Universidade Federal do Rio Grande do Sul
Faculdade de Medicina
Programa de Pós-Graduação em Epidemiologia

Tese de Doutorado

Protocolos de terapia de indução em pacientes portadores de mieloma múltiplo em primeira linha de tratamento: revisão sistemática e metanálise por *mixed treatment comparison*

Aluno: Leo Sekine
Orientador: Prof. Dr. Rodrigo Antonini Ribeiro
Co-orientadora: Profª Drª Patrícia Klarmann Ziegelmann

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“The evil that is in the world almost always comes of ignorance, and good intentions may do as much harm as malevolence if they lack understanding.”

- Albert Camus.

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Sumário

Abreviaturas e Siglas

Abreviatura/Sigla	Significado
A-HPCT	*Autologous Hematopoietic Progenitor Cell Transplantation*
ANVISA	Agência Nacional de Vigilância Sanitária
auto/RICallo	Transplante autótologo seguido de um transplante alogênico com condicionamento reduzido
B	*Bortezomib*
B2M	Beta-2-microglobulina
BCNU	*Carmustine*
CI	*Confidence Interval*
CIBMTR	*Center for International Blood and Marrow Transplant Research*
CKD-EPI	*Chronic Kidney Disease Epidemiology Collaboration*
CPR	Ciclofosfamida, prednisona e lenalidomida
CR	*Complete Response*
CRAB	*Calcium (Hypercalcemia), Renal failure, Anemia and Bone fractures/lesions* (Acrônimo das principais manifestações clínicas do MM)
CrI	*Credible Interval*
CTD	Ciclofosfamida, talidomida e dexametasona
CTH	Células Tronco Hematopoéticas
CVAD	Ciclofosfamida, vincristina, doxorrubicina e dexametasona
Dex	Dexametasona em altas doses (Monoterapia)
EBMT-NMAM200	*European Group for Blood and Marrow Transplantation Non-Myeloablative Allogeneic Stem Cell transplantation in MM*
ECR	Ensaio Clínico Randomizado
EUA	Estados Unidos da América
FDA	*Food and Drug Administration*
FISH	*Fluorescence in situ hybridization*
HCT-CI	*Hematopoietic Cell Transplantation-Comorbidity Index*
HDAC	*Histone Deacetylase Inhibitors*
HR	*Hazard Ratio*
IADL	*Instrumental Activities of Daily Living*
IMiDs	*Immunomodulatory imide Drugs*
IMWG	*International Multiple Myeloma Working Group*
ISS	*International Staging System*
L	*Lenalidomide*
Ld	Lenalidomida e dexametasona em número pré-determinado de ciclos
LD	Lenalidomida e altas doses de dexametasona

Ldc	Lenalidomida e dexametasona em ciclos ininterruptos até progressão
LDH	*Lactate Dehydrogenase*
mABs	*Monoclonal Antibodies*
MCNU	*Ranimustine*
MD	Melfalano e dexametasona
MDRD	*Modification of Diet in Renal Disease*
MGUS	*Monoclonal Gammopathy of Undetermined Significance*
MM	Mieloma Múltiplo/Multiple Myeloma
MP	Melfalano e prednisona
MPR	Melfalano, prednisona e lenalidomida
MPR-R	Melfalano, prednisona e lenalidomida e manutenção com lenalidomida
MPT	Melfalano, prednisona e talidomida
MPT-T	Melfalano, prednisona e talidomida e manutenção com talidomida
mSMART	Mayo Stratification for Myeloma and Risk-Adapted Therapy
MTC	*Mixed Treatment Comparison*
NMA	*Network Meta-Analysis*
NPS	Neoplasia Primária Secundária (Nova neoplasia como resultado de um tratamento oncológico anterior)
NU-based	Regime baseado em nitrosouréia (BCNU ou MCNU)
OR	*Overall Response*
OS	*Overall Survival*
PAD	Bortezomibe, doxorrubicina and dexametasona
PCR	Proteína C Reativa
PET	*Positron emission tomography*
PFS	*Progression Free Survival*
PIs	*Proteasome Inhibitors*
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta- Analyses*
R-ISS	*Revised International Staging System*
RC	Resposta Completa
RCT	*Randomized Clinical Trial*
RD	Lenalidomida e Dexametasona
RM	Ressonância Magnética
RR	*Risk Ratio*
RS	Revisão Sistemática
RVD	Lenalidomida, bortezomibe e dexametasona
SG	Sobrevida Global
SLP	Sobrevida Livre de Doença
SMM	*Smoldering Multiple Myeloma*
SR	*Systematic Review*
SUCRA	*Surface Area Under de Cumulative Ranking*

T	*Thalidomide*
TAD	Talidomida , doxorrubicina e dexametasona
TADoses	Terapia de altas doses
TBI	*Total Body Irradiation*
TCPH	Transplante de Células Progenitoras Hematopoéticas
TCPH-Auto	Transplante de Células Progenitoras Hematopoéticas Autólogo
TD	Talidomida e dexametasona
TFG	Taxa de filtração glomerular
TP	Tempo para Progressão
TR	Taxa de Resposta
TT2+Thal	*Total Therapy 2* com talidomida. É um protocolo de múltiplas drogas e regimes sequenciais.
UK	*United Kingdom*
VAD	Vincristina, doxorubicina e dexametasona
Vd	Bortezomibe e dexametasona
VGPR	*Very Good Partial Response*
VMCP	Vincristina, melfalano, ciclofosfamida e prednisona intermitente
VMCPc	Vincristina, melfalano, ciclofosfamida e prednisona contínua
VMP	Bortezomibe, melfalano e prednisona
VMPT-VT	Bortezomibe, melfalano, prednisona e talidomida
VRd	Bortezomibe, lenalidomida e dexametasona
VTd	Bortezomibe, talidomida e dexametasona em dose reduzida
VTD	Bortezomibe, talidomida e dexametasona
VTDC	Bortezomibe, talidomida, dexametasona e ciclofosfamida
VTP	Bortezomibe, talidomida e prednisona
Z-Dex	Idarrubicina e dexametasona

Resumo

Introdução: o mieloma múltiplo (MM) é uma enfermidade de crescente incidência devido à melhora da expectativa de vida de diversas populações ao redor do mundo. Seu tratamento é composto por duas estratégias primordiais que separam os pacientes recém-diagnosticados em dois grupos: aqueles elegíveis a transplante de células progenitoras hematopoéticas autólogo (TCPH-Auto) e aqueles que não o são. Tal divisão é determinada por fatores inerentes ao paciente, como idade, performance status e comorbidades.

O número de tratamentos disponíveis para esta doença tem se multiplicado de forma rápida nos últimos anos. Devido a diversos fatores logísticos e econômicos, a comparação simultânea dessas abordagens terapêuticas em um ensaio clínico randomizado (ECR) é improvável. Dessa forma, a comparação de eficácia e segurança entre estes diversos protocolos, no intuito de determinar a melhor opção, só pode ser alcançada através de ferramentas como a revisão sistemática (RS) seguida por metanálise em rede.

Métodos: com base nessa premissa, realizamos uma RS e metanálise em rede por *mixed treatment comparison* (MTC) compreendendo tratamentos citotóxicos de indução (primeira linha) para pacientes com diagnóstico recente de MM. Este estudo utilizou-se da já estabelecida divisão terapêutica deste seguimento de pacientes: elegíveis e inelegíveis a TCPH-Auto. A revisão sistemática utilizou uma estratégia de busca sensível com incorporação de um filtro para ECR e consultou as bases de dados PubMed/MEDLINE, EMBASE, Cochrane CENTRAL SciELO e LILACS. Ao todo, foram avaliadas 15.091 referências após a retirada de duplicatas. Tais referências foram então revisadas por pares de pesquisadores de forma paralela, para inclusão em um dos dois grupos em avaliação.

Resultados: o estudo de pacientes elegíveis selecionou 18 publicações envolvendo 9 ECR, totalizando 4.432 pacientes arrolados entre 10 abordagens diferentes de tratamento. Similaridade entre tratamentos pareceu adequada em relação ao delineamento, metodologia e amostra selecionada. Homogeneidade e consistência não puderam ser aferidas devido à rede apresentar apenas comparações indiretas. O desfecho de sobrevida global (SG) apontou o PAD (bortezomibe,

doxorrubicina e dexametasona) como protocolo de melhor resultado em relação aos demais tratamentos, enquanto o VTD (bortezomibe, talidomida e dexametasona) foi o melhor protocolo no que tange a sobrevida livre de progressão (SLP). Na análise de perfil de resposta ao tratamento, a resposta completa e a resposta global (desfecho combinado de níveis diferenciados de resposta, incluindo a completa) também se mostrou mais frequente com o esquema VTD. Uma análise de segurança foi realizada compreendendo eventos adversos de grau 3 e 4 infeciosos, cardíacos, gastrointestinais, neurológicos, trombóticos e hematológicos. O risco de eventos trombóticos foi maior com o esquema TAD (talidomida, doxorrubicina e dexametasona), neurológicos com o PAD, infecciosos com o Dex (altas doses de dexametasona), hematológicos com o Z-Dex (idarrubicina e dexametasona), gastrointestinais com o VTD e cardíacos com o PAD. Um desfecho combinado considerando os ranqueamentos (probabilidades de ser o melhor tratamento) dos tratamentos para cada um dos desfechos (realizado através do SUCRA – surface under the cumulative ranking curve) foi calculado para os desfechos de sobrevida, resposta e toxicidade e indicou o VTD, seguido pelo PAD e TAD como os melhores tratamentos em geral. Nosso estudo mostrou que para os tratamentos de primeira linha em pacientes elegíveis a TCPH-Auto a melhor opção de tratamento envolveria o uso de um triplet (tratamento composto por três drogas), principalmente incluindo o uso de novos agentes: drogas imunomodulatórias (IMiDs) e inibidores do proteasoma (PIs).

O estudo de pacientes inelegíveis selecionou 54 publicações envolvendo 27 ECR, totalizando 11.967 pacientes arrolados entre 23 abordagens diferentes de tratamento. Similaridade entre tratamentos pareceu adequada em relação ao delineamento, metodologia e amostra selecionada. Foi encontrada heterogeneidade moderada a alta entre os estudos que comparavam os mesmos tratamentos para os desfechos de sobrevida (SG e SLP) e para 3 desfechos de toxicidade (hematológico, gastrointestinal e cardíaco). Não foi encontrada inconsistência entre as evidências diretas e indiretas das medidas de efeito que compuseram a medida da MTC. Análise de SG identificou a superioridade do VRd (bortezomibe, lenalidomida e dexametasona), VMPT-VT (bortezomibe, melfalano, prednisona e talidomida), MPR-R (melfalano, prednisona, lenalidomida), Ldc (lenalidomida e dexametasona) e CPR (ciclofosfamida, prednisona e lenalidomida). A SLP foi maior com MPR-R, seguido do MPT-T (melfalano,

prednisona e talidomida), VMPT-VT, Ldc e VRd. A resposta completa foi mais comum com regimes contendo bortezomibe (VMPT-VT, VTP – bortezomibe, talidomida e prednisona, VMP – bortezomibe, melfalano e prednisona, Vd – bortezomibe e dexametasona, e VRd), enquanto a resposta global foi liderada também pelo VMPT-VT, seguido por Vd, VTd (bortezomibe, talidomida e dexametasona), LD (lenalidomida e dexametasona em altas doses) e VTP. Um desfecho compilado de toxicidade (hematológica, gastrointestinal, neurológica, cardíaca, trombótica e infecciosa) apontou o Dex e o MP (melfalano e prednisona) como os regimes mais com a menor incidência de eventos adversos, embora também tenham sido os tratamentos com os piores resultados no quesito sobrevida e resposta. Uma vez ponderadas as diversas probabilidades de ser o melhor tratamento, considerando sobrevida, resposta e toxicidade, ficou indicado o regime VMPT-VT como a melhor abordagem terapêutica, seguida do VRd, MPR-R, VMP e Ldc. Por outro lado, os regimes com piores posicionamentos foram o Dex, TD (talidomida e dexametasona em altas doses), VMPC (vincristina, melfalano, prednisona e ciclofosfamida) com ou sem prednisona contínua, MP e MD (melfalano e dexametasona).

Conclusão: os resultados do presente trabalho favorecem o uso de esquemas *triplets* e *triplets* ou *quadruplets* (contendo agentes IMiDs e PIs) para pacientes elegíveis e inelegíveis a TCPH-Auto, respectivamente. Além disso, para os pacientes inelegíveis, estratégias que incluam o uso continuado de lenalidomida, devem ser priorizadas em relação a outros esquemas.

Abstract

Introduction: Multiple myeloma (MM) is a disease of growing incidence due to the widening of population life span in several populations around the world. Its management is composed by two main strategies that separate newly diagnosed patients in two groups: those that are eligible to autologous hematopoietic progenitor cell transplantation (A-HPCT) and those that are ineligible. This classification is determined by factors inherent to the patient such as age, performance status and comorbidities.

The amount of available treatments for this disease have been multiplying in a rapid pace over the last years. Due to several logistic and economic factors, the simultaneous comparison of therapeutic approaches in a randomized clinical trial is unlikely. As a result, the comparison of efficacy and safety among this many treatments, in order to find the best overall option, can only be attained through approaches like systematic review (SR) followed by a network meta-analysis.

Methods: With this in mind, we performed a SR and MTC meta-analysis involving induction (frontline) cytotoxic treatment for patients with recently diagnosed MM. This study followed current management framework where transplant eligibility defines the path of treatment. This systematic review used a very sensitive search strategy along with an ECR filter while consulting PubMed/MEDLINE, EMBASE, SciELO and LILACS databases. A total of 15.091 references, after duplicates exclusion, were peer-reviewed and allocated to one of the two main population groups.

Results: For transplant eligible patients, final search resulted in 18 publications involving 9 different randomized clinical trials, enrolling 4,432 patients and comparing 10 different treatment regimens that were evaluated regarding survival, response and safety outcomes. Similarity among study designs, methodology and population was considered adequate. The available network allowed only for indirect evidence analysis, thus consistency and homogeneity tests were not applicable. Overall survival (OS) analysis showed superiority of PAD (bortezomib, doxorubicin and dexamethasone) over other regimens, while for progression-free survival (PFS) outcome, VTD (bortezomib, thalidomide and dexamethasone) was considered the best treatment option. Also, for complete response and overall response, once more VTD showed clear superiority

among analyzed protocols. Safety profile evaluated infectious, cardiac, gastrointestinal, neurological, thrombotic and hematological grade 3-4 adverse events. Risk of thrombotic events was higher with TAD (thalidomide, doxorubicin, dexamethasone), neurological with PAD, infectious with high dose dexamethasone (Dex), hematological with Z-Dex (Idarubicin and dexamethasone), gastrointestinal with VTD and cardiac with PAD. A compiled outcome considering best ranked treatments (in regard to being the best choice among all) concerning survival, response and toxicity (using SUCRA value) indicated that VTD, followed by PAD and TAD were superior treatments overall.

The transplant-ineligible patients study comprised 27 randomized clinical trials, enrolling 11.967 patients and comparing 23 different treatment regimens regarding survival, response and safety outcomes. Similarity among study designs, methodology and population was considered adequate. Heterogeneity was found for identical pairwise comparison studies concerning survival outcomes and 3 adverse event outcomes (hematological, gastrointestinal and cardiac). No significant inconsistency was found for all endpoints. OS analysis showed superiority of VRd (bortezomib, lenalidomide and dexamethasone), VMPT-VT (bortezomib, melphalan, prednisone and thalidomide), MPR-R (melphalan, prednisone and lenalidomide), Ldc (lenalidomide and dexamethasone) and CPR (cyclophosphamide, prednisone and lenalidome). PFS was longer with MPR-R, followed by MPT-T (melphalan, prednisone and thalidomide), VMPT-VT, Ldc and VRd. Complete remission was more common with bortezomib-containing regimens (VMPT-VT, VTP – bortezomib, thalidomide and prednisone, VMP – bortezomib, melphalan and prednisone, Vd – bortezomib and dexamethasone, and VRd), while overall response rate was also leaded by VMPT-VT, followed by Vd, VTd (bortezomib, thalidomide and dexamethasone), LD (lenalidomide and high dose dexamethasone) and VTP. Safety profile evaluated infectious, cardiac, gastrointestinal, neurological, thrombotic and hematological grade 3-4 adverse events. A compound toxicity analysis presented high dose dexamethasone (Dex) and MP (melphalan and prednisone) as regimens with the lowest incidence of adverse events, although with also the lowest survival and/or response rates. A compiled outcome considering best ranked treatments regarding survival, response and toxicity indicated that VMPT-VT, followed by VRd, MPR-R, VMP and Ldc. On the other hand, last ranked treatments overall were Dex, TD (thalidomide and dexamethasone), VMPC (vincristine, melphalan, prednisone

and cyclophosphamide) with and without continuous prednisone, MP and MD (melphalan and dexamethasone)

Conclusion: our results favor the use of *triplets* and *triplets* or *quadruplets* (containing IMiDs an PIs) for transplant eligible and ineligible patients, respectively. Moreover, for transplant-ineligible patients, regimens comprising long term use of lenalidomide, should be preferred.

1. Apresentação

Este trabalho consiste na tese de doutorado intitulada “Protocolos de terapia citotóxica de indução em pacientes portadores de mieloma múltiplo em primeira linha de tratamento: revisão sistemática e metanálise por *mixed treatment comparison*”, apresentada ao Programa de Pós-Graduação em Epidemiologia da Universidade Federal do Rio Grande do Sul, no dia 08 de janeiro de 2018. O trabalho é apresentado em três partes, na ordem que segue:

1. Introdução, Revisão da Literatura e Objetivos
2. Artigo(s)
3. Conclusões e Considerações Finais.

Documentos de apoio estão apresentados nos anexos.

2. Introdução

O mieloma múltiplo (MM) é uma neoplasia que tem um tropismo especial pela medula óssea e tecidos ósseos adjacentes (pelve, coluna e costelas) e é resultado da proliferação desordenada de plasmócitos clonais, que são linfócitos B pós-centro germinativo que se tornaram autonomamente regulados. Os plasmócitos são células pertencentes ao sistema imunológico normal e têm por função primordial a produção de anticorpos, via expansão clonal regida por diversos mecanismos regulatórios. No MM, estas células tornam-se não senescentes e retroalimentam sua própria expansão clonal via liberação de interleucinas, passando a produzir quantidades excessivas de um anticorpo aberrante, uma imunoglobulina monoclonal, chamada de proteína M. Os mecanismos inerentes ao desenvolvimento de linhagens clonais neoplásicas de plasmócitos são ligados a translocações cromossômicas envolvendo os genes ligados às cadeias de imunoglobulinas além de aneuploidia (via de regra, hiperdiploidia). Duas etapas primordiais compõe a série de alterações mutacionais que resultam no MM: uma resposta inadequada ao estímulo antigênico e desregulação do controle do ciclo celular culminando em vias de escape em relação ao processo normal de apoptose. À medida que as células neoplásicas se acumulam, o funcionamento da medula óssea fica comprometido, seja pela interferência funcional nas demais células do microambiente medular, seja pela limitação do espaço intramedular para proliferação das células saudáveis. Em fases mais avançadas da doença, os plasmócitos neoplásicos migram para fora do ambiente medular, dando origem aos plasmocitomas extramedulares e à leucemia de células plasmáticas. (Cejalvo 2017, Engelhardt 2014, Kumar 2017, Lonial 2011, Picot 2011, Rollig 2015)

O MM é a segunda neoplasia hematológica mais comum no mundo (logo após o linfoma), representando cerca de 1,7% de todas as neoplasias existentes, e cerca de 10 a 13% das neoplasias hematológicas. Em 2007, foram diagnosticados 3.357 novos casos de MM na Inglaterra e aproximadamente 86.000 novos casos de MM ocorrem todos os anos no mundo, com uma incidência de cerca de 4,5-6,0 casos novos para cada 100.000 habitantes/ano, na Europa e EUA. (Kumar 2003, Kumar 2017, Moreau 2017, Rajkumar 2016, Rollig 2015) A mortalidade é de cerca de 3,4 a 4,1/100.000 habitantes/ano, e esta taxa teve um aumento progressivo até os anos 2000, quando

foram introduzidos os novos agentes anti-neoplásicos, da classe de imunomoduladores e inibidores do proteasoma. (Kumar 2017, Moreau 2015, Moreau 2017, Rollig 2015, Torimoto 2015) Uma frequência maior pode ser encontrada em países desenvolvidos como EUA, Austrália e países da Europa Ocidental, devido muito provavelmente a um maior acesso à saúde, melhores técnicas de detecção, maior índice de suspeição dos profissionais de saúde e maior expectativa de vida. (Kumar 2017) A maior incidência ocorre entre 75 e 79 anos de idade com uma mediana de idade de cerca de 69 a 72 anos, com mais de 61,9% dos pacientes possuindo mais de 65 anos no diagnóstico. (Moreau 2017, Rollig 2015) Raramente é observado antes dos 40 anos (apenas 2% dos pacientes). (Rajkumar 2016) É mais comum em homens em relação a mulheres, e afrodescendentes em relação a hispânicos e asiáticos. (Rajkumar 2016) A incidência é cerca de 2 a 3 vezes maior em afro-americanos (a *monoclonal gammopathy of undetermined significance* também é mais frequente neste grupo), sendo a principal neoplasia hematológica neste grupo étnico. (Rajkumar 2016) A Cancer Research UK estimou, através de dados epidemiológicos dos anos de 2001-2005, que a estimativa do risco de desenvolver MM durante a vida é de cerca de 1/148 em homens e 1/186 em mulheres. (Ludwig 2010, Picot 2011)

Diversos fatores predisponentes já foram estudados, embora as conclusões sejam ainda pouco consistentes. Possíveis fatores de risco externos que já foram avaliados são: radiação ionizante, pesticidas, solventes, agentes infecciosos, atividade rural, corantes de cabelo, benzeno e derivados do petróleo. No entanto, as evidências e medidas de efeito encontradas ainda são muito escassas e de pequena magnitude para tecer conclusões definitivas. (Kumar 2017) Quanto à possível predisposição genética, observou-se que algumas famílias já foram identificadas com incidência aumentada de casos da doença, além do fato de que familiares de primeiro grau de pacientes com MGUS tem um risco aumentado em 2 vezes de apresentar a mesma desordem. Estudos de *genome-wide association* já conseguiram identificar múltiplos *loci* gênicos associados com um aumento no risco para MM. (Kumar 2017)

A doença tende a ter um início insidioso, com evolução gradativa. Praticamente todos os pacientes evoluem de uma fase pré-maligna assintomática chamada de *monoclonal gammopathy of undetermined significance (MGUS),* embora devido à sua natureza silenciosa apenas 10% dos pacientes com diagnóstico novo de MM tenham

diagnóstico anterior de *MGUS*. (Kumar 2017, Moreau 2017, Rajkumar 2016) A *MGUS* pode ser observada em 3 a 4% da população em geral após os 50 anos de idade. (Kumar 2017, Moreau 2017) Observou-se ainda que os pacientes com MM que já eram acompanhados clinicamente em função do diagnóstico de *MGUS* mostraram melhor sobrevida do que aqueles diagnosticados já com doença estabelecida e, destes, aqueles com pico monoclonal inferior a 0,5 g/dL mostravam pior sobrevida global (SG) do que aqueles com pico entre 0,5 e 3,0 g/dL. (Kumar 2017) A taxa de progressão da *MGUS* para MM é de cerca de 1% ao ano e, ao todo, cerca de 15% dos pacientes tornar-se-ão portadores de MM, além de outros cerca de 5% que progredirão para outras neoplasias hematológicas (amiloidose, macroglobulinemia de Waldenström ou outra desordem linfoproliferativa), num período de observação de até 25 anos. (Kumar 2016, Kumar 2017, Moreau 2017, Rajkumar 2016) Em outros pacientes, uma fase pré-maligna intermediária, pode ser identificada chamada de *smouldering* ou *indolent multiple myeloma* (SMM). (Moreau 2017, Rajkumar 2016) O SMM progride para MM a uma taxa de 10% ao ano nos primeiros 5 anos do diagnóstico, 3% ao ano nos 5 anos subsequentes, e 1,5% ao ano nos anos posteriores. (Moreau 2017)

Inicialmente a progressão para MM pode levar à fadiga, perda de peso e susceptibilidade a infeções. Com o avanço da doença, pode haver comprometimento ósseo com lesões líticas, fraturas patológicas, hipercalcemia e dor incapacitante. O acometimento da medula óssea pode levar a citopenias como anemia, leucopenia e plaquetopenia. Outra manifestação característica da doença é a insuficiência renal, via de regra multifatorial, mas principalmente precipitada pela hiperproteinemia e hipercalcemia. (Lonial 2011, Picot 2011, Rollig 2015)

A avaliação do paciente suspeito de MM inclui a realização de exames como proteína total no soro, proteinograma e imunofixação (séricas e em urina de 24 horas), pesquisa de cadeias leves livres (e a relação Kappa/Lambda, especificamente a concentração de cadeia clonal/não-clonal >100, que também possui informação prognóstica), hemograma completo, creatinina e uréia, eletrólitos, cálcio, LDH, albumina e β2-microglobulina. (Kumar 2017, Moreau 2017, Pratt 2017) A ausência de resultado anormal na eletroforese de proteínas séricas e urinárias não exclui a probabilidade do diagnóstico e deve receber complementação diagnóstica se a suspeita for proeminente. (Moreau 2017, Pratt 2017) A biópsia com trefina e o aspirado de

medula óssea também fazem parte inerente da avaliação. O medulograma deve ser utilizado primariamente para avaliar o percentual de infiltração enquanto a citometria de fluxo deve ser utilizada para a confirmação do imunofenótipo anômalo e clonal das células plasmocitárias (além de ser útil na monitorização do clone durante o tratamento). (Moreau 2017, Pratt 2017) Além das avaliações morfológicas e fenotípicas, é importante encaminhar o material para a realização do *FISH* (*fluorescence in situ hybridization*) para identificação de anormalidades cromossômicas com mau prognóstico como t(4;14), t(14;16), amplificação do 1q21, del(1p) e del(17p) (deleção TP53). (Moreau 2017) Além destas também é importante a detecção da t(14;20), t(11;14) e hiperdiploidia. (Pratt 2017) No fragmento de biópsia, deve ser pesquisada a expressão de marcadores como Ki-67 e o p53, que também possuem conotação prognóstica. (Pratt 2017)

Exame de imagem deve ser realizado em todos os pacientes com suspeita de MM para a detecção de lesões líticas características da doença. O exame recomendado é a ressonância magnética (RM) de corpo inteiro ou, caso inacessível, a tomografia computadorizada (TC) de baixa dose de corpo inteiro. O PET (Positron Emission Tomography) pode ser útil em algumas situações específicas (possui sensibilidade cerca de 20-30 vezes maior do que um *screening* com radiografias comuns, embora sua especificidade não seja ideal). (Landgren 2016) Radiografias devem ser reservadas apenas para os pacientes sem possibilidade de realizar os exames previamente citados, por serem pouco sensíveis. (Moreau 2017, Pratt 2017) Cintilografia óssea não deve fazer parte da avaliação do paciente com MM. (Pratt 2017)

O diagnóstico é usualmente firmado através da identificação de uma proteína monoclonal (soro ou urina), plasmocitose acima de 10% na medula óssea e lesão em órgão alvo, avaliada classicamente pelo acrônimo em inglês *CRAB*: hipercalcemia (cálcio sérico com aumento igual ou superior a 1 mg/dL acima do limite máximo do valor de referência), falência renal (creatinina superior a 2 mg/dL ou uma taxa de filtração glomerular (TFG) inferior a 40 ml/min estimada via MDRD ou CKD-EPI), anemia (redução de 2 g/dL de hemoglobina ou mais além do limite mínimo do valor de referência) e doença óssea, conforme critérios atualizados pelo IMWG (International Myeloma Working Group). (Kumar 2017, Moreau 2017) Lesões líticas podem ser definidas por TC, PET-CT ou mesmo por radiografias. (Moreau 2017) Alguns pacientes são, mesmo após

extensa investigação, considerados não-secretores, portanto a presença de um pico monoclonal não é obrigatória para a definição diagnóstica. (Kumar 2017) Pacientes que não apresentem manifestações clássicas de lesão em órgão alvo, ainda podem ser diagnosticados como portadores de MM se apresentarem biomarcadores da doença como: plasmocitose medular clonal superior a 60% (mensurada por mielograma, exame anatomopatológico ou citometria de fluxo, o que for maior), relação de cadeia leve clonal/não clonal maior do que 100 ou duas ou mais lesões focais na RM (cada lesão focal deve medir pelo menos 5 mm). (Landgren 2016, Moreau 2017) Plasmocitose inferior a 10% mas com proteína monoclonal acima de 3 g/dL também são diagnósticas, caso hajam manifestações pertinentes. Pacientes não secretores de proteína monoclonal, necessitam de mais de 30% de plasmocitose, ou presença de plasmocitomas para diagnóstico. Um plasmocitoma isolado (ósseo ou em sítio extra-ósseo), com menos de 10% de plasmocitose, medular é chamado de plasmocitoma solitário e se comporta distintamente do MM, tanto no prognóstico quando no tratamento. Como citado anteriormente, outras classificações envolvem estágios da doença onde não há identificação de lesão em órgão alvo (pré-malignas) e compreendem o *SMM* (quando há plasmocitose entre 10% e 60% na medula, e/ou pico monoclonal sérico IgG/IgA acima de 3 g/dL e/ou urinário acima de 500 mg/24 horas, na ausência de manifestações atribuíveis à doença) e o *MGUS* (quando existe pico monoclonal, mas não é preenchido o critério mínimo para SMM). (Moreau 2017)

Alguns parâmetros avaliados no momento do diagnóstico podem predizer o prognóstico destes pacientes tais como ß2-microglobulina (B2M), albumina, proteína C reativa (PCR) e desidrogenase láctica (LDH). O *ISS (International Staging System)* leva em consideração os valores laboratoriais da B2M e a da albumina para estratificar os pacientes em 3 estágios de doença, sendo o que o estágio III é o de pior prognóstico. (Kumar 2017, Moreau 2017) A função renal (cerca de 50% dos pacientes terão taxa de filtração glomerular estimada menor do que 60 mL/min), as alterações citogenéticas (como a t(4;14), t(14;16), t(14;20), deleção do braço curto do cromossomo 17 além de qualquer cariótipo não-hiperdiplóico), imunoparesia, número de plasmócitos circulantes, presença de doença extramedular, taxa de proliferação plasmocitária elevada, morfologia plasmablástica e fragilidade do paciente (mensurada por várias escalas, isoladas ou combinadas) também são fatores preponderantes. (Kumar 2017,

Moreau 2015, Rollig 2015, Torimoto 2015) Em um estudo de fatores prognósticos, uma análise multivariada evidenciou que a fragilidade do paciente foi o fator prognóstico mais importante a determinar a SG do paciente com MM, sendo mais importante inclusive do que o *ISS* e as alterações citogenéticas. (Moreau 2015, Moreau 2017) Recentemente, uma versão revisada do *ISS (R-ISS,* que também conta com 3 categorias*)* que considera o resultado do *FISH* e do LDH em conjunto com *ISS* mostrou melhor poder discriminativo em desfechos como SG e sobrevida livre de progressão (SLP). (Kumar 2017, Moreau 2017) Com base nesse fato, o *IMWG* propôs um escore de fragilidade (baseado em idade, comorbidades e condições cognitivas e físicas) capaz de predizer a mortalidade e o risco de toxicidade relacionada ao tratamento entre os pacientes. (Moreau 2017) *Gene expression profiling* também é uma técnica de estratificação prognóstica baseada na mensuração de atividade de alguns genes específicos e foi incorporada num escore prognóstico publicado pela Mayo Clinic em 2013, o mSMART. Esta técnica se mostrou capaz de identificar pacientes de alto risco e potencialmente guiar decisões terapêuticas, mas suas metodologias não são adequadamente padronizadas e seu custo é muito elevado, sendo ainda pouco acessível para o público em geral. (Genadieva-Stavric 2017, Kumar 2017, Moreau 2017) Embora bastante informativos, o uso de escores prognósticos como o *ISS* e *R-ISS* para determinar estratégias de tratamento para estes pacientes ainda não é consenso. (Kumar 2017)

O MM é convencionalmente incurável (Cejalvo 2017) (embora algumas alternativas curativas existam para alguns subgrupos selecionados de pacientes, como o transplante alogênico de células progenitoras hematopoéticas), mas pode ser controlado por longos períodos de tempo com uma combinação de medidas de suporte e quimioterapia para prolongar a sobrevida e melhorar a qualidade de vida. Nestes termos, a expectativa de sobrevida média para alguns subgrupos pode chegar a mais de 10 anos. (Cejalvo 2017, Kumar 2017, Landgren 2016, Picot 2011) Atualmente, correntes de pesquisadores debatem o dilema “cura x controle” dentro do âmbito terapêutico do MM, no entanto, a capacidade de estratificação de risco e de performance ainda pouco discriminativas limitam a segregação de pacientes para uma ou outra alternativa de tratamento de forma adequada. (Genadieva-Stavric 2017)

O tratamento do MM tem por objetivo primordial incrementar o tempo de sobrevida e a qualidade de vida através da redução das manifestações da doença e seus

sinais e sintomas correlatos, ao mesmo tempo que procura minimizar os efeitos adversos do tratamento. Com o tratamento, almeja-se alcançar um período de estabilidade de doença (fase de *plateau*) pelo maior tempo possível. Um dos grandes parâmetros para determinação de linha de tratamento é a elegibilidade para transplante de células progenitoras hematopoéticas autólogo (TCPH-Autouto). Pacientes elegíveis tendem a ser tratados de forma mais agressiva até a obtenção da resposta máxima antes do momento do transplante. Pacientes inelegíveis costumeiramente são tratados com terapias de menor toxicidade por períodos de tempo mais prolongados, ou mesmo apenas tratamento de suporte. (Dingli 2010, Picot 2011)

Após o tratamento de primeira linha, a maioria dos pacientes apresenta alguma resposta, classificada através da redução percentual da quantidade do componente monoclonal em remissão parcial até completa. No entanto, em teoria, todos invariavelmente irão recidivar sua doença em algum momento. Uma minoria dos pacientes não responderá a terapias de primeira linha, sendo considerado refratários. (Kapoor 2012, Picot 2011)

Por se tratar, portanto, de uma neoplasia com características de doença crônica e com múltiplos momentos de indicação de terapia durante sua história natural, muitas alternativas terapêuticas foram desenvolvidas ao longo das décadas. Algumas caíram em desuso, outras se sedimentaram pela sua tradição e experiência, e muitas têm entrado no cenário terapêutico nas últimas décadas. Optar por uma ou outra alternativa tem se tornado cada vez mais difícil dada esta multiplicidade de alternativas e a falta de comparações diretas entre as mesmas. Existe uma crescente necessidade de olhar criticamente para estes novos fármacos e contrapô-los aos que já possuem larga experiência de uso de forma a embasar, ou refutar, uma proposta de mudança de paradigmas. No entanto, a plausibilidade de um grande ensaio clínico randomizado que possa abranger tal objetivo é absolutamente improvável na atualidade. Outras alternativas de responder este questionamento devem, portanto, ser implementadas.

3. Revisão da Literatura

É consenso que o paciente portador de gamopatia monoclonal com manifestações clínico-laboratoriais atribuíveis à condição de base tem indicação inequívoca de tratamento. Grande parte das diretrizes não recomendam o tratamento em fases anteriores da doença, onde lesões em órgão alvo ainda inexistam. No entanto, a definição e detecção destas lesões tem passado por um contínuo processo de aprimoramento (tornando obsoleto o acrônimo *CRAB*, citado anteriormente), reduzindo a certeza da delimitação entre doença sintomática e assintomática. (Engelhardt 2014) Um estudo relativamente recente de selecionou pacientes com SMM e alto risco de progressão e randomizou-os para tratamento com lenalidomida e dexametasona ou placebo. (Mateos 2013) Os resultados demonstraram benefício na taxa de progressão para MM e na SG dos pacientes tratados. Tais evidências colocam em discussão os determinantes para indicação de tratamento para MM, mas carecem de replicação em outros cenários antes de serem traduzidas para a prática diária.

As terapias específicas para o MM iniciaram na década de 60 com a tradicional combinação do melfalano e prednisona (MP), e este esquema manteve-se como tratamento padrão por mais de 40 anos. Até então, grande parte das alternativas terapêuticas descritas em literatura eram rigorosamente ineficazes. Embora muitos esquemas de drogas combinadas tenham sido desenvolvidos até os anos 2000 com o objetivo de superar o MP (e efetivamente alguns mostraram taxas de resposta superiores), estes acabaram falhando em demonstrar benefício claro em SG, e não se firmaram no rol de alternativas terapêuticas. Neste cenário, a terapia de altas doses (TADoses) com melfalano e o transplante/resgate de células progenitoras hematopoéticas autólogo (TCPH-Auto), estabeleceu-se como terapia de escolha para pacientes com menos de 65 anos por seus resultados até então incomparáveis na taxa de resposta (TR) e na SLP. (Moreau 2015, Torimoto 2015)

Na última década, um dos maiores avanços no manejo do MM foi a introdução de novos agentes farmacológicos, tais como talidomida, bortezomibe e lenalidomida, na terapia inicial ou de primeira linha em pacientes candidatos ou não a transplante. Estas drogas contribuíram de forma importante para a taxa de remissão completa (RC), sem aumentar substancialmente a incidência de efeitos adversos, e além disso

permitiram o aumento do tempo para progressão (TP), SLP e SG. (Genadieva-Stavric 2017, Moreau 2015, Torimoto 2015) Ainda, outros tratamentos mais inovadores como anticorpos monoclonais (daratumumabe, elotuzumabe, siltuximabe, nivolumabe, pembrolizumabe), inibidores de proteasoma de segunda geração (carfilzomibe, ixazomibe, marizomibe, oprozomibe), imunomoduladores de terceira geração (pomalidomida) e inibidores de histona deacetilase (panobinostat), muitos ainda no *"pipeline"*, têm se mostrado como valiosas promessas terapêuticas para os pacientes em situação de recidiva. (Cejalvo 2017, Engelhardt 2014, Genadieva-Stavric 2017) A evolução farmacológica acompanhada pela melhoria na terapia de suporte tornou possível o aumento na mediana de SG nesses pacientes de 2,5 anos antes de 2001, para 4,6 anos entre 2001 e 2005, e para 6,1 anos entre 2006 e 2010. (Genadieva-Stavric 2017)

As abordagens de tratamento dependem do *"fitness"* do paciente, sendo a idade ainda um forte fator discriminante para a seleção de terapia. A avaliação inicial dos pacientes inclui uma análise sobre a elegibilidade do paciente para TADoses e TCPH-Auto baseada na idade, status da *performance* (diz respeito a susceptibilidade do paciente a complicações ligadas ao tratamento quimioterápico), e comorbidades. (Genadieva-Stavric 2017, Moreau 2015) Atualmente, um escore de fragilidade desenvolvido pelo IMWG (citado anteriormente também como marcador prognóstico), publicado em 2015, tem ganhado popularidade na avaliação da plausibilidade das diversas alternativas terapêuticas. Neste escore os pacientes podem ser classificados como "*fit"*, *"intermediate"* e *"frail"*. Pacientes *"fit"* podem ser submetidos a terapias triplas em dose plena; enquanto pacientes *"intermediate"* são submetidos a terapia triplas menos intensivas ou duplas; e pacientes *"frail"* podem se beneficiar de terapias duplas atenuadas ou mesmo terapia paliativa (Genadieva-Stavric 2017). O preenchimento dos critérios de elegibilidade para TCPH-Auto é um grande "divisor de águas" para o paciente portador de MM, determinando planejamentos terapêuticos diversos.

Um estudo retrospectivo da *Mayo Clinic* pôde determinar que nenhuma diferença concreta se observou em relação à sobrevida mediana dos paciente com MM entre 1971 e 2001, mas um aumento significativo de sobrevida foi visto entre 2001 e 2006, como citado acima. (Kumar 2008) Este benefício foi visto principalmente em pacientes mais jovens tratados com TCPH-Auto. Adiante, outro aumento na sobrevida

mediana dos pacientes com MM foi observado entre os anos de 2006 e 2010. (Kumar 2014) Desta vez, os pacientes mais beneficiados foram aqueles com mais de 65 anos, e foi intimamente ligado à aplicação de novas drogas no tratamento do MM. Os pacientes mais jovens e submetidos à transplante sofreram um menor impacto destas terapias, preponderando a influência do próprio TCPH-Auto neste subgrupo. (Torimoto 2015) Assim, particularidades em termos de resposta e resiliência à terapia determinam a alocação inicial daqueles recém diagnosticados entre elegíveis e inelegíveis a TCPH-Auto.

O transplante alogênico de células progenitoras hematopoéticas é considerado ainda uma terapia de cunho experimental para o MM. Isso devido ao número reduzido de pacientes que se mostrariam candidatos efetivos a este tipo de terapia, dada sua toxicidade (mortalidade associada ao transplante de 10-20% e doença do enxerto contra o hospedeiro). Todavia, uma publicação do EBMT-NMAM200 com 96 meses de seguimento demonstrou que pacientes de até 69 anos que possuíam doador aparentado e eram submetidos a protocolo auto/RICallo (um transplante autólogo seguido de um transplante alogênico aparentado com regime de condicionamento reduzido) tinham melhor SLP (22%) e SG (49%) quando comparados aos pacientes que realizavam apenas TCPH-Auto (12% e 36%, respectivamente, P=0,027) (Gahrton 2013). Outro estudo publicado pelo CIBMTR, avaliou o transplante alogênico em 1207 pacientes portadores de MM e mostrou uma SLP e SG projetada em 5 anos de 14% (IC: 9-20%) e 29% (IC: 23%-35%), respectivamente. Na análise multivariada, foram considerados fatores de pior prognóstico a idade avançada, tempo prolongado entre o diagnóstico e o transplantes e doadores não aparentados. (Kumar 2011) De forma geral, o transplante alogênico atualmente deve ser proposto apenas para pacientes com MM de alto risco, em especial os jovens com ISS II-III associados a del 1p/1q gain, t(4;14), de(17p) ou t(14;16), nos quais a expectativa de SLP e SG em 4 anos não exceda 11% e 33%, respectivamente, idealmente dentro de um protocolo de pesquisa. (Engelhardt 2014)

3.1 Pacientes elegíveis a TCPH-Auto

TCPH-Auto é a terapia de escolha para os pacientes com 65 anos ou menos. É capaz de prolongar a SLP, SG e melhorar a qualidade de vida. (Engelhardt 2014,

Genadieva-Stavric 2017) O tratamento dos pacientes elegíveis a TCPH-Auto pode ser dividido em fases: Indução, TCPH propriamente dito, consolidação e manutenção.

O propósito da terapia de indução é reduzir a massa tumoral de células plasmocitárias, controlar sintomas e permitir a coleta de células tronco hematopoéticas (CTH) para o TCPH-Auto. (Engelhardt 2014) Agentes alquilantes como o melfalano estão associados a dano citotóxico às células tronco e podem impactar negativamente na coleta de CTH. Por esse motivo, o uso do protocolo VAD (vincristina, adriamicina, dexametasona), que exercia mínima influência sobre os resultados da coleta e permitia uma rápida citorredução tumoral, foi usado de forma sistemática para pacientes elegíveis a TCPH-Auto durante muitos anos, embora seus resultados em termos de remissão de doença ainda deixassem bastante a desejar (cerca de 15% apenas de resposta parcial muito boa – do inglês *very good partial remission/VGPR*). Após a introdução de novos agentes (talidomida, bortezomibe e lenalidomida), verificou-se que os mesmos também permitiam coletas de CTH favoráveis, não comprometendo os planos de transplante, além de serem consideravelmente mais eficazes na obtenção de respostas terapêuticas (VGPR de até 70% para algumas combinações). (Moreau 2015) Assim, o VAD foi sendo lentamente substituído por outras combinações farmacológicas. (Torimoto 2015) Atualmente, a recomendação para terapia de indução neste grupo de pacientes inclui poliquimioterapia com esquemas de pelo menos 3 drogas, dentre as 4 classes farmacológicas principais (corticoides, inibidores do proteasoma - PI's, imunomoduladores - IMiD e agentes alquilantes), incluindo bortezomibe e dexametasona, por no máximo 3 a 6 ciclos tratamento, idealmente. (Engelhardt 2014, Moreau 2015, Rollig 2015) Esquemas com 4 drogas não parecem agregar maior benefício até o momento (além de aumentar a toxicidade), e pacientes com intolerância a regimes triplos podem ser tratados com protocolos de 2 drogas. (Engelhardt 2014, Kumar 2012, Rollig 2015)

A TAD ainda hoje é realizada eminentemente com o uso de melfalano (em doses de 200 mg/m^2), embora a irradiação corporal total (do inglês *total body irradiation – TBI*) com 8 Gy e o uso combinado de bortezomibe já tenham sido testados, sem agregar benefício concreto. Atualmente, estuda-se a possibilidade de combinações com busulfano e bendamustina. (Moreau 2015, Torimoto 2015) Alguns pesquisadores já questionaram o papel da TAD neste novo cenário de terapias de alta eficácia atual,

acreditando que o TCPH-Auto poderia ser reservado apenas para pacientes recidivados/refratários. (Moreau 2015, Rollig 2015) Uma das principais argumentações é que com a utilização de drogas de nova geração (claramente mais eficazes e potentes do que os tratamentos antigos), a função do TCPH-Auto em aprofundar respostas obtidas pelos esquemas menos efetivos do passado tornou-se fútil, ao menos para alguns pacientes. (Engelhardt 2014, Moreau 2015, Rollig 2015, Torimoto 2015) Todavia, estudos como o de Palumbo *et al* (Palumbo 2014) e Gay *et al* (Gay 2015) mostram que o papel do TCPH-Auto permanece relevante no cenário terapêutico, quando comparado ao uso exclusivo de poliquimioterapia, demonstrando resultados superiores em SLP e SG mesmo quando confrontado com novos agentes (lenalidomida). Outro ponto de discussão é o momento do TCPH-Auto, pois uma alternativa após a coleta de células progenitoras hematopoéticas periféricas seria a de seguir realizando o tratamento de indução até progressão, reservando o transplante autólogo para um segundo momento. (Engelhardt 2014)

A terapia de consolidação com o uso de TCPH-Auto em *tandem* (definido pela realização de dois TCPH-Auto em curto espaço de tempo que permita apenas a recuperação medular) se mostrou eficaz em prolongar o SLP e SG, especialmente para pacientes nos quais não se conseguia atingir pelo menos *VGPR* no primeiro transplante. No entanto, o uso de terapias de manutenção utilizando os novos agentes imunomoduladores e inibidores do proteasoma foi também capaz aprofundar o grau de resposta pós-transplante, colocando o papel do transplante *tandem* em discussão. (Rollig 2015, Torimoto 2015) Na realidade, a consolidação com o *tandem transplantation* ou mesmo com fármacos utilizados na indução encontrava seu nicho em meio a um cenário onde a toxicidade do tratamento (interferon, corticoides, etc) inibia terapias duradouras no longo prazo. Os novos agentes têm quebrado este paradigma, mostrando-se capazes de serem utilizados por períodos prolongados de tempo, sustentando maiores períodos de SLP e possivelmente de SG, ainda que agregando paraefeitos e comprometendo de certa forma a qualidade de vida do paciente. (Engelhardt 2014, Rollig 2015)

A terapia de manutenção pós-transplante tem sido alvo frequente de estudos na última década. O uso da talidomida ou lenalidomida resultou em efetivo aumento da SLP e SG. No entanto, o uso da talidomida em longo prazo determina piora na qualidade

de vida dos pacientes como resultado de seu perfil desfavorável de efeitos adversos. (Moreau 2015) Além disso, a utilização da lenalidomida também foi associada ao aumento de neoplasias primárias secundárias (NPS) à quimioterapia. Em uma metanálise (Palumbo 2014), o risco cumulativo de NPS em 5 anos em pacientes tratados com lenalidomida foi de 6,9% (contra 4,8% no grupo placebo, *p*=0,037). Subgrupos com maior risco foram aqueles pacientes expostos a melfalano oral e com idade mais avançada. Deve haver cautela, portanto, na indicação de manutenção para pacientes com MM, embora o benefício seja solidamente demonstrado. (Engelhardt 2014, Rollig 2015, Torimoto 2015)

Alguns pesquisadores apostam na incorporação de novos agentes em múltiplas fases de tratamento com o objetivo de otimizar ao máximo a sobrevida dos pacientes. Exemplos de estudos com tal estrutura são o "Total Therapy III" (Usmani 2013) (onde se atingiu taxas de SG e SLP de 73% e 62%, respectivamente, muito próximas às da população sem MM com a mesma idade) e o "IFM 2008-01" (Roussel 2014) (que foi desenhado para utilizar bortezomibe, lenalidomida e dexametasona – RVD – na indução, realizar TCPH-Auto com melfalano 200 mg/m2, consolidar os pacientes novamente com RVD e realizar manutenção com lenalidomida por 1 ano, já demonstrando resultados impressionantes em SLP e SG, com taxa de doença residual mínima indetectável em significativa parte dos pacientes e nenhuma recidiva até o momento da publicação).

3.2 Pacientes inelegíveis a TCPH-Auto

Cerca de 70% dos pacientes portadores de MM diagnosticados não serão elegíveis a TCPH-Auto, devido a idade e/ou presença de comorbidades. (Torimoto 2015) Hoje, a idade torna-se cada vez menos importante como marcador biológico do que outros tipos de avaliação para classificar o paciente como *fit* ou *unfit*. Fatores como o Karnofsky Performance Status e o número de falências orgânicas (principalmente renal e pulmonar) tornam-se parte de escores como o Freiburg Comorbidity Index, HCT-CI, Charlson Comorbidity Index e o Kaplan-Feinstein Index, auxiliando na estratificação dos pacientes. Além disso, ferramentas como o teste *"timed up and go"* e o IADL (instrumental activities of daily living) ajudam a ponderar a importância de outros aspectos do cotidiano do paciente nesta avaliação. (Engelhardt 2014) Pacientes podem

apresentar-se, dentro desse contexto, como aptos a receber terapias em dose plena ou fragilizados o suficiente para receber apenas tratamento de suporte.

Uma vez avaliadas as condições do paciente, o cerne do tratamento consiste na terapia citotóxica, com medidas paralelas de suporte para o tratamento de complicações da doença. Estes pacientes possuem uma fase de indução mais prolongada que os pacientes elegíveis a TCPH-Auto, com o objetivo de alcançar o *plateau* em termos de resposta (máxima resposta possível, onde existe uma retificação da curva de redução da proteína monoclonal). Após atingido este marco, existe também uma fase de manutenção. (Moreau 2015, Torimoto 2015)

O MP foi durante muitas décadas o tratamento de escolha para este seguimento de pacientes, antes da introdução dos novos agentes farmacológicos. No entanto, ele ainda tem sido indicado para pacientes com *unfit* e para aqueles que necessitaram interrupção do tratamento com agentes mais novos devido à toxicidade. (Torimoto 2015)

A adição da talidomida ao esquema MP aumentou SG (39,3 meses vs 32,7 meses, p=0,04) e SLP (20,3 meses vs 14,9 meses, p<0,0001) em pacientes inelegíveis a TCPH-Auto, além de aumentar a taxa de resposta em 1 ano do tratamento.(Fayers 2011) Seus efeitos colaterais principais são a neuropatia periférica e a trombose venosa profunda.

O uso da lenalidomida, que é um derivado da talidomida, também já teve sua eficácia demonstrada neste segmento de pacientes. Um estudo randomizado demonstrou que o uso de lenalidomida, associada ao MP, com lenalidomida também em manutenção (MPR-R, R de Revlimid – nome comercial da lenalidomida) ou não (MPR) foram superiores ao esquema MP isolado em TR (MPR-R 77% vs MPR 68% vs MP 50%) e que MPR-R foi superior a MPR e MP em SLP (MPR-R 31 meses vs MPR 14 meses, p<0,01 e vs MP 13 meses, p<0,01). (Palumbo 2012) O uso combinado com dexametasona também parece promissor. Em um estudo, o uso de lenalidomida com altas doses de dexametasona (RD) mostrou benefício em SLP em 1 ano e TR global, embora demonstrando um perfil de toxicidade desfavorável em termos de neutropenia e eventos tromboembólicos. (Zonder 2010) Mais tarde o uso de doses mais baixas de dexametasona (Rd), quando comparada ao RD, mostrou benefício em SG em 1 ano (RD 87% vs Rd 96%, p=0,0002) além de possuir um melhor perfil de efeitos adversos.

(Rajkumar 2010) O uso deste esquema em administração contínua, comparado ao convencional (Rd por 18 meses) e com o MPT (Melfalano, Prednisona e Talidomida, também por 18 meses), demonstrou melhora em SLP (Rd contínuo 25,5 meses vs Rd 20,7 meses e vs MPT 21,2 meses, p<0,001 para ambas comparações) e em SG em 4 anos (Rd contínuo 59% vs MPT 51%, p=0,02), na comparação com MPT. (Benboubker 2014)

O uso do inibidor do proteasoma bortezomibe também tem mostrado eficácia no grupo de pacientes inelegíveis para TCPH-Auto. Um ensaio clínico randomizado (ECR) comparou o uso de MP combinado com bortezomibe (VMP, V de Velcade – nome comercial do bortezomibe) com o MP e mostrou benefício em SG depois de 5 anos de seguimento (VMP 56,4 meses vs MP 43,1 meses, p<0,001). (Mateos 2010, San Miguel 2013) De forma interessante, o uso de bortezomibe demonstrou eficácias comparáveis em pacientes com ou sem comprometimento renal e com ou sem alterações citogenéticas como t(4;14), t(14;16) ou del(17p), reconhecidos marcadores de pior prognóstico. (Torimoto 2015) Um dos efeitos adversos limitantes ao uso do bortezomibe é a neuropatia periférica. O uso desta medicação em regime semanal (VMP modificado) não se mostrou inferior ao regime convencional (duas aplicações semanais) e reduziu sensivelmente a incidência de neuropatia periférica (VMP modificado 8% vs VMP 28%, p<0,001) e a taxa de descontinuação do tratamento dada por este paraefeito (VMP modificado 5% vs VMP 15%, p<0,001).(Bringhen 2010) O uso de bortezomibe via subcutânea também está associado à redução deste efeito colateral. (Moreau 2011)

Terapia de manutenção para pacientes inelegíveis a TCPH-Auto ainda é um campo de incerteza. Mesmo com a adição de novos agentes quimioterápicos, benefício concreto em SG ainda não foi determinado, embora haja uma clara melhora em SLP. No entanto, esse benefício vem acompanhado de um aumento considerável na taxa de paraefeitos, sendo portanto uma escolha a ser individualizada. Ainda assim, qual o esquema a ser utilizado e suas doses também são alvo de grande controvérsia na atualidade. (Moreau 2015, Torimoto 2015)

3.3 Comparação simultânea de múltiplos tratamentos

As metanálises tradicionais são métodos de sumarização de informação que possibilitam a comparação entre duas alternativas de tratamento confrontadas em ensaios clínicos. É possível compilar os dados em uma medida sumário (como risco

relativo ou diferença de médias), de forma a agregar em um único parâmetro todos os resultados observados nos estudos considerados. No entanto, em grande parte das situações clínicas, é comum encontrar variadas abordagens terapêuticas e um incontável arsenal de alternativas farmacológicas. É frequente a indisponibilidade de estudos contemplando todas as combinações possíveis de fármacos, necessárias à realização de metanálises, uma vez que estas dependem da existência de comparações diretas entre pares de tratamento (Caldwell 2005) para determinar a relação hierárquica de eficácia entre as escolhas disponíveis.

Parece lógico que a realização de ensaios clínicos que contemplem comparações diretas inexistentes ou, ainda mais, que congreguem todas as alternativas terapêuticas para uma mesma condição clínica em único estudo seria a forma mais adequada de determinar superioridade entre tratamentos ainda não comparados. No entanto, tais estudos são muitas vezes impraticáveis, seja por financiamento insuficiente ou mesmo por falta de interesse da indústria farmacêutica (Jansen 2011). Em tais situações, é possível determinar a relação de eficácia entre diversos tipos de intervenção através de comparações indiretas.

Comparações indiretas podem ser realizadas de diversas formas. Uma forma considerada potencialmente inadequada é através da comparação das frações de resposta dos grupos randomizados de interesse em diferentes estudos, ignorando o efeito placebo e o risco basal de desfecho da amostra de cada estudo (*Naive Indirect Comparison)*. Este tipo de comparação tem valor semelhante ao de estudos observacionais, não preserva o benefício da randomização, e sua utilização é, portanto, desencorajada.

Outra forma de estabelecer uma relação entre resultados de estudos independentes é comparar as estimativas pontuais e intervalo de confiança de 95% das medidas de efeito de estudos comparando duas determinadas alternativas terapêuticas contra um tratamento em comum *(Informal Indirect Comparison)*. No entanto, este tipo de comparação não é capaz de determinar medidas de efeito nem estabelecer a presença de diferenças estatisticamente significativas entre tratamentos (Jansen 2011).

Tendo em vista a imprecisão das formas de comparação indireta anteriormente citadas, foram desenvolvidos métodos capazes de preservar, ao menos em parte, a randomização dos ensaios clínicos agregados *(Adjusted/Anchored Indirect*

Comparison). Seu racional é baseado no estabelecimento de relações entre estudos que, por exemplo, comparam fármacos A e C e que comparam fármacos B e C, sendo possível a partir de um ponto de relação comum (tratamento C), comparar indiretamente os fármacos A e B, e determinar se existem diferenças estatisticamente significativas entre seus resultados.

Em boa parte das vezes, no entanto, necessitamos de comparações que permitam analisar múltiplos fármacos simultaneamente, e, para este objetivo em específico, é necessária a utilização de outras formas de comparações indiretas. Quando os dados envolvem mais de dois ensaios clínicos e mais de duas intervenções, indica-se a utilização da *Network Meta-analysis* (NMA). NMA (entre outras denominações encontradas na literatura) é um tipo de estrutura de análise que permite que diversos tratamentos possam ser comparados entre si sem que, necessariamente, eles estejam originalmente presentes em um mesmo estudo. Além da comparação par a par para todos os tratamentos incluídos na metanálise, esta forma de compilação permite classificar (ranquear) os tratamentos de acordo com sua probabilidade de ser o mais efetivo dentre os demais.

Existem situações onde é possível encontrar comparações diretas para os fármacos de interesse, no entanto o volume de evidência é pequeno ou inconsistente. Neste contexto, é possível condensar comparações diretas e indiretas de forma a tornar mais robusta a evidência disponível, como no método denominado *mixed treatment comparison* (MTC). Este método também oferece a vantagem de classificar os diferentes tratamentos testados em relação à probabilidade de serem efetivamente melhores em relação aos demais, segundo uma abordagem Bayesiana, o que facilitaria na tomada de decisão (Cooper 2011, Hoaglin 2011, Jansen 2011).

A utilização do MTC necessita que alguns pressupostos sejam satisfeitos (Cooper 2011, Hoaglin 2011, Jansen 2011):

- Os estudos a serem sintetizados devem formar uma rede onde não existem tratamentos que estejam isolados e não comparados com pelo menos um outro tratamento presente na rede. Para uma MTC, deve haver comparações diretas suficientes para serem combinadas com as indiretas, chamadas *loops* (Figura 1).

- Deve haver similaridade entre os estudos agregados, ou seja, a população estudada, a definição e mensuração dos desfechos, os protocolos terapêuticos, o tempo

de seguimento e a qualidade metodológica dos estudos devem ser homogêneos. O não cumprimento deste pressuposto pode levar ao viés de confundimento.

- Deve haver consistência entre as comparações diretas e indiretas no sentido de demonstrarem resultados semelhantes. Quando surgem discrepâncias, elas são investigadas e, caso não sejam esclarecidas, os resultados diretos devem ser considerados mais fidedignos em detrimento das comparações indiretas.

3.4 Necessidade do presente trabalho

Com base nesta breve revisão sobre o tratamento do MM, pode-se imaginar o grande dilema que o médico assistente tem que enfrentar diante de um paciente com um diagnóstico novo. Esquemas de maior e menor toxicidade, perfis de efeitos adversos variados, combinações múltiplas de drogas, são apenas algumas das ponderações necessárias ao médico neste momento. Tais ponderações levam a questionamentos que muitas vezes não foram respondidos em lugar algum da literatura. Muitas vezes a comparação entre duas estratégias de tratamento sequer foi testada. Além disso, por razões inerentes ao mercado de produtos farmacêuticos, via de regra os novos agentes não são testados contra o melhor esquema disponível na atualidade e sim contra esquemas já considerados obsoletos.

Revisões sistemáticas e metanálises são metodologias que permitem compilar dados de múltiplos estudos, de forma que as informações encontradas nestes possam ser agregadas e potencialmente mostrar diferenças que até então não puderam ser detectadas dadas as limitações de cada estudo individualmente. Durante a revisão de literatura, pudemos avaliar 41 estudos reportando revisões sistemáticas com metanálises versando sobre o tratamento do MM (Buchberger 2016, Buchberger 2015, Cartier 2015, Fayers 2011, Gao 2016, Gregory 1992, Hicks 2008, Hu 2017, Huang 2014, Kapoor 2011, Koreth 2007, Kortuem 2014, Kuhr 2016, Kumar 2011, Leiba 2014, Levy 2005, Liu 2017, Liu 2015, Lyu 2016, Myeloma Trialists' Collaborative 2001, Naumann-Winter 2012, Nooka 2013, Palumbo 2013, Qiao 2015, Satta 2015, Scott 2016, Scott 2015, Sonneveld 2013, Teh 2016, Trialists 1998, van de Velde 2007, Wang 2012, Wang 2012, Wang 2014, Wang 2016, Weisel 2016, Yang 2013, Zeng 2013, Zhu 2016, Zou 2014, Zou 2013). Destes, 30 estudos utilizavam metodologia convencional de metanálise, com sumarização de resultados de comparações diretas(Buchberger 2015, Fayers 2011, Gao

2016, Gregory 1992, Hicks 2008, Hu 2017, Huang 2014, Kapoor 2011, Koreth 2007, Kuhr 2016, Kumar 2011, Leiba 2014, Levy 2005, Liu 2015, Lyu 2016, Myeloma Trialists' Collaborative 2001, Nooka 2013, Palumbo 2013, Qiao 2015, Scott 2016, Scott 2015, Sonneveld 2013, Teh 2016, Trialists 1998, van de Velde 2007, Wang 2012, Wang 2012, Wang 2014, Wang 2016, Yang 2013, Zeng 2013, Zhu 2016, Zou 2014, Zou 2013), abordagem esta que é claramente insuficiente para determinar de forma abrangente a melhor estratégia de tratamento, dentre tamanha pluralidade de opções, restringindo-se basicamente a comparar pares de alternativas. Em 3 estudos (Cartier 2015, Kortuem 2014, Naumann-Winter 2012), não foi possível a realização de metanálise devido a heterogeneidade dos dados encontrados, ou mesmo se realizou uma compilação de dados com objetivo diverso da comparação entre tratamentos. Em outros 4 estudos (Buchberger 2015, Kuhr 2016, Kumar 2011, Zou 2013), além da abordagem tradicional de metanálise, utilizou-se uma metodologia de comparações indiretas baseadas em um comparador em comum (método de Bucher) (Bucher 1997). Por fim, em 4 estudos (Buchberger 2016, Liu 2017, Satta 2015, Weisel 2016) (todos publicados a partir de 2016) lançou-se mão de uma metodologia mais abrangente de metanálise de estudos, a *network meta-analysis* (NMA). Todos estes 4 estudos versaram sobre a população de pacientes inelegíveis a transplante, no entanto contiveram número discrepante de estudos entre si, o que pode ser sinal de uma revisão sistemática pouco sensível, sendo que tal fato pode influenciar de forma negativa o resultado da metanálise. Além disso, não identificamos uma NMA ou assemelhada envolvendo pacientes elegíveis a TCPH-Auto.

Assim, existe necessidade contínua de que abordagens de compilação das informações na literatura sejam sistematicamente aplicadas aos dados existentes, e àqueles que surgem diariamente. Metodologias como a NMA e assemelhadas são uma promessa para as limitações impostas pela forma que os estudos individuais são tratados atualmente. O presente trabalho tem a expectativa de, ao realizar abrangente revisão sistemática, agregar informação ao conhecimento estabelecido de forma a confirmar ou refutar o conteúdo de outras metanálises prévias para a população de pacientes inelegíveis, além de aplicar pela primeira vez essa mesma estrutura de análise para os pacientes elegíveis.

4. Objetivos

4.1 Justificativa

O MM é ainda hoje um grande desafio terapêutico para hemato-oncologistas clínicos devido à natureza crônica de sua evolução e pluralidade de terapias disponíveis para seu tratamento. Embora seja lógico pensar que quanto maior o número de terapias disponíveis para uma determinada enfermidade, melhor será sua condução após o diagnóstico, a heterogeneidade e multiplicidade de esquemas quimioterápicos existentes torna difícil o encadeamento, estruturado em evidências, de uma ordenação de protocolos segundo uma hierarquia de eficácia e efetividade.

Desde alguns séculos atrás, medicamentos variados foram sendo aplicados no combate ao MM, com maior ou menor sucesso. Aqueles que obtinham resultado favorável eram então combinados sucessivamente até que seu sinergismo fosse esgotado. Evoluindo da monoterapia de estudos de fase I e II, até esquemas complexos, sequenciais e aditivos, em estudos de fase III, a terapia desta doença alcançou a marca de dezenas de protocolos utilizados ativamente de forma intercambiável nas diferentes regiões do mundo. Ainda assim, pouca argumentação existe que possa sustentar um esquema em detrimento de outro.

É dentro deste cenário que pretendemos alocar nossos esforços neste trabalho com o intuito de dirimir as dúvidas inerentes à decisão terapêutica tomada pelo médico no momento de indicar tratamento para seu paciente. Propomo-nos, através de uma abordagem estatística ainda pouco utilizada nesse contexto, comparar diversos protocolos quimioterápicos quanto à sua efetividade e segurança.

4.2 Objetivo Geral

Realizar revisão sistemática (RS) de ensaios clínicos randomizados (ECR) que envolvam protocolos de tratamento quimioterápico para pacientes com MM em primeira linha de tratamento, elegíveis ou não a transplante de células progenitoras hematopoéticas (TCPH).

Realizar metanálise por *mixed treatment comparison* (MTC) dos ECR encontrados e que cumpram os critérios de inclusão.

4.3 Objetivos Específicos

Comparar diferentes abordagens de tratamento de indução e determinar através de abordagem Bayesiana qual a alternativa de tratamento com maior probabilidade de ser a melhor dentre aquelas estudadas, segundo os desfechos considerados (taxa resposta global, taxa de remissão completa, SLP, SG e perfil de segurança/eventos adversos).

Realizar análise de qualidade metodológica, conforme descrito pela Cochrane (Higgins 2008), dos trabalhos incluídos.

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6. Artigo 1:

Tratamento de indução para pacientes portadores de mieloma múltiplo elegíveis a transplante autólogo de células progenitoras hematopoéticas: revisão sistemática e metanálise por mixed treatment comparison de 4.432 pacientes.

Frontline treatment for transplant-eligible multiple myeloma patients: a 4,432 patients systematic review and mixed treatment comparison meta-analysis.

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A ser enviado ao periódico Blood.

Frontline treatment for transplant-eligible multiple myeloma patients: a 4,432 patients systematic review and network meta-analysis.

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Abstract

Autologous transplantation continues to be a cornerstone of young and fit multiple myeloma patients. It is known that frontline induction therapy before transplantation can influence post-transplant results. Therefore, best frontline treatment for transplant-eligible patients should be based on best available evidence to guide therapy. We performed a systematic review and mixed treatment comparison meta-analysis of 9 randomized clinical trials, enrolling 4,432 patients and comparing 10 different treatment regimens regarding survival, response and safety outcomes. Similarity among study designs, methodology and population was considered adequate. Available network allowed only for indirect evidence analysis, thus consistency and homogeneity tests were not applicable. OS analysis showed superiority of PAD (bortezomib, doxorubicin and dexamethasone) over other regimens, while for PFS outcome, VTD (bortezomib, thalidomide and dexamethasone) was considered the best treatment option. Also, for complete response and overall response, once more VTD showed clear superiority among analyzed protocols. Safety profile evaluated infectious, cardiac, gastrointestinal, neurological, thrombotic and hematological grade 3-4 adverse events. Risk of thrombotic events was higher with TAD (thalidomide, doxorubicin, dexamethasone), neurological with PAD, infectious with high dose dexamethasone (Dex), hematological with Z-Dex (Idarubicin and dexamethasone), gastrointestinal with VTD and cardiac with PAD. A compiled outcome considering best ranked treatments regarding survival, response and toxicity indicated that VTD, followed by PAD and TAD were superior treatments overall. Our study suggests that for transplant-eligible patients' frontline treatment, a triplet combination treatment, especially when including both classes of

novel agents (immunomodulatory drugs and proteasome inhibitors) should be preferred over other regimens.

Keywords: Multiple Myeloma; Transplantation, Autologous; Network Meta-analysis; Induction Chemotherapy.

Introduction

Multiple myeloma (MM) is currently the second most common hematologic malignancy worldwide[1,2] and its incidence has been increasing steadily (specially among some specific ethnic groups, such as non-Hispanic whites and non-Hispanic black men)[3]. Over the last two decades, the introduction of different classes of highly active agents has improved overall survival expectancy for both autologous transplant eligible and ineligible patients.[3,4] This therapeutic arsenal includes proteasome inhibitors (PIs), immunomodulatory imide drugs (IMiDs), histone deacetylase (HDAC) inhibitors, monoclonal antibodies (mAbs), along with corticosteroids, anthracyclines and alkylating drugs.[5] Frontline treatment for transplant-eligible MM patients is an essential treatment step and should be carefully planned in order to obtain a maximal response without excessive toxicity, while allowing for hematopoietic graft harvest. Quality of induction therapy response has been shown to improve post-transplant survival.[6] However, as new agents are continuously being developed, selecting a specific combination of drugs becomes an ever-increasing challenge, and unfortunately clarification is far beyond clinical trials structure.

To fulfill this methodological gap, an innovative approach of network meta-analysis, the mixed treatment comparison (MTC), has been developed allowing for simultaneous multiple comparisons among treatments through direct and indirect evidence, also ranking therapeutic approaches according to their probability of being the best among those tested. With this tool, all selected treatments, that were and probably would not be compared on a clinical trial setting, can have their relative effects weighted against each other simultaneously.[7-9]

In order to define, among currently available therapeutic options, the best frontline treatment approaches for patients eligible to transplant, we have conducted a systematic review and MTC meta-analysis.

Methods

Information Sources and Search Strategy

We have performed a comprehensive systematic review in order to identify all clinical trials comparing treatment approaches enrolling MM patients. Search strategy comprised terms defining MM and related disorders, available active drugs and a sensitive filter strategy for randomized clinical trials.[10-12] Included databases were MEDLINE, Embase, LILACS, SciELO, Cochrane CENTRAL and proceedings from major international meetings in hematology and oncology. We have also hand searched references from all retrieved randomized clinical trials and prior systematic reviews. Search strategy for databases screened are available as supplementary material (Appendix 1).

Duplicates were excluded before proceeding to study selection. All titles and abstracts retrieved were screened independently by teams of two researchers. Full-text articles also had its eligibility evaluated by two independent researchers. The last date of the search was January 22, 2017. We have followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting this study and reporting our results.[13,14] PRISMA flow diagram is shown in Figure 1.

Eligibility Criteria

Selected patient population involved newly diagnosed transplant-eligible MM patients. Only randomized phase 2 and 3 clinical trials comparing two or more therapeutic approaches for MM, with or without blinding were included in the study. Abstracts or unpublished data were allowed to be included if they report sufficient data to extraction. No language or age restriction were applied.

Studies were excluded if there were no randomization procedure reported or if study design was considered unclear. No prior treatment was allowed except for brief corticosteroid exposure. Refractory/relapsed MM patients' studies were also excluded. Ancillary treatment approaches as bisphosphonates, kyphoplasty/vertebroplasty, radiation therapy, colony stimulating factors or erythropoietin were allowed if they were evenly distributed on trial arms, but trials comparing only bisphosphonate use were not considered for the purpose of this meta-analysis. Interferon treatment was

also not included in the systematic review due to its obsolescence within current therapy. Studies were also excluded if they did not report data on overall survival (OS) and/or progression free survival (PFS), or similar endpoint, hazard ratios (HR).

Study Selection and Data Extraction

Eight reviewers (L.S., F.S.F., M.R.R., M.S., C.F.P., V.D.M., A.P.S., D.M.) participated in the screening and full-text evaluation. All abstracts screened and articles selected were reviewed and extraction proceeded by two of the eight reviewers, while a third reviewer would intervene (R.A.R.) if there was any discordance over data extracted. Data extracted was: title and reference details (first author, year of publication, study acronym, period of patient enrollment, site of the study), study population characteristics (age, sex, median follow up, prognostic assessment), inclusion of therapy phase other than induction, ancillary treatments, number of enrolled patients, number of patients in each treatment arm, type of interventions and outcome data. For each trial, we evaluated hazard ratios (HRs) with 95% confidence intervals (CI) of overall survival (OS) and progression-free survival (PFS). Event-free survival and time to next treatment were also evaluated where PFS was unavailable. If CI was not reported, we extracted P-value of the HR tests to derive CI. Binary outcomes such as rate of complete response (CR) and overall response (OR), as well as safety analysis (rate of grade 3 and/or 4 hematological, gastrointestinal, cardiac, neurological, infectious or thrombotic adverse events) were extracted as absolute frequency. Definition of CR and OR relied in the criteria utilized within each study. Frequency of adverse events was considered to be the total number of patients experiencing any grade 3-4 events (1 or more episodes) during study period. If there were any data not clearly reported on manuscripts from reviewed articles or supplemental material, correspondent authors were contacted and asked to provide needed information. All data were extracted independently and registered on separate electronic spreadsheets, which were compiled and compared afterwards.

Quality Assessment

Selected studies were assessed for quality and risk of bias considering recommendations from The Cochrane Collaboration[15] group (including items such as

random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data outcome, selective reporting). We have also evaluated early trial interruption due to efficacy as a potential bias[16]. This evaluation was also peer-reviewed and disparities were resolved by a third author. Where information for bias assessment was not reported, correspondent author was contacted and asked to provide study details. If no contact could be established, evaluated item was ranked unclear.

Mixed Treatment Comparison Meta-Analysis

MTC[17] uses a Bayesian hierarchical framework to simultaneously compare multiple treatments via common comparators. It is a generalized linear model for network meta-analysis. This approach combines direct and indirect evidence to summarize a comparison effect measure (point estimate and credible interval), whether a risk ratio (RR) or a HR. Contribution from this technique is that precision of estimates can be improved pending on completeness of meta-analysis network, also allowing inclusion of more than two-arm trials. Also, this method of meta-analysis is able to rank all treatments in order to quantify probability of being best ranked overall (for each specific outcome).

Goodness of fit of the models was evaluated by means of residual deviance and deviance information criteria (DIC). MTC analyses were performed considering a fixed effect model due to the fact that all comparisons had only one study available. Similarity assumption (based on the premise that the true treatment effect comparing any two interventions would be similar across all trials[18]) was evaluated by judging and comparing baseline characteristics, methodological quality and outcome measurement outcomes from each individual study. Consistency checking was not performed for this meta-analysis because we had no closed loop in the network. Also, homogeneity of retrieved trials could not be evaluated since only one trial was available for each pair of treatments.

Outcomes reported are relative effects of treatments as HR for OS and PFS, and RR for binary outcomes (CR, OR and adverse events) along with corresponding 95% credible intervals (Bayesian equivalent for confidence intervals). For ranking probabilities evaluation, we chose to use the surface under the cumulative ranking

(SUCRA) curve[19-21], which provides a numerical summary of the rank distribution of each treatment schedule on the different endpoints. The larger the SUCRA curve value (up to 1), the better the rank of the intervention. Pairwise meta-analysis and MTC was carried out with R software by using *meta* and *gemtc* packages.

Results

Study Selection

PRISMA flowchart for study selection and search strategy is depicted in Figure 1. In the time frame covered by this systematic review, a total of 15.091 studies, including full articles or meeting abstracts, were peer-reviewed. From these articles, 18 publications deriving from 9 RCT, with a total of 4,432 patients, were eventually considered eligible for inclusion in meta-analysis.[22-39] One trial (with four publications) did not report HR data on OS and were excluded from OS analyses.[27,28,31,34] All selected RCT reported HR data on PFS and frequency of gastrointestinal AE, while 8 reported data on CR[22-24,26-39] and OR[22,24,25,27-39], 7 on hematological[22-26,30,32,33,35-39], infectious[22,24,25,27,28,30-39] and thrombotic[23-38] AE and 5 on cardiac[23-31,33,34,38] AE. Characteristics of the 9 selected RCT are shown in Table 1. All studies performed transplantation with a melphalan-only conditioning, dose ranging from 140 to 200 mg/m^2 (both tandem or single transplantation). Studies were considered similar with respect to population, trial design, general methodology and outcome measurement. Follow up intervals ranged from 19 to 91.4 months, though 77.8% of trials had follow up times of four years or more.

Quality Assessment

Quality assessment summary is presented in Table 2. Overall, risk assessment was compromised by underreporting of randomization and concealment methods in 7 of the trials, while blinding of participants and personnel was thoroughly not pursued.

Treatment Group Allocation and Network Assembling

We have arbitrarily allocated similar multidrug protocols (MDP) based on their drug profile and constituents, resulting in 10 individual treatment groups. Those

treatment groups were: TT2+Thal[23,26] (Doxorubicin, Etoposide, Cisplatin, Cyclophosphamide, Dexamethasone, Vincristine and Thalidomide), VAD-Based Regimen[22-26,29,30,32,33,38,39] (mainly Doxorubicin, Dexamethasone, Vincristine - and variants including Cyclophosphamide and/or Etoposide, but not Thalidomide, Lenalidomide or Bortezomib), TD-Based Regimen[27,28,31,32,34] (Thalidomide and Dexamethasone, with or without Cyclophosphamide), VTD[27,28,31,34-37] (Bortezomib, Thalidomide and Dexamethasone), VTDC[35-37] (Bortezomib, Thalidomide, Dexamethasone and Cyclophosphamide), Z-Dex[22] (Idarubicin and Dexamethasone), TAD[29] (Thalidomide, Doxorubicin and Dexamethasone), DVd[24,25] (Pegylated Doxorubicin, Vincristine and Dexamethasone), PAD[30,33,38] (Bortezomib, Doxorubicin and Dexamethasone) and Dex[39] (High Dose Dexamethasone Monotherapy). Network plot depicting treatment inter-relations is presented in Figure 2.

Survival Analysis

Survival outcomes (PFS and OS) HR with 95% credible intervals (CrI) of all treatment pairs evaluated through the network simultaneous comparisons are shown in Figure 3. Overall, therapeutic protocols including thalidomide (T) and/or bortezomib (B) performed better than those relying on antracyclic backbones. PFS results significantly favored VTD, PAD, TAD and TT2+Thal over regimens not containing T and/or B. Also, VTD, TAD and TT2+Thal resulted in significantly longer PFS than TD-based regimens. OS analysis resulted in few significant differences among treatment alternatives. Of note, however, Z-Dex protocol showed the worst results concerning OS, being signicantly inferior to PAD, TAD, TD-based and VAD-based regimens, and even Dex.

Complete Remission and Overall Response Rate

Complete response and OR RR with 95% CrI of all treatment pairs evaluated through the network simultaneous comparisons are shown in Figure 4. Analogous to survival outcomes, treatments incorporating T and/or B showed higher rates of complete response than other regimens. VTD showed significant superiority over TT2+Thal, TD-based, VAD-based, Z-Dex and Dex regimens when concerning CR rate. PAD performed significantly better than TT2+Thal, VAD-based, Z-Dex and Dex regimens. TAD

was superior to TD-based, VAD-based, Z-Dex and Dex regimens. TT2+Thal and TD-based regimen resulted in superior CR rates when compared to VAD and Z-Dex.

Concerning OR, trends on T and/or B containing regimens behaved similarly to their performance in CR. Again, VTD resulted in significantly better response rates than all other treatments, except for VTDC and PAD, while VTDC, PAD and TD-based regimens showed significantly superior OR rates than VAD-based and Z-Dex protocols.

Safety/Toxicity

We have evaluated the risk of 6 different grade 3-4 adverse event groups: thromboembolic, neurological, infectious, hematological, gastrointestinal and cardiac events. Simultaneous comparisons of all treatments through RR with 95% CrI can be found in Table 3.

Adverse events were seen predominantly in low frequencies (inferior to 15%), except for hematological events (with a global mean of 27.6%). The lowest frequency was found with cardiac events (4.8%).

As expected, T containing regimens presented higher rates of thromboembolic events when compared to other treatment options. Among these thalidomide regimens, TAD and TT2+Thal showed the worst results.

Neurologic adverse events were found more common in T and B containing regimens, especially when compared to VAD-based regimens. Also, combined B and T (VTD) fared worse than a thalidomide only protocol (CTD).

Infectious events were more common in anthracycline containing regimens, like VAD-based and PAD regimens, than in other treatment groups. Of note, high dose dexamethasone monotherapy also showed an unfavorable profile, resulting in significant more infectious events than PAD, VAD, Z-Dex and VTD and showing the same behavior trend towards other treatment groups.

Hematological adverse events were also found more frequently in anthracycline containing regimens (especially Z-Dex, VAD-based and PAD regimens), except for TT2+Thal that has also shown a higher rate of events when compared to CTD, DVd and Dex.

Gastrointestinal adverse events occurred significantly more frequently in VTD, CTD, TAD and TT2+Thal regimens when compared to VAD and Z-Dex.

Cardiac events were significantly more common with TAD regimen over TT2+Thal and DVd, and with TT2+Thal over VAD-based regimen.

Ranking of Treatment Regimens

For each outcome evaluated, it was possible to calculate the SUCRA curve values for each treatment option and hierarchically organize them according to the probability of being best among those analyzed. Also, we compiled SUCRA curve values from different outcomes (survival, response and a summarized toxicity parameter) to estimate a global ranking of treatments, balancing efficacy and safety. These results are shown in Figure 5.

Overall, survival and response outcomes were leaded by T and B containing regimens. PAD ranked first in OS outcome, followed by Dvd and TD-based regimens (VTD and VTDC data on OS was not available). VTD was the best treatment in PFS outcome, followed by TAD and TT2+Thal, and ranked similarly for OR (followed VTDC and PAD) and CR (followed closely by PAD and TAD).

Safety analysis demonstrated major toxicity profiles occurring in regimens which contained anthracyclines (TAD, PAD and TT2+Thal), while TD-based and VTDC regimens seemed to be safer regimens.

When considering the average SUCRA from compilation of outcomes (both probabilities of attaining longer OS and PFS, reaching higher response rates and dealing with lower incidence of adverse events), VTD resulted in the highest probability of being best over all other treatments, followed by PAD, TAD and VTDC, with minor differences of probability among those latter regimens.

Discussion

The primary intent in performing this study was to thoroughly analyze all therapeutic options for MM in a network meta-analysis structure. Indeed, a relevant amount of RCT have been reported comparing individual treatments, but there is little hope that a simultaneous direct comparison of regimens, both traditional and novel ones, will exist in the future. Therefore, many gaps and unanswered questions still linger on MM treatment, many of them inferred on but seldom effectively demonstrated. This

study aimed at fulfilling at least some of these lacunae. Additionally, the MTC structure allow us not only to compare treatments through indirect comparisons, but also hierarchically classify from best to worst treatment probability, granting the possibility of regimen stratification based on their overall performance.

Selected studies included trials performed on the last two decades, mainly in Europe and USA. Median age and sex distributions were comparable among studies. Follow-up time ranged from 19 to 91.4 months, more than half of them beyond 4 years of follow-up. Although this study aimed at transplant-eligible patients, one study reported a rate of only 30% of transplantation[25], possibly due to a shorter follow up. For the remaining trials, more than half of patients underwent transplantation, attaining an impressing 100% rate in one of them[39]. Bisphosphonate use was reported in the majority of trials.

Risk of bias was systematically present in included trials to a variable extent. Most of it was due to limitations in blinding and/or concealment, or underreporting of methodology details. Although this is undoubtedly a quality shortcoming, most of current RCT in this area follow a similar structure, thus this group of studies would be considered representative of available evidence.

Survival outcomes in this systematic review corroborated current practice of incorporating novel agents (T and/or B) into first-line treatments for transplant-eligible patients. Based on our results we would recommend against the use of any protocol not including at least one of these agents and, even more, we would endorse the use of T and B concomitantly, as in VTD, as the treatment of choice for this population, at least when PFS is concerned. OS data was not available for VTD, but leading treatments were mainly both T or B containing regimens. DVd[25] ranked unexpectedly well on OS among these protocols, possibly due to a shorter follow-up time.

Response outcomes reflected findings on survival, again recommending against protocols not containing novel agents (that should be abandoned now on). Also, VTD ranked first on both OR/CR, corroborating previous recommendations for first-line treatment.

Adverse events had a low overall rate, and those regimens containing anthracyclines would possibly be responsible for an important amount of them.

Anthracyclines were a main part of older regimens but, considering results from the current study, its use on current therapy of MM should be questioned.

Some limitations to this study should be acknowledged. We opted to use a very sensitive search strategy and as a result a vast number of references were screened throughout the initial part of this study. While more than 250 articles were eventually selected for full text analysis, more than half of these studies were withdrawn due to the lack of HR reporting. As we noticed, HR as an effect measure was only gradually incorporated in MM clinical trials after the 1980s, gaining more awareness on the 1990s. Therefore, a significant amount of studies was not included in this meta-analysis due to data unavailability, although comprising mainly older therapeutic options, what possibly would have minor impact on our results. We also chose not to apply graphical data extraction approaches[40] because we felt that this could lead to undesired inaccuracy to estimates. Moreover, it is important to emphasize that HR extracted from Cox regression model analyses are prone to bias and incorrectness pending on their non-compliance with model assumptions, a limitation that has been unequivocally demonstrated previously[41]. Also, grouping of treatments was complex due to intrinsic minor differences among some of the protocols included in the same arm of comparison, although we have based our similarity assumption on backbone constituents of each regimen. Specifications of each protocol are available as supplementary material (Appendix 2). Heterogeneity among protocols included in the same group of comparison should not be overlooked while acknowledging these results. Meta-analysis is no more than a heuristic approach to solve a complex problem, and as so, one should consider that heterogeneity and complexity of patients, treatments and study designs could all influence to some point its results.

To the best of our knowledge, this is the first network meta-analysis of RCT to study first-line transplant-eligible patients' induction treatment. Our results endorse the use of T and/or B containing regimens for this population of patients (chiefly VTD, PAD and TAD regimens) due to favorable effects on OS and PFS, high complete and overall response rates and acceptable toxicity profiles. Further studies comparing directly these treatment approaches (also with newer available agents) should be able to establish anthracycline role on current therapy and clarify optimal sequence of protocols to be applied on conventional practice.

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Figure 1. PRISMA Flowchart for study selection and review.

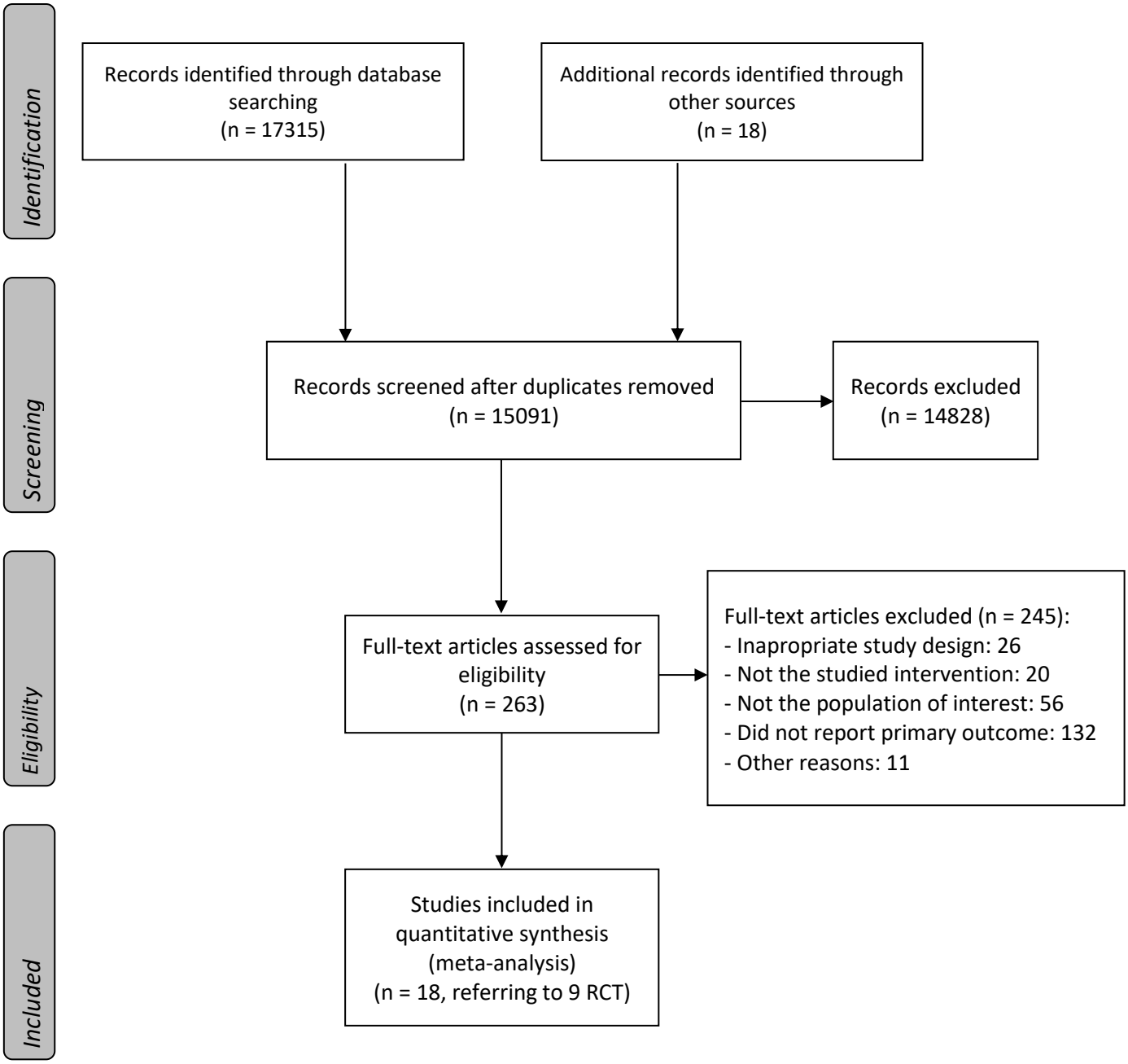

Figure 2. Network Plot.

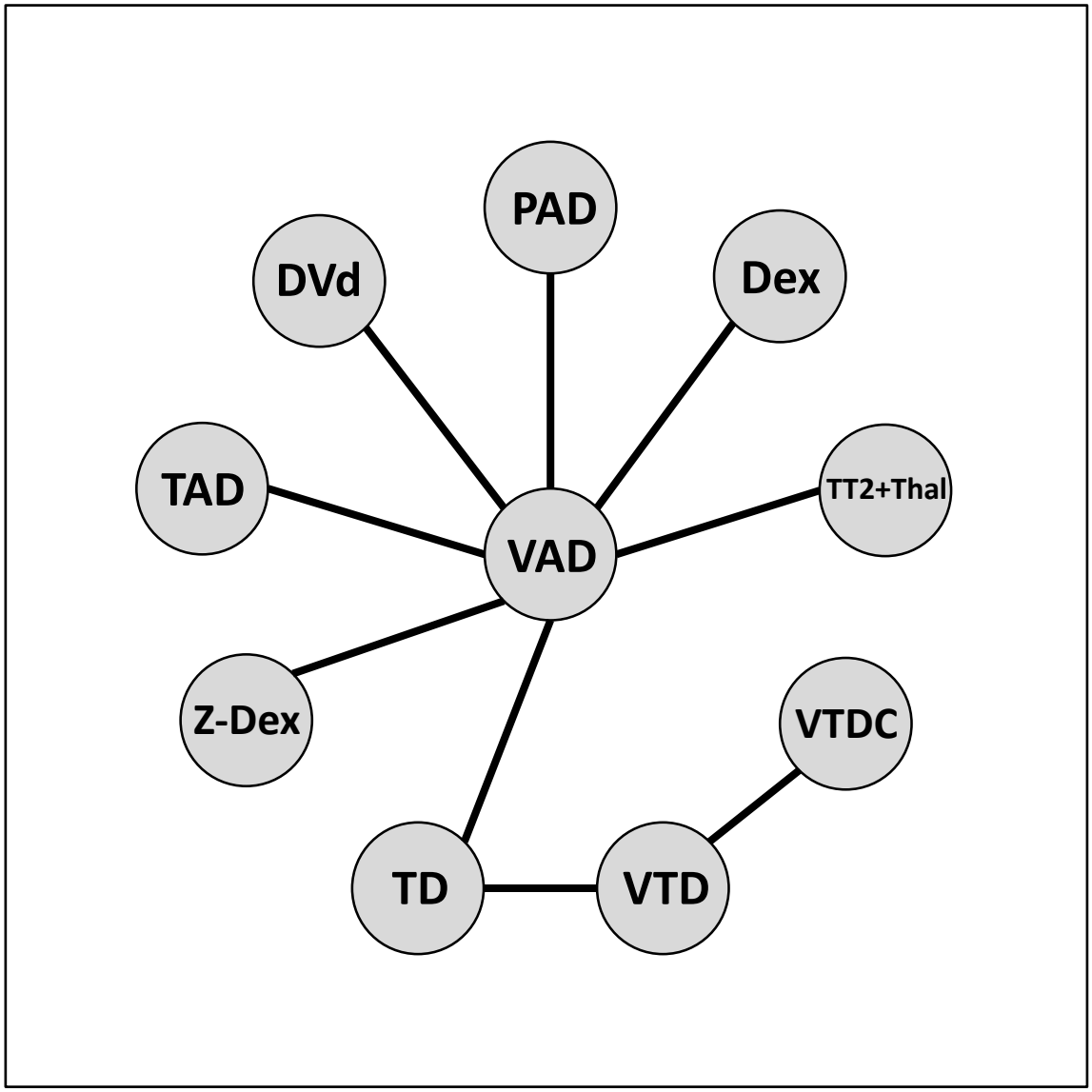

Figure 3. OS and PFS HR with 95% CrI for head-to-head simultaneous comparisons over treatments.

VTD	0.73 (0.43-1.23)	0.82 (0.58-1.16)	0.92 (0.65-1.31)	0.92 (0.65-1.31)	**0.66 (0.51-0.84)**	0.55 (0.31-1.00)	**0.61 (0.46-0.82)**	**0.42 (0.22-0.78)**	**0.62 (0.42-0.93)**
–	**VTDC**	1.13 (0.60-2.13)	1.26 (0.67-2.40)	1.26 (0.67-2.40)	0.90 (0.50-1.62)	0.76 (0.34-1.69)	0.84 (0.46-1.55)	0.57 (0.25-1.31)	0.85 (0.44-1.66)
–	–	**PAD**	1.11 (0.85-1.47)	1.11 (0.84-1.47)	0.79 (0.62-1.01)	0.67 (0.39-1.16)	**0.75 (0.62-0.90)**	**0.50 (0.28-0.91)**	0.75 (0.54-1.05)
–	–	0.84 (0.58-1.21)	**TAD**	1 (0.75-1.33)	**0.71 (0.56-0.91)**	0.60 (0.34-1.04)	**0.66 (0.54-0.81)**	**0.45 (0.25-0.82)**	**0.67 (0.48-0.94)**
–	–	0.78 (0.52-1.18)	0.93 (0.61-1.40)	**TT2 +Thal**	**0.71 (0.55-0.92)**	0.60 (0.34-1.04)	**0.66 (0.54-0.82)**	**0.45 (0.25-0.82)**	**0.67 (0.48-0.94)**
–	–	0.87 (0.63-1.22)	1.04 (0.74-1.45)	1.12 (0.76-1.63)	**TD-Based**	0.84 (0.49-1.44)	0.94 (0.80-1.09)	0.63 (0.35-1.13)	0.94 (0.69-1.29)
–	–	0.91 (0.48-1.74)	1.08 (0.57-2.07)	1.16 (0.60-2.27)	1.04 (0.56-1.94)	**DVd**	1.11 (0.66-1.85)	0.75 (0.35-1.59)	1.12 (0.63-2.00)
–	–	0.80 (0.62-1.04)	0.95 (0.73-1.24)	1.03 (0.74-1.41)	0.92 (0.75-1.13)	0.88 (0.48-1.58)	**VAD-Based**	0.67 (0.39-1.18)	1.01 (0.77-1.32)
–	–	**0.42 (0.22-0.83)**	**0.50 (0.26-0.98)**	0.54 (0.27-1.08)	**0.48 (0.25-0.92)**	0.46 (0.19-1.08)	**0.52 (0.28-0.97)**	**Z-Dex**	1.48 (0.80-2.76)
–	–	0.84 (0.60-1.17)	0.99 (0.71-1.39)	1.07 (0.72-1.56)	0.95 (0.71-1.28)	0.91 (0.48-1.71)	1.03 (0.84-1.28)	**1.96 (1.03-3.75)**	**Dex**

Treatments are shown in the dark gray area (middle oblique line). At the OS analysis area (white/bottom), HR represents column-defining treatment compared to line-defining treatment with 95% Credible Intervals (CrI). At the PFS analysis area (light gray/top), HR represents line-defining treatment compared to column-defining treatment with 95% Credible Intervals (CrI). Statistically significant HR are highlighted in blue.

Figure 4. CR and OR RR with 95% CrI for head-to-head simultaneous comparisons over treatments.

VTD	1.06 (0.98-1.19)	1.07 (0.96-1.19)	**1.12 (1.002-1.26)**	–	**1.07 (1.02-1.13)**	1.17 (0.83-1.63)	**1.25 (1.14-1.36)**	**1.61 (1.23-2.22)**	**1.29 (1.01-1.63)**
1.13 (0.47-2.85)	**VTDC**	1.01 (0.83-1.14)	1.05 (0.90-1.20)	–	1.01 (0.90-1.11)	1.09 (0.76-1.56)	**1.17 (1.03-1.31)**	**1.51 (1.12-2.08)**	1.21 (0.90-1.56)
0.99 (0.58-1.66)	0.83 (0.29-2.38)	**PAD**	1.04 (0.90-1.16)	–	1.01 (0.90-1.11)	1.09 (0.76-1.53)	**1.16 (1.08-1.25)**	**1.51 (1.14-2.08)**	1.20 (0.90-1.53)
1.06 (0.76-1.49)	0.90 (0.34-2.38)	1.07 (0.62-1.92)	**TAD**	–	0.96 (0.90-1.06)	1.04 (0.76-1.47)	**1.11 (1.03-1.20)**	**1.44 (1.08-1.96)**	1.14 (0.90-1.47)
1.53 (1.01-2.38)	1.35 (0.5-3.57)	**1.56 (1.06-2.32)**	1.47 (0.90-2.32)	**TT2 +Thal**	**–**	–	–	–	–
1.40 (1.17-1.69)	1.23 (0.5-3.03)	1.42 (0.83-2.38)	**1.33 (1.01-1.78)**	0.90 (0.62-1.33)	**TD-Based**	1.08 (0.76-1.51)	**1.16 (1.08-1.23)**	**1.49 (1.13-2.04)**	1.20 (0.90-1.51)
–	–	–	–	–	–	**DVd**	1.06 (0.76-1.47)	1.38 (0.90-2.12)	1.11 (0.71-1.63)
2.22 (1.49-3.33)	1.92 (0.71-5.1)	**2.27 (1.58-3.33)**	**2.08 (1.33-3.33)**	**1.44 (1.25-1.66)**	**1.58 (1.11-2.22)**	–	**VAD-Based**	1.29 (0.99-1.75)	1.04 (0.83-1.29)
4.34 (1.51-14.4)	3.84 (0.90-16.3)	**4.34 (1.56-14.7)**	**4.16 (1.38-13.8)**	**2.85 (1.05-9.09)**	**3.12 (1.09-10.1)**	–	1.96 (0.71-6.25)	**Z-Dex**	0.76 (0.55-1.13)
3.03 (1.35-6.66)	2.63 (0.76-8.33)	**3.03 (1.40-7.14)**	**2.85 (1.25-6.66)**	1.96 (0.96-4.16)	2.12 (0.99-4.76)	–	1.36 (0.66-2.77)	0.66 (0.18-2.38)	**Dex**

Treatments are shown in the dark gray area (middle oblique line). At the CR analysis area (white/bottom), RR represents column-defining treatment compared to line-defining treatment with 95% Credible Intervals (CrI). At the OR analysis area (light gray/top), RR represents line-defining treatment compared to column-defining treatment with 95% Credible Intervals (CrI). Statistically significant RR are highlighted in blue.

Figure 5. Ranking of treatments included in meta-analysis.

Regimen	OS	PFS	OR	CR	Thrombotic Adverse Events	Neurological Adverse Events	Infectious Adverse Events	Hematological Adverse Events	Gastrointestinal Adverse Events	Cardiological Adverse Events	Average Toxicity	Average SUCRA*
VTD		0.893	0.952	0.838	0.751	0.324	0.892		0.107		0.519	0.800
PAD	0.837	0.671	0.697	0.830	0.451	0.218	0.282	0.310	0.597	0.415	0.379	0.683
TAD	0.528	0.816	0.519	0.780	0.056	0.463	0.678		0.430	0.840	0.494	0.627
VTDC		0.511	0.697	0.676	0.839	0.491	0.484		0.614		0.607	0.623
TD-Based	0.623	0.389	0.653	0.508	0.557	0.876		0.769	0.355		0.639	0.562
TT2/Thal	0.403	0.814		0.455	0.165	0.379		0.253	0.509	0.840	0.429	0.525
Dvd	0.637	0.240	0.469		0.765		0.402	0.732	0.266	0.604	0.554	0.475
VAD-Based	0.411	0.283	0.246	0.227	0.416	0.747	0.383	0.393	0.780	0.609	0.555	0.344
Dexa	0.525	0.316	0.240	0.130			0.095	0.977	0.431		0.501	0.342
Z-Dex	0.035	0.067	0.028	0.056			0.783	0.067	0.912		0.587	0.155

*Average SUCRA is an arithmetic mean of OS, PFS, CR, OR and Average Toxicity outcomes.

Table 1. Characteristics of the studies included in meta-analysis.

Main Author	Acronym	Number of Publications	Publication Year	Enrollment Period	Region	Total Study Population	Median Age	Male Sex	Median Follow Up	Prognostic Information	Proportion of Patients Undergoing Autologous BMT	High Risk Cytogenetic Profile	Bisphosphonate Use	Study Intervention	Control Arm
Barlogie	TT2	2	2006-2008	10/1998-02/2004	USA	668	532/668 (79.6%) younger than 65 years	396/668 (59.3%)	72 months (2008)*	Albumin < 3.5 (119/664 - 17.9%) and B2M > 3.5 (243/668 - 36.4%)	67% Tandem Auto-Transplant	188/634 (29.7%)	Not Reported	TT2 + Thal[¥]	VAD-Based Regimen
Cavo	GIMEMA-MMY-3006	4	2010-2013	05/2006-04/2008	Italy	474	57/58 years	273/474 (57.6%)	59 months (2013)*	ISS III - 77/474 (16.2%)	69.6% Tandem Auto-Transplant	110/474 (23.2%)	Not Reported	Bortezomib + Thalidomide + Dexamethasone (VTD)	TD-Based Regimen
Cook	WOS MM1	1	2004	10/1996-11/2002	UK	106	57 years	55/106 (58%)	19 months	B2M (4-8 ou >8): 33/106 (31%)	48%	Not Reported	Yes (Allowed, but not part of protocol)	Idarubicin + Dexamethasone (Z-Dex)	VAD-Based Regimen
Lokhorst	HOVON-50/GMMG-HD3	1	2010	11/2001-05/2005	Belgium, Germany e Netherlands	536	56 years	337/536 (63%)	52 months	ISS III - 97/536 (25%)	82%	101/294 (34%)	Not Reported	Thalidomide + Doxorubicin + Dexamethasone (TAD)	VAD-Based Regimen
Ludwig	Not defined	3	2013-2015	10/2007-09/2008	Austria, Portugal, Hungary, Israel, Poland, Czech Republic, Spain, France	98	57-58 years	51/98 (52%)	64.8 months (2015)*	ISS III - 32/98 (32.7%)	89.80%	Not Reported	Yes (Allowed, but not part of protocol)	VTD + Cyclophosphamide (VTDC)	VTD
Morgan	MRC Myeloma IX Trial	1	2012	2003-2007	UK	1111	59 years	692/1111 (62.3%)	47 months	ISS III - 343/1111 (30.9%)	67.20%	293/626 (47%)	Yes - Randomization to Zoledronate or Clodronate until progression	TD-Based Regimen	VAD-Based Regimen
Porter	Not defined	2	2006-2007	01/2001-08/2003	EUA	192	60 years	115/192 (59.9%)	21 months	Mean B2M 3.96 and 4.99 mg/L (per group) Mean albumin 3.51 e 3.29 g/dL (per group)	30%	Not Reported	Not Reported	Pegylated Doxorubcin + Vincristine + Dexamethasone (DVd)	VAD-Based Regimen
Sonneveld	HOVON-65/GMMG-HD4	3	2010-2015	05/2005-05/2008	Belgium, Germany e Netherlands	827	57 years	500/827 (60.5%)	91.4 months (2015)*	ISS III - 188/827 (22.7%)	84.50%	**t(4;14) –** 70/512 (13.7%) **del(17p13)** – 65/602 (10.8%)	Yes (Allowed, but not part of protocol: Pamidronate or Zoledronate)	Bortezomib + Doxorubicin + Dexamethasone (PAD)	VAD-Based Regimen
Straka	DSMM	1	2016	08/2001-08/2006	Germany	420	65 years	236/420 (56.2%)	62.4 months	Durie-Salmon III (A or B) - 333/420 (79.3%)	100%	44/210 (20.9%)	Yes (Allowed, but not part of protocol)	VAD-Based Regimen	Dexamethasone Monotherapy

*For multiple publication RCT we have considered the longer follow up report for each outcome. [¥]Multidrug, multi-phase regimen, detailed in supplementary material (Appendix 1).

Table 2. Quality assessment of included studies.

Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Early Interruption
Barlogie	**2006-2008**	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Cavo	**2010-2013**	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Cook	**2004**	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Lokhorst	**2010**	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Ludwig	**2013-2015**	Unclear	Unclear	High Risk	High Risk	Low Risk	Low Risk	No
Morgan	**2012**	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Porter	**2006-2007**	Unclear	Unclear	High Risk	Low Risk	Unclear	Unclear	No
Sonneveld	**2010-2015**	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Straka	**2016**	Unclear	Unclear	High Risk	Unclear	Unclear	Unclear	No

Table 3. Adverse events risk ratios with 95% credible intervals.*

Comparison	Thrombotic	Neurologic	Infectious	Hematological	Gastrointestinal	Cardiac
Z-Dex/VAD	-	-	**0.46 (0.24-0.79)**	**1.38 (0.94-2.10)**	0.84 (0.68-1.01)	-
TT2+Thal/VAD	**1.73 (1.30-2.31)**	**1.62 (1.21-2.19)**	-	1.03 (0.98-1.09)	**1.63 (1.05-2.56)**	**2.94 (1.66-5.52)**
TAD/VAD	3.22 (0.94-14.94)	**1.46 (1.10-1.98)**	**0.57 (0.42-0.75)**	-	**1.89 (1.06-3.57)**	0.57 (0.12-2.32)
CTD/VAD	0.85 (0.66-1.11)	0.42 (0.01-5.32)	-	**0.38 (0.24-0.59)**	**2.29 (1.06-5.22)**	-
Dvd/VAD	0.48 (0.13-1.48)	-	0.99 (0.22-4.28)	**0.42 (0.20-0.81)**	3.32 (0.74-23.81)	1.01 (0.59-1.70)
PAD/VAD	1.01 (0.23-4.31)	**2.22 (1.13-4.72)**	1.19 (0.69-2.09)	1.01 (0.36-2.72)	1.40 (0.57-3.75)	1.36 (0.47-4.21)
VTD/VAD	0.53 (0.20-1.28)	2.07 (0.06-31.95)	**0.33 (0.12-0.85)**	-	**6.51 (1.10-57.52)**	-
VTDC/VAD	0.22 (0.01-3.17)	1.34 (0.03-26.82)	0.81 (0.05-28.71)	-	1.22 (0.03-24.33)	-
Dex/VAD	-	-	1.74 (1.22-2.54)	**0.21 (0.10-0.38)**	2.11 (0.38-17.28)	-
TT2+Thal/Z-Dex	-	-	-	0.75 (0.49-1.10)	**1.94 (1.21-3.19)**	-
TAD/Z-Dex	-	-	1.22 (0.66-2.42)	-	**2.26 (1.22-4.39)**	-
CTD/Z-Dex	-	-	-	**0.28 (0.15-0.49)**	**2.73 (1.22-6.36)**	-
Dvd/Z-Dex	-	-	2.15 (0.43-10.40)	**0.30 (0.13-0.65)**	3.97 (0.87-29.07)	-
PAD/Z-Dex	-	-	**2.58 (1.19-6.02)**	0.73 (0.24-2.12)	1.67 (0.66-4.50)	-
VTD/Z-Dex	-	-	0.70 (0.22-2.21)	-	**7.77 (1.29-70.15)**	-
VTDC/Z-Dex	-	-	1.77 (0.10-66.01)	-	1.45 (0.03-29.04)	-
Dex/Z-Dex	-	-	3.77 (1.95-7.95)	**0.15 (0.07-0.31)**	2.51 (0.44-20.48)	-
TAD/TT2+Thal	1.87 (0.53-8.99)	0.90 (0.59-1.37)	-	-	1.17 (0.55-2.51)	**5.23 (1.11-28.54**)
CTD/TT2+Thal	**0.49 (0.33-0.73)**	0.26 (0.01-3.32)	-	**0.37 (0.23-0.58)**	1.41 (0.57-3.59)	-
Dvd/TT2+Thal	**0.28 (0.07-0.89)**	-	-	**0.41 (0.20-0.79)**	2.04 (0.42-15.32)	1.78 (0.39-9.40)
PAD/TT2+Thal	0.58 (0.13-2.56)	1.37 (0.65-3.11)	-	0.98 (0.35-2.63)	0.85 (0.31-2.47)	2.45 (0.41-16.20)
VTD/TT2+Thal	**0.30 (0.11-0.77)**	1.28 (0.03-20.07)	-	-	3.98 (0.64-36.28)	-
VTDC/TT2+Thal	0.13 (0.01-1.87)	0.82 (0.02-16.90)	-	-	0.74 (0.02-15.65)	-
Dex/TT2+Thal	-	-	-	**0.20 (0.10-0.37)**	1.30 (0.22-11.10)	-
CTD/TAD	**0.26 (0.06-0.93)**	0.29 (0.01-3.69)	-	-	1.20 (0.44-3.32)	-
Dvd/TAD	**0.14 (0.02-0.82)**	-	1.75 (0.39-7.80)	-	1.75 (0.35-13.77)	**0.34 (0.15-0.75)**
PAD/TAD	0.31 (0.04-2.07)	1.52 (0.72-3.47)	2.11 (1.15-3.95)	-	0.73 (0.24-2.31)	0.46 (0.13-1.61)
VTD/TAD	**0.16 (0.03-0.74)**	1.41 (0.04-22.06)	0.58 (0.21-1.42)	-	3.42 (0.52-33.20)	-
VTDC/TAD	0.07 (0.01-1.37)	0.90 (0.02-18.92)	1.42 (0.09-50.68)	-	0.64 (0.02-13.79)	-
Dex/TAD	-	-	**3.08 (1.96-4.92)**	-	1.11 (0.18-9.83)	-
Dvd/CTD	0.56 (0.15-1.77)	-	-	1.11 (0.46-2.43)	1.46 (0.26-11.94)	-
PAD/CTD	1.18 (0.26-5.40)	2.26 (0.45-11.85)	-	2.64 (0.86-7.92)	0.61 (0.18-2.12)	-
VTD/CTD	0.62 (0.24-1.45)	**4.87 (2.02-14.76)**	-	-	2.78 (0.57-21.56)	-
VTDC/CTD	0.26 (0.01-3.61)	3.24 (0.64-16.94)	-	-	0.53 (0.01-9.81)	-
Dex/CTD		-	-	0.54 (0.23-1.16)	0.93 (0.14-8.50)	
PAD/Dvd	1.18 (0.26-5.21)	-	1.21 (0.25-5.94)	2.40 (0.72-8.30)	0.42 (0.05-2.40)	1.35 (0.41-4.76)
VTD/Dvd	1.11 (0.25-5.53)	-	0.33 (0.06-1.88)	-	1.96 (0.14-27.44)	-
VTDC/Dvd	0.47 (0.01-9.31)	-	0.84 (0.04-35.86)	-	0.34 (0.01-10.85)	-
Dex/Dvd	-	-	1.77 (0.38-8.22)	0.49 (0.19-1.27)	0.62 (0.05-8.06)	-
VTD/PAD	0.52 (0.09-2.88)	0.92 (0.02-16.09)	**0.27 (0.09-0.82)**	-	4.67 (0.60-48.82)	-
VTDC/PAD	0.21 (0.01-4.66)	0.59 (0.01-13.47)	0.69 (0.04-25.27)	-	0.87 (0.02-21.00)	-
Dex/PAD	-	-	1.5 (0.74-2.90)	**0.20 (0.06-0.69)**	1.53 (0.21-14.20)	-
VTDC/VTD	0.43 (0.01-5.27)	0.66 (0.17-2.27)	2.46 (0.19-79.56)	-	0.19 (0.01-1.48)	-
Dex/VTD	-	-	5.36 (1.94-15.83)	-	0.33 (0.02-4.92)	-
Dex/VTDC	-	-	2.17 (0.06-34.98)	-	1.79 (0.05-120.2)	-

* Significant comparisons are highlightened in bold.

Appendix 1. Search strategies for included databases.

MEDLINE

Population	("Multiple Myeloma"[Mesh] OR "Myeloma"[All Fields] OR "Multiple Myeloma"[All Fields] OR "Multiple Myelomas"[All Fields] OR "Plasma-Cell Myeloma"[All Fields] OR "Plasma-Cell Myelomas"[All Fields] OR "Myelomatosis"[All Fields] OR "Myelomatoses"[All Fields] OR "Plasma Cell Myeloma"[All Fields] OR "Plasma Cell Myelomas"[All Fields] OR "Kahler Disease"[All Fields]) OR ("Paraproteinemias"[Mesh] OR "Paraproteinemia"[All Fields] OR "Plasma Cell Dyscrasias"[All Fields] OR "Plasma Cell Dyscrasia"[All Fields] OR "Monoclonal Gammopathy"[All Fields] OR "Monoclonal Gammopathies"[All Fields] OR "Monoclonal Gammapathy"[All Fields] OR "Monoclonal Gammapathies"[All Fields])
Intervention	(("dexamethasone"[Mesh] OR "dexamethasone"[All Fields]) OR ("prednisone"[Mesh] OR "prednisone"[All Fields]) OR ("prednisolone"[Mesh] OR "prednisolone"[All Fields]) OR ("methylprednisolone"[Mesh] OR "methylprednisolone"[All Fields]) OR ("betamethasone"[Mesh] OR "betamethasone"[All Fields]) OR ("cyclophosphamide"[Mesh] OR "cyclophosphamide"[All Fields]) OR ("melphalan"[Mesh] OR "melphalan"[All Fields]) OR ("bendamustine" [Supplementary Concept] OR "bendamustine"[All Fields]) OR ("bortezomib" [Supplementary Concept] OR "bortezomib"[All Fields]) OR ("carfilzomib" [Supplementary Concept] OR "carfilzomib"[All Fields]) OR ("marizomib" [Supplementary Concept] OR "marizomib"[All Fields]) OR ("MLN 9708" [Supplementary Concept] OR "ixazomib"[All Fields] OR "MLN9708"[All Fields] OR "MLN2238"[All Fields]) OR ("oprozomib"[All Fields] OR "ONX0912"[All Fields]) OR ("delanzomib" [Supplementary Concept] OR "delanzomib"[All Fields] OR "CEP-18770"[All Fields]) OR ("Thalidomide"[Mesh] OR "Thalidomide"[All Fields]) OR ("lenalidomide" [Supplementary Concept] OR "lenalidomide"[All Fields]) OR ("pomalidomide" [Supplementary Concept] OR "pomalidomide"[All Fields]) OR ("vorinostat" [Supplementary Concept] OR "vorinostat" [All Fields]) OR ("panobinostat" [Supplementary Concept] OR "panobinostat"[All Fields]) OR ("2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide" [Supplementary Concept] OR "ACY-1215"[All Fields] OR "ricolinostat"[All Fields]) OR ("JNJ 26481585" [Supplementary Concept] OR "quisinostat"[All Fields] OR "JNJ26481585"[All Fields] OR "JNJ-26481585"[All Fields]) OR ("elotuzumab" [Supplementary Concept] OR "elotuzumab"[All Fields]) OR ("daratumumab" [Supplementary Concept] OR "daratumumab"[All Fields]) OR ("SAR650984"[All Fields]))
Comparison	Omitted.
Outcome	Omitted (for increased sensitivity).
Study Design	((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

Embase

Population	('multiple myeloma'/exp OR 'multiple myeloma' OR 'myeloma' OR 'multiple myelomas' OR 'plasma-cell myeloma' OR 'plasma-cell myelomas' OR 'myelomatosis' OR 'myelomatoses' OR 'plasma cell myeloma' OR 'plasma cell myelomas' OR 'kahler disease' OR 'POEMS')
Intervention	('dexamethasone'/exp OR 'dexamethasone') OR ('prednisone'/exp OR 'prednisone') OR ('prednisolone'/exp OR 'prednisolone') OR ('methylprednisolone'/exp OR 'methylprednisolone') OR ('betamethasone'/exp OR 'betamethasone') OR ('cyclophosphamide'/exp OR 'cyclophosphamide') OR ('melphalan'/exp OR 'melphalan'/exp) OR ('bendamustine'/exp OR 'bendamustine') OR ('bortezomib'/exp OR 'bortezomib') OR ('carfilzomib'/exp OR 'carfilzomib') OR ('salinosporamide A'/exp OR 'salinosporamide A' OR 'Marizomib' OR 'NPI 0052' OR 'NPI-0052') OR ('ixazomib'/exp OR 'ixazomib' OR 'MLN9708' OR 'MLN2238') OR ('oprozomib'/exp OR 'oprozomib' OR 'ONX0912') OR ('delanzomib'/exp OR 'delanzomib' OR 'CEP-18770' OR 'CEP18770' OR 'CEP 18770') OR ('thalidomide'/exp OR 'thalidomide') OR ('lenalidomide'/exp OR 'lenalidomide') OR ('pomalidomide'/exp OR 'pomalidomide') OR ('vorinostat'/exp OR 'vorinostat') OR ('panobinostat'/exp OR 'panobinostat'/exp) OR ('ricolinostat'/exp OR 'ricolinostat' OR '2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide' OR 'ACY-1215') OR ('quisinostat'/exp OR 'quisinostat' OR 'JNJ 26481585' OR 'JNJ26481585' OR 'JNJ-26481585') OR ('elotuzumab'/exp OR 'elotuzumab') OR ('daratumumab'/exp OR 'daratumumab') OR ('isatuximab'/exp OR 'isatuximab' OR 'SAR650984')
Comparison	Omitted.
Outcome	Omitted (for increased sensitivity).
Study Design	'crossover procedure'/exp AND [embase]/lim OR ('prospective study'/exp AND [embase]/lim) OR ('follow up'/exp AND [embase]/lim) OR ('placebo'/exp AND [embase]/lim) OR ('clinical trial'/exp AND [embase]/lim) OR ('single blind procedure'/exp AND [embase]/lim) OR ('double blind procedure'/exp AND [embase]/lim) OR ('randomization'/exp AND [embase]/lim) OR ('controlled clinical trial'/exp AND [embase]/lim) OR ('randomized controlled trial'/exp AND [embase]/lim)

LILACS

Population	(Mieloma AND Múltiplo) or (Multiple AND Myeloma) or (Kahler) or (Mieloma AND Multiplo)
Intervention	((dexamethasone) OR (prednisone) OR (prednisolone) OR (methylprednisolone) OR (betamethasone) OR (cyclophosphamide) OR (melphalan) OR (bendamustine) OR (bortezomib) OR (carfilzomib) OR (salinosporamide A OR Marizomib OR NPI 0052 OR NPI-0052) OR (ixazomib OR MLN9708 OR MLN2238) OR (oprozomib OR ONX0912) OR (delanzomib OR CEP-18770 OR CEP18770 OR CEP 18770) OR (thalidomide) OR (lenalidomide) OR (pomalidomide) OR (vorinostat) OR (panobinostat) OR (ricolinostat OR 2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide OR ACY-1215) OR (quisinostat OR JNJ 26481585 OR JNJ26481585 OR JNJ-26481585) OR (elotuzumab) OR (daratumumab) OR (isatuximab OR SAR650984))
Comparison	Omitted.
Outcome	Omitted (for increased sensitivity).
Study Design	Omitted (for increased sensitivity).

SciELO

Population	(Mieloma AND Múltiplo) or (Multiple AND Myeloma) or (Kahler) or (Mieloma AND Multiplo)
Intervention	((dexamethasone) OR (prednisone) OR (prednisolone) OR (methylprednisolone) OR (betamethasone) OR (cyclophosphamide) OR (melphalan) OR (bendamustine) OR (bortezomib) OR (carfilzomib) OR (salinosporamide A OR Marizomib OR NPI 0052 OR NPI-0052) OR (ixazomib OR MLN9708 OR MLN2238) OR (oprozomib OR ONX0912) OR (delanzomib OR CEP-18770 OR CEP18770 OR CEP 18770) OR (thalidomide) OR (lenalidomide) OR (pomalidomide) OR (vorinostat) OR (panobinostat) OR (ricolinostat OR 2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide OR ACY-1215) OR (quisinostat OR JNJ 26481585 OR JNJ26481585 OR JNJ-26481585) OR (elotuzumab) OR (daratumumab) OR (isatuximab OR SAR650984))
Comparison	Omitted.
Outcome	Omitted (for increased sensitivity).
Study Design	Omitted (for increased sensitivity).

Appendix 2. Treatment details of included studies.

Main Author	Publication Year	Intervention Treatment	Control Treatment
Barlogie	2006-2008	TT2+Thal - C1 VAD (Vincristine 0.5 mg/day D1-D4 + Doxorubicin 10 mg/m2 D1-D4 + Dexamethasone 40 mg D1-D4, D9-D12 and D17-D20) + C2 DCEP (Cyclophosphamide 400 mg/m2 D1-D4, Etoposide 40 mg/m2 D1-D4, Cisplatin 10 mg/m2 D1-D4 and Dexamethasone 40 mg D1-D4) + C3 CAD (Cyclophosphamide 400 mg/m2 D1-D4 + Doxorubicin 15 mg/m2 D1+D4 + Dexamethasone 40 mg D1-D4) + C4 DCEP. Accompanying Thalidomide 400 mg/day.	Conventional TT2 - C1 VAD (Vincristine 0.5 mg/day D1-D4 + Doxorubicin 10 mg/m2 D1-D4 + Dexamethasone 40 mg D1-D4, D9-D12 and D17-D20) + C2 DCEP (Cyclophosphamide 400 mg/m2 D1-D4, Etoposide 40 mg/m2 D1-D4, Cisplatin 10 mg/m2 D1-D4 and Dexamethasone 40 mg D1-D4) + C3 CAD (Cyclophosphamide 400 mg/m2 D1-D4 + Doxorubicin 15 mg/m2 D1+D4 + Dexamethasone 40 mg D1-D4) + C4 DCEP. No thalidomide allowed.
Cavo	2010-2013	VTD - Bortezomib 1,3 mg/m2 D1, D4, D8 and D11 + Dexamethasone 40 mg D1-D4 and D9-D12 + Thalidomide 200 mg/m2.	TD - Dexamethasone 40 mg D1-D4 and D9-D12 + Thalidomide 200 mg/m2.
Cook	2004	Z-Dex - Idarubicin 10 mg/m2/day D1-D4 +Dexamethasone 40 mg/day D1-D4 every 28 days.	VAD - Vincristine 0,4 mg/day D1-D4 + Doxorubicin 10 mg/m2/day D1-D4 + Dexamethasone 40 mg/day D1-D4 every 28 days.
Lokhorst	2010	TAD - Doxorubicin 9 mg/m2 D1-D4 + Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 28/28 days + Thalidomide 200 - 400 mg/day.	VAD - Vincristine 0,4 mg/day D1-D4 + Doxorubicin 10 mg/m2/day D1-D4 + Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 every 28 days.
Ludwig	2013-2015	VTDC - Cyclophosphamide 400 mg/m2 D1 and D8 + Bortezomib 1,3 mg/m2 D1, D4, D8 and D11 + Dexamethasone 40 mg D1-D4 and D9-D12 + Thalidomide 100 mg/day (every 21 days).	VTD - Bortezomib 1,3 mg/m2 D1, D4, D8 and D11 + Dexamethasone 40 mg D1-D4 and D9-D12 + Thalidomide 100 mg/day (every 21 days).
Morgan	2012	CTD - Cyclophosphamide 50 mg/day + Dexamethasone 40 mg D1-D4, D15-D18 + Thalidomide 100-200 mg/day	CVAD - Cyclophosphamide 500 mg/weekly +Vincristine 0,4 mg/day + Doxorubicin 9 mg/m2/day D1-D4 + Dexamethasone 40 mg/day D1-D4 and D12-D15.
Porter	2006-2007	DVd - Pegylated Doxorubicin 40 mg/m2 D1 + Vincristine 1,4 mg/m2 D1 + Dexamethasone 40 mg D1-D4.	VAD - Vincristine 0,4 mg/day D1-D4 + Doxorubicin 10 mg/m2/day D1-D4 + Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 every 28 days.
Sonneveld	2010-2015	PAD - Bortezomib 1,3 mg/m2 D1, D4, D8 and D11 + Doxorubicin 9 mg/m2/day D1-D4 + Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 evey 28 days.	VAD - Vincristine 0,4 mg/day D1-D4 + Doxorubicin 10 mg/m2/day D1-D4 + Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 every 28 days.
Straka	2016	Dexamethasone 40 mg D1-D4 and D8-D11.	Anthracycline-Based Induction (ID 67%, VAD 25% or CAD 6% - 2% received only dexamethasone)

7. Artigo 2:

Tratamento de indução para pacientes portadores de mieloma múltiplo não-candidatos a transplante autólogo de células progenitoras hematopoéticas: revisão sistemática e metanálise por mixed treatment comparison de 11.967 pacientes em 27 ensaios clínicos randomizados.

Frontline treatment for transplant-ineligible multiple myeloma patients: a systematic review and mixed treatment comparison meta-analysis of 11,967 patients in 27 randomized clinical trials.

Leo Sekine, Doutorando em Epidemiologia pela UFRGS;

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL (UFRGS)

A ser enviado ao periódico Blood.

Frontline treatment for transplant-ineligible multiple myeloma patients: a systematic review and network meta-analysis of 11,967 patients in 27 randomized clinical trials.

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Abstract

World has seen a relevant proliferation of active drugs for multiple myeloma management. Best frontline treatment should be constantly reevaluated under this context. We performed a systematic review and mixed treatment comparison meta-analysis of 27 randomized clinical trials, enrolling 11,967 patients and comparing 23 different treatment regimens regarding survival, response and safety outcomes. Similarity among study methodology, outcome measurement, follow up and population were considered adequate. No significant inconsistency was found. We performed ranking of treatments for each outcome analyzed. Overall survival analysis showed superiority of VRd, VMPT-VT, MPR-R, continuous Ld (Ldc) and CPR. Progression-free survival was longer with MPR-R, MPT-T, VMPT-VT, Ldc and VRd. Complete remission was more common with bortezomib-containing regimens (VMPT-VT, VTP, VMP, Vd and VRd), while overall response rate was also leaded by VMPT-VT, followed by Vd, VTd, LD and VTP. Safety profile evaluated infectious, cardiac, gastrointestinal, neurological, thrombotic and hematological grade 3-4 adverse events. A compound toxicity analysis presented high dose dexamethasone (Dex) and MP as regimens with the lowest incidence of adverse events, although with also the lowest survival and/or response rates. A compiled ranking outcome demonstrated that the best treatment option was VMPT-VT, followed by VRd, MPR-R, VMP and Ldc. On the other hand, last ranked treatments overall were Dex, TD, VMPC with and without continuous prednisone, MP and MD. Our analysis suggests that for transplant-ineligible patients, strategies combining novel agents (immunomodulatory imide drugs and proteasome inhibitors) in triplets or quadruplets and/or those comprising long term use of lenalidomide should be preferred.

Keywords: Multiple Myeloma; Frail Elderly; Network Meta-analysis; Induction Chemotherapy.

Introduction

Multiple myeloma (MM) comprises almost 2% of all malignancies worldwide and has an incidence of 6.08 new cases per 100.000 persons every year.[1-3] More than half of these patients are older than 65 years, with a major incidence between 75 to 79 years.[4,5] Elderly patients have inherent biological frailties, frequently accompanied by a number of comorbidities, which preclude almost 70% of them from being eligible to transplant.[6] Transplant-ineligible patients are warranted multidrug treatment regimens for an extended period of time, aiming at symptoms control and quality of life improvement.[7]

Within the last two decades a plethora of new active drug classes have rapidly been added to MM treatment like proteasome inhibitors (PIs), immunomodulatory imide drugs (IMiDs), histone deacetylase (HDAC) inhibitors, monoclonal antibodies (mAbs), along with corticosteroids and alkylating drugs.[8] The choice of one frontline regimen over another has been increasingly challenging due to the lack of comprehensive clinical trials comparing drug combinations and inability of conventional meta-analysis design to thoroughly aggregate data. Also, network meta-analysis approach has already been recently applied to this subgroup of patients[9-12], but with divergent results and discrepant number of captured trials.

MTC is a network meta-analysis approach that allows both direct and indirect comparisons to be accounted for in treatment effect estimation, also performing ranking of probabilities of being the best combination of drugs among all.[13-15] In order to summarize current knowledge on frontline multidrug treatment regimens for transplant-ineligible MM patients we have conducted a comprehensive systematic review and mixed treatment comparison (MTC) meta-analysis of all available therapeutic approaches.

Methods

Information Sources and Search Strategy

We have performed a comprehensive systematic review in order to identify all clinical trials comparing treatment approaches enrolling MM patients. Search strategy

comprised terms defining MM and related disorders, available active drugs and a sensitive filter strategy for randomized clinical trials.[16-18] Included databases were MEDLINE, Embase, LILACS, SciELO, Cochrane CENTRAL and proceedings from major international meetings in hematology and oncology. We have also hand searched references from all retrieved randomized clinical trials and prior systematic reviews. Search strategy for databases screened are available as supplementary material (Appendix 1).

Duplicates were excluded before proceeding to study selection. All titles and abstracts retrieved were screened independently by teams of two researchers. Full-text articles also had its eligibility evaluated by two independent researchers. The last date of the search was January 22, 2017. We have followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting this study and reporting our results.[19,20] PRISMA flow diagram is shown in Figure 1.

Eligibility Criteria

Selected patient population involved newly diagnosed transplant-ineligible MM patients. Only randomized phase 2/3 clinical trials, with or without blinding were included in the study. Abstracts or unpublished data were allowed to be included if they report sufficient data to extraction. No language or age restriction were applied.

Studies were excluded if there were no randomization procedure reported or if design was considered unclear. No prior treatment was allowed except for brief corticosteroid exposure. Refractory/Relapsed MM patients' studies were also excluded. Ancillary treatment approaches as bisphosphonates, kyphoplasty/vertebroplasty, radiation therapy, colony stimulating factors or erythropoietin were allowed if they were evenly distributed on trial arms, but trials comparing only bisphosphonate use were not considered for the purpose of this meta-analysis. Studies were also excluded if they did not report data on overall survival (OS) and/or progression free survival (PFS) hazard ratios (HR).

Study Selection and Data Extraction

Eight reviewers (L.S., F.S.F., M.R.R., M.S., C.F.P., V.D.M., A.P.S., D.M.) participated in the screening and full-text evaluation. All abstracts screened and articles

selected were reviewed and extraction proceeded by two of the eight reviewers, while a third reviewer would intervene (L.S) if there was any discordance over data extracted. Data extracted was: title and reference details (first author, year of publication, study acronym, period of patient enrollment, site of the study), study population characteristics (age, sex, median follow up, prognostic assessment), inclusion of therapy phase other than induction, ancillary treatments, number of enrolled patients, number of patients in each treatment arm, type of interventions and outcome data. For each trial, we evaluated hazard ratios (HRs) with 95% confidence intervals (CI) of overall survival (OS) and progression-free survival (PFS). Event-free survival and time to next treatment were also evaluated where PFS was unavailable. If CI was not reported, we extracted P-value of the HR tests to derive CI. Binary outcomes such as rate of complete response (CR) and overall response (OR), as well as safety analysis (rate of grade 3 and/or 4 hematological, gastrointestinal, cardiac, neurological, infectious or thrombotic adverse events) were extracted as absolute frequency. Definition of CR and OR relied in the criteria utilized within each study. Frequency of adverse events was considered to be the total number of patients experiencing any grade 3-4 events (1 or more episodes) during study period. If there were any data not clearly reported on manuscripts from reviewed articles or supplemental material, correspondent authors were contacted and asked to provide needed information. All data were extracted independently and registered on separate electronic spreadsheets, which were compiled and compared afterwards.

Quality Assessment

Selected studies were assessed for quality and risk of bias considering recommendations from The Cochrane Collaboration[21] group (including items such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data outcome, selective reporting). We have also evaluated early trial interruption due to efficacy as a possible bias[22]. This evaluation was also peer-reviewed and disparities were resolved by a third author. Where information for bias assessment was not reported, correspondent author was contacted and asked to provide study details. If no contact could be established, evaluated item was ranked unclear.

Mixed Treatment Comparison Meta-Analysis

MTC[23] uses a Bayesian hierarquical framework to simultaneously compare multiple treatments via common comparators. It is a generalized linear model for network meta-analysis. This approach combines direct and indirect evidence to summarize a comparison effect measure (point estimate and credible interval) whether a risk ratio (RR) or a HR. Contribution from this technique is that precision of estimates can be improved pending on completeness of meta-analysis network, also allowing inclusion of more than two-arm trials and heterogeneous between-trials variability. Also, this method of meta-analysis is able to rank treatments against each other in order to quantify probability of being best ranked overall (for each specific outcome).

Goodness of fit of the models was evaluated by means of residual deviance and deviance information criteria (DIC). DIC value was used as a parameter to compare model adjustment between random and fixed models. Eventually, MTC analyses were performed considering a fixed effect model. Similarity assumption (based on the premise that the true treatment effect comparing any two interventions would be similar across all trials[24]) was evaluated by judging and comparing baseline characteristics, methodological quality and outcome measurement outcomes from each individual study. Were similarity to be questioned, subgroup analysis would be performed to assess adequacy of the assumption. Homogeneity assumption among trials comparing similar treatments was tested through I^2 statistic. Consistency assumption was assessed through posterior plots and the Bayesian P-values produced by the node-splitting method described by Dias *et al*[25].; significance level was set to 0.05/k (k=number of comparisons) to adjust for multiple comparisons.

Outcomes reported are relative effects of treatments as HR for OS and PFS, and RR for binary outcomes (CR, OR and adverse events) along with corresponding 95% credible intervals (Bayesian equivalent for confidence intervals). For ranking probabilities evaluation, we chose to use the surface under the cumulative ranking (SUCRA) curve[26-28], which provides a numerical summary of the rank distribution of each treatment schedule on the different endpoints. The larger the SUCRA curve value (up to 1), the better the rank of the intervention. Pairwise meta-analysis and MTC was carried out with R software by using *meta* and *gemtc* packages.

Results

Study Selection

The PRISMA flowchart illustrating study selection process is shown in Figure 1. We have chosen to cover up the whole period of each database indexing, from inception to present time. A total of 15,091 references were retrieved from databases and peer-reviewed after exclusion of duplicates, including both full articles and meeting abstracts. From these studies, eventually 54 reports published from 1990 to 2016, concerning 27 RCT, were sorted out for inclusion in meta-analysis.[29-82] These RCT comprised a total of 11,967 patients, with a balanced distribution over gender, and mainly older age (70.4% of selected studies had a population median age superior to 70 years), enrolled in study sites throughout Europe, Asia, North America and South America. Median follow-up ranged from 18 to 82.8 months and prognostic information from patients was considered reasonably homogeneous. The majority of studies (74.1%) reported bisphosphonate use allowance. Overall, studies were considered similar with respect to population, trial design, general methodology and outcome measurement.

Only two trials[39,53] did not report OS HR, other two trials[29,49] did not report PFS HR. OR data was available for all studies, while CR data was missing in two[29,37] of them. Among adverse events, data was not available in four trials[29,31,34,50] for hematological, five trials[29,34,37,52,55,65,77] for neurological, two trials[42,65,77] for infectious, four trials[30,32,33,37] for thrombotic, eleven trials [30,34,37,40-42,44,47,50,51,53,54,58,60,65,76,77,80] for cardiac, and six trials[29,37,39,49,56,57,59,61,62,67-75,79,81] for gastrointestinal events. Details on the 27 included RCT are available in Table 1.

Quality Assessment

Risk of bias was evaluated as recommended by the Cochrane Collaboration[21], aiming at 7 different study attributes: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and early interruption of the trial. Overall, studies were of low to moderate risk of bias, although non-blinding of participants and personnel was a major drawback for most of them. Still, underreporting on

randomization and concealment method compromised the evaluation of some studies. Details on quality assessment can be seen in Table 2.

Treatment Group Allocation and Network Assembling

A total of 59 therapeutic arms over 27 RCT were reviewed and categorized under 23 treatment groups. Those treatment groups were allocated based on main constituents of each protocol, where slightly different doses and few additional ancillary drugs were tolerated. Summarized definition of treatment groups was as follows: Dex[34,39] (high dose dexamethasone), VMCP[29,32,33] (vincristine, melphalan, cyclophosphamide and intermittent prednisone), VMCPc[33] (same as previous except for continuous prednisone), Nitrosourea (NU) based regimen[30,32] (MCNU or BCNU, vincristine, melphalan, cyclophosphamide and prednisone), VAD[31,36] (vincristine, doxorubicin and high dose dexamethasone), MD[37] (melphalan and high dose dexamethasone), MP[29-31,34-38,40-44,47,50-55,60] (melphalan and prednisone), MPT[35,36,38,42,50,53,56,61,62,67-75,79,80] (melphalan, prednisone and thalidomide), MPT-T[65,66,77,82] (same as MPT, but with thalidomide maintenance), VMP[40,41,44,45,47,48,54,58,60,63,64,76] (bortezomib, melphalan and prednisone), VTP[46,63] (bortezomib, thalidomide and prednisone), VMPT-VT[45,48,64] (bortezomib, melphalan, prednisone and thalidomide), TD[39,43] (thalidomide and high dose dexamethasone), CTD[51,80] (cyclophosphamide, thalidomide and high dose dexamethasone), CPR[57,59,81] (cyclophosphamide, prednisone and lenalidomide), MPR[52,55,57,59,81] (melphalan, prednisone and lenalidomide), MPR-R[52,55,65,66,77,82] (same as MPR, but with lenalidomide maintenance), Ld[56,57,59,61,62,67-75,78,79,81] (lenalidomide and low dose dexamethasone, for a limited time period), Ldc[56,57,59,61,62,67-75,78,79,81] (same as Ld, but treatment continued until progression), LD[49] (lenalidomide and high dose dexamethasone), Vd[58,76] (bortezomib and low dose dexamethasone), VTd[58,76] (bortezomib, thalidomide and low dose dexamethasone) and VRd[78] (bortezomib, lenalidomide and low dose dexamethasone). Details on study therapeutic protocols are available as supplementary material (Appendix 2).

Survival Analysis

Comparison among treatment options concerning OS and PFS, through HR with 95% CrI, are shown in Figure 3. Overall, concerning OS, lenalidomide (L) containing regimens fared better than other combinations, except for LD. Among bortezomib (B) and thalidomide (T) containing regimens, the combination of the two (VMPT-VT) resulted in superior results than both agents separately, although VTP and VTd combinations did not perform similarly. Regimens lacking the incorporation of novel agents (L, T or B) definitely performed worse than their counterparts. Noticeably, LD and TD, high dose dexamethasone containing regimens, showed poorer results in OS, corroborating current knowledge upon high dose dexamethasone toxicity over this subgroup of patients.

While considering PFS, Dex resulted in the worst profile, being significantly inferior to all other treatments compared. MP also demonstrated poor results in face of novel agents' incorporation. Regimens comprising maintenance phases, whether L or T (VRd, MPR-R, VMPT-VT and MPT-T) fared better than other treatments, but still L containing regimens seemed to attain more favorable results overall.

There were three pairwise comparisons with more than one study for survival outcomes (MPT/MP, VAD/MP and MPR-R/MPT-T). Moderate to high heterogeneity was found when evaluating I^2 statistic for some comparisons regarding OS (MPT/MP 61.9%, VAD/MP 84.7% and MPR-R/MPT-T 59.7%) and PFS (VAD/MP 88.5% and MPR-R/MPT-T 74.7%). No significant inconsistency was found between direct and indirect evidence for these outcomes.

Complete Remission and Overall Response Rate

Results for simultaneous comparisons among included treatments, presenting RR 95% and CrI, are shown in Figure 4. Results on CR analysis derived few significant differences among treatments. Dex and MP regimens fared undoubtedly worse than other treatments, but among novel agents' containing regimens no obvious pattern of superiority could be drawn. Of note, CPR performed unsatisfactorily when compared to T, B and other L containing regimens.

OR analysis presented an overall significant inferiority of non-T/B/L containing protocols (namely, Dex, NU-based, VMCPc, VMCP, MP, MD and VAD), TD and MPT in

comparison to other regimens. Also, some B-containing regimens showed better results than L-containing treatments (Vd, VTd, VMP and VMPT-VT when compared to MPR and CPR, and also to Ldc and Ld versus VMPT-VT).

Pairwise comparisons for response outcomes were the same as in survival outcomes. No relevant heterogeneity was found when evaluating I^2 statistic for CR (0%-34%) and PFS (0%-39%) for those studies. No significant inconsistency was found between direct and indirect evidence for these outcomes.

Safety/Toxicity

We have assessed six different categories of adverse events (thromboembolic, neurological, infectious, hematological, gastrointestinal and cardiac). RR with 95% CrI for all simultaneous head-to-head comparisons for each adverse event evaluated are listed in Table 3. Overall rates of adverse events reported were considered low across studies (overall mean inferior to 15%), except for hematological adverse events (34.9%).

Concerning hematological adverse events, L containing agents were associated with more events than B containing regimens (MPR and MPR-R against VTd and Vd) and T containing protocols (MPR and MPR-R against TD). Also, regimens containing melphalan showed higher rates of toxicity than their counterparts (VMPT-VT, VMP and MPT against VTd, Vd and TD). VAD also showed relevant hematological toxicity when compared to T (CTD and TD) and V (Vd and VTD) containing regimens. Dex, as expected, resulted in inferior toxicity compared to other treatments.

While observing cardiac events, a trend towards a higher toxicity was observed with LD and VAD regimens. Underreporting of this outcome compromised further conclusions due to lack of information from more than 40% of the included studies. Gatrointestinal events were particularly frequent with B containing regimens, with or without T (Vd, VTd, VMP and VMPT-VT). Infectious events were seen especially with L containing regimens, mainly with LD. VAD also showed an unfavorable performance compared to other treatments. Thrombotic events were shown to be associated with L and T regimens, especially LD, along with T containing regimens (TD, MPT and CTD) and T and B combined (VTd and VTP).

There were two pairwise comparisons with more than one study for hematological events (MPT/MP and MPR-R/MPT-T); and other two for infectious,

gastrointestinal, thrombotic and cardiac events (MPT/MP and VAD/MP). Only one pairwise comparison had more than one study concerning neurological events. Moderate to high heterogeneity was found in some of such comparisons when evaluating I^2 statistic, such as in hematological (MPT/MP 61%% and MPR-R/MPT-T 92.8%), gastrointestinal (MPT/MP 61%) and cardiac (VAD/MP 77%) events. Only low to moderate heterogeneity was found with thrombotic (0%-49%), neurological (15%) and infectious events (0%-31%). Also, no significant inconsistency was found between direct and indirect evidence for these outcomes.

Ranking of Treatment Regimens

Aside from computing effect measures comparing treatments, MTC meta-analysis can also rank treatments on their probability of being best among all alternatives analyzed. The SUCRA curve value, an estimate of the probability of being the best regimen, was calculated for each treatment under all outcomes evaluated. With the intent to summarize rankings from different outcomes and eventually select the preferred regimens based on their efficacy on survival and response, while accounting for their safety profile, a compilation of SUCRA curve values was performed (considering a compound toxicity outcome, an arithmetic mean of SUCRA from adverse events). The results of this compilation are shown in Figure 5.

OS outcome was leaded by VRd, followed by VMPT-VT, MPR-R, Ldc and CPR. Except for VMPT-VT, all regimens contained L. Also, only one regimen (CPR) did not contain at least two novel agent classes (proteasome inhibitors and immunomodulatory drugs). PFS showed a similar pattern, with MPR-R ranking best, followed by MPT-T, VRd, VMPT-VT and Ldc. Of note, regimens with continuous treatment structures (MPR-R, MPT-T, VRd and Ldc) were found on both set of best treatments group, concerning OS and PFS.

When analyzing response parameters, CR was attained more often in B containing regimens (with and without immunomodulatory drugs), leaded by VMPT-VT, and followed by VTP, VMP, Vd and VRd. OR results presented an equivalent pattern to CR, VMPT-VT also leading this outcome, followed by Vd, VTd, LD and VTP.

Lowest ranked treatments for thrombotic events were LD, CPR, Ldc, VTP and Vd. Neurological events were found in higher rates with B with or without T containing

regimens (VTd, VTP, VMPT-VT, Vd and VMP in this order). Infectious events presented the most unfavorable results with VAD (the only anthracycline containing regimen among those analyzed), but also frequent among the worst ranked treatments concerning this adverse events were those regimens containing L (LD, Ldc, MPR, VRd and Ld). Hematological events were mostly seen with VAD and melphalan containing regimens combined with T or L. (MPR, MPR-R, MPT and VMPT-VT). The worst profile in gastrointestinal events were seen mainly with combinations of B, T and melphalan containing regimens (Vd, VTd, MD, VMP and VMPT-VT, in this order). Finally, cardiac events were more prone to result from older regimens (VAD, VMPC and VMPCc) but also with LD.

When considering the average SUCRA from compilation of outcomes (both probabilities of attaining longer OS and PFS, reaching higher response rates and dealing with lower incidence of adverse events), best designated treatment was VMPT-VT, followed closely by VRd, MPR-R, VMP and Ldc. Worst ranked regimens were those including high dose dexamethasone (Dex and TD) and older treatments not incorporating novel agents (MP, MD, VMCP, VMCPc, NU-based and VAD regimens).

Discussion

Treatment for transplant-ineligible MM patients has evolved enormously during last two decades, resulting in a proliferation of new drugs and protocols. Although this impressively productive pipeline is undoubtedly welcomed by attending physicians worldwide, the rapid pace in what new technologies are incorporated into practice prevent adequate judgement on what would be the best option among all alternatives. Into this context, the present study aims at defining a new horizon of efficacy stratification for the treatment of MM.

Previous meta-analyses using this same statistical framework were already published. Liu *et al*[10] reported a network meta-analysis (NMA) concerning first-line treatment for transplant-ineligible patients. However, only 19 studies were eventually included in this study, evaluating a total of 7,235 patients distributed over 17 different treatments. As the number of included studies were lower than the amount we have evaluated, this report could not assemble a complete network for PFS and therefore had

to analyze two separate subnetworks. This study also did not aim at evaluating safety/toxicity outcomes, and so could not attain a final balanced ranking including this information. This study did not add information to the report from Weisel *et al*. Weisel *et al*[12] performed a NMA comprising a similar context of patients, including 18 RCT and managed to extract HR from Kaplan-Meier curves through a graphical approach. Again, as the number of selected studies were lower, this study had to deal with two separate networks (preventing simultaneous comparisons of all treatments), and no safety/toxicity analysis was pursued. Other published meta-analyses found for this specific population had a conventional framework (and therefore were restricted to pairwise comparisons) or are already obsolete.

In our study, we managed to comprehensively and systematically review current and past medical literature and select all of the already attempted treatment strategies for transplant-ineligible MM patients. As a result, more than 20 different regimens, epitomes of the history of MM management, could be weighed against each other and their use reinforced or challenged. Such an information would only be possible through a mixed treatment comparison meta-analysis structure.

OS and PFS outcomes were unanimous in highlight the importance of L as part of the first line treatment of transplant-ineligible patients. Although B and T were also reasonable options, one seeking for longer survival endpoints should clearly incorporate L in its management. Usage of doublets, both L + B and T + B would also be strongly recommended. Response outcomes underscored the characteristic deep effect of B on lowering tumor burden. It was part of the five best treatments in attaining CR and also in 4 out of 5 best regimens in inducing OR. Safety analysis corroborated current knowledge upon toxicity profile, such as gastrointestinal events in B, thrombotic events in T and L and neurologic events in B and T containing regimens. It also ratified the abandonment of high dose dexamethasone for this set of patients.

Finally, compilation of SUCRA curve results in the ranking of treatments provided a complete and broad panorama of regimens hierarchical framework, conducting VMPT-VT to the leading treatment in this study, among others similarly efficacious protocols (namely, VRd, MPR-R, Ldc and VMP) also corroborating current knowledge with concrete evidence. Moreover, not a mere coincidence, the best ranked treatment presented one of the most toxic profiles among regimens, and on the other

hand, the “safest” of them all (Dex) showed the poorest result when concerning survival and response outcomes, eventually being considered the worst ranked treatment. This adds to the understanding that effective control comes at the inherent cost of side effects, and that one seeking for longer survival times will inevitably have quality of life compromised. Balancing among these parameters with each individual patient is the oncologist/hematologist conundrum.

However, limitations to this study should be also discussed. We assembled a very sensitive search strategy and as a result a great number of references were evaluated. Eventually, more than 250 articles were selected for full text review, but regrettably more than half of these studies were withdrawn due to the lack of HR reporting. HR as an effect measure was only incorporated in MM clinical trials after the 1980s, gradually gaining popularity on the 1990s. Thus, a significant amount of evidence was not included in this meta-analysis because of lack of appropriate information. Still, much of this research comprised older therapeutic options, implying minor impact on reported results. We did not apply graphical extraction techniques[83] due to possible inaccuracy of resulting estimates. Another important aspect is that HR extracted from Cox regression model analyses are susceptible to bias and imprecision as a result of non-compliance with specific model assumptions, a limitation that has been unequivocally demonstrated previously[84].

Furthermore, allocation of treatments in therapeutic groups, as we did, is susceptible to doubts regarding equivalence owing to intrinsic specific differences among some of the protocols included arbitrarily in the same group of comparison, although we have based our similarity assumption on known main drugs of each regimen. Thus, variation in treatment effect due to arbitrary allocation should not be disregarded. Instability of effect measures for some outcomes is possibly a result of this shortcoming. Meta-analysis is no more than a heuristic approach to solve a complex problem, and as so, one should consider that heterogeneity and complexity of patients, treatments and study designs could all influence to some point its results.

Similarity assumption over population characteristics, study design and endpoint measurements was considered adequate, but significant heterogeneity was present for some outcomes, and this should also be accounted for while examining the present results. No significant inconsistency was found in examining direct and indirect

evidence. For some reports, lack of available data and difficulties in contacting authors had also impacted negatively in completeness of information.

The present systematic review, as far as we are concerned, have compiled the greatest number of studies in a network meta-analysis yet. It was our objective to include older regimens together with novel agents to definitely establish their obsolescence in face of newer protocols. Novel agents, especially L and B should be essential part of MM current treatment, assembled in triplets or quadruplets and incorporating L in maintenance phase until progression or toxicity. The role of HDAC, mAbs, second generation PIs and IMiDs within this framework should be settled on further prospective studies in newly diagnosed MM patients.

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Figure 1. PRISMA Flowchart for study selection and review.

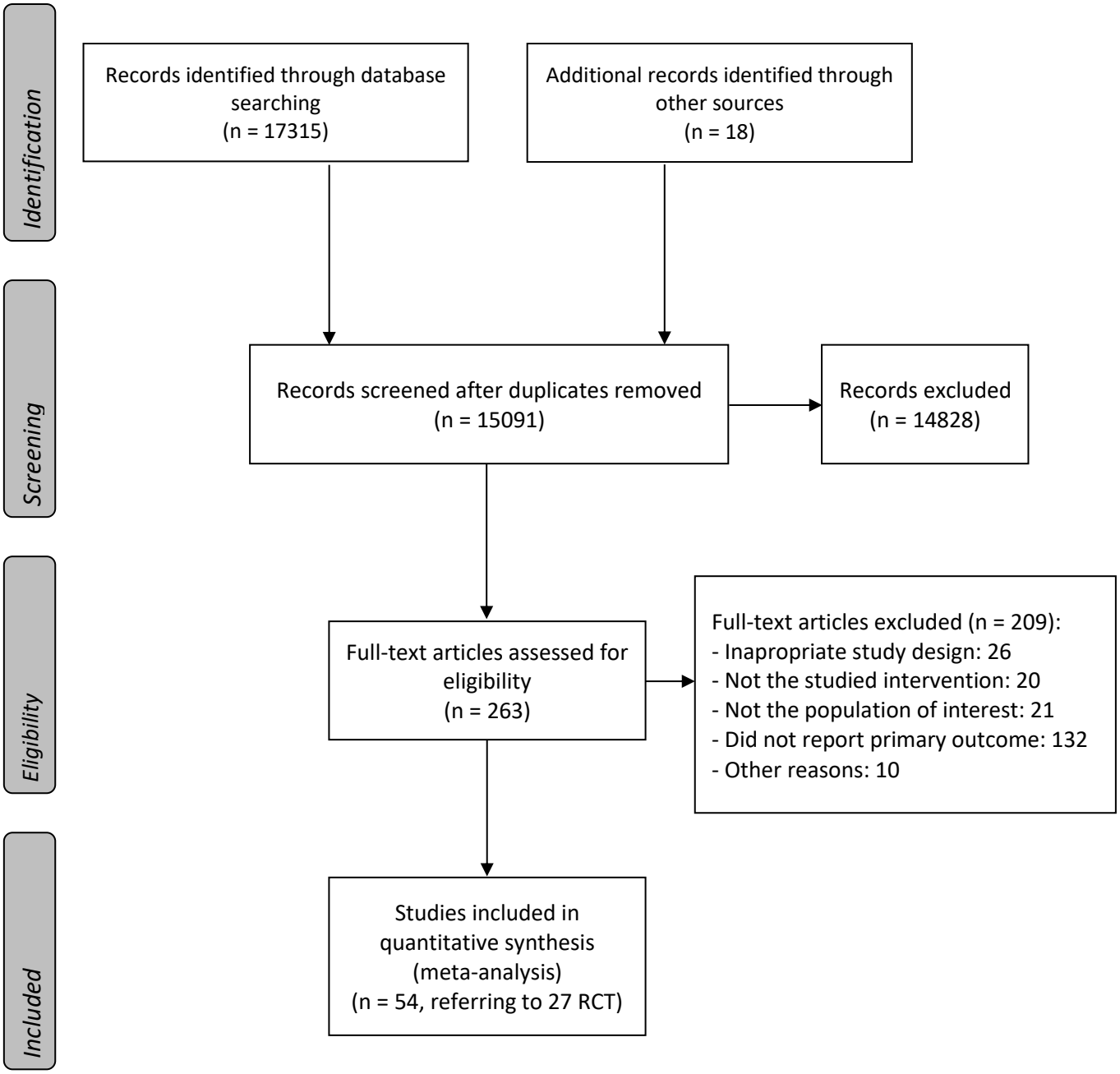
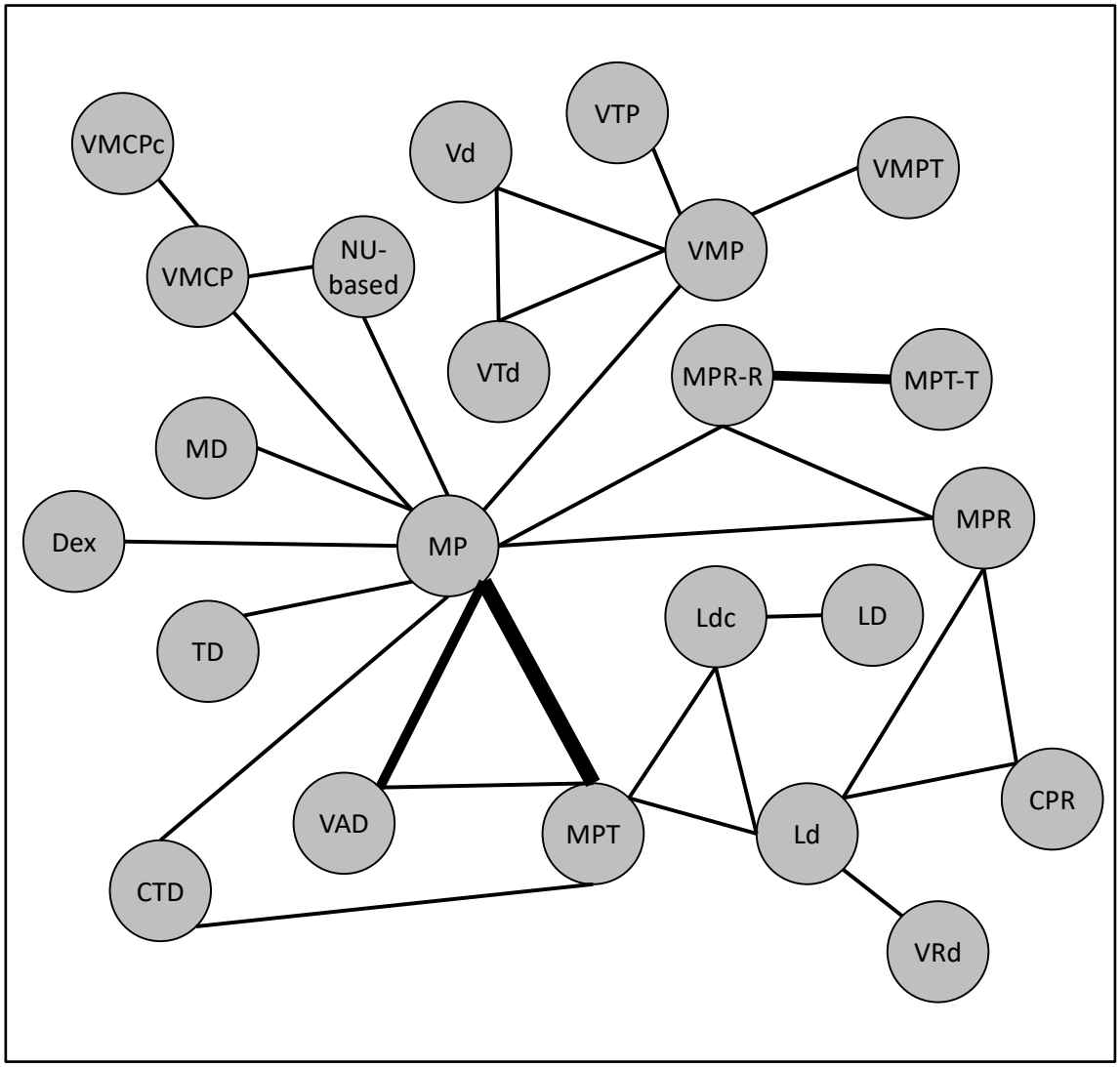


Figure 2. Network plot.*



*MPT x MP, 5 studies. VAD x MP, 2 studies. MPR-R x MPT-T, 2 studies. Three-arm trials: VAD x MPT x MP, Ldc x Ld x MPT, MPR x Ld x CPR, MPR-R x MPR x MP and VTd x Vd x VMP.

Figure 3. OS and PFS HR with 95% CrI for head-to-head simultaneous comparisons over treatments.

VRd	1.09 (0.41-2.85)	0.55 (0.23-1.25)	0.71 (0.41-1.26)	0.5 (0.22-1.03)	0.47 (0.19-1.12)	–	1 (0.32-2.85)	0.55 (0.21-1.42)	1.09 (0.4-3.12)	0.62 (0.20-1.92)	0.52 (0.16-1.56)	0.52 (0.25-1.11)	0.45 (0.15-1.40)	**0.4 (0.16-0.97)**	**0.29 (0.11-0.71)**	0.43 (0.18-1.03)	**0.34 (0.13-0.90)**	**0.30 (0.14-0.66)**	–	–	–	**0.17 (0.07-0.41)**
0.92 (0.5-1.7)	**MPR-R**	**0.5 (0.27-0.90)**	0.66 (0.30-1.42)	**0.43 (0.22-0.90)**	**0.43 (0.2-0.90)**	–	0.83 (0.33-2.32)	0.5 (0.22-1.14)	1 (0.66-1.49)	0.58 (0.20-1.58)	0.47 (0.17-1.28)	**0.47 (0.25-0.90)**	0.41 (0.15-1.16)	**0.35 (0.17-0.76)**	**0.26 (0.12-0.55)**	**0.38 (0.19-0.83)**	**0.32 (0.14-0.71)**	**0.27 (0.15-0.52)**	–	–	–	**0.15 (0.07-0.33)**
0.73 (0.46-1.1)	0.79 (0.53-1.2)	**MPR**	1.33 (0.71-2.5)	0.90 (0.55-1.40)	0.83 (0.5-1.44)	–	1.72 (0.71-4.34)	1 (0.5-2.12)	2 (0.97-4.16)	1.14 (0.45-2.94)	0.90 (0.37-2.38)	0.90 (0.58-1.58)	0.83 (0.33-2.17)	0.71 (0.38-1.40)	0.52 (0.27-1.03)	0.76 (0.43-1.47)	0.62 (0.31-1.33)	**0.55 (0.34-0.90)**	–	–	–	**0.31 (0.16-0.58)**
0.82 (0.58-1.2)	0.89 (0.51-1.6)	1.1 (0.76-1.7)	**Ldc**	0.66 (0.4-1.09)	0.66 (0.32-1.26)	–	1.31 (0.5-3.33)	0.76 (0.35-1.63)	1.49 (0.62-3.57)	0.83 (0.33-2.27)	0.71 (0.27-1.85)	0.71 (0.43-1.20)	0.62 (0.23-1.66)	0.55 (0.28-1.08)	**0.4 (0.19-0.83)**	0.58 (0.31-1.14)	0.47 (0.22-1.04)	**0.41 (0.24-0.71)**	–	–	–	**0.23 (0.11-0.47)**
0.74 (0.55-1.0)	0.8 (0.48-1.4)	1.02 (0.72-1.4)	0.9 (0.75-1.1)	**Ld**	1 (0.58-1.56)	–	1.96 (0.83-4.76)	1.13 (0.55-2.38)	**2.22 (1.02-5)**	1.28 (0.52-3.33)	1.05 (0.41-2.70)	1.06 (0.71-1.69)	0.90 (0.37-2.43)	0.83 (0.45-1.56)	0.58 (0.30-1.14)	0.90 (0.5-1.63)	0.71 (0.34-1.49)	0.62 (0.4-1.02)	–	–	–	**0.35 (0.18-0.66)**
0.79 (0.56-1.1)	0.86 (0.51-1.5)	1.11 (0.77-1.5)	0.97 (0.75-1.3)	1.1 (0.9-1.3)	**CPR**	–	2.04 (0.76-5.55)	1.17 (0.52-2.70)	2.32 (1-5.55)	1.33 (0.5-3.70)	1.09 (0.41-3.03)	1.11 (0.62-2.08)	1 (0.35-2.70)	0.83 (0.41-1.85)	0.62 (0.28-1.35)	0.90 (0.45-1.92)	0.76 (0.33-1.72)	0.66 (0.35-1.23)	–	–	–	**0.37 (0.16-0.76)**
0.33 (0.17-0.63)	**0.36 (0.16-0.78)**	**0.45 (0.23-0.89)**	**0.4 (0.23-0.7)**	**0.44 (0.25-0.8)**	**0.42 (0.23-0.77)**	**LD**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
0.93 (0.56-1.6)	1.01 (0.51-1.96)	1.3 (0.74-2.2)	1.1 (0.74-1.7)	1.3 (0.82-1.9)	1.18 (0.77-1.85)	**2.8 (1.4-5.7)**	**VMPT-VT**	0.58 (0.33-1)	1.14 (0.4-3.33)	0.66 (0.29-1.47)	0.55 (0.24-1.19)	0.55 (0.24-1.21)	0.47 (0.21-1.07)	0.41 (0.17-1.02)	**0.30 (0.12-0.71)**	0.45 (0.19-1.07)	**0.37 (0.14-0.90)**	**0.32 (0.14-0.71)**	–	–	–	**0.18 (0.07-0.43)**
0.65 (0.42-0.99)	0.71 (0.38-1.3)	0.89 (0.56-1.4)	0.79 (0.58-1.1)	0.88 (0.65-1.2)	0.83 (0.59-1.16)	**2.0 (1.1-3.7)**	**0.7 (0.53-0.93)**	**VMP**	1.96 (0.83-5)	1.13 (0.62-2.04)	0.90 (0.52-1.66)	0.90 (0.52-1.72)	0.83 (0.45-1.49)	0.71 (0.37-1.47)	0.52 (0.25-1.05)	0.76 (0.4-1.51)	0.62 (0.29-1.35)	**0.55 (0.32-0.95)**	–	–	–	**0.31 (0.15-0.62)**
0.84 (0.44-1.6)	0.91 (0.75-1.1)	1.2 (0.74-1.8)	1.03 (0.57-1.9)	1.1 (0.65-2.0)	1.06 (0.59-1.89)	**2.6 (1.1-5.8)**	0.91 (0.45-1.8)	1.3 (0.68-2.5)	**MPT-T**	0.58 (0.19-1.72)	0.47 (0.16-1.38)	0.47 (0.22-1.02)	0.41 (0.14-1.23)	**0.35 (0.15-0.83)**	**0.26 (0.11-0.62)**	0.4 (0.17-0.90)	**0.32 (0.12-0.76)**	**0.27 (0.13-0.58)**	–	–	–	**0.15 (0.06-0.37)**
0.6 (0.34-1.03)	0.65 (0.32-1.3)	0.82 (0.46-1.5)	0.73 (0.46-1.2)	0.81 (0.51-1.3)	0.77 (0.45-1.23)	1.8 (0.88-3.8)	0.64 (0.41-1.01)	0.92 (0.65-1.3)	0.71 (0.34-1.5)	**VTd**	0.83 (0.45-1.47)	0.83 (0.35-1.92)	0.71 (0.32-1.69)	0.62 (0.25-1.58)	0.45 (0.17-1.13)	0.66 (0.28-1.66)	0.55 (0.21-1.44)	0.5 (0.21-1.08)	–	–	–	**0.27 (0.10-0.66)**
0.58 (0.34-1.0)	0.63 (0.31-1.3)	0.8 (0.45-1.4)	0.71 (0.45-1.1)	0.78 (0.5-1.2)	0.71 (0.45-1.19)	1.8 (0.86-3.7)	**0.63 (0.4-0.98)**	0.89 (0.64-1.3)	0.69 (0.33-1.4)	0.97 (0.69-1.4)	**Vd**	1.01 (0.43-2.32)	0.90 (0.38-2.04)	0.76 (0.32-1.96)	0.55 (0.22-1.38)	0.83 (0.35-2.04)	0.66 (0.25-1.75)	0.58 (0.27-1.31)	–	–	–	**0.33 (0.13-0.83)**
0.62 (0.43-0.87)	0.67 (0.38-1.2)	0.84 (0.57-1.2)	**0.75 (0.62-0.9)**	**0.83 (0.69-0.99)**	0.78 (0.6-1.0)	**1.9 (1.04-3.4)**	**0.66 (0.45-0.96)**	0.95 (0.74-1.2)	0.73 (0.4-1.3)	1.03 (0.67-1.6)	1.1 (0.69-1.6)	**MPT**	0.90 (0.38-2.04)	0.76 (0.47-1.21)	**0.55 (0.32-0.90)**	0.83 (0.55-1.26)	0.66 (0.37-1.20)	**0.58 (0.45-0.76)**	–	–	–	**0.33 (0.19-0.52)**
0.44 (0.26-0.74)	**0.47 (0.24-0.93)**	0.6 (0.34-1.04)	**0.53 (0.34-0.82)**	**0.59 (0.38-0.91)**	**0.56 (0.34-0.91)**	1.3 (0.66-2.7)	**0.47 (0.31-0.72)**	**0.67 (0.49-0.91)**	0.52 (0.25-1.1)	0.73 (0.46-1.2)	0.75 (0.47-1.2)	0.71 (0.48-1.1)	**VTP**	0.83 (0.35-2.17)	0.62 (0.24-1.56)	0.90 (0.38-2.32)	0.76 (0.28-2)	0.66 (0.30-1.49)	–	–	–	**0.37 (0.14-0.90)**
0.52 (0.34-0.78)	0.56 (0.31-1.02)	0.71 (0.46-1.1)	**0.63 (0.47-0.84)**	**0.7 (0.53-0.93)**	**0.67 (0.48-0.91)**	1.6 (0.84-2.9)	**0.56 (0.38-0.83)**	0.8 (0.61-1.04)	0.62 (0.33-1.2)	0.87 (0.56-1.3)	0.89 (0.58-1.4)	0.84 (0.68-1.05)	1.2 (0.78-1.8)	**CTD**	0.71 (0.37-1.35)	1.08 (0.62-1.92)	0.90 (0.43-1.75)	0.76 (0.5-1.17)	–	–	–	**0.43 (0.22-0.76)**
0.29 (0.17-0.5)	**0.32 (0.16-0.63)**	**0.4 (0.23-0.7)**	**0.36 (0.23-0.55)**	**0.39 (0.25-0.61)**	**0.37 (0.23-0.59)**	0.89 (0.44-1.8)	**0.31 (0.19-0.52)**	**0.45 (0.29-0.69)**	**0.35 (0.17-0.71)**	**0.49 (0.28-0.85)**	**0.5 (0.29-0.87)**	**0.47 (0.32-0.71)**	0.67 (0.39-1.1)	**0.56 (0.37-0.86)**	**TD**	1.49 (0.83-2.77)	1.20 (0.58-2.5)	1.06 (0.66-1.72)	–	–	–	**0.58 (0.37-0.90)**
0.59 (0.38-0.91)	0.64 (0.35-1.2)	0.81 (0.51-1.3)	**0.72 (0.52-0.99)**	0.8 (0.58-1.1)	0.77 (0.53-1.08)	1.8 (0.95-3.4)	**0.64 (0.41-0.98)**	0.91 (0.66-1.2)	0.7 (0.37-1.3)	0.99 (0.62-1.6)	1.01 (0.64-1.6)	0.96 (0.74-1.2)	1.4 (0.87-2.1)	1.1 (0.84-1.5)	**2.04 (1.3-3.2)**	**VAD**	0.83 (0.41-1.56)	0.71 (0.47-1.04)	–	–	–	**0.4 (0.21-0.71)**
0.5 (0.32-0.76)	**0.54 (0.29-0.99)**	0.67 (0.44-1.08)	**0.63 (0.46-0.83)**	**0.67 (0.5-0.91)**	**0.63 (0.44-0.91)**	1.52 (0.83-2.86)	**0.53 (0.36-0.83)**	0.77 (0.59-1.02)	0.59 (0.31-1.12)	0.83 (0.53-1.32)	0.83 (0.56-1.33)	0.83 (0.63-1.03)	1.14 (0.77-1.72)	0.96 (0.73-1.3)	**1.70 (1.11-2.63)**	0.83 (0.63-1.16)	**MD**	0.90 (0.52-1.51)	–	–	–	**0.5 (0.23-0.99)**
0.45 (0.31-0.66)	**0.49 (0.28-0.87)**	**0.62 (0.41-0.94)**	**0.55 (0.44-0.69)**	**0.61 (0.49-0.76)**	**0.56 (0.43-0.77)**	1.4 (0.75-2.5)	**0.49 (0.34-0.69)**	**0.7 (0.57-0.85)**	**0.54 (0.29-0.99)**	0.76 (0.51-1.1)	0.78 (0.52-1.2)	**0.74 (0.64-0.84)**	1.04 (0.72-1.5)	0.87 (0.73-1.1)	**1.5 (1.1-2.3)**	**0.77 (0.6-0.98)**	0.91 (0.74-1.1)	**MP**	–	–	–	**0.55 (0.35-0.83)**
0.5 (0.32-0.78)	0.55 (0.29-1.02)	0.69 (0.43-1.1)	**0.61 (0.44-0.85)**	**0.68 (0.49-0.94)**	**0.63 (0.44-0.92)**	1.5 (0.8-2.9)	**0.54 (0.35-0.83)**	0.77 (0.56-1.1)	0.6 (0.31-1.2)	0.84 (0.53-1.3)	0.86 (0.54-1.4)	0.82 (0.62-1.1)	1.2 (0.74-1.8)	0.97 (0.72-1.3)	**1.7 (1.1-2.7)**	0.85 (0.6-1.2)	1.0 (0.74-1.4)	1.1 (0.88-1.4)	**VMCP**	–	–	–
0.43 (0.25-0.74)	**0.47 (0.23-0.94)**	0.59 (0.34-1.05)	**0.61 (0.44-0.85)**	**0.59 (0.37-0.92)**	**0.55 (0.33-0.89)**	1.3 (0.64-2.7)	**0.47 (0.27-0.79)**	0.67 (0.43-1.04)	0.52 (0.25-1.1)	0.73 (0.41-1.3)	0.75 (0.43-1.3)	0.7 (0.47-1.1)	0.99 (0.58-1.7)	0.84 (0.54-1.3)	1.5 (0.86-2.6)	0.73 (0.46-1.2)	0.87 (0.56-1.4)	0.96 (0.65-1.4)	0.86 (0.63-1.2)	**VMCPc**	–	–
0.52 (0.33-0.8)	0.56 (0.3-1.04)	0.71 (0.44-1.1)	**0.63 (0.46-0.88)**	**0.7 (0.5-0.97)**	**0.65 (0.45-0.95)**	1.6 (0.83-3.03)	**0.56 (0.37-0.85)**	0.8 (0.58-1.1)	0.62 (0.32-1.2)	0.87 (0.54-1.4)	0.89 (0.56-1.4)	0.84 (0.64-1.1)	1.2 (0.77-1.8)	1.0 (0.74-1.4)	**1.8 (1.1-2.8)**	0.88 (0.62-1.2)	1.0 (0.76-1.4)	1.1 (0.91-1.5)	1.03 (0.97-1.1)	1.2 (0.87-1.6)	**NU-based**	–
0.39 (0.26-0.59)	**0.42 (0.23-0.78)**	**0.54 (0.34-0.84)**	**0.48 (0.35-0.64)**	**0.53 (0.39-0.71)**	**0.49 (0.35-0.69)**	1.2 (0.63-2.2)	**0.42 (0.28-0.63)**	**0.6 (0.45-0.79)**	**0.46 (0.25-0.88)**	0.65 (0.42-1.02)	0.67 (0.43-1.04)	**0.63 (0.5-0.8)**	0.89 (0.59-1.4)	**0.75 (0.58-0.99)**	1.3 (0.87-2.04)	0.66 (0.49-0.9)	0.59 (0.78-1.04)	0.86 (0.71-1.05)	0.78 (0.57-1.1)	0.9 (0.58-1.4)	0.75 (0.55-1.02)	**Dex**

Treatments are shown in the dark gray area (middle oblique line). At the OS analysis area (white/bottom), HR represents column-defining treatment compared to line-defining treatment with 95% Credible Intervals (CrI). At the PFS analysis area (light gray/top), HR represents line-defining treatment compared to column-defining treatment with 95% Credible Intervals (CrI). Statistically significant HR are highlighted in blue.

Figure 4. CR and OR RR with 95% CrI for head-to-head simultaneous comparisons over treatments.

VRd	1.08 (0.90-1.33)	**1.19 (1.01-1.40)**	1.05 (0.90-1.20)	1.08 (0.96-1.23)	1.17 (0.99-1.38)	0.90 (0.71-1.06)	0.83 (0.62-1.04)	0.90 (0.71-1.12)	1.09 (0.90-1.35)	0.83 (0.62-1.13)	0.83 (0.62-1.12)	**1.25 (1.08-1.42)**	0.90 (0.66-1.14)	0.90 (0.76-1.14)	**1.53 (1.21-1.92)**	1.26 (0.98-1.61)	**1.51 (1.20-1.92)**	**1.81 (1.53-2.12)**	**2.04 (1.58-2.70)**	**2 (1.44-2.77)**	**1.49 (1.20-1.81)**	**2.32 (1.81-2.85)**
1.51 (0.33-6.67)	**MPR-R**	1.09 (0.96-1.25)	1 (0.83-1.13)	1 (0.83-1.16)	1.07 (0.90-1.28)	**0.83 (0.66-0.99)**	**0.76 (0.58-0.95)**	0.83 (0.66-1.03)	1.01 (0.90-1.07)	0.76 (0.58-1.04)	0.76 (0.58-1.03)	1.14 (0.97-1.33)	0.83 (0.62-1.05)	0.83 (0.71-1.05)	**1.40 (1.12-1.75)**	1.14 (0.90-1.47)	**1.40 (1.09-1.78)**	**1.66 (1.42-1.96)**	**1.88 (1.44-2.43)**	**1.81 (1.31-2.5)**	**1.36 (1.09-1.66)**	**2.12 (1.66-2.63)**
3.22 (0.83-11.76)	2.08 (0.76-5.88)	**MPR**	0.90 (0.76-1)	0.90 (0.83-1.02)	1 (0.83-1.12)	**0.76 (0.62-0.90)**	**0.66 (0.55-0.83)**	**0.76 (0.62-0.90)**	0.90 (0.76-1.06)	**0.71 (0.55-0.90)**	**0.71 (0.55-0.90)**	1.04 (0.90-1.17)	**0.76 (0.58-0.90)**	**0.76 (0.66-0.90)**	**1.28 (1.04-1.58)**	1.05 (0.83-1.33)	**1.28 (1.03-1.58)**	**1.51 (1.33-1.75)**	**1.72 (1.35-2.17)**	**1.66 (1.21-2.27)**	**1.25 (1.03-1.49)**	**1.92 (1.56-2.38)**
1.56 (0.5-4.35)	1 (0.27-3.85)	0.47 (0.15-1.52)	**Ldc**	1.03 (0.97-1.09)	1.12 (0.98-1.28)	**0.83 (0.76-0.90)**	**0.76 (0.62-0.96)**	0.83 (0.71-1.04)	1.04 (0.90-1.25)	0.83 (0.62-1.05)	0.83 (0.62-1.05)	**1.19 (1.11-1.28)**	0.83 (0.66-1.06)	0.90 (0.76-1.05)	**1.44 (1.20-1.78)**	1.19 (0.97-1.49)	**1.44 (1.17-1.78)**	**1.72 (1.53-1.92)**	**1.96 (1.56-2.5)**	**1.88 (1.40-2.56)**	**1.40 (1.19-1.66)**	**2.17 (1.78-2.70)**
1.72 (0.76-4)	1.13 (0.34-4.17)	0.55 (0.19-1.56)	1.09 (0.62-2.44)	**Ld**	1.07 (0.96-1.21)	**0.83 (0.71-0.90)**	**0.76 (0.62-0.90)**	0.83 (0.66-1)	1.01 (0.83-1.20)	0.76 (0.58-1.02)	0.76 (0.58-1.01)	**1.14 (1.07-1.23)**	0.83 (0.66-1.03)	0.83 (0.71-1.01)	**1.40 (1.16-1.69)**	1.16 (0.90-1.44)	**1.40 (1.13-1.72)**	**1.66 (1.49-1.85)**	**1.88 (1.49-2.38)**	**1.81 (1.35-2.43)**	**1.36 (1.14-1.61)**	**2.12 (1.75-2.56)**
9.09 (1.53-76.92)	5.88 (0.98-55.55)	2.77 (0.55-21.73)	**5.55 (1.13-52.63)**	**5 (1.08-38.46)**	**CPR**	**0.76 (0.62-0.90)**	**0.71 (0.55-0.90)**	**0.76 (0.62-0.90)**	0.90 (0.76-1.12)	**0.71 (0.55-0.96)**	**0.71 (0.55-0.96)**	1.06 (0.90-1.20)	**0.76 (0.58-0.97)**	**0.76 (0.66-0.97)**	**1.29 (1.04-1.61)**	1.07 (0.83-1.36)	**1.29 (1.03-1.63)**	**1.53 (1.33-1.78)**	**1.75 (1.35-2.27)**	**1.69 (1.23-2.32)**	**1.26 (1.03-1.53)**	**1.96 (1.56-2.43)**
1.26 (0.26-5.56)	0.83 (0.15-4.55)	0.38 (0.08-1.82)	0.83 (0.27-2.38)	0.71 (0.19-2.5)	0.14 (0.013-1.02)	**LD**	0.90 (0.71-1.17)	1.02 (0.83-1.28)	**1.25 (1.01-1.53)**	1 (0.71-1.28)	1 (0.71-1.28)	**1.40 (1.23-1.61)**	1 (0.76-1.29)	1.05 (0.83-1.29)	**1.72 (1.38-2.17)**	**1.42 (1.11-1.81)**	**1.72 (1.35-2.17)**	**2.04 (1.75-2.43)**	**2.32 (1.78-3.03)**	**2.27 (1.63-3.12)**	**1.66 (1.36-2.08)**	**2.63 (2.08-3.33)**
0.52 (0.09-2.22)	0.34 (0.06-1.67)	**0.16 (0.03-0.71)**	0.34 (0.07-1.25)	0.31 (0.07-1)	**0.058 (0.0049-0.4)**	0.41 (0.06-2.33)	**VMPT-VT**	**1.09 (1.01-1.19)**	**1.35 (1.05-1.72)**	1.04 (0.83-1.25)	1.03 (0.83-1.25)	**1.51 (1.25-1.85)**	1.08 (0.90-1.25)	1.13 (0.90-1.42)	**1.85 (1.47-2.38)**	**1.53 (1.17-2)**	**1.85 (1.44-2.38)**	**2.22 (1.85-2.63)**	**2.5 (1.92-3.33)**	**2.43 (1.75-3.33)**	**1.81 (1.44-2.27)**	**2.77 (2.22-3.57)**
0.83 (0.17-2.94)	0.52 (0.12-2.17)	**0.25 (0.06-0.91)**	0.52 (0.15-1.59)	0.47 (0.12-1.32)	**0.091 (0.009-0.56)**	0.66 (0.12-3.13)	1.56 (0.76-3.23)	**VMP**	1.21 (0.97-1.56)	1 (0.83-1.12)	0.90 (0.76-1.12)	**1.38 (1.14-1.69)**	1 (0.90-1.11)	1.03 (0.83-1.28)	**1.69 (1.35-2.12)**	**1.40 (1.08-1.81)**	**1.69 (1.33-2.17)**	**2.04 (1.72-2.38)**	**2.27 (1.75-2.94)**	**2.22 (1.61-3.03)**	**1.63 (1.35-2.04)**	**2.56 (2.04-3.22)**
2.12 (0.43-10.3)	1.36 (0.76-2.63)	0.66 (0.19-2.13)	1.36 (0.33-5.88)	1.21 (0.30-4.76)	0.23 (0.024-1.6)	1.69 (0.28-10.2)	4 (0.76-23.8)	2.63 (0.55-12.82)	**MPT-T**	0.76 (0.58-1.04)	0.76 (0.58-1.03)	1.13 (0.95-1.35)	0.83 (0.62-1.05)	0.83 (0.66-1.05)	**1.38 (1.09-1.75)**	1.14 (0.90-1.47)	**1.38 (1.08-1.78)**	**1.63 (1.38-1.96)**	**1.85 (1.42-2.43)**	**1.81 (1.29-2.5)**	**1.35 (1.08-1.66)**	**2.08 (1.63-2.63)**
1.01 (0.12-7.14)	0.66 (0.09-5)	0.31 (0.04-2.13)	0.66 (0.10-3.85)	0.58 (0.09-3.23)	0.11 (0.0072-1.1)	0.83 (0.09-6.67)	1.92 (0.41-9.09)	1.23 (0.32-5)	0.47 (0.05-3.7)	**VTd**	1 (0.83-1.16)	**1.44 (1.13-1.88)**	1.04 (0.83-1.28)	1.08 (0.83-1.42)	**1.78 (1.35-2.38)**	**1.47 (1.08-2)**	**1.78 (1.33-2.38)**	**2.12 (1.69-2.70)**	**2.38 (1.75-3.33)**	**2.32 (1.61-3.33)**	**1.72 (1.33-2.27)**	**2.70 (2-3.57)**
0.83 (0.10-5.26)	0.52 (0.07-3.85)	0.25 (0.03-1.64)	0.52 (0.08-2.94)	0.47 (0.07-2.5)	**0.092 (0.006-0.85)**	0.66 (0.07-5)	1.56 (0.37-6.67)	1.01 (0.27-3.85)	0.38 (0.04-2.94)	0.83 (0.19-3.33)	**Vd**	**1.47 (1.13-1.88)**	1.04 (0.83-1.28)	1.09 (0.83-1.44)	**1.81 (1.35-2.38)**	**1.49 (1.08-2.04)**	**1.78 (1.33-2.43)**	**2.12 (1.69-2.70)**	**2.43 (1.78-3.33)**	**2.32 (1.63-3.33)**	**1.75 (1.33-2.27)**	**2.70 (2.04-3.57)**
2.5 (0.76-6.25)	1.61 (0.5-5.26)	0.76 (0.26-2.13)	1.63 (0.71-3.03)	1.47 (0.62-2.5)	0.28 (0.032-1.3)	2 (0.52-6.67)	4.76 (1.49-15.38)	**3.03 (1.20-8.33)**	1.17 (0.30-4.35)	2.43 (0.45-13.15)	2.94 (0.58-15.87)	**MPT**	**0.71 (0.55-0.90)**	**0.76 (0.62-0.90)**	**1.23 (1.02-1.47)**	1.01 (0.83-1.25)	1.21 (1-1.49)	**1.44 (1.33-1.61)**	**1.63 (1.31-2.08)**	**1.58 (1.19-2.12)**	**1.19 (1.01-1.38)**	**1.85 (1.53-2.22)**
0.58 (0.1-2.56)	0.37 (0.07-1.85)	**0.17 (0.03-0.77)**	0.37 (0.08-1.43)	0.33 (0.07-1.16)	**0.064 (0.005-0.46)**	0.45 (0.07-2.63)	1.09 (0.37-3.23)	0.71 (0.32-1.56)	0.27 (0.04-1.47)	0.58 (0.11-2.7)	0.71 (0.14-3.23)	**0.23 (0.06-0.77)**	**VTP**	1.05 (0.83-1.35)	**1.72 (1.33-2.22)**	**1.42 (1.06-1.88)**	**1.72 (1.31-2.27)**	**2.04 (1.66-2.5)**	**2.32 (1.75-3.12)**	**2.22 (1.58-3.12)**	**1.66 (1.31-2.12)**	**2.56 (2-3.33)**
1.31 (0.30-4.35)	0.83 (0.21-3.33)	0.4 (0.10-1.39)	0.83 (0.27-2.22)	0.76 (0.23-1.89)	**0.15 (0.015-0.83)**	1.04 (0.21-4.55)	2.5 (0.66-10)	1.58 (0.52-5)	0.62 (0.13-2.7)	1.29 (0.20-7.69)	1.58 (0.27-9.09)	0.52 (0.23-1.15)	2.27 (0.58-9.09)	**CTD**	**1.63 (1.33-2.04)**	**1.35 (1.06-1.72)**	**1.63 (1.31-2.04)**	**1.96 (1.69-2.27)**	**2.22 (1.72-2.85)**	**2.12 (1.56-2.94)**	**1.58 (1.31-1.92)**	**2.5 (2-3.03)**
5.88 (1.04-31.25)	3.84 (0.71-22.72)	1.85 (0.35-10)	3.84 (0.83-17.85)	3.44 (0.76-15.15)	0.65 (0.054-5.3)	4.76 (0.76-29.41)	**11.3 (2.22-62.5)**	**7.14 (1.66-35.71)**	2.77 (0.45-17.85)	5.88 (0.76-47.61)	7.14 (0.99-58.82)	2.38 (0.62-10)	**10.3 (1.88-58.82)**	**4.54 (1.08-20.83)**	**TD**	0.83 (0.62-1.06)	1 (0.76-1.26)	**1.19 (1.01-1.38)**	**1.35 (1.04-1.75)**	1.29 (0.90-1.78)	1 (0.76-1.19)	**1.49 (1.29-1.75)**
1.58 (0.38-5)	1.02 (0.27-4)	0.5 (0.13-1.59)	1.02 (0.34-2.56)	0.90 (0.29-2.17)	**0.18 (0.018-0.97)**	1.25 (0.27-5.26)	3.03 (0.83-10.98)	1.92 (0.66-5.56)	0.71 (0.16-3.13)	1.56 (0.26-9.09)	1.88 (0.33-10.86)	0.62 (0.30-1.3)	2.70 (0.71-10.2)	1.20 (0.43-3.23)	0.26 (0.05-1.11)	**VAD**	1.20 (0.90-1.58)	**1.44 (1.17-1.75)**	**1.63 (1.21-2.17)**	**1.58 (1.12-2.22)**	1.17 (0.90-1.49)	**1.81 (1.40-2.38)**
–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	**MD**	1.19 (1-1.42)	**0.76 (0.55-0.97)**	**1.35 (1.03-1.75)**	1 (0.76-1.20)	**1.51 (1.19-1.92)**
6.66 (1.88-18.18)	**4.16 (1.36-13.88)**	2.04 (0.71-5.56)	**4.34 (1.75-9.09)**	**3.84 (1.49-7.14)**	0.74 (0.083-3.6)	**5.26 (1.29-19.23)**	**12.5 (4.16-37.03)**	**8.33 (3.44-19.23)**	3.03 (0.83-11.11)	**6.66 (1.23-32.25)**	**7.69 (1.66-38.46)**	**2.63 (1.72-4.17)**	**11.3 (3.70-35.71)**	**5 (2.43-10.75)**	1.09 (0.29-3.85)	**4.16 (2.12-8.33)**	–	**MP**	1.12 (0.90-1.38)	1.09 (0.83-1.44)	**0.83 (0.71-0.90)**	**1.26 (1.07-1.49)**
–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	**VMCP**	1 (0.83-1.16)	**0.71 (0.58-0.90)**	1.12 (0.83-1.44)
–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	**VMCPc**	**0.76 (0.55-0.98)**	1.16 (0.83-1.58)
–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	**NU-based**	**1.56 (1.26-1.92)**
13.6 (2.32-71.42)	**9.09 (1.61-50)**	4.16 (0.83-22.72)	**9.09 (1.96-40)**	**7.69 (1.69-34.48)**	1.51 (0.12-12.82)	**10.8 (1.69-71.42)**	**26.3 (5-147.05)**	**16.6 (3.70-83.33)**	**6.66 (1.03-41.66)**	**13.6 (1.75-105.2)**	**16.6 (2.22-125)**	**5.55 (1.44-22.22)**	**23.8 (4.16-136.9)**	**6.67 (1.20-66.67)**	2.27 (0.90-6.25)	**8.33 (2.08-40)**	–	2.08 (0.58-8.33)	–	–	–	**Dex**

Treatments are shown in the dark gray area (middle oblique line). At the CR analysis area (white/bottom), RR represents column-defining treatment compared to line-defining treatment with 95% Credible Intervals (CrI). At the OR analysis area (light gray/top), RR represents line-defining treatment compared to column-defining treatment with 95% Credible Intervals (CrI). Statistically significant RR are highlighted in blue.

Figure 5. Ranking of treatments included in meta-analysis.

Regimen	OS	PFS	CR	OR	Thrombotic Adverse Events	Neurological Adverse Events	Infectious Adverse Events	Hematological Adverse Events	Gastrointestinal Adverse Events	Cardiological Adverse Events	Average Toxicity	Average SUCRA*
VMPT-VT	0.888	0.853	0.914	0.939	0.515	0.099	0.386	0.310	0.303		0.323	0.783
VRd	0.931	0.866	0.721	0.692	0.476	0.753	0.321	0.496		0.304	0.470	0.736
MPR-R	0.867	0.903	0.564	0.565	0.844		0.614	0.132	0.557	0.693	0.568	0.693
VMP	0.620	0.557	0.773	0.804	0.797	0.218	0.603	0.435	0.217		0.454	0.642
Ldc	0.824	0.734	0.543	0.622	0.283	0.764	0.147	0.473		0.397	0.413	0.627
VTd	0.520	0.638	0.673	0.868	0.332	0.094	0.679	0.860	0.121		0.417	0.623
MPT-T	0.782	0.892	0.419	0.545	0.727		0.453	0.320	0.350	0.537	0.477	0.623
VTP	0.216	0.414	0.882	0.824	0.296	0.098	0.978	0.646	0.561		0.516	0.570
Ld	0.723	0.456	0.481	0.556	0.453	0.942	0.331	0.522		0.668	0.583	0.560
Vd	0.333	0.493	0.740	0.878	0.311	0.148	0.351	0.882	0.029		0.344	0.558
CTD	0.369	0.308	0.614	0.782	0.342	0.502	0.410	0.570	0.577		0.480	0.511
MPR	0.690	0.557	0.272	0.416	0.403	0.901	0.282	0.130	0.717	0.766	0.533	0.494
LD	0.095		0.622	0.849	0.077	0.686	0.033	0.663		0.067	0.305	0.468
CPR	0.792	0.427	0.100	0.443	0.181	0.877	0.503	0.437		0.668	0.533	0.459
MPT	0.554	0.524	0.330	0.365	0.488	0.434	0.514	0.244	0.721	0.581	0.497	0.454
VAD	0.512	0.367	0.533	0.379	0.740	0.799	0.021	0.055	0.469	0.190	0.379	0.434
NU-based	0.389			0.242		0.312	0.779	0.346	0.808		0.561	0.397
VMCP	0.492			0.060		0.312	0.722	0.551	0.485	0.231	0.460	0.337
MD	0.327	0.236		0.225			0.430	0.545	0.186		0.387	0.294
MP	0.217	0.136	0.119	0.121	0.821	0.641	0.801	0.460	0.919	0.786	0.738	0.266
VMCPc	0.212			0.084		0.244	0.723	0.583	0.678	0.075	0.460	0.252
TD	0.030	0.132	0.165	0.223	0.502	0.460	0.519	0.893	0.656	0.735	0.628	0.235
Dex	0.115	0.006	0.036	0.017	0.913	0.715	0.902	0.947	0.648	0.802	0.821	0.199

*Average SUCRA is an arithmetic mean of OS, PFS, CR, OR and Average Toxicity outcomes.

Table 1. Characteristics of the studies included in meta-analysis.

Main Author	Acronym	Number of Studies	Publication Year	Enrollment Period	Region	Total Study Population	Median Age	Male Sex	Median Follow Up	Prognostic Information	Follow Up Includes Maintenance Phase	Patients were allowed to undergo BMT	High Risk Cytogenetic Profile	Bisphosphonate Use	Study Intervention	Control Arm
Durie	SWOG S0777	1	2016	04/2008-02/2012	USA	471	43% > 65 years	275/471 (58.4%)	55 months	ISS III - 157/471 (33%)	No	Yes, at discretion of the attending physician. Patients were censored.	Not reported	Not reported	VRd	Ld
Facon	IFM 95-01	1	2006	06/1995-09/1998	France and Belgium	488	70 years	249/488 (51%)	82.8 months	ISS III - 293/488 (60%)	No	No	Not reported	Yes - Pamidronate	MP	Dex
Facon	IFM 99-06	1	2007	05/2000-08/2005	France, Belgium and Switzerland	447	183/447 (41%) > 70 years	238/447 (53.2%)	51.5 months	ISS III - 127/410 (31%)	No	Yes, patients underwent attenuated dose melphalan conditioning.	t(11:14) 37/223 (17%) and t(4:14) 24/222 (11%)	Yes - Clodronate	MPT	MP
Hjorth		1	1990	10/1983-12/1986	Sweden	162	69 years	94/162 (58%)	45 months	Durie-Salmon III (A or B) - 108/162 (66.7%)	Yes	No	Not reported	Not reported	MP	VMCP
Hulin	IFM 01/01	1	2009	04/2002-12/2006	France and Belgium	229	78.5 years	104/229 (45.4%)	47.5 months	ISS III - 65/202 (32%)	Yes	No	Not reported	Yes - Clodronate	MPT	MP
Hulin, Facon, Benboubker, Dimopoulos	FIRST Trial (MM-020/IFM07-01)	13	2013-2016	08/2008-03/2011	18 countries (not discriminated)	1623	73 years	854/1623 (52.6%)	45.5 months (2016)*	ISS III - 659/1623 (40.6%)	No	No	142/762 (18.6%)	Yes (Allowed, but not defined by protocol)	Ldc	Ld
Hungria		1	2016	07/2006-04/2013	Brazil and Argentina	82	72.2 years	36/82 (43.9%)	37.5 months	ISS III - 32/82 (39%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	MPT	CTD
Ludwig		1	2005	05/1994-12/2001	Austria, Germany, Switzerland, Belgium, Hungary, Slovakia, Greece and the Czech Republic	292	67 years	141/292 (48%)	49 months	Durie-Salmon III (A or B) - 197/292 (67%)	Yes	No	Not reported	Not reported	VMCPc	VMCP
Ludwig		1	2009	08/2001-10/2007	Austria, Czech Republic, Slovakia, Hungary and Croatia	289	72 years	144/288 (50%)	28.1 months	ISS III - 193/288 (67%)	Yes	No	Not reported	Yes - Zoledronate	TD	MP
Magarotto, Palumbo		3	2013-2016	08/2009-09/2012	Italy and Czech Republic	654	74 years	322/662 (48.6%)	39 months (2016)*	ISS III - 179/662 (27%)	No	No	133/525 (25.3%)	Not reported	CPR	MPR
Mateos	GEM2005	2	2010-2014	03/2006-10/2008	Spain	260	73 years	130/260 (50%)	72 months (2014)*	ISS III - 87/260 (33.4%)	Yes	No	27/260 (10.4%)	Yes (Allowed, but not defined by protocol)	VTP	VMP
Mateos, Dimopoulos, San Miguel	VISTA Trial	6	2008-2013	12/2004-09/2006	22 countries (not discriminated)	682	71 years	341/682 (50%)	60.1 months (2013)*	ISS III - VMP 35% e MP 34%	No	No	20/163 (12.2%)	Yes (Allowed, but not defined by protocol)	VMP	MP
Morgan	MRC Myeloma IX	1	2011	2003-2007	UK	849	73 years	473/849 (55.7%)	44 months	ISS III - 333/849 (39.2%)	Yes	No	186/849 (21.9%)	Yes - Randomization to Zoledronate or Clodronate until progression	CTD	MP
Niesvizky	UPFRONT	2	2013-2015	06/2007-03/2010	USA	502	74.5 years	261/502 (51.9%)	42.7 months (2015)*	ISS III - 157/502 (31.3%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	VTd	Vd

Table 1. Continued.

Main Author	Acronym	Number of Studies	Publication Year	Enrollment Period	Region	Total Study Population	Median Age	Male Sex	Median Follow Up	Prognostic Information	Follow Up Includes Maintenance Phase	Patients were allowed to undergo BMT	High Risk Cytogenetic Profile	Bisphosphonate Use	Study Intervention	Control Arm
Oken		1	1997	08/1979-07/1983	USA	465	64 years	112/425 (24.1%)	29 months	Durie-Salmon III (A or B) - MP 58/230 (25.2%) e VBMCP 58/235 (24.7%)	Yes	No	Not reported	Not reported	MP	Nitrosourea (NU) Based Regimen
Palumbo	M97G Trial	1	2004	10/1997-12/2000	Italy	194	65 years	105/194 (54.1%)	39 months	Durie-Salmon III (A or B) - 58/95 (61%) e 62/99 (62.6%)	No	Yes, patients underwent attenuated dose melphalan conditioning.	Not reported	Not reported	VAD	MP
Palumbo		2	2006-2008	01/2002-05/2005	Italy	331	72 years	Not reported	38.4 months (2008)*	Durie-Salmon III (A or B) - 206/331 (62.2%)	Yes	No	Not reported	Not reported	MPT	MP
Palumbo		3	2009-2014	05/2006-01/2009	Italy	511	71 years	252/511 (49.3%)	54 months (2014)*	ISS III - 104/407 (25.5%)	Yes	No	180/376 (47.9%)	Yes - Pamidronate or Clodronate allowed	VMPT-VT	VMP
Palumbo	MM-015	2	2011-2012	02/2007-09/2008	European countries, Australia and Israel	459	72 years	228/459 (49.7%)	30 months (2012)*	ISS III - 226/459 (49.2%)	Yes	No	31/184 (16.8%)	Yes (Allowed, but not defined by protocol)	MPR-R	MPR
Rajkumar		1	2008	03/2003-04/2005	USA	470	64.4 years	238/470 (50.6%)	18 months	Durie-Salmon III (A or B) - 157/235 (66.8%) e 145/235 (61.7%)	No	Yes, at discretion of the attending physician. Patients were censored.	Not reported	Yes (Allowed, but not defined by protocol)	TD	Dex
Rajkumar	ECOG-ACRIN E4A03	1	2010	11/2004-04/2006	USA	445	66 years	253/457 (55.4%)	35.8 months	ISS III - 107/445 (24%)	No	Yes, at discretion of the attending physician. Patients were censored.	Not reported	Yes - Pamidronate or Zoledronate allowed	Ldc	LD
Sacchi		1	2011	01/2005-12/2008	Italy	118	79 years	55/118 (46.6%)	30 months	ISS III - 30/118 (25.4%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	MPT	MP
Shustik		1	2007	06/1995-07/2003	Canada	466	70.9 years	188/466 (40%)	62.4 months	Durie-Salmon III (A or B) - 331/466 (71%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	MD	MP
Stewart	E1A06	2	2014-2015	02/2008-11/2011	USA	306	76.6 years	167/306 (54.6%)	40.7 months (2015)*	ISS III - 95/306 (31%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	MPT-T	MPR-R
Takenaka		1	2004	07/1993-08/1998	Japan	210	63 years	106/210 (5%)	43 months	Durie-Salmon III (A or B) - 123/210 (58%)	No	No	Not reported	Not reported	Nitrosourea (NU) Based Regimen	VMCP
Wijermans	HOVON49	1	2010	09/2002-07/2007	Belgium, Netherlands, Norway, Sweden, Denmark	333	73 years	186/333 (55.8%)	39 months	ISS III - 61/225 (27.1%)	Yes	No	33/182 (18.1%)	Yes - Pamidronate or Clodronate allowed	MPT	MP
Zweegman	HOVON87/ NMSG18	2	2014-2016	03/2009-10/2012	Belgium, Netherlands, Norway, Sweden, Denmark	637	73 years	346/637 (54.3%)	36 months (2016)*	ISS III - 165/637 (25.9%)	Yes	No	7.50%	Yes (Allowed, but not defined by protocol)	MPT-T	MPR-R

*For multiple publication RCT we have considered the longer follow up report for each outcome (date of publication between parentheses).

Table 2. Quality assessment of included studies.

Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Early Interruption
Durie	2016	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Facon	2006	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Facon	2007	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Hjorth	1990	Unclear	Unclear	High Risk	Unclear	High Risk	High Risk	No
Hulin	2009	Unclear	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Yes
Hulin	2013-2016	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	No
Hungria	2016	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Ludwig	2005	Low Risk	Low Risk	Unclear	Unclear	Low Risk	Low Risk	No
Ludwig	2009	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Magarotto	2013-2016	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Mateos	2010-2014	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Mateos	2008-2013	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	No
Morgan	2011	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Niesvizky	2013-2015	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Oken	1997	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Palumbo	2004	Low Risk	Low Risk	High Risk	Unclear	Unclear	Unclear	No
Palumbo	2006-2008	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	No
Palumbo	2009-2014	Unclear	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	No
Palumbo	2011-2012	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Rajkumar	2008	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	No
Rajkumar	2010	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Yes
Sacchi	2011	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Shustik	2007	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Stewart	2014-2015	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Takenaka	2004	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Wijermans	2010	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Zweegman	2014-2016	Unclear	Unclear	High Risk	Unclear	Unclear	Unclear	No

Table 3. Adverse events RR with 95% CrI (significant results are shown in bold).

Comparison	Hematological	Cardiac	Gastrointestinal	Infectious	Neurological	Thrombotic
MD/Dex	8.33 (0.90-83.3)	NA	6.66 (0.58-222.2)	**2.38 (1.17-4.76)**	NA	NA
VMCPc/Dex	7.14 (0.5-116.)	**21.2 (1.44-833.3)**	0.83 (0.03-33.3)	1.38 (0.47-4.16)	**24.3 (1.29-500)**	NA
VMCP/Dex	8.33 (0.71-105.)	8.33 (0.66-303.0)	1.66 (0.07-62.5)	1.44 (0.58-3.57)	**18.5 (1.03-357.1)**	NA
NU-based/Dex	**12.9 (1.42-131.)**	NA	0.66 (0.12-2.85)	1.36 (0.71-2.63)	**17.5 (1.75-208.3)**	NA
CPR/Dex	**10.8 (1.11-119.)**	1.56 (0.26-9.09)	NA	2.17 (0.90-4.76)	0.29 (0.01-5.88)	**8.33 (2.43-28.5)**
MP/Dex	**10.3 (1.49-83.3)**	1.25 (0.29-5.26)	0.47 (0.1-1.92)	1.35 (0.83-2.22)	1.44 (0.16-14.2)	1.51 (0.76-3.03)
VAD/Dex	**34.4 (4-357.1)**	**6.66 (1.11-38.4)**	1.72 (0.31-7.69)	**7.14 (3.84-13.3)**	0.55 (0.03-8.33)	2 (0.71-5.26)
TD/Dex	1.78 (0.5-7.14)	1.23 (0.52-3.03)	1 (0.16-5)	2.04 (0.90-5)	**5.26 (1.25-38.4)**	**3.70 (1.92-7.69)**
CTD/Dex	8.33 (1-76.9)	NA	1.25 (0.21-6.66)	**2.43 (1.29-4.54)**	4.16 (0.47-45.4)	**5.26 (2.27-11.9)**
VTP/Dex	6.25 (0.52-83.3)	NA	1.38 (0.13-11.3)	0.35 (0.04-1.72)	**66.6 (5-1063.8)**	8.33 (0.47-333.3)
MPT/Dex	**15.8 (2.17-138.8)**	1.85 (0.35-9.09)	0.83 (0.16-3.44)	**2.12 (1.21-3.70)**	6.66 (0.76-66.6)	**4 (1.75-9.09)**
Vd/Dex	2.04 (0.15-29.4)	NA	**16.6 (2.43-103.0)**	**2.70 (1.02-7.14)**	**52.6 (4.76-769.2)**	6.66 (0.71-62.5)
VTd/Dex	2.32 (0.18-33.3)	NA	**8.33 (1.20-55.5)**	1.56 (0.55-4.34)	**62.5 (5.26-909.0)**	6.25 (0.71-55.5)
MPT-T/Dex	**14.4 (1.42-166.)**	2.04 (0.30-13.8)	2.63 (0.25-32.2)	2.27 (0.90-5.55)	NA	1.63 (0.17-10.5)
VMP/Dex	**10.8 (1.20-111.)**	NA	4.76 (0.76-25)	1.85 (0.90-3.70)	**45.4 (4-625)**	1.51 (0.22-10)
VMPT-VT/Dex	**14.7 (1.28-192.)**	NA	3.44 (0.5-20.4)	**2.5 (1.07-5.88)**	**58.8 (5.26-909.0)**	3.44 (0.41-29.4)
LD/Dex	5.88 (0.5-83.3)	**26.3 (1.92-960)**	NA	**2.70 (1.47-5)**	0.20 (0.01-3.03)	**12.3 (4.54-34.4)**
Ld/Dex	**9.09 (1.07-90.9)**	**26.3 (1.92-960)**	NA	**2.70 (1.47-5)**	0.20 (0.01-3.03)	**12.3 (4.54-34.4)**
Ldc/Dex	**10 (1.08-107.)**	2.56 (0.5-13.3)	NA	**3.70 (2.04-6.66)**	0.71 (0.07-8.33)	**5.88 (2.32-14.2)**
MPR/Dex	**23.2 (2.70-217.3)**	1.29 (0.25-6.66)	0.76 (0.06-10)	**2.94 (1.47-5.88)**	0.25 (0.01-5)	**4.54 (1.44-15.6)**
MPR-R/Dex	**23.8 (2.63-238.0)**	1.47 (0.25-8.33)	1.38 (0.14-15.8)	1.85 (0.83-4.16)	NA	1.20 (0.13-7.14)
VRd/Dex	10 (0.83-114.)	3.70 (0.58-23.8)	NA	**2.77 (1.33-5.88)**	0.66 (0.03-10)	**4 (1.35-11.7)**
VMCPc/MD	0.83 (0.1-7.69)	NA	0.11 (0.001-6.25)	0.58 (0.19-1.75)	NA	NA
VMCP/MD	1 (0.15-5.88)	NA	0.23 (0.004-12.0)	0.62 (0.23-1.53)	NA	NA
NU-based/MD	1.51 (0.33-7.14)	NA	**0.1 (0.003-0.66)**	0.58 (0.29-1.13)	NA	NA
CPR/MD	1.26 (0.25-6.25)	NA	NA	0.90 (0.4-2.08)	NA	NA
MP/MD	1.20 (0.41-3.44)	NA	**0.07 (0.002-0.45)**	**0.58 (0.34-0.96)**	NA	NA
VAD/MD	4.16 (0.98-16.9)	NA	0.25 (0.01-1.75)	**3.03 (1.56-5.55)**	NA	NA
TD/MD	0.21 (0.03-1.20)	NA	0.14 (0.005-1.12)	0.90 (0.37-2.08)	NA	NA
CTD/MD	0.90 (0.24-3.84)	NA	0.18 (0.006-1.47)	1.03 (0.52-1.96)	NA	NA
VTP/MD	0.71 (0.10-4.76)	NA	0.2 (0.005-2.43)	**0.14 (0.01-0.71)**	NA	NA
MPT/MD	1.85 (0.55-6.25)	NA	**0.12 (0.004-0.83)**	0.90 (0.5-1.61)	NA	NA
Vd/MD	0.23 (0.03-1.66)	NA	2.43 (0.07-22.7)	1.14 (0.43-3.12)	NA	NA
VTd/MD	0.27 (0.03-1.96)	NA	1.25 (0.04-11.9)	0.66 (0.22-1.92)	NA	NA
MPT-T/MD	1.69 (0.32-9.09)	NA	0.38 (0.01-6.25)	1 (0.38-2.38)	NA	NA
VMP/MD	1.26 (0.27-5.55)	NA	0.71 (0.02-5.55)	0.76 (0.38-1.61)	NA	NA
VMPT-VT/MD	1.72 (0.27-10.8)	NA	0.5 (0.01-4.54)	1.06 (0.43-2.56)	NA	NA
LD/MD	0.71 (0.10-4.76)	NA	NA	1.13 (0.58-2.12)	NA	NA
Ld/MD	1.07 (0.26-4.54)	NA	NA	1.13 (0.58-2.12)	NA	NA
Ldc/MD	1.16 (0.25-5.55)	NA	NA	1.56 (0.83-2.85)	NA	NA
MPR/MD	2.70 (0.71-10.6)	NA	0.11 (0.002-2)	1.23 (0.58-2.5)	NA	NA

Comparison	Hematological	Cardiac	Gastrointestinal	Infectious	Neurological	Thrombotic
MPR-R/MD	2.77 (0.62-12.1)	NA	0.20 (0.005-3.22)	0.76 (0.33-1.78)	NA	NA
VRd/MD	1.09 (0.18-6.66)	NA	NA	1.17 (0.55-2.56)	NA	NA
VMCP/VMCPc	1.11 (0.37-3.22)	**0.4 (0.14-0.96)**	**1.96 (1.16-3.44)**	1.04 (0.58-1.81)	0.76 (0.4-1.36)	NA
NU-based/VMCPc	1.75 (0.38-8.33)	NA	0.76 (0.02-10.7)	1 (0.35-2.70)	0.71 (0.11-4.54)	NA
CPR/VMCPc	1.47 (0.16-13.3)	**0.07 (0.002-0.83)**	NA	1.56 (0.47-5)	**0.01 (0.0005-0.2)**	NA
MP/VMCPc	1.40 (0.22-9.09)	**0.05 (0.002-0.55)**	0.58 (0.01-8.33)	1 (0.37-2.56)	**0.05 (0.007-0.45)**	NA
VAD/VMCPc	4.76 (0.58-38.4)	0.31 (0.009-3.70)	2.04 (0.06-31.2)	**5.26 (1.78-14.4)**	**0.02 (0.001-0.29)**	NA
TD/VMCPc	0.24 (0.02-2.5)	**0.05 (0.001-0.76)**	1.19 (0.03-19.6)	1.49 (0.43-5)	0.22 (0.01-2.70)	NA
CTD/VMCPc	1.09 (0.14-9.09)	NA	1.49 (0.04-25)	1.75 (0.62-5)	0.17 (0.01-1.49)	NA
VTP/VMCPc	0.83 (0.07-9.09)	NA	1.63 (0.03-37.0)	0.25 (0.02-1.53)	2.70 (0.22-37.0)	NA
MPT/VMCPc	2.17 (0.32-14.9)	**0.09 (0.002-0.90)**	1 (0.03-14.9)	1.53 (0.55-4.16)	0.27 (0.03-2.27)	NA
Vd/VMCPc	0.27 (0.02-3.12)	NA	19.6 (0.5-370.3)	1.96 (0.52-7.14)	2.22 (0.19-27.0)	NA
VTd/VMCPc	0.32 (0.02-3.70)	NA	10.2 (0.25-192.3)	1.12 (0.29-4.34)	2.5 (0.22-30.3)	NA
MPT-T/VMCPc	1.96 (0.21-18.8)	0.1 (0.002-1.26)	3.22 (0.06-90.9)	1.63 (0.47-5.55)	NA	NA
VMP/VMCPc	1.47 (0.17-12.1)	NA	5.55 (0.15-90.9)	1.33 (0.43-4)	1.85 (0.17-21.7)	NA
VMPT-VT/VMCPc	2 (0.18-21.2)	NA	4.16 (0.10-71.4)	1.81 (0.55-6.25)	2.5 (0.22-30.3)	NA
LD/VMCPc	0.83 (0.07-10)	1.25 (0.02-66.6)	NA	1.92 (0.66-5.55)	**0.008 (0.0005-0.10)**	NA
Ld/VMCPc	1.25 (0.16-10)	1.25 (0.02-66.6)	NA	1.92 (0.66-5.55)	**0.008 (0.0005-0.10)**	NA
Ldc/VMCPc	1.35 (0.15-11.9)	0.12 (0.003-1.31)	NA	2.63 (0.90-7.69)	**0.03 (0.002-0.28)**	NA
MPR/VMCPc	3.12 (0.41-25)	**0.06 (0.001-0.66)**	0.90 (0.01-26.3)	2.08 (0.71-6.25)	**0.01 (0.0005-0.17)**	NA
MPR-R/VMCPc	3.22 (0.4-26.3)	**0.07 (0.002-0.76)**	1.66 (0.03-45.4)	1.31 (0.4-4.16)	NA	NA
VRd/VMCPc	1.28 (0.12-12.9)	0.17 (0.005-2.22)	NA	2 (0.66-6.25)	**0.02 (0.001-0.33)**	NA
NU-based/VMCP	1.58 (0.55-4.54)	NA	0.4 (0.01-5)	1 (0.41-2.17)	1 (0.17-5.55)	NA
CPR/VMCP	1.31 (0.19-9.09)	0.19 (0.006-1.81)	NA	1.49 (0.52-4.16)	**0.01 (0.0008-0.25)**	NA
MP/VMCP	1.26 (0.27-5.55)	0.15 (0.005-1.12)	0.29 (0.009-4)	0.90 (0.43-2.08)	**0.07 (0.01-0.55)**	NA
VAD/VMCP	4.34 (0.71-25.6)	0.83 (0.02-7.69)	1.03 (0.03-15.1)	**5 (2.04-11.7)**	**0.03 (0.001-0.35)**	NA
TD/VMCP	0.22 (0.02-1.72)	0.15 (0.004-1.56)	0.62 (0.01-9.09)	1.42 (0.5-4.16)	0.29 (0.02-3.44)	NA
CTD/VMCP	1 (0.17-5.88)	NA	0.76 (0.02-12.1)	1.69 (0.71-4)	0.23 (0.02-1.85)	NA
VTP/VMCP	0.76 (0.09-6.25)	NA	0.83 (0.01-17.8)	0.24 (0.02-1.35)	3.57 (0.31-45.4)	NA
MPT/VMCP	1.96 (0.4-9.09)	0.22 (0.007-1.92)	0.5 (0.01-7.14)	1.49 (0.66-3.44)	0.37 (0.04-2.77)	NA
Vd/VMCP	0.25 (0.02-2.27)	NA	10.1 (0.26-178.5)	1.88 (0.58-5.88)	2.94 (0.28-33.3)	NA
VTd/VMCP	0.28 (0.03-2.63)	NA	5.26 (0.13-100)	1.08 (0.32-3.70)	3.33 (0.33-38.4)	NA
MPT-T/VMCP	1.75 (0.25-13.3)	0.25 (0.007-2.63)	1.61 (0.03-45.4)	1.58 (0.52-4.76)	NA	NA
VMP/VMCP	1.31 (0.20-8.33)	NA	2.85 (0.08-45.4)	1.29 (0.5-3.33)	2.5 (0.25-27.0)	NA
VMPT-VT/VMCP	1.78 (0.21-14.4)	NA	2.08 (0.05-35.7)	1.75 (0.58-5)	3.33 (0.33-38.4)	NA
LD/VMCP	0.71 (0.08-6.66)	3.12 (0.06-151.5)	NA	1.85 (0.76-4.34)	**0.01 (0.0007-0.12)**	NA
Ld/VMCP	1.11 (0.19-6.66)	3.12 (0.06-151.5)	NA	1.85 (0.76-4.34)	**0.01 (0.0007-0.12)**	NA
Ldc/VMCP	1.21 (0.19-7.69)	0.32 (0.01-2.77)	NA	**2.56 (1.09-5.88)**	**0.04 (0.004-0.35)**	NA
MPR/VMCP	2.85 (0.5-16.1)	0.16 (0.005-1.40)	0.47 (0.009-12.9)	2 (0.83-5)	**0.01 (0.0007-0.21)**	NA
MPR-R/VMCP	2.85 (0.47-17.2)	0.18 (0.005-1.66)	0.83 (0.01-22.2)	1.28 (0.45-3.57)	NA	NA
VRd/VMCP	1.16 (0.14-9.09)	0.45 (0.01-4.76)	NA	1.92 (0.76-5)	**0.03 (0.002-0.41)**	NA
CPR/NU-based	0.83 (0.16-4.34)	NA	NA	1.56 (0.71-3.44)	**0.01 (0.001-0.13)**	NA
MP/NU-based	0.83 (0.27-2.32)	NA	0.71 (0.43-1.21)	1 (0.62-1.53)	**0.08 (0.02-0.18)**	NA
VAD/NU-based	2.70 (0.66-11.2)	NA	**2.56 (1.20-5.55)**	**5.26 (2.85-9.09)**	**0.03 (0.003-0.18)**	NA

Comparison	Hematological	Cardiac	Gastrointestinal	Infectious	Neurological	Thrombotic
TD/NU-based	**0.14 (0.02-0.83)**	NA	1.49 (0.58-4)	1.49 (0.66-3.44)	0.30 (0.06-1.75)	NA
CTD/NU-based	0.62 (0.16-2.56)	NA	1.88 (0.71-5.26)	1.75 (0.99-3.12)	**0.24 (0.07-0.71)**	NA
VTP/NU-based	0.47 (0.07-3.12)	NA	2.12 (0.35-11.1)	0.25 (0.03-1.20)	3.70 (0.66-23.2)	NA
MPT/NU-based	1.23 (0.38-4)	NA	1.26 (0.66-2.38)	1.53 (0.90-2.63)	0.38 (0.12-1.03)	NA
Vd/NU-based	0.15 (0.02-1.09)	NA	**25 (7.69-90.9)**	1.96 (0.76-5.26)	3.03 (0.66-16.9)	NA
VTd/NU-based	0.18 (0.02-1.26)	NA	**12.8 (3.84-50)**	1.13 (0.4-3.12)	3.44 (0.76-19.2)	NA
MPT-T/NU-based	1.11 (0.21-6.25)	NA	4 (0.66-35.7)	1.66 (0.66-4)	NA	NA
VMP/NU-based	0.83 (0.18-3.70)	NA	**7.14 (2.77-20.8)**	1.35 (0.71-2.63)	2.5 (0.58-13.5)	NA
VMPT-VT/NU-based	1.12 (0.17-7.14)	NA	**5.26 (1.69-18.1)**	1.81 (0.83-4.34)	3.44 (0.71-19.2)	NA
LD/NU-based	0.45 (0.07-3.12)	NA	NA	**1.96 (1.11-3.44)**	**0.01 (0.001-0.06)**	NA
Ld/NU-based	0.71 (0.17-2.94)	NA	NA	**1.96 (1.11-3.44)**	**0.01 (0.001-0.06)**	NA
Ldc/NU-based	0.76 (0.16-3.57)	NA	NA	**2.70 (1.53-4.76)**	**0.04 (0.01-0.15)**	NA
MPR/NU-based	1.78 (0.45-7.14)	NA	1.19 (0.16-10.8)	**2.12 (1.11-4.16)**	**0.01 (0.001-0.11)**	NA
MPR-R/NU-based	1.81 (0.41-8.33)	NA	2.08 (0.38-17.2)	1.33 (0.58-2.94)	NA	NA
VRd/NU-based	0.71 (0.12-4.34)	NA	NA	2.04 (1-4.16)	**0.03 (0.004-0.20)**	NA
MP/CPR	1 (0.27-3.22)	0.76 (0.29-2.17)	NA	0.62 (0.33-1.21)	4.76 (0.76-45.4)	**0.18 (0.06-0.5)**
VAD/CPR	3.22 (0.71-14.7)	**4.16 (1.19-15.6)**	NA	**3.33 (1.63-6.66)**	1.88 (0.12-28.5)	**0.24 (0.07-0.76)**
TD/CPR	0.16 (0.02-1.07)	0.76 (0.17-3.70)	NA	1 (0.37-2.56)	**18.1 (1.88-277.7)**	0.45 (0.13-1.51)
CTD/CPR	0.76 (0.17-3.33)	NA	NA	1.12 (0.52-2.43)	**14.0 (2-147.0)**	0.62 (0.20-1.88)
VTP/CPR	0.58 (0.07-4.16)	NA	NA	**0.16 (0.01-0.83)**	**222.2 (21.2-3571.4)**	1.01 (0.05-43.4)
MPT/CPR	1.47 (0.43-5)	1.17 (0.5-2.77)	NA	1 (0.52-1.88)	**22.2 (3.70-208.3)**	0.47 (0.17-1.23)
Vd/CPR	0.18 (0.02-1.42)	NA	NA	1.25 (0.43-3.70)	**181.8 (19.6-2564.1)**	0.76 (0.08-8.33)
VTd/CPR	0.21 (0.02-1.72)	NA	NA	0.71 (0.23-2.27)	**204.0 (21.7-2857.1)**	0.76 (0.07-7.69)
MPT-T/CPR	1.33 (0.27-6.66)	1.29 (0.31-5.55)	NA	1.05 (0.43-2.56)	NA	0.20 (0.02-1.12)
VMP/CPR	1 (0.2-5)	NA	NA	0.83 (0.38-2)	**151.5 (16.9-2083.3)**	0.18 (0.02-1.40)
VMPT-VT/CPR	1.35 (0.19-10)	NA	NA	1.16 (0.45-3.12)	**204.0 (21.7-2857.1)**	0.41 (0.04-4)
LD/CPR	0.55 (0.1-3.44)	**16.1 (1.96-500)**	NA	1.23 (0.71-2.27)	0.71 (0.20-2.27)	1.49 (0.5-4.16)
Ld/CPR	0.83 (0.29-2.43)	**16.1 (1.96-500)**	NA	1.23 (0.71-2.27)	0.71 (0.20-2.27)	1.49 (0.5-4.16)
Ldc/CPR	0.90 (0.23-3.84)	1.66 (0.71-3.84)	NA	1.69 (0.90-3.22)	2.43 (0.33-25.6)	0.71 (0.25-1.78)
MPR/CPR	2.12 (0.76-5.88)	0.83 (0.37-1.88)	NA	1.35 (0.76-2.5)	0.83 (0.27-2.63)	0.55 (0.23-1.31)
MPR-R/CPR	2.17 (0.52-9.09)	0.90 (0.28-3.12)	NA	0.83 (0.37-1.92)	NA	**0.14 (0.01-0.76)**
VRd/CPR	0.90 (0.2-3.84)	2.38 (0.76-7.69)	NA	1.29 (0.62-2.77)	2.17 (0.58-7.69)	0.47 (0.16-1.36)
VAD/MP	**3.33 (1.29-9.09)**	**5.26 (2-14.4)**	**3.44 (2-6.25)**	**5.26 (3.57-7.69)**	0.4 (0.05-1.72)	1.29 (0.58-2.70)
TD/MP	**0.17 (0.03-0.71)**	1 (0.31-3.22)	2.04 (0.96-4.76)	1.51 (0.76-3.12)	**3.57 (1.09-17.2)**	**2.38 (1.26-4.76)**
CTD/MP	0.76 (0.33-1.92)	NA	**2.56 (1.14-6.25)**	**1.78 (1.20-2.63)**	**2.94 (1.53-5.88)**	**3.33 (2.17-5.55)**
VTP/MP	0.58 (0.12-2.77)	NA	2.94 (0.52-13.8)	0.25 (0.03-1.13)	**43.4 (11.6-232.5)**	5.55 (0.34-204.0)
MPT/MP	1.53 (0.90-2.63)	1.47 (0.71-3.12)	**1.72 (1.21-2.5)**	**1.56 (1.17-2.08)**	**4.54 (2.85-7.69)**	**2.56 (1.66-4)**
Vd/MP	0.19 (0.03-1.02)	NA	**33.3 (11.9-116.2)**	2 (0.83-4.76)	**35.7 (12.0-166.6)**	4.16 (0.55-35.7)
VTd/MP	0.22 (0.04-1.17)	NA	**17.5 (5.88-62.5)**	1.14 (0.45-2.94)	**40 (13.6-185.1)**	4 (0.5-33.3)
MPT-T/MP	1.38 (0.4-5.26)	1.63 (0.47-5.55)	5.55 (0.99-45.4)	1.66 (0.76-3.57)	NA	1.08 (0.12-5.88)
VMP/MP	1.04 (0.35-3.03)	NA	**9.09 (4.54-25.6)**	1.36 (0.83-2.27)	**29.4 (10.8-131.5)**	1 (0.16-5.55)
VMPT-VT/MP	1.40 (0.31-6.25)	NA	**7.14 (2.56-22.2)**	1.85 (0.90-3.84)	**40 (13.6-185.1)**	2.27 (0.30-17.2)
LD/MP	0.58 (0.12-2.85)	**20 (2.56-625)**	NA	**1.96 (1.38-2.85)**	**0.15 (0.02-0.58)**	**8.33 (3.84-16.9)**

Comparison	Hematological	Cardiac	Gastrointestinal	Infectious	Neurological	Thrombotic
Ld/MP	0.90 (0.34-2.32)	**20 (2.56-625)**	NA	**1.96 (1.38-2.85)**	**0.15 (0.02-0.58)**	**8.33 (3.84-16.9)**
Ldc/MP	1 (0.32-2.94)	2.08 (0.95-4.54)	NA	**2.70 (1.92-3.84)**	0.52 (0.17-1.31)	**3.70 (2.08-7.14)**
MPR/MP	2.22 (0.90-5.55)	1.04 (0.47-2.32)	1.61 (0.24-13.8)	**2.12 (1.33-3.57)**	0.18 (0.01-1.19)	**3.03 (1.19-8.33)**
MPR-R/MP	2.27 (0.83-6.66)	1.17 (0.45-3.03)	2.85 (0.58-21.7)	1.35 (0.66-2.63)	NA	0.76 (0.1-4)
VRd/MP	0.90 (0.22-3.84)	3.03 (0.99-10)	NA	**2.04 (1.16-3.57)**	0.47 (0.06-1.92)	**2.63 (1.13-5.88)**
TD/VAD	**0.05 (0.008-0.28)**	**0.19 (0.04-0.90)**	0.58 (0.22-1.56)	**0.28 (0.13-0.66)**	**9.09 (1.31-109.8)**	1.85 (0.71-5.26)
CTD/VAD	**0.23 (0.07-0.83)**	NA	0.71 (0.27-2.08)	**0.34 (0.19-0.58)**	**7.14 (1.49-62.5)**	**2.56 (1.11-6.25)**
VTP/VAD	0.17 (0.02-1.05)	NA	0.83 (0.13-4.34)	**0.05 (0.006-0.23)**	**114.9 (14.9-1449.2)**	4.16 (0.23-166.6)
MPT/VAD	0.45 (0.17-1.20)	**0.28 (0.1-0.76)**	**0.5 (0.27-0.90)**	**0.30 (0.20-0.43)**	**11.4 (2.63-90.9)**	1.96 (0.97-4.34)
Vd/VAD	**0.05 (0.008-0.4)**	NA	**10 (2.94-37.0)**	**0.38 (0.15-0.98)**	**90.9 (14.0-1063.8)**	3.22 (0.35-31.2)
VTd/VAD	**0.06 (0.01-0.45)**	NA	**5 (1.40-19.6)**	**0.22 (0.07-0.58)**	**105.2 (16.1-1219.5)**	3.12 (0.34-29.4)
MPT-T/VAD	0.41 (0.08-2.04)	0.31 (0.06-1.44)	1.56 (0.25-14.0)	**0.32 (0.14-0.71)**	NA	0.83 (0.09-5.26)
VMP/VAD	0.31 (0.07-1.28)	NA	**2.70 (1.04-8.33)**	**0.26 (0.13-0.5)**	**76.9 (12.3-833.3)**	0.76 (0.11-5)
VMPT-VT/VAD	0.41 (0.06-2.43)	NA	2 (0.62-7.14)	**0.35 (0.15-0.83)**	**106.3 (15.8-1204.8)**	1.75 (0.20-14.9)
LD/VAD	0.17 (0.02-1.05)	4 (0.41-123.4)	NA	**0.38 (0.24-0.58)**	0.37 (0.03-4.16)	**6.25 (2.43-16.3)**
Ld/VAD	**0.26 (0.07-0.96)**	4 (0.41-123.4)	NA	**0.38 (0.24-0.58)**	0.37 (0.03-4.16)	**6.25 (2.43-16.3)**
Ldc/VAD	0.28 (0.07-1.16)	0.4 (0.12-1.14)	NA	**0.52 (0.33-0.83)**	1.28 (0.22-11.1)	**2.85 (1.26-7.14)**
MPR/VAD	0.66 (0.18-2.38)	**0.20 (0.06-0.62)**	0.45 (0.06-4.16)	**0.41 (0.23-0.71)**	0.45 (0.03-6.66)	2.32 (0.76-7.69)
MPR-R/VAD	0.66 (0.17-2.70)	**0.22 (0.05-0.83)**	0.83 (0.14-6.66)	**0.25 (0.12-0.55)**	NA	0.58 (0.06-3.57)
VRd/VAD	0.27 (0.05-1.42)	0.58 (0.14-2.27)	NA	**0.4 (0.21-0.76)**	1.14 (0.1-13.3)	2 (0.71-5.88)
CTD/TD	4.54 (0.90-28.5)	NA	1.25 (0.4-4)	1.17 (0.52-2.63)	0.83 (0.15-3.22)	1.40 (0.62-3.12)
VTP/TD	3.44 (0.41-30.3)	NA	1.42 (0.20-8.33)	**0.16 (0.02-0.90)**	**12.1 (1.58-100)**	2.22 (0.12-90.9)
MPT/TD	**9.09 (1.96-47.6)**	1.47 (0.37-5.88)	0.83 (0.34-1.96)	1.04 (0.47-2.17)	1.26 (0.24-4.54)	1.06 (0.47-2.38)
Vd/TD	1.12 (0.12-10.9)	NA	**16.6 (4.54-71.4)**	1.31 (0.43-4)	**10 (1.44-66.6)**	1.75 (0.19-16.1)
VTd/TD	1.29 (0.14-13.1)	NA	**8.33 (2.17-37.0)**	0.76 (0.23-2.43)	**11.3 (1.69-76.9)**	1.66 (0.18-15.3)
MPT-T/TD	**8.33 (1.21-66.6)**	1.63 (0.30-9.09)	2.63 (0.4-25)	1.11 (0.38-3.03)	NA	0.45 (0.04-2.77)
VMP/TD	**5.88 (1.03-41.6)**	NA	**4.76 (1.51-15.8)**	0.90 (0.37-2.12)	**8.33 (1.26-55.5)**	0.4 (0.06-2.63)
VMPT-VT/TD	**8.33 (1.02-71.4)**	NA	3.44 (0.95-13.5)	1.21 (0.43-3.33)	**11.3 (1.66-76.9)**	0.90 (0.11-7.69)
LD/TD	3.33 (0.41-31.2)	**20.8 (1.81-714.2)**	NA	1.29 (0.58-2.85)	**0.04 (0.003-0.26)**	**3.33 (1.21-9.09)**
Ld/TD	5 (0.90-32.2)	**20.8 (1.81-714.2)**	NA	1.29 (0.58-2.85)	**0.04 (0.003-0.26)**	**3.33 (1.21-9.09)**
Ldc/TD	5.55 (0.90-38.4)	2.08 (0.5-8.33)	NA	1.78 (0.83-3.84)	**0.13 (0.02-0.66)**	1.56 (0.62-3.70)
MPR/TD	**12.6 (2.5-83.33)**	1.05 (0.25-4.16)	0.76 (0.10-7.69)	1.40 (0.58-3.22)	**0.04 (0.003-0.47)**	1.25 (0.4-4.16)
MPR-R/TD	**13.1 (2.27-90.90)**	1.19 (0.26-5.26)	1.38 (0.23-12.3)	0.90 (0.33-2.32)	NA	0.32 (0.03-1.88)
VRd/TD	5.26 (0.71-43.4)	3.03 (0.58-15.3)	NA	1.35 (0.55-3.33)	**0.12 (0.01-0.90)**	1.07 (0.37-3.12)
VTP/CTD	0.76 (0.12-4.34)	NA	1.13 (0.16-6.66)	**0.14 (0.01-0.66)**	**15.1 (3.33-90.9)**	1.61 (0.1-62.5)
MPT/CTD	1.96 (0.76-4.76)	NA	0.66 (0.26-1.56)	0.90 (0.55-1.40)	1.56 (0.71-3.33)	0.76 (0.41-1.40)
Vd/CTD	0.25 (0.03-1.61)	NA	**13.1 (3.33-55.5)**	1.12 (0.43-2.94)	**12.3 (3.33-62.5)**	1.25 (0.15-11.1)
VTd/CTD	0.28 (0.04-1.78)	NA	**6.66 (1.61-30.3)**	0.62 (0.23-1.75)	**13.8 (3.84-71.4)**	1.17 (0.14-10.4)
MPT-T/CTD	1.78 (0.38-8.33)	NA	2.12 (0.31-20.8)	0.90 (0.4-2.22)	NA	0.32 (0.03-1.88)
VMP/CTD	1.31 (0.32-5)	NA	**3.70 (1.13-12.9)**	0.76 (0.4-1.47)	**10.2 (3.03-50)**	0.29 (0.04-1.75)
VMPT-VT/CTD	1.81 (0.30-10.1)	NA	2.77 (0.71-10.9)	1.04 (0.45-2.38)	**13.8 (3.84-71.4)**	0.66 (0.08-5.26)
LD/CTD	0.71 (0.13-4.16)	NA	NA	1.11 (0.66-1.85)	**0.05 (0.006-0.22)**	**2.38 (1.02-5.55)**
Ld/CTD	1.12 (0.33-3.70)	NA	NA	1.11 (0.66-1.85)	**0.05 (0.006-0.22)**	**2.38 (1.02-5.55)**
Ldc/CTD	1.21 (0.32-4.54)	NA	NA	1.51 (0.90-2.56)	**0.17 (0.05-0.52)**	1.11 (0.52-2.32)

Comparison	Hematological	Cardiac	Gastrointestinal	Infectious	Neurological	Thrombotic
MPR/CTD	2.85 (0.83-9.09)	NA	0.62 (0.07-6.25)	1.20 (0.66-2.27)	**0.06 (0.005-0.43)**	0.90 (0.32-2.70)
MPR-R/CTD	2.94 (0.76-10.8)	NA	1.12 (0.18-10)	0.76 (0.34-1.63)	NA	0.23 (0.02-1.26)
VRd/CTD	1.16 (0.22-5.88)	NA	NA	1.14 (0.58-2.27)	**0.15 (0.01-0.71)**	0.76 (0.30-1.96)
MPT/VTP	2.56 (0.5-13.5)	NA	0.58 (0.11-3.44)	**5.88 (1.31-47.6)**	**0.10 (0.01-0.43)**	0.47 (0.01-7.69)
Vd/VTP	0.32 (0.05-1.81)	NA	**11.6 (2.85-66.6)**	**7.69 (1.58-62.5)**	0.83 (0.31-2.04)	0.83 (0.02-9.09)
VTd/VTP	0.37 (0.07-2.04)	NA	**5.88 (1.40-34.4)**	4.34 (0.83-37.0)	0.90 (0.35-2.32)	0.76 (0.02-8.33)
MPT-T/VTP	2.32 (0.32-18.1)	NA	1.92 (0.17-27.7)	**6.66 (1.19-58.8)**	NA	0.18 (0.003-5.26)
VMP/VTP	1.72 (0.58-5.26)	NA	3.22 (0.98-15.6)	**5.26 (1.29-38.4)**	0.71 (0.28-1.56)	0.19 (0.006-1.47)
VMPT-VT/VTP	2.32 (0.5-11.1)	NA	2.38 (0.58-12.8)	**7.14 (1.61-55.5)**	0.90 (0.35-2.27)	0.43 (0.01-4.34)
LD/VTP	1 (0.10-9.09)	NA	NA	**7.69 (1.63-58.8)**	**0.003 (0.0002-0.02)**	1.49 (0.03-25.6)
Ld/VTP	1.47 (0.24-9.09)	NA	NA	**7.69 (1.63-58.8)**	**0.003 (0.0002-0.02)**	1.49 (0.03-25.6)
Ldc/VTP	1.58 (0.24-10.8)	NA	NA	**10.4 (2.22-83.3)**	**0.01 (0.001-0.05)**	0.71 (0.01-11.4)
MPR/VTP	3.70 (0.62-22.2)	NA	0.55 (0.04-8.33)	**8.33 (1.69-66.6)**	**0.003 (0.0002-0.04)**	0.55 (0.01-10.3)
MPR-R/VTP	3.84 (0.58-24.3)	NA	1.01 (0.10-13.8)	5.26 (0.99-45.4)	NA	0.13 (0.002-3.57)
VRd/VTP	1.51 (0.18-12.3)	NA	NA	**7.69 (1.58-66.6)**	**0.01 (0.0007-0.07)**	0.47 (0.01-8.33)
Vd/MPT	**0.12 (0.02-0.71)**	NA	**19.6 (6.66-66.6)**	1.26 (0.52-3.12)	**7.69 (2.27-38.4)**	1.63 (0.2-14.4)
VTd/MPT	**0.14 (0.02-0.83)**	NA	**10.1 (3.12-37.0)**	0.71 (0.27-1.96)	**9.09 (2.63-43.4)**	1.56 (0.18-13.6)
MPT-T/MPT	0.90 (0.23-3.57)	1.11 (0.28-4.16)	3.12 (0.55-27.7)	1.07 (0.5-2.27)	NA	0.41 (0.05-2.27)
VMP/MPT	0.66 (0.20-2.17)	NA	**5.55 (2.38-15.3)**	0.83 (0.47-1.56)	**6.66 (2.04-30.3)**	0.38 (0.06-2.32)
VMPT-VT/MPT	0.90 (0.18-4.54)	NA	**4 (1.40-13.3)**	1.17 (0.55-2.56)	**9.09 (2.63-43.4)**	0.90 (0.11-7.14)
LD/MPT	0.37 (0.08-1.72)	**13.5 (1.96-384.6)**	NA	1.25 (0.99-1.58)	**0.03 (0.004-0.11)**	**3.12 (1.72-5.88)**
Ld/MPT	0.58 (0.23-1.40)	**13.5 (1.96-384.6)**	NA	1.25 (0.99-1.58)	**0.03 (0.004-0.11)**	**3.12 (1.72-5.88)**
Ldc/MPT	0.62 (0.22-1.72)	1.40 (0.98-2)	NA	**1.72 (1.38-2.17)**	**0.11 (0.04-0.24)**	1.44 (0.96-2.22)
MPR/MPT	1.44 (0.55-3.70)	0.71 (0.33-1.51)	0.90 (0.13-8.33)	1.36 (0.83-2.22)	**0.04 (0.004-0.23)**	1.16 (0.47-3.12)
MPR-R/MPT	1.47 (0.47-4.54)	0.83 (0.26-2.27)	1.63 (0.32-12.9)	0.83 (0.43-1.69)	NA	0.30 (0.03-1.53)
VRd/MPT	0.58 (0.14-2.32)	2 (0.83-5.26)	NA	1.31 (0.76-2.17)	**0.10 (0.01-0.37)**	1.01 (0.5-2.08)
VTd/Vd	1.16 (0.27-5)	NA	**0.52 (0.28-0.90)**	0.58 (0.27-1.16)	1.13 (0.76-1.63)	0.90 (0.47-1.88)
MPT-T/Vd	7.14 (0.90-62.5)	NA	0.16 (0.01-1.72)	0.83 (0.27-2.63)	NA	0.25 (0.01-3.70)
VMP/Vd	**5.26 (1.47-20.8)**	NA	**0.28 (0.12-0.55)**	0.66 (0.34-1.33)	0.83 (0.55-1.25)	**0.23 (0.06-0.66)**
VMPT-VT/Vd	**7.14 (1.33-41.6)**	NA	**0.20 (0.07-0.52)**	0.90 (0.38-2.17)	1.13 (0.66-1.96)	0.55 (0.11-2.32)
LD/Vd	2.94 (0.31-31.2)	NA	NA	1 (0.38-2.5)	**0.004 (0.0003-0.02)**	1.92 (0.20-17.2)
Ld/Vd	4.54 (0.66-32.2)	NA	NA	1 (0.38-2.5)	**0.004 (0.0003-0.02)**	1.92 (0.20-17.2)
Ldc/Vd	5 (0.66-38.4)	NA	NA	1.35 (0.52-3.44)	**0.01 (0.002-0.06)**	0.90 (0.1-7.69)
MPR/Vd	**11.3 (1.72-83.3)**	NA	**0.04 (0.005-0.5)**	1.07 (0.4-2.85)	**0.004 (0.0003-0.04)**	0.71 (0.07-7.14)
MPR-R/Vd	**11.6 (1.63-90.9)**	NA	**0.08 (0.01-0.83)**	0.66 (0.22-2)	NA	0.18 (0.01-2.5)
VRd/Vd	4.76 (0.52-41.6)	NA	NA	1.03 (0.37-2.85)	**0.01 (0.001-0.08)**	0.62 (0.06-5.55)
MPT-T/VTd	6.25 (0.76-50)	NA	0.31 (0.03-3.44)	1.47 (0.43-4.76)	NA	0.26 (0.01-3.84)
VMP/VTd	**4.54 (1.28-16.3)**	NA	0.55 (0.23-1.20)	1.19 (0.52-2.63)	0.71 (0.5-1.08)	**0.25 (0.07-0.66)**
VMPT-VT/VTd	**6.25 (1.20-32.2)**	NA	0.4 (0.13-1.09)	1.61 (0.62-4.16)	1 (0.58-1.69)	0.58 (0.11-2.43)
LD/VTd	2.56 (0.27-25)	NA	NA	1.72 (0.62-4.76)	**0.003 (0.0003-0.02)**	2 (0.21-18.1)
Ld/VTd	3.84 (0.58-25.6)	NA	NA	1.72 (0.62-4.76)	**0.003 (0.0003-0.02)**	2 (0.21-18.1)
Ldc/VTd	4.16 (0.58-31.2)	NA	NA	2.38 (0.83-6.66)	**0.01 (0.002-0.05)**	0.90 (0.10-8.33)

Comparison	Hematological	Cardiac	Gastrointestinal	Infectious	Neurological	Thrombotic
MPR/VTd	**10 (1.51-66.6)**	NA	0.09 (0.01-1.02)	1.85 (0.66-5.26)	**0.004 (0.0002-0.04)**	0.76 (0.07-7.14)
MPR-R/VTd	**10 (1.40-71.4)**	NA	0.16 (0.02-1.69)	1.17 (0.37-3.70)	NA	0.19 (0.01-2.63)
VRd/VTd	4 (0.45-35.7)	NA	NA	1.78 (0.58-5.26)	**0.01 (0.0009-0.07)**	0.66 (0.06-5.88)
VMP/MPT-T	0.76 (0.13-3.84)	NA	1.78 (0.18-12.8)	0.83 (0.33-2)	NA	0.90 (0.07-14.0)
VMPT-VT/MPT-T	1.01 (0.13-7.14)	NA	1.29 (0.12-10.1)	1.11 (0.38-3.12)	NA	2.12 (0.15-40)
LD/MPT-T	0.41 (0.05-2.94)	**12.6 (1.16-416.6)**	NA	1.17 (0.55-2.56)	NA	**7.14 (1.28-66.6)**
Ld/MPT-T	0.62 (0.14-2.63)	**12.6 (1.16-416.6)**	NA	1.17 (0.55-2.56)	NA	**7.14 (1.28-66.6)**
Ldc/MPT-T	0.66 (0.13-3.44)	1.26 (0.33-5)	NA	1.61 (0.76-3.57)	NA	3.44 (0.62-30.3)
MPR/MPT-T	1.61 (0.43-5.88)	0.62 (0.18-2.22)	0.29 (0.05-1.38)	1.26 (0.66-2.56)	NA	2.77 (0.58-21.7)
MPR-R/MPT-T	1.63 (0.71-3.44)	0.71 (0.33-1.56)	**0.52 (0.28-0.90)**	0.83 (0.55-1.13)	NA	0.71 (0.43-1.17)
VRd/MPT-T	0.66 (0.10-3.84)	1.81 (0.4-9.09)	NA	1.21 (0.5-3.03)	NA	2.38 (0.4-22.2)
VMPT-VT/VMP	1.35 (0.47-4)	NA	0.71 (0.38-1.36)	1.35 (0.83-2.27)	1.35 (0.90-1.96)	2.27 (0.90-6.66)
LD/VMP	0.55 (0.08-3.84)	NA	NA	1.44 (0.76-2.70)	**0.004 (0.0004-0.02)**	**8.33 (1.21-55.5)**
Ld/VMP	0.83 (0.20-3.57)	NA	NA	1.44 (0.76-2.70)	**0.004 (0.0004-0.02)**	**8.33 (1.21-55.5)**
Ldc/VMP	0.90 (0.2-4.34)	NA	NA	**2 (1.07-3.70)**	**0.01 (0.002-0.07)**	3.84 (0.58-24.3)
MPR/VMP	2.17 (0.52-8.33)	NA	0.16 (0.02-1.63)	1.56 (0.76-3.22)	**0.005 (0.0004-0.05)**	3.12 (0.41-22.7)
MPR-R/VMP	2.22 (0.5-10)	NA	0.29 (0.04-2.70)	1 (0.41-2.27)	NA	0.76 (0.05-8.33)
VRd/VMP	0.90 (0.15-5.26)	NA	NA	1.51 (0.71-3.22)	**0.01 (0.001-0.09)**	2.63 (0.38-18.1)
LD/VMPT-VT	0.41 (0.04-3.70)	NA	NA	1.06 (0.47-2.38)	**0.003 (0.0003-0.02)**	3.57 (0.41-30.3)
Ld/VMPT-VT	0.62 (0.10-3.84)	NA	NA	1.06 (0.47-2.38)	**0.003 (0.0003-0.02)**	3.57 (0.41-30.3)
Ldc/VMPT-VT	0.66 (0.10-4.54)	NA	NA	1.47 (0.66-3.22)	**0.01 (0.002-0.05)**	1.63 (0.2-13.6)
MPR/VMPT-VT	1.58 (0.27-9.09)	NA	0.22 (0.02-2.38)	1.14 (0.47-2.77)	**0.004 (0.0002-0.04)**	1.33 (0.13-12.3)
MPR-R/VMPT-VT	1.61 (0.26-10.1)	NA	0.4 (0.05-4)	0.71 (0.27-1.92)	NA	0.34 (0.01-4.54)
VRd/VMPT-VT	0.66 (0.08-5.26)	NA	NA	1.11 (0.43-2.77)	**0.01 (0.0009-0.07)**	1.14 (0.12-10)
Ld/LD	1.53 (0.33-6.66)	**15.3 (2.22-434.7)**	NA	**0.4 (0.22-0.71)**	0.18 (0.01-1.40)	NA
Ldc/LD	1.66 (0.52-5)	**0.10 (0.003-0.71)**	NA	**0.55 (0.32-0.90)**	0.66 (0.16-2.32)	**0.47 (0.30-0.71)**
MPR/LD	3.84 (0.71-19.6)	**0.05 (0.001-0.41)**	NA	**0.43 (0.21-0.90)**	0.22 (0.01-2.43)	0.37 (0.13-1.08)
MPR-R/LD	4 (0.62-23.8)	**0.05 (0.001-0.52)**	NA	**0.27 (0.11-0.66)**	NA	**0.1 (0.01-0.52)**
VRd/LD	1.58 (0.24-10)	0.14 (0.004-1.25)	NA	**0.41 (0.20-0.83)**	0.58 (0.05-4.54)	**0.32 (0.14-0.71)**
Ldc/Ld	1.08 (0.4-3.12)	**0.10 (0.003-0.71)**	NA	**0.55 (0.32-0.90)**	0.66 (0.16-2.32)	**0.47 (0.30-0.71)**
MPR/Ld	**2.5 (1.02-6.25)**	**0.05 (0.001-0.41)**	NA	**0.43 (0.21-0.90)**	0.22 (0.01-2.43)	0.37 (0.13-1.08)
MPR-R/Ld	2.56 (0.76-9.09)	**0.05 (0.001-0.52)**	NA	**0.27 (0.11-0.66)**	NA	**0.1 (0.01-0.52)**
VRd/Ld	1.03 (0.34-2.94)	0.14 (0.004-1.25)	NA	**0.41 (0.20-0.83)**	0.58 (0.05-4.54)	**0.32 (0.14-0.71)**
MPR/Ldc	2.32 (0.66-7.69)	0.5 (0.23-1.09)	NA	0.76 (0.47-1.29)	0.35 (0.03-2.63)	0.83 (0.32-2.12)
MPR-R/Ldc	2.38 (0.55-10)	0.55 (0.18-1.66)	NA	**0.5 (0.24-0.99)**	NA	0.21 (0.02-1.06)
VRd/Ldc	1 (0.21-4)	1.42 (0.58-3.70)	NA	0.76 (0.47-1.25)	0.90 (0.11-4.34)	0.71 (0.34-1.40)
MPR-R/MPR	1.02 (0.35-2.85)	1.12 (0.43-2.85)	1.75 (0.41-9.09)	0.62 (0.33-1.12)	NA	0.26 (0.03-1.11)
VRd/MPR	0.4 (0.10-1.61)	2.85 (0.99-9.09)	NA	1 (0.5-1.81)	2.56 (0.66-9.09)	0.83 (0.29-2.43)
VRd/MPR-R	0.4 (0.07-2.04)	2.5 (0.66-10.1)	NA	1.51 (0.66-3.44)	NA	3.33 (0.58-29.4)

NA, comparison not available.

Appendix 1. Search strategies for included databases.

MEDLINE

Population	("Multiple Myeloma"[Mesh] OR "Myeloma"[All Fields] OR "Multiple Myeloma"[All Fields] OR "Multiple Myelomas"[All Fields] OR "Plasma-Cell Myeloma"[All Fields] OR "Plasma-Cell Myelomas"[All Fields] OR "Myelomatosis"[All Fields] OR "Myelomatoses"[All Fields] OR "Plasma Cell Myeloma"[All Fields] OR "Plasma Cell Myelomas"[All Fields] OR "Kahler Disease"[All Fields]) OR ("Paraproteinemias"[Mesh] OR "Paraproteinemia"[All Fields] OR "Plasma Cell Dyscrasias"[All Fields] OR "Plasma Cell Dyscrasia"[All Fields] OR "Monoclonal Gammopathy"[All Fields] OR "Monoclonal Gammopathies"[All Fields] OR "Monoclonal Gammapathy"[All Fields] OR "Monoclonal Gammapathies"[All Fields])
Intervention	(("dexamethasone"[Mesh] OR "dexamethasone"[All Fields]) OR ("prednisone"[Mesh] OR "prednisone"[All Fields]) OR ("prednisolone"[Mesh] OR "prednisolone"[All Fields]) OR ("methylprednisolone"[Mesh] OR "methylprednisolone"[All Fields]) OR ("betamethasone"[Mesh] OR "betamethasone"[All Fields]) OR ("cyclophosphamide"[Mesh] OR "cyclophosphamide"[All Fields]) OR ("melphalan"[Mesh] OR "melphalan"[All Fields]) OR ("bendamustine" [Supplementary Concept] OR "bendamustine"[All Fields]) OR ("bortezomib" [Supplementary Concept] OR "bortezomib"[All Fields]) OR ("carfilzomib" [Supplementary Concept] OR "carfilzomib"[All Fields]) OR ("marizomib" [Supplementary Concept] OR "marizomib"[All Fields]) OR ("MLN 9708" [Supplementary Concept] OR "ixazomib"[All Fields] OR "MLN9708"[All Fields] OR "MLN2238"[All Fields]) OR ("oprozomib"[All Fields] OR "ONX0912"[All Fields]) OR ("delanzomib" [Supplementary Concept] OR "delanzomib"[All Fields] OR "CEP-18770"[All Fields]) OR ("Thalidomide"[Mesh] OR "Thalidomide"[All Fields]) OR ("lenalidomide" [Supplementary Concept] OR "lenalidomide"[All Fields]) OR ("pomalidomide" [Supplementary Concept] OR "pomalidomide"[All Fields]) OR ("vorinostat" [Supplementary Concept] OR "vorinostat" [All Fields]) OR ("panobinostat" [Supplementary Concept] OR "panobinostat"[All Fields]) OR ("2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide" [Supplementary Concept] OR "ACY-1215"[All Fields] OR "ricolinostat"[All Fields]) OR ("JNJ 26481585" [Supplementary Concept] OR "quisinostat"[All Fields] OR "JNJ26481585"[All Fields] OR "JNJ-26481585"[All Fields]) OR ("elotuzumab" [Supplementary Concept] OR "elotuzumab"[All Fields]) OR ("daratumumab" [Supplementary Concept] OR "daratumumab"[All Fields]) OR ("SAR650984"[All Fields]))
Comparison	Omitted.
Outcome	Omitted (for increased sensitivity).
ECR Filter	((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

Embase

Population	('multiple myeloma'/exp OR 'multiple myeloma' OR 'myeloma' OR 'multiple myelomas' OR 'plasma-cell myeloma' OR 'plasma-cell myelomas' OR 'myelomatosis' OR 'myelomatoses' OR 'plasma cell myeloma' OR 'plasma cell myelomas' OR 'kahler disease' OR 'POEMS')
Intervention	('dexamethasone'/exp OR 'dexamethasone') OR ('prednisone'/exp OR 'prednisone') OR ('prednisolone'/exp OR 'prednisolone') OR ('methylprednisolone'/exp OR 'methylprednisolone') OR ('betamethasone'/exp OR 'betamethasone') OR ('cyclophosphamide'/exp OR 'cyclophosphamide') OR ('melphalan'/exp OR 'melphalan'/exp) OR ('bendamustine'/exp OR 'bendamustine') OR ('bortezomib'/exp OR 'bortezomib') OR ('carfilzomib'/exp OR 'carfilzomib') OR ('salinosporamide A'/exp OR 'salinosporamide A' OR 'Marizomib' OR 'NPI 0052' OR 'NPI-0052') OR ('ixazomib'/exp OR 'ixazomib' OR 'MLN9708' OR 'MLN2238') OR ('oprozomib'/exp OR 'oprozomib' OR 'ONX0912') OR ('delanzomib'/exp OR 'delanzomib' OR 'CEP-18770' OR 'CEP18770' OR 'CEP 18770') OR ('thalidomide'/exp OR 'thalidomide') OR ('lenalidomide'/exp OR 'lenalidomide') OR ('pomalidomide'/exp OR 'pomalidomide') OR ('vorinostat'/exp OR 'vorinostat') OR ('panobinostat'/exp OR 'panobinostat'/exp) OR ('ricolinostat'/exp OR 'ricolinostat' OR '2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide' OR 'ACY-1215') OR ('quisinostat'/exp OR 'quisinostat' OR 'JNJ 26481585' OR 'JNJ26481585' OR 'JNJ-26481585') OR ('elotuzumab'/exp OR 'elotuzumab') OR ('daratumumab'/exp OR 'daratumumab') OR ('isatuximab'/exp OR 'isatuximab' OR 'SAR650984')
Comparison	Omitted.
Outcome	Omitted (for increased sensitivity).
ECR Filter	'crossover procedure'/exp AND [embase]/lim OR ('prospective study'/exp AND [embase]/lim) OR ('follow up'/exp AND [embase]/lim) OR ('placebo'/exp AND [embase]/lim) OR ('clinical trial'/exp AND [embase]/lim) OR ('single blind procedure'/exp AND [embase]/lim) OR ('double blind procedure'/exp AND [embase]/lim) OR ('randomization'/exp AND [embase]/lim) OR ('controlled clinical trial'/exp AND [embase]/lim) OR ('randomized controlled trial'/exp AND [embase]/lim)

LILACS

Population	(Mieloma AND Múltiplo) or (Multiple AND Myeloma) or (Kahler) or (Mieloma AND Multiplo)
Intervention	((dexamethasone) OR (prednisone) OR (prednisolone) OR (methylprednisolone) OR (betamethasone) OR (cyclophosphamide) OR (melphalan) OR (bendamustine) OR (bortezomib) OR (carfilzomib) OR (salinosporamide A OR Marizomib OR NPI 0052 OR NPI-0052) OR (ixazomib OR MLN9708 OR MLN2238) OR (oprozomib OR ONX0912) OR (delanzomib OR CEP-18770 OR CEP18770 OR CEP 18770) OR (thalidomide) OR (lenalidomide) OR (pomalidomide) OR (vorinostat) OR (panobinostat) OR (ricolinostat OR 2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide OR ACY-1215) OR (quisinostat OR JNJ 26481585 OR JNJ26481585 OR JNJ-26481585) OR (elotuzumab) OR (daratumumab) OR (isatuximab OR SAR650984))
Comparison	Omitted.
Outcome	Omitted (for increased sensitivity).
ECR Filter	Omitted (for increased sensitivity).

SciELO

Population	(Mieloma AND Múltiplo) or (Multiple AND Myeloma) or (Kahler) or (Mieloma AND Multiplo)
Intervention	((dexamethasone) OR (prednisone) OR (prednisolone) OR (methylprednisolone) OR (betamethasone) OR (cyclophosphamide) OR (melphalan) OR (bendamustine) OR (bortezomib) OR (carfilzomib) OR (salinosporamide A OR Marizomib OR NPI 0052 OR NPI-0052) OR (ixazomib OR MLN9708 OR MLN2238) OR (oprozomib OR ONX0912) OR (delanzomib OR CEP-18770 OR CEP18770 OR CEP 18770) OR (thalidomide) OR (lenalidomide) OR (pomalidomide) OR (vorinostat) OR (panobinostat) OR (ricolinostat OR 2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide OR ACY-1215) OR (quisinostat OR JNJ 26481585 OR JNJ26481585 OR JNJ-26481585) OR (elotuzumab) OR (daratumumab) OR (isatuximab OR SAR650984))
Comparison	Omitted.
Outcome	Omitted (for increased sensitivity).
ECR Filter	Omitted (for increased sensitivity).

Appendix 2. Details on treatments from included studies.

Study	Treatment Details
Durie, 2016	Ld - Lenalidomide 25 mg D1-D21 + Dexamethasone 40 mg D1, D8, D15, D22 every 28 days x 6 cycles + Maintenance with same regimen until progression
	VRd - Bortezomib 1.3 mg/m2 D1, D4, D8, D11 + Lenalidomide 25 mg D1-D14 + Dexamethasone 20 mg D1, D2, D4, D5, D8, D9, D11, D12 every 21 days x 8 cycles + Maintenance with Ld (as above)
Facon, 2006	Dex - Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 (2 cycles) and after D1-D4 only + Dex-IFN - IFN A2B 3 MU 3x/week + Dexamethasone dose from Dex
	MP - Melphalan 0.25 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 every 6 weeks + M-Dex - Melphalan dose from MP and Dexamethasone dose from Dex
Facon, 2007	MP - Melphalan 0.25 mg/kg + Prednisone 2 mg/kg
	MPT - Melphalan 0.25 mg/kg + Prednisone 2 mg/kg + Thalidomide up to 400 mg/day
	VAD - Dexamethasone 40 mg/day D1-D4 + Doxorubicin 50 mg/m2 D1 + Vincristine 1 mg D1 (2 cycles) + 2 reduced conditioning auto-transplant (Melphalan 100 mg/m2) 2 months apart
Hjorth, 1990	MP - Melphalan 0.25 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 cycle every 6 weeks
	VMCP - Vincristine 1 mg D1 + Melphalan 5 mg/m2 D1-D4 + Cyclophosphamide 100 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D3 alternating every 3 weeks with VBAP - Vincristine 1 mg D1 + BCNU 30 mg/m2 D1 + Doxorubicin 30 mg/m2 D1 + Prednisone 60 mg/m2 D1-D4
Hulin, 2009	MP - Melphalan 0.2 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 every 6 weeks
	MPT - Melphalan 0.2 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Thalidomide 100 mg/day every 6 weeks
Hulin, 2016	Ldc - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1, D8, D15 and D22 every 28 days continuously
	Ld - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1, D8, D15 and D22 every 28 days x 18 cycles
	MPT - Melphalan 0.25 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Thalidomide 200 mg/day every 6 weeks x 12 cycles
Hungria, 2016	CTD - Cyclophosphamide 50 mg/d + Dexamethasone 40 mg D1-D4 and D15-D18 (for 2 cycles and only D1-D4 thereafter) + Thalidomide 100-200 mg/day
	MPT - Melphalan 4 mg/m2 + Prednisone 40 mg/m2 D1-D7 every 4 weeks + Thalidomide 100-200 mg/day
Ludwig, 2005	VMCP - Vincristine 2 mg D1 + Melphalan 15 mg/m2 D1 + Cyclophosphamide 450 mg/m2 D1 + Prednisolone 40 mg D1-D7 and 25 mg 3x/sem D8-D14 every 4 weeks
	VMCPc - Vincristine 2 mg D1 + Melphalan 15 mg/m2 D1 + Cyclophosphamide 450 mg/m2 D1 + Prednisolone 40 mg D1-D7 and 25 mg 3x/week D8-D28 every 4 weeks
Ludwig, 2009	MP - Melphalan 0.25 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 every 4-6 weeks
	TD - Thalidomide 50-400 mg/day + Dexamethasone 40 mg D1-D4 and D15-D18 (even cycles) and D1-D4 (odd cycles)

Magarotto/Palumbo, 2016	CPR - Lenalidomide 25 mg/day D1-D21 + Cyclophosphamide 50 mg D1-D21 + Prednisone 25 mg alternate days x 9 cycles + Maintenance with Lenalidomide 10 mg D1-D21 with or without Prednisone until progression/toxicity
	Ld - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1, D8, D15 and D22 every 28 days x 9 cycles + Maintenance with Lenalidomide 10 mg D1-D21 with or without Prednisone until progression/toxicity
	MPR - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 x 9 cycles + Maintenance with Lenalidomide 10 mg D1-D21 with or without Prednisone until progression/toxicity
Mateos, 2010	VMP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 first 4 cycles and D1, D8, D22, D29 C5-C9) every 6 weeks until progression/toxicity
	VTP - Thalidomide 100 mg/day + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 in C1 and D1, D8, D15 and D22 thereafter) every 6 weeks until progression/toxicity
San Miguel, 2013	MP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 every 6 weeks fo 9 cycles
	VMP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 first 4 cycles and D1, D8, D22, D29 C5-C9) every 6 weeks for 9 cycles
Morgan, 2011	CTDa - Cyclophosphamide 500 mg/weekl + Thalidomide 200 mg + Dexamethasone 20 mg D1-D4 and D15-D18 every 28 days
	MP - Melphalan 7 mg/m2 D1-D4 + Prednisone 40 mg/m2 D1-D4 every 4 weeks
Niesvizky, 2013	VD - Bortezomib 1.3 mg/m2 D1, D4, D8, D11 + Dexamethasone 20 mg D1, D2, D4, D5 D8, D9, D11, D12 (4 cycles) and D1, D2, D4, D5 (5-8 cycles) x 8 cycles
	VMP - Bortezomib 1.3 mg/m2 D1, D4, D8, D11 + Melphalan 9 mg/m2 and Prednisone 60 mg/m2 D1-D4 x 8 cycles
	VTD - Bortezomib 1.3 mg/m2 D1, D4, D8, D11 + Dexamethasone 20 mg D1, D2, D4, D5 D8, D9, D11, D12 (4 cycles) and D1, D2, D4, D5 (5-8 cycles) + Thalidomide 100 mg x 8 cycles
Oken, 1997	MP - Melphalan 8 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 every 4 weeks
	NU-Based Regimen - Melphalan 8 mg/m2/day D1-D4 + Carmustine (BCNU) 20 mg/m2 D1 + Cyclophosphamide 400 mg/m2 D1 + Vincristine 1.2 mg/m2 D1 + Prednisone 40 mg/m2/day D1-D7 (and 20 mg/m2 D8-D14 first 3 cycles) every 35 days
Palumbo, 2004	MP - Melphalan 6 mg/m2 + Prednisone 60 mg/m2 D1-D7 every 4 weeks
	VAD - Dexamethasone 40 mg/day D1-D4 + Doxorubicin 50 mg/m2 D1 + Vincristine 1 mg D1 (2 cycles) + 1 reduced conditioning auto-transplant (Melphalan 100 mg/m2)
Palumbo, 2008	MP - Melphalan 4 mg/m2 + Prednisone 40 mg/m2 D1-D7 every 4 weeks
	MPT - Melphalan 4 mg/m2 + Prednisone 40 mg/m2 D1-D7 + Thalidomide 100 mg/day every 4 weeks
Palumbo, 2012	MP - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4
	MPR - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21
	MPR-R - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 + Maintenance with Lenalidomide 10 mg D1-D19

Palumbo, 2014	VMP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 first 4 cycles and D1, D8, D22, D29 C5-C9) every 6 weeks
	VMPT-VT - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 first 4 cycles and D1, D8, D22, D29 C5-C9) + Thalidomide 50 mg/day every 6 weeks + Maintenance with Bortezomib 1.3 mg/m2 every 2 weeks + Thalidomide 50 mg/day
Rajkumar, 2008	Dex - Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 every 4 weeks
	TD - Thalidomide 200 mg/day contínuo + Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 every 4 weeks
Rajkumar, 2010	LD - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1-D4, D9-D12 and D17-D20 every 28 days
	Ld - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1, D8, D15 and D22 every 28 days
Sacchi, 2011	MP - Melphalan 0.25 mg/kg D1-D4 + Prednisone 60 mg/m2 D1-D4 every 28 days
	MPT - Melphalan 0.25 mg/kg D1-D4 + Prednisone 60 mg/m2 D1-D4 + Thalidomide 100 mg/day every 28 days
Shustik, 2007	MD - Melphalan 9 mg/m2 D1-D4 + Dexamethasone 40 mg/day for 4 days every 14 days
	MP - Melphalan 9 mg/m2 D1-D4 + Prednisone 100 mg D1-D4 every 4 weeks
Stewart, 2015	MPR-R - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 + Maintenance with Lenalidomide 10 mg D1-D20
	MPT-T - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Thalidomide 200 mg D1-D28 every 28 days + Maintenance with Thalidomide 100 mg/day
Takenaka, 2004	mCOP/MP - Cyclophosphamide 350 mg/m2 D1 and D8 + Vincristine 1 mg/m2 D1 and D8 + Prednisolona 40 mg/m2 D1-D3, D8-D10 and D22-D24 + Melphalan 3 mg/m2 D22-D24 every 6 weeks
	NU-Based Regimen - Ranimustine (MCNU) 50 mg/m2 D1 + Cyclophosphamide 350 mg/m2 D1 and D22 + Vincristine 1 mg/m2 D1 and D22 + Prednisolone 60 mg/m2 D1-D3 and D22-D24 + Melphalan 3 mg/m2 D1-D3 and D22-D24 every 6 weeks
Wijermans, 2010	MP - Melphalan 0.25 mg/kg + Prednisone 1 mg/kg
	MPT - Melphalan 0.25 mg/kg + Prednisone 1 mg/kg + Thalidomide 200 mg/day
Zweegman, 2016	MPR-R - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 + Maintenance with Lenalidomide 10 mg D1-D21
	MPT-T - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Thalidomide 200 mg D1-D28 every 28 days + Maintenance with 100 mg/day

Sumário dos Artigos em Português

Artigo 1:

Tratamento de indução para pacientes portadores de mieloma múltiplo elegíveis a transplante autólogo de células progenitoras hematopoéticas: revisão sistemática e metanálise por mixed treatment comparison de 4.432 pacientes.

O transplante autólogo continua a ser fundamental para o tratamento de pacientes jovens e com poucas comorbidades portadores de mieloma múltiplo. A terapia de indução antes do transplante pode influenciar os resultados pós-transplante. Portanto, a melhor terapia de primeira linha para estes pacientes deve ser baseada na melhor evidência disponível para guiar a terapia. Nós realizamos uma revisão sistemática e metanálise por mixed treatment comparison de 9 ensaios clínicos randomizados, arrolando 4.432 pacientes e comparando 10 tratamentos diferentes avaliando sobrevida, resposta e segurança. A similaridade entre os desenhos, metodologia e população dos estudos foi considerada adequada. A rede compilada permitiu apenas comparações indiretas, portanto análises de homogeneidade e consistência não foram aplicadas. A análise de sobrevida global (SG) mostrou superioridade do PAD (bortezomibe, doxorrubicina e dexametasona) sobre os outros regimes, enquanto para a sobrevida livre de doença, o VTD (bortezomibe, talidomida e dexametasona) foi considerado o melhor tratamento. Além disso, para resposta completa e resposta global, mais uma vez o VTD mostrou clara superioridade entre os protocolos analisados. O perfil de segurança avaliou eventos adversos infeciosos, cardíacos, gastrointestinais, neurológicos, trombóticos e hematológicos de grau 3-4. O risco de eventos trombóticos foi superior com o TAD (talidomida, doxorrubicina e dexametasona), neurológicos com o PAD, infecciosos com doses elevadas de dexametasona (Dex), hematológicos com o Z-Dex (Idarrubicina e dexametasona), gastrointestinais com o VTD e cardíacos com o PAD. Um desfecho compilado considerando os tratamentos melhor ranqueados incorporando sobrevida, resposta e toxicidade indicou o VTD, seguido pelo PAD e TAD, como melhores tratamentos em relação aos demais. Nosso estudo sugere que para o tratamento de indução de pacientes elegíveis a transplante, uma combinação de três drogas, especialmente

incluindo ambas as classes de novos agentes (imunomoduladores e inibidores do proteasoma) deveriam ser preferidos em relação a outros regimes.

Artigo 2:

Tratamento de indução para pacientes portadores de mieloma múltiplo não-candidatos a transplante autólogo de células progenitoras hematopoéticas: revisão sistemática e metanálise por mixed treatment comparison de 11.967 pacientes em 27 ensaios clínicos randomizados.

O mundo testemunhou uma importante proliferação de drogas ativas para o tratamento do mieloma múltiplo. A melhor opção de tratamento de indução deve ser constantemente reavaliada dentro deste contexto. Nós realizamos uma revisão sistemática and metanálise por mixed treatment comparison de 27 ensaios clínicos randomizados, arrolando 11.967 pacientes e comparando 23 regimes de tratamento diferentes, avaliando sobrevida, resposta e desfechos de segurança. A similaridade da organização, metodologia e população entre os estudos foi considerada adequada. Nenhuma inconsistência significativa foi encontrada. Nós ranqueamos os tratamentos para cada desfecho analisado. A análise de sobrevida global mostrou superioridade do VRd, VMPT-VT, MPR-R, Ld contínuo (Ld) e CPR. A sobrevida livre de progressão foi superior com o MPR-R, MPT-T, VMPT-VT, Ldc e VRd. A resposta completa foi mais comum com regimes contendo bortezomibe (VMPT-T, VTP, VMP, Vd e VRd), enquanto a taxa de resposta global foi liderada pelo VMPT-VT, seguido por Vd, VTd, LD e VTP. O perfil de segurança avaliou eventos adversos infeciosos, cardíacos, gastrointestinais, neurológicos, trombóticos e hematológicos de grau 3-4. Um desfecho ponderado de toxicidade (levando em consideração todos estes eventos) demonstrou a dexametasona em altas doses (Dex) e o MP como os regimes com a menor incidência de eventos adversos, muito embora estes também tenha sido aqueles com resultados inferiores em sobrevida e/ou resposta. Um desfechos compilado considerando os ranqueamentos de todos os tratamentos indicou o VMPT-VT, seguido pelo VRd, MPR-R, VMP e Ldc, foram os melhores tratamentos entre os demais. Por outro lado, os tratamentos ranqueados por último foram Dex, TD, VMPC com ou sem prednisona contínua, MP e MD. Nossa análise sugere que, para os pacientes inelegíveis a transplante, estratégias combinando

novos agentes (imunomoduladores e inibidores do proteasoma) em regimes de 3 ou 4 drogas, ou aqueles regimes incorporando o uso de lenalidomida a longo prazo, deveriam ser priorizados.

8. Conclusões e Considerações Finais

O tratamento do MM é alvo de intensa pesquisa nos dias de hoje, dado que sua importância dentro da área de onco-hematologia só tende a crescer nas próximas décadas e, muito além disso, a sobrevida prolongada destes pacientes acaba suscitando a necessidade de cada vez mais possibilidades de medicamentos que possam ser usados de forma sequencial de modo que, a cada falha de manejo, haja uma nova alternativa a ser oferecida ao paciente. Essa necessidade resultou no crescente número de publicações e estudos multicêntricos que vão se tornando parte do cotidiano de assistência destes pacientes, inclusive no Brasil.

Dado que o manejo destes pacientes é bastante dispendioso e oneroso ao sistema de saúde, seja público ou privado, e considerando que já na presente realidade um grande contingente de pacientes encontra-se em situação de esgotamento de alternativas terapêuticas dentro de seu cenário de tratamento, a cada nova droga introduzida no mercado observa-se um significativo e rápido processo de adesão. Muitas vezes baseado em achados meramente preliminares, não replicados e não comparados. Impõe-se um grande dilema pois a premente necessidade dos pacientes acaba sendo contraposta à carência de evidências de eficácia ponderada aos demais regimes disponíveis, e muitas drogas incorporam-se ao cotidiano sem ter seu nicho hierárquico bem definido perante os demais protocolos.

O presente trabalho é uma tentativa, como outras já existentes na literatura, de dirimir este dilema. Seus resultados, já extensamente discutidos, vão ao encontro das inferências atualmente estabelecidas no sentido de agregar cada vez mais agentes de alta eficácia, combinados, já no tratamento de primeira linha destes pacientes, fazendo uso de *triplets* e *quadruplets* e, sobretudo no grupo de pacientes inelegíveis, num contexto ininterrupto até a progressão. Isto já poderia ser considerado uma quebra de paradigmas, pois não há muito tempo atrás a discussão ainda colocava em cheque a necessidade de manutenção.

Ao longo deste trabalho pode-se avaliar de forma abrangente e profunda a literatura médica disponível envolvendo o tratamento do MM, ao menos em sua fase inicial. Uma característica notável e quase que sistemática entre os trabalhos avaliados é a carência de descrição metodológica de quesitos básicos de um ECR tal como o

método de randomização, as medidas adotadas para o sigilo de alocação de tratamento e sobretudo a falta de cegamento. Esperamos que, com o aperfeiçoamento dos métodos de avaliação crítica da literatura, estudos com cada vez mais qualidade metodológica possam fazer parte de trabalhos como este.

É importante citar que dentro do cenário brasileiro existe um inegável déficit estrutural que dificulta muito o manejo dos pacientes (como se a dificuldade inerente do tratamento oncológico não fosse *per se* já um grande desafio), mesmo para aplicação de terapias já consolidadas. Um grande exemplo disso é uma das drogas apresentadas no presente trabalho como parte integrante dos melhores protocolos para pacientes inelegíveis, a lenalidomida. Este medicamento foi inicialmente estudado no final da década de 1990, e em 2006 foi aprovado pelo FDA para tratamento de MM com pelo menos uma linha de tratamento anterior, sendo rapidamente incorporado também na primeira linha de tratamento. Desde então, a totalidade das diretrizes na área recomenda o uso deste medicamento. Todavia, há mais de 9 anos sua aprovação tramitava na ANVISA, sendo influenciada por diversos fatores político-econômicos, sendo felizmente aprovada em Dezembro de 2017.

O presente trabalho é fruto do esforço conjunto de um grande número de profissionais e teve por objetivo demarcar, ao menos até o presente momento, um panorama de recomendações acerca desta enfermidade. Mas este é um ciclo, na realidade, inexorável. O incansável ímpeto da pesquisa em busca de novas alternativas de tratamento, seja para esta doença como para tantas outras, sempre fará indispensável a recondução deste processo. Como para Sísifo, nossa rocha acaba de rolar ao pé da montanha novamente.