

## The Third Fani Job Meeting in Hematology – Cellular Therapy and beyond

### III Encontro Fani Job de Hematologia – Terapia Celular e além

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Transplant physicians have tried to win the battle against Graft-versus-Host Disease (GvHD) since as early as the seventies. Much has been done since then. Today, the Treatment Related Mortality (TRM) can be as low as 20%, including all causes, depending on the cancer center. Acute and chronic GvHD, however, still poses a major challenge to both patients and physicians since it carries a significant morbidity.

The third Fani Job Meeting in Hematology was programmed to consider the stunning progression of the cellular and molecular therapies with hazardous myeloablative and non-myeloablative Bone Marrow Transplantation (BMT) techniques for the treatment of hematological cancers.

Recently it has been demonstrated that stem cells can originate from cardiac, neural, skeletal muscle, hepatic, and of course, bone marrow tissues. These tissues can be grown in vitro and their clinical applications are obvious. Although the precise mechanisms or the fate determinants of stem cells as well as their origins are still far from being defined, there are clinical applications being tested with some success.<sup>1,2</sup> So, it seems like we can make stem cells develop to a defined tissue, in other words, to function in a defined way.

We can select a particular subset of hematopoietic cells, activate them, and cause them to proliferate for the treatment of infections or tumors (viral infected cells or residual tumor cells). It is also possible to select, in vivo, a desired cell (or function) and utilize its cytotoxic activity against

the affected target.<sup>3,4</sup> There are several cytokines available on the market, whose action is to create an environment for anti-tumor cells to become activated and attack their targets, breaking down the acquired immuno-tolerance of the organism to its resident tumor.<sup>5</sup>

Stem cell engraftment to form bone marrow tissue is a common practice. There are many ways to do this. Different sources of stem cells (and maybe different types): bone marrow, peripheral blood or cord blood stem cells, and different techniques of transplantation are used. Utilizing bone marrow or cord blood as a source using the myeloablative approach, requires long hospitalizations, several intravascular lumen devices, and the employment of several, very expensive anti-infection drugs. Chemo- and radiotherapeutic conditioning adds an environment where infections and acute GvHD become very hazardous. The TRM of the BMT is more common in this transplant modality.

A partially ablative, immunosuppressive, environment is used for the non-myeloablative modality. It allows the donor's stem cell to engraft and regenerate the bone marrow as full chimera in recipients,<sup>6</sup> with early hospital release, low early TRM, and immune anti-tumor effect.<sup>7</sup> However, there still has a long way to go to overcome the chronic GvHD that is severe in 30% of the patients submitted to non-myeloablative BMT.<sup>8</sup>

There are no doubts that Graft-versus-Tumor (GvT) effect is a byproduct of GvHD. The latter's intensity, however, does not correlate with the GvT effect.<sup>9,10</sup> Separation of the GvHD from the GvT effect has been attempted for years. Recently, it has been

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shown that this ideal situation can be accomplished by NK cell mismatch transplants which have a remarkable result: a long EFS and possible cure of patients submitted to such transplants.<sup>11,12</sup>

A very low amount of minimal residual disease, before transplant, has being shown to be important for its curative effect in the treatment of childhood high risk LLA<sup>13</sup> and adult B-LLA.<sup>14</sup> A remarkable tumor shrink can be achieved with new drugs such as imatinib for CML<sup>15</sup> and monoclonal antibodies for the lymphoproliferative diseases.<sup>16</sup> Some of these options can probably even cure the disease without the need for transplants. On the other hand, several different approaches are being developed to hasten the autologous immune system to overcome minimal residual diseases such as the dendritic cell technology<sup>4</sup> and the above mentioned immune modulators.

The translation of these new technical achievements to the clinical setting, however, has been comparatively slow. There are several aspects related to this. The main one is the experimental nature and the developmental velocity of these technologies. There has to be a careful transference of new developments to our patients. They have to be enrolled in clinical trials controlled by experimented physicians. On the other hand, drugs like imatinib, fludarabine, peg interferon's or monoclonal antibodies, whose effects are undoubtedly superior to anything else available for their indications should be available to the patient as soon as possible. There are several such drugs being tested now. They are however, extremely expensive. Several clinical trials from good cancer centers are hampered by the amount of money that has to be spent on diagnosis and treatment. The costs are high even for developed countries.

In Brazil, the costs of treatment rely mainly on the public health system. While there are still issues like high infant mortality, hunger and the other consequences of an underdeveloped society, there is cancer in Brazil too. By our constitution the individual patient has the right to receive the best treatment there is. The amount of resources spent for the treatment of a single patient submitted to BMT, for instance, who develops GvHD, cytomegalovirus and a fungal pulmonary infection, would probably pay for the food and basic medicines to an entire community. This does not include the costs for the clinical treatment of

chronic myeloid leukemia patients throughout the country.<sup>17</sup>

If cancer is to be treated, or its treatment developed, a rationalized use of such tools should be enforced. This issue should not be dealt with by organizations affected by political or financial aspects, particularly where the health care system is entirely dependent on the public budget. Experienced experts should be consulted for treatment designs and their application centralized.<sup>17</sup> The continental size of Brazil along with its different cultural backgrounds, however, calls for regional centralization. It is mandatory though that medical care tools should become affordable since human life should not be part of a profit-making business.

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