The medical importance of autologous hematopoietic stem cell transplantation

A importancia médica do transplante de células tronco hematopoiéticas

In 1979, Dicke e col. (1) reported the first series of patients with relapsed acute leukemia treated with high dose chemotherapy and total body irradiation followed by the infusion of cryopreserved autologous bone marrow derived hematopoietic stem cell (HSC) infusion. Since then, autologous stem cell transplant (ASCT) has evolved into a medical therapy using not only bone marrow as a source of HSC but also peripheral blood. The findings of an increase in peripheral blood HSC following chemotherapy (2) and/or hematopoietic growth factors (3), and the demonstration that peripheral blood HSC engraft earlier than BM derived HSC (4), made peripheral blood stem cells to became the standard HSC source for ASCT. As for its indications, although still been tested for prognostically favorable acute myeloid leukemia (5) ASCT became the standard of care for Multiple Myeloma and Mantle Cell Lymphoma in first remission; and diffuse large B cell lymphomas, follicular lymphomas and Hodgkin lymphomas that are in chemosensitive relapsed or after second complete remission (CR2) (6). As for solid tumors, according the European School of Haematology, it is considered a standard of care for high risk or beyond CR2 Ewing's sarcoma, high risk or beyond CR1 Neuroblastoma, and an option for breast cancer as an adjuvant strategy. The rationale behind its role in the treatment of malignant diseases is to allow the utilization of sub-lethal doses of chemotherapy followed by autologous HSC rescue.

For Multiple Myeloma (MM) the most common plasma cell disorder, except for patients with a compromised performance status, ASCT is the standard of care irrespectively of the stage or of the cytogenetic and/or molecular abnormality or yet, other laboratory tests recognized as risk factors for response to therapy or overall survival (OS). Accordingly, MM is currently the most common indication for ASCT in US and Europe. ASCT has indubitably increased the OS from a median of three to a median of five years. (7, 8). There are no incidence studies of MM in Brazil. Based on the US incidence, provided there are no ethnical differences, which is very unlikely, we could say that there are roughly 9000 new cases a year in Brazil. Although there are several very active anti-MM drugs either been tested or already incorporated as a standard of care for initial pre-ASCT treatment, ASCT still remains the ideal treatment, remaining to be defined if two (Tandem) transplants are superior to one for patients in partial remission after the first ASCT (9). Toxicity has to be taken into consideration for the decision of a second transplant, as well as the emerging target drugs presently under investigation might change this scenario (10). In any case, ASCT will still be the standard of care for MM in the next few years representing a tremendous burden for the ASCT teams in Brazil since the diagnosis and proper referral of patients are improving in the country, and at least a fourth of the patients will need two transplants.

The second most frequent indication for ASCT is the B cell lymphomas. The most common types are diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL) accounting for 30.6 and 22.1% of all lymphomas, respectively. Mantle cell lymphoma, for which ASCT is a standard of care as stated above, accounts for 6% (11).

Annually, 50.000 new cases of non-Hodgkin lymphoma are diagnosed in US (12) and its incidence and mortality rates increased steadily during the 1970s and 1980s at 3% to 4% per year (13). During the past decade, however, overall rates have reached a plateau because of a significant decrease in males aged 25 to 54 of all races, believed to be related to the falling incidence of human immunodeficiency virus (HIV) infection. As stated above, ASCT is the standard of care for relapsed, in second CR and/or chemosensitive DLBCL and FL. DLBCL can be cured with chemotherapy including Rituximab, but stage, cellular or molecular factors and age (international prognostic index – IPI) have an impact in the relapse free survival at five years that varies from 70 to 40%. There are no data about non-Hodgkin lymphoma incidence in Brazil, but based in the US figures we probably should be offering ASCT for a significant number of patients. The same holds true for Hodgkin Lymphomas (HL) which is less common and more curable with the appropriated chemotherapy or radio-chemotherapy, but still, in CR2 or relapsed chemosensitive cases ASCT is indicated.

An emerging role for ASCT in the treatment of autoimmune diseases such as Systemic sclerosis, Rheumatoid arthritis, Multiple sclerosis, Lupus erythematosus and

Crohn's disease is currently being defined. For these diseases, the rationale for autologous HSCT is the ablation of an aberrant or self-reactive immune system by chemotherapy and regeneration of new and hopefully self-tolerant immune system from HSC infusion. In the past 15 years, more than 1500 patients enrolled in clinical trials worldwide have received HSCT for the treatment of autoimmune diseases with variable results pointing to a better role of HSCT in less advanced diseases, preferentially with an exuberant inflammatory component (14). In Brazil, Voltarelli and col (15) published the first series of recently diagnosed type I Diabetes Mellitus treated with auto HSCT as a proof of principle that also for this disease the ablation of self reactive immune system might have a role in its cure.

Analyzing the world HSCT activity, a recent World Bone Marrow Transplant (WBMT) registry publication, including all transplants reported to the several international registries in a period of three years (2006-2008) the authors were able to show that ASCT accounted for 55% of all 146.808 transplants reported in that period, and peripheral blood was the HSC source in 98% of these procedures. Lymphoproliferative disorders were the main indication (84%), followed by solid tumors (9%) and nonmalignant conditions (1%) (16).

In Brazil, of the 20.458 HSCT reported to the Brazilian Society of Bone Marrow Transplantation – SBTMO, up to December 2012, 10.972 (54%) were ASCT, a figure that matches with the world activities. However, only 33 of the 61 centers authorized to perform HSCT reported to SBTMO or published their results (17). The series of 120 ASCT performed between 1996 and 2011, reported by Pereira et al. in this issue of the Revista da AMRIGS, reflects the world activity since 85% of their patients had lymphoproliferative disorders and in 100% of the procedures peripheral blood HSC was utilized, adding a valuable experience and a hope that we will be able to transplant all patients in need, as more of these experienced transplantation teams increases in the country.

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