HEMATOLOGY IN DEVELOPING COUNTRIES

The Mexican approach to conduct allogeneic stem cell transplantation: Braking dogmata and facing the Matthew effect

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Introduction

The dogmata

Dogmata are principles, maxims or tenets; settled opinions adopted through authority instead of reason or experience. The progress and evolution of knowledge very frequently rely on the breakage of dogmata [1]. Historically, the development of allogeneic hematopoietic stem cells (HSC) transplantation has relied on high dose myeloablative chemo or radiotherapy with three main dogmatic goals: (1) to eradicate underlying disease, (2) to create bone marrow space for the incoming HSC, and (3) to suppress the recipient’s immune system in preparation for the allograft so that rejection of the donor stem cell graft does not occur [2].

The broken dogmata

The evolution of knowledge has proven as wrong the first two above mentioned dogmata: In 1978, Odom et al. [3] described two patients with acute lymphoblastic leukemia who achieved a remission as a result of the development of graft versus host disease (GVHD). The concept of “graft versus leukemia” effect was then introduced. Later on, researchers from the group of the Nobel-laureate, Dr. E. Donnall Thomas in Seattle, USA, published a paper on the anti-leukemic effect of the GVHD [4]; this publication is now considered as one of the landmark papers in hematology of the twentieth century [5]. The documentation that donor-lymphocyte infusions (DLI) with no additional chemotherapy following induction of host versus graft unresponsiveness resulted in remission, thus suggesting that once given the chance by prevention of rejection, alloreactive lymphocytes can eliminate leukemia, a concept entertained by Kolb et al. [6] and Slavin et al. [7,8] was followed by focusing on durable engraftment of lymphocytes rather than myeloablation of tumor cells, resulting in the development of the non-myeloablative stem cell transplantation (NST) methods starting in Jerusalem and then in Houston [9,10]. Accordingly, it is now well known that the anti-tumor effect of the GVHD induced by HSC allografts is responsible for the control of certain malignancies, and that HSC create their own marrow space through GVHD reactions [5–17]. We have learned that certain malignancies are more susceptible than others to the graft versus tumor effect; for example: Chronic myelogenous leukemia is substantially more sensitive to this effect than acute lymphoblastic leukemia [13,14], this being probably one of the reasons of the different results obtained when allografting individuals with these diseases.

The consequences of braking dogmata

(1) Having proved that the graft versus tumor effect is the responsible for the control of certain malignancies in individuals given allogeneic HSC grafts, and that the bone marrow space does not need to be created by ablative chemo or radiotherapy, the obvious question was: It is possible to induce graft versus tumor effect by allogeneic HSC without producing a severe damage to the recipient’s bone marrow, immune system and other organs? The answer to this question is yes; it is now well known that current intensive and toxic cytoreductive conditioning therapy can be replaced by nonmyeloablative immunosuppression to facilitate...
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allogeneic engraftment; in lieu of intensive chemotherapy before transplantation, engrafted donor T cells are used to accomplish the task of eradicating the host’s malignant cells [5–19]. Accordingly, it seems now clear that two immunological barriers must be overcome to successfully establish HSC allografts: One is host versus graft disease (HVGD/rejection), whereas the other is the opposite, the graft versus host reaction, which includes GVHD. Traditionally, the therapeutic regimens administered to prevent HVGD are delivered before transplant and aimed to eradicate the host’s immune response, whereas the therapeutic regimens to prevent GVHD focus on the grafted donor immune cells are delivered after transplant and ideally, should only affect those donor immune cells that react with alloantigens for which the donor and host are mismatched [5–19].

(2) Widespread application of HSC transplantation had been limited by the toxicity associated with the myeloablative conditioning regimens. In attempts to achieve maximal tumor eradication, conditioning regimens had been intensified to a point at which serious non-hematopoietic organ toxicities were common and resulted in morbidity and mortality [19]. In addition, the pancytopenia induced by the high-dose regimens carries the risks of serious and even lethal infections despite the use of prophylactic broad-spectrum antibiotics; even more, the regimen-related toxicity, particularly to the liver and kidney, frequently restricts the ability to give optimal post-grafting immunosuppression therapy, which is necessary to avoid GVHD. As a result, at most transplant centers, the severity of the complications from myeloablative chemotherapy and allografts to a median of two (range 1 to 4), thus diminishing costs of the procedures and of the disposable apheresis sets.

(3) Another salient point which is frequently overlooked in papers dealing with bone marrow transplantation coming from developed countries is the cost of the procedure. In our experience (vide infra), non-myeloablative stem cell transplantation (NST) is substantially cheaper than conventional ablative stem cell allografting [17,19–31]; as a result, allogeneic HSC can be offered now to more patients as a therapeutic option, this observation being critical for individuals living in developing countries. The fact that over two-thirds if the inhabitants of the world live in developing countries should be born in mind when reading these lines.

The ways of braking these dogmata

Many transplantation groups have reported encouraging results using a number of reduced-intensity or non-myeloablative conditioning regimens for patients with hematological malignancies and solid tumors [6–17]. Different approaches have been used to conduct NST: The Jerusalem approach, the Houston approach, the Bethesda approach, the Genoa approach, the Boston approach, the Seattle approach, the Dresden approach, the London approach and the Mexican approach [32,33]; all these approaches address the immunosuppressive effect more than the myeloablative effect of the conditioning regimens.

The Mexican way to brake these dogmata

In 1999, we elected to employ a regimen to conduct NST, based in those employed in Jerusalem [7], Houston [6] and Genoa [34], introducing some changes with the main goal of decreasing the cost of the procedure. The salient changes of our approach are:

Use of cheapest and available drugs. Since both intravenous melphalan and anti-thymocyte globulin are expensive and unavailable in Mexico, we chose to use available and affordable drugs by means of the following scheme: Oral busulphan, 4 mg kg\(^{-1}\) on days \(-6\) and \(-5\); i.v. cyclophosphamide, 350 mg/m\(^2\) on days \(-4\), \(-3\) and \(-2\); i.v. fludarabine, 30 mg/m\(^2\) on days \(-4\), \(-3\) and \(-2\); oral cyclosporin A (CyA) 5 mg kg\(^{-1}\) was started on day \(-1\) and i.v. methotrexate 5 mg/m\(^2\) was delivered on days \(+1\), \(+3\), \(+5\) and \(+11\) [7,18,19].

Tailored number of apheresis sessions. We used initially three sessions of apheresis to obtain peripheral blood HSC from the donors [18], but we learned afterwards that, with the goal of obtaining between 1 and \(6 \times 10^6\) viable CD34 cells kg\(^{-1}\) of recipient’s body weight [12] we could cut down the number of sessions of apheresis to a median of two (range 1 to 4), thus diminishing costs of the procedures and of the disposable apheresis sets.

Elimination of prophylactic ganciclovir and intravenous IgG. Probably as a result of the reduced bone marrow damage during NST, the prompt recovery of both the hematopoiesis and immune function in this type of allografts and the use of peripheral blood, there is a very low prevalence of cytomegalovirus (CMV) disease despite a high prevalence of CMV infection in these individuals. We have faced no CMV-related deaths in patients given NST using our method [21] and have elected to eliminate the prophylactic use of both ganciclovir and intravenous IgG, thus reducing
costs; it is interesting that other NST schedules including anti-CD52 monoclonal antibody (Campath) are related to higher prevalences of CMV disease and mortality [21].

**Outpatient conduction.** Since the duration of both granulocytopenia and thrombocytopenia during NST is shorter than those during autologous stem cell transplants or during myeloablative chemotherapy, we elected to conduct NST on an outpatient basis provided certain conditions are fulfilled. Only patients asymptomatic, fully active, able to stay in their homes, with relatives or friends or in nearby-hotels, and with a fair educational level can be offered this program. Fundamental to the success of this approach is the availability of a 7 day-a-week clinic where medications and transfusions can be rapidly and efficiently provided [23,26,27].

**Reduced number of blood products transfusions.** Stemming also from the prompt recovery of the bone marrow, NST can be conducted in some instances without transfusion of blood products. In our experience, approximately one out of three individuals does not need red blood cells or platelets transfusions. The median of transfused red blood cells units is 6, range 0–19, whereas the median of platelet transfusion sessions was 2, range 0–5. Twenty percent of the patients given NST using our method do not require red blood cells nor platelet transfusions at all [25]. It is obvious that this policy results in decreases of both costs and risks derived from exposure to human blood derivatives.

**Reduced donor-lymphocyte infusions.** Donor lymphocyte infusions (DLI) are delivered only if the patients, on day 30, have not displayed either of the following. An evidence of partial or complete chimerism [22], GVHD or molecular remission of the malignancy. As a result of this policy, less than 10% of the patients need late DLI, thus diminishing costs as well.

**Results**

Using our method, we have conducted over 200 allografts in patients with different diseases: Chronic myelogenous leukemia (CML), acute myelogenous leukemia, acute lymphoblastic leukemia, myelodysplasia, thalassemia major, relapsed Hodgkin’s disease, Blackfan-Diamond syndrome, adrenoleukodystrophy, aplastic anemia and solid tumors. In the whole group, the median granulocyte recovery time to $0.5 \times 10^{9}/L$ was 13 days, whereas the median platelet recovery time to $20 \times 10^{9}/L$ was 12 days. Around one third of the patients did not need red blood cell transfusions and also one third did not need platelet transfusions. In about 80% of the cases, the procedure could be completed fully on an outpatient basis. Follow-up times range between 30 and 1500 days. Fifteen patients failed to engraft and recovered endogenous hemopoiesis; half of them developed acute GVHD, whereas 33% developed chronic GVHD. The median post-transplant survival (SV) has not been reached, whereas the 1500 day overall SV is 58%. The 100-day mortality was 18% and the transplant-related mortality was 24%. The best results of our program have been obtained in CML, whereas the worse in acute lymphoblastic leukemia; these differences may be related with the susceptibility of the malignancy to the graft versus tumor effect. It is now clear that certain neoplasias such as CML are very sensitive to this effect whereas ALL and other malignancies are less susceptible to this immune effect. In the total group of patients, the median cost of each NST procedure was 18 000 US dollars [20–27], a figure which contrasts with that informed from the US for conventional bone marrow transplantation, which is 300 000 US dollars [2]. As a result and an example, it is now clear that, using our method, it is cheaper to allograft an individual with CML than to provide treatment with imatinib mesilate for one year.

Within the group of patients with chronic myelogenous leukemia (CML), 21 have been published [23]: Eleven were grafted in chronic phase, six in blast phase and four in accelerated phase; the median age of the patients was 43 years, with a range of 20 to 61; ten individuals were above 45 years old. The median post-transplant survival of the patients is above 750 days, whereas the 750-day survival is 60%. Four of the six patients grafted in blast phase have died. Twelve patients (57%) developed acute GVHD and 12/17 (70%) developed grade I-II chronic GVHD. All the patients engrafted and achieved hematological remissions; in 15 individuals a molecular remission could be recorded. We have also grafted 21 children [21]; the median age of this group was 13 years. The median post-transplant overall survival of the children is above 1350 days, whereas the 34-month survival is 55%; 4/21 patients (19%) developed acute GVHD and 2/15 (13%) developed chronic GVHD. The 34-month survival of children with non-malignant diseases was 83%, whereas the 25-month survival of those with malignant disorders was 44% ($P < 0.01$) (Figure 3). The NST methods which we have chosen allows also allografting of umbilical blood cells [30,31].

In acute myelogenous leukemia (AML), we have grafted individuals who could have received conventional grafts: 25 allografts were prospectively given to 24 patients with AML, eligible for conventional allografting; two individuals had secondary forms of AML. The median age of the patients was 35 years, with a range of 12 to 56. All patients engrafted; median time to achieve an absolute neutrophil count
Recent advances in stem cell transplantation have revolutionized the treatment of hematologic malignancies and non-malignant hematopoietic disorders. The Mexican approach to conduct allogeneic stem cell transplantation, particularly in the context of aplastic anemia, has been one of the most exciting developments in the last five years [19]. However, NST should not be envisioned as an “easy way” to conduct allogeneic bone marrow transplantation [36–40]. Worldwide, NST is still a therapeutic modality that has been reserved for certain individuals: aged, debilitated or afflicted by other diseases. In some centers in México and in other developing countries, NST has been adopted as the conventional method to conduct bone marrow transplantation mainly because of its affordability. Consideration of costs should not be overlooked in any part of the world, but they are particularly critical in developing countries [15,41–46]. Eighty percent of children with cancer worldwide die of the illness because lifesaving treatments, such as HSC transplantation, are not available in under-developed countries [41–46]. In some developing countries, the cost of the “Mexican approach to conduct NST has been shown to be 15–20 times lower than that of a conventional allograft in developed countries.

The consequences of breaking dogmata

NST has been one of the most exciting developments in the treatment of hematologic malignancies in the last five years [19]; however NST should not be envisioned as an “easy way” to conduct allogeneic bone marrow transplantation [36–40]. Worldwide, NST is still a therapeutic modality that has been reserved for certain individuals: aged, debilitated or afflicted by other diseases. In some centers in México and in other developing countries, NST has been adopted as the conventional method to conduct bone marrow transplantation mainly because of its affordability. Consideration of costs should not be overlooked in any part of the world, but they are particularly critical in developing countries [15,41–46]: Eighty percent of children with cancer worldwide die of the illness because lifesaving treatments, such as HSC transplantation, are not available in under-developed countries [41–46]. In some developing countries, the cost of the “Mexican approach to conduct NST has been shown to be 15–20 times lower than that of a conventional allograft in developed countries.
The Matthew effect

A verse in the biblical book of Matthew reads: “Unto every one that hath shall be given... , but from him that hath not shall be taken away even that which he hath” supports the origin of the concept of “the Matthew effect”, described in a classic paper in Science by Robert K. Merton [47]; he noticed that in science, credit for a discovery or knowledge tends to go to the most famous researcher associated with it rather than to the most deserving one [48, 49]. C.N. R. Rao notes that “the Matthew effect” is not uncommon even for work done in advanced countries, but hurts a person in a developing country much more because he does research with great difficulty; sometimes it takes many years to complete the work and then get no credit is very disappointing and frustrating [48]. The “Mexican approach” to conduct bone marrow transplantation has not escaped the “Matthew effect”: the method, which has been used in several countries, and is endowed with several advantages over other procedures to conduct NST, is frequently overlooked in reviews or papers dealing with the topic [36].

Conclusions

Most patients who have been allografted in México and other developing countries using the “Mexican approach” to conduct NST could not have afforded the cost of a conventional or more expensive stem cell transplant. Prospective studies will define if NST will eventually replace conventional stem cell grafting [45, 46, 52]; however, very frequently in developing countries, the decision for a given patient is not between offering either a conventional bone marrow transplant or a NST; the decision has to be made between NST or no other effective treatment. Because of its cost, NST could be considered as an early treatment option in countries where limited resources currently prevent usual allogeneic bone marrow transplantation; role-definition and appropriate timing for this therapeutic approach in patients are required. We are learning which malignancies are more susceptible to the graft versus tumor effect, one of the main effects of NST in addition to the replacement of the bone marrow cells, and as a consequence, we are also learning in which malignancies NST is more useful. The “Mexican approach” to conduct NST has been shown to be effective for allografting individuals with malignant and non-malignant conditions. Despite the fact that most studies with reduced intensity conditioning have a relatively short follow up, there is information which indicates that the procedure is related with a lower prevalence and severity of GVHD [53], and with a similar efficacy as that of conventional allografting. Since this method is more feasible and affordable for patients and physicians in developing countries, the number of allografts in these places has increased substantially, as well as the publications related to bone marrow transplantation stemming from places where this therapeutic maneuver was considered as unaffordable previous to the development of this technology [46].

Despite the fact that allografting with reduced intensity conditioning may be related with several disadvantages such as mixed chimerism and relapse of the malignancy, braking several dogmata related to bone marrow allografting has resulted not only in the progress of knowledge, but also in the accessibility of many patients to sophisticated therapeutic actions, in some cases, the only true curative option for these individuals. Braking dogmata has been proved to be worthwhile in the case of HSC transplantation.

References


