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REVIEW

Hematopoietic stem cell transplantation in Egypt

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Hematopoietic SCT is now an established treatment modality with definitive indications for many hematological disorders. However, this line of treatment requires tremendous resources, and it becomes increasingly difficult for transplanters practicing in the developing world to reconcile the difference between what is possible and what is available. On the basis of 18 years of experience and more than 1300 transplants, this article will focus on special issues, which we think are important for hematopoietic SCT practices in developing countries, taking the program in Egypt as an example that may be applicable to other countries in the developing world. The SCT program in Egypt started in 1989 on a narrow scale. In 1997, the transplant rate increased dramatically with the opening of the SCT unit at the Nasser Institute. Our team is registered in the Center for International Blood and Marrow Transplant Research. The total number of transplants performed till June 2007 is 1362; 80% of the cases are allogeneic and 20% autologous. There are seven other centers in Egypt performing mainly autologous transplants.
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Introduction

Hematopoietic SCT is now an established treatment modality with definitive indications for many hematological disorders. However, this line of treatment requires tremendous resources, and it becomes increasingly difficult for transplanters practicing in the developing world to reconcile the difference between what is possible and what is available.

On the basis of 18 years of experience and more than 1300 transplants, this chapter will focus on special issues, which we think are important for hematopoietic SCT practices in developing countries, taking the program in Egypt as an example that may be applicable to other countries in the developing world.

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Total population and transplant centers

The total population in Egypt in 2007 is 75 million with only eight transplant centers performing about 210 transplants per year. The biggest center is at the Nasser Institute, which contains 20 cabins equipped with high efficiency particulate air (HEPA) filters, positive pressure and vertical laminar air flow. We perform around 170 transplants per year; 80% of the transplants are allogeneic and 20% autologous. The other seven centers (two of them under construction) have 32 rooms equipped for SCT and practice mainly autologous transplants. The transplant rate in Egypt is about 2.8 transplants per million, compared to an average of 30–42 transplants per million in developed countries.

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Lack of matched unrelated donor transplants

Approximately 25–30% of patients who have siblings can be expected to have an HLA genotypically identical donor. This figure is somewhat higher, reaching up to 40% in our community owing to larger family size. The chance of finding a match depends on several factors, including the size of the panel, the frequency of a specific HLA type in the population and the ethnic background of the donor and recipient. It is a well-known fact that less than 3% of donors listed in international registries are of oriental origin, which makes it difficult to find a match for our patients, and this demonstrates how urgent it is to set up a donor registry for oriental populations.[1]

Stem cell source

For many years, the pendulum has been swinging gently toward PBSCs in place of marrow stem cells for clinical practice. In most cases, engraftment of neutrophils and platelets appeared to be more rapid when compared to marrow-derived stem cells. The incidence of severe GVHD was not increased.[2]

For this purpose, a study was conducted at National Cancer Institute, Cairo University in the period between January 1995 and March 1997 comparing allogeneic PBSC transplants with conventional BMT as regards engraftment, incidence of GVHD and cost. This study clearly demonstrated that allogeneic PBSC transplants show more rapid engraftment, judged by neutrophil and platelet recovery and less days of neutropenic fever, leading to shorter hospital stays and less antibiotic and antifungal consumption. The incidence of acute GVHD in the PBSC transplant group was not higher.[3]

In our community, donors definitely appreciate the option of avoiding general anesthesia, and, indeed, leukapharesis may be safer than anesthesia in a normal person. So, our program was shifted totally from BMT to PBSC transplants during the last 10 years. Donor follow-up during this period did not show any problems.

Distribution of disease entities

CML used to constitute about 31% of the allogeneic transplants per year; however, in the era of imatinib, this figure decreased to 20% as we still offer transplants to young *de novo* cases of CML in the chronic phase owing to financial reasons. The cost is estimated to be about 59 million US dollars per year to treat all patients with imatinib, which is beyond our capabilities.

AML and ALL constitute 25 and 12%, respectively, of yearly transplants, several aplastic anemia 21%, β-thalassemia 7%, myelodysplastic syndrome 7% and other diseases 5% (Fanconi anemia, immune deficiency disorders).

Autologous transplants are performed mainly for lymphomas and multiple myeloma.

Allogeneic SCT for β-thalassemia major

β-thalassemia is the most common hereditary hemolytic anemia in Egypt, with a carrier state varying between 6 and 10%.[4]

Considering the chronicity of the disease, the huge psychological, social and financial burden on both the patient and his family, as well as the different complications associated with the conventional therapy available,[5,6] it becomes clear that we were interested in initiating a transplant program in Egypt for this entity in an effort to offer a radical cure or at least a stable chimeric state that makes it possible to avoid regular blood transfusion and chelation. It is obvious that the strategy for thalassemia in the developing world should be primarily preventive. However, there is no doubt that in a country like Egypt, the economic advantage of SCT for thalassemia is compelling. The major reason for transplant failure is graft rejection due to previous poly transfusions. As most of our patients are referred relatively late to the transplant center owing to logistic and administrative problems, we had to look for an innovative approach for such candidates. In an attempt to overcome the problem of graft rejection, we have added antithymocyte globulin to the conditioning regimen to increase immunosuppression of recipients, and we also shifted our program from allogeneic BMT to allogeneic PBSC to take advantage of the higher T-cell content of PBSC grafts, which in turn is known to have a graft-letting effect.[7,8]

With these changes, the overall and disease-free survival rates for β-thalassemia major patients post allogeneic SCT at our center are 90 and 85%, respectively, at a median follow-up of 3 years (61 patients) (Figure 1).

New protocols

We started to implement new protocols for conditioning severe aplastic anemia by using Cy 50 mg/kg for 4 days (D-5 to D-2) and fludarabine (Flu) as 30 mg/m^2 for 3 days D-3 to D-1 (Flu/Cy) instead of the standard Cy/ATG, and our preliminary results with the first 17 cases showed a disease-free survival of about 88% with lower cost and toxicity than the standard Cy/ATG protocol.[9] The number now reached 62 cases with a median follow-up of 2 years; the disease-free survival is 82% compared to 68% in the Cy/ATG protocol ($P = 0.04$) (Figure 2).

Non-myeloablative transplants are used for some diseases, such as myelodysplastic syndrome, and for medically infirm patients. We were using the Seattle protocol Flu 30 mg/m^2 for 3 days (D-4 to D-2) and TBI 2 Gy on day 1 (Flu/TBI), and our preliminary results for the first 54 patients showed a disease-free survival of 47%.[10]

Then we shifted our conditioning in non-myeloablative transplants to Flu 30 mg/m^2 for 5 days (D-8 to D-4) and melphalan 70 mg/m^2 for 2 days (D-3 and D-2) (Flu/Melph) protocol with promising results for our preliminary results.

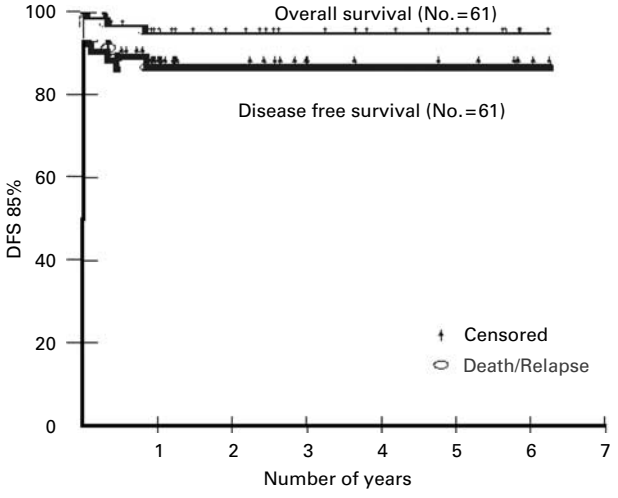

Figure 1 Allogeneic SCT for β-thalassemia major.

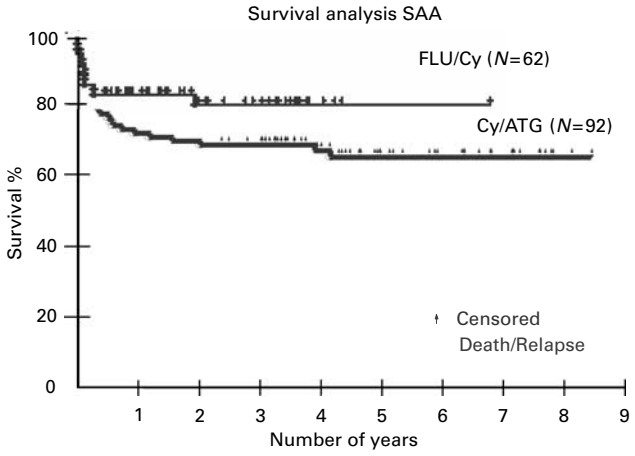

Figure 2 Severe aplastic anemia disease-free survival analysis.

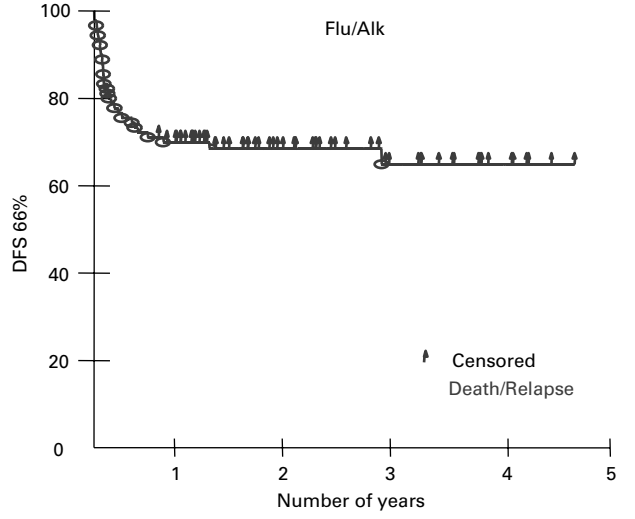

Figure 3 Reduced-intensity transplant.

We transplanted 30 patients (23 myelodysplastic syndrome, three AML, one CML, one non-Hodgkin lymphoma, one multiple myeloma (MM), one CLL), and with a median follow-up of 3 years the disease-free survival was 66% (Figure 3).

Also, we underwent modifications of the standard Bu/Cy protocol by applying spacing (48-h rest period) between Bu and Cy. We randomized 40 patients to receive the spaced protocol versus the unspaced one (20 in each arm). Follow-up of these patients for the incidence of veno-occlusive disease (VOD) and hemorrhagic cystitis showed 5 and 0% for VOD and hemorrhagic cystitis as compared to 25 and 35%, respectively (Figure 4).

Another new conditioning regimen is the Flu/Bu, Flu as 30 mg/m^2 for 5 days (D-10 to D-9, then D-4 to D-2) and Bu 16 mg/m^2 divided over 4 days (D-8 to D-5), which is used for myeloid malignancies with excellent results of engraftment kinetics and reduced toxicity profile, especially VOD and hemorrhagic cystitis. Our preliminary results of the first 36 cases showed a disease-free survival of 81%,

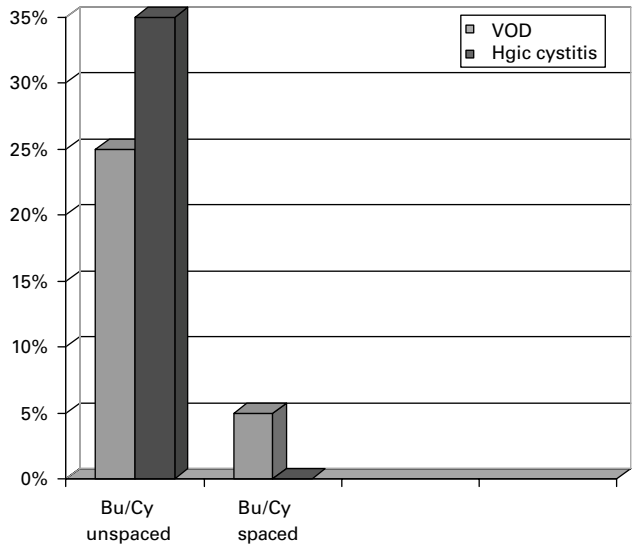

Figure 4 Incidence of veno-occlusive disease and hemorrhagic cystitis.

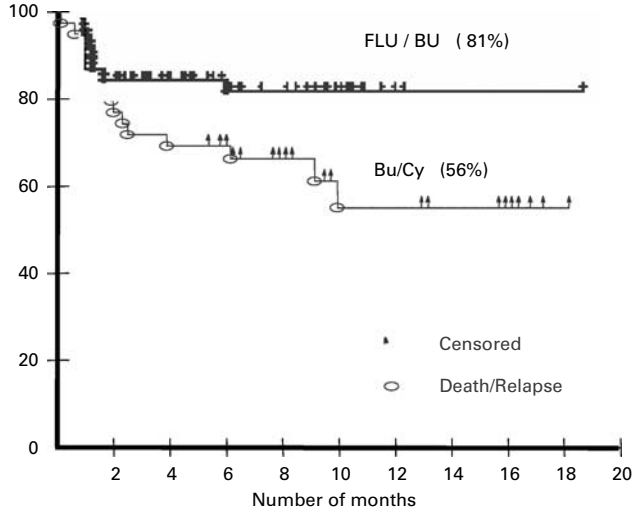

Figure 5 Disease-free survival analysis.

compared to 56% for a historical control group using matched pair analysis for patients who received the Bu/Cy protocol ($P = 0.02$) (Figure 5).

Liver toxicity and veno-occlusive disease

The development of hepatic complications in allogeneic BMT occurs mainly secondary to toxicity from cytoreductive regimens, GVHD, VOD and infections.[11]

In Egypt, two problems further complicate the situation.

Schistosomiasis

Schistosomiasis is one of 'the great neglected diseases of mankind,' being primarily a problem of the developing world. Among our first 89 allogeneic bone marrow

transplants, we have realized that all patients who had previous contact with schistosomiasis and showed clinically silent mild periportal fibrosis of the liver have developed severe fatal VOD in spite of normal pretransplant liver functions and absence of portal hypertension. The relative risk of developing VOD was calculated to be 17-fold higher, compared to normal recipients, and consequently, for many years, schistosomal periportal fibrosis was regarded as a relative contraindication to transplant in our center.[12]

Hepatitis

The population of Egypt has a heavy burden of liver diseases. The overall prevalence of antibody to hepatitis C virus in the general population is around 15–20%. Patients who are PCR-positive for hepatitis C virus are estimated to be around 8%. For hepatitis B, the incidence of exposed patients who are HBVcAb-positive is around 25%, whereas the HBsAg carrier rate is 3%.[13–15] Pretransplant hepatitis C and B viral infections are reported to be independent risk factors for VOD.[16]

However, patients infected with hepatitis B or C virus should not be excluded from transplantation programs. The decision to proceed to transplantation must balance the absolute risk of death from VOD against risks from the underlying disease.[17]

Recipients who are positive for any hepatitis B virus marker are treated with lamivudine therapy, and hepatitis C virus-positive recipients are treated with interferon-α in combination with ribavirin.

We hope that this policy will decrease the incidence of hepatic toxicity and VOD among our patients, as the preliminary data are very promising.[18]

Cost of the transplant in Egypt

The average cost of the transplant in Egypt is about 15 000 USD, and it is totally sponsored by medical insurance or the Ministry of Health.

Follow-up and socioeconomic problems

In the post-transplant period, follow-up and strict hygienic conditions at home are of supreme importance. Unfortunately, the follow-up dropout rate is relatively high among our patients (20%). Many patients also find it difficult to comply with post-transplant hygienic rules, even if the treatment is provided free of cost. But, this is the milieu in which hematopoietic SCT is practiced in the developing world, where the state can provide some help, but the socioeconomic status of the individual plays a major role in the success of the treatment. In our opinion, there is no doubt that developing countries should have the expertise to offer 'state of the art' treatment, including hematopoietic SCT. This will provide treatment locally at a much lower cost than abroad, thus saving valuable foreign currency and, most important, improving the quality of services in tertiary referral centers.

However, it is still clear that in the developing world, food, sanitation, immunization, population control and prevention of communicable diseases are the most important public health priorities where low cost inputs yield high dividends.[19]

Conflict of interest

None of the authors declared any financial interests.

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