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Review Article

Hematopoietic Stem Cell Transplantation in Egypt: *Challenges and Opportunities*

Mahmoud H.K.[1], Fathy G.M.[2], Elhaddad A.[1], Fahmy O.A.[3], Abdel-Mooti M.[1], Abdelfattah R.[1] and Bokhary M.[2].

[1] National Cancer Institute, Hematology and Bone Marrow Transplantation unit.
[2] Nasser Institute Hospital for research and treatment, Hematology and Bone Marrow Transplantation unit.
[3] Kasr Alainy, faculty of medicine, Cairo University, Hematology and Bone Marrow Transplantation unit.

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Abstract. Hematopoietic stem cell transplantation (HSCT) is now an established treatment modality with definitive indications for many hematological disorders. However, HSCT requires tremendous resources, and it is increasingly challenging for transplantation experts to practice in the developing world and to reach a compromise between requirements and available resources. Based on 30 years of experience and 4256 transplants (60% allogeneic and 40% autologous), this article focuses on the challenges our HSCT program encountered since it started in 1989 and what opportunities we see to solve them. Since 1997, HSCT procedures increased dramatically with the opening of 15 HSCT units distributed all over Egypt.

Keywords: HSCT rate; Challenges; Opportunities; Donor availability; HCV; GVHD.

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Correspondence to: Mahmoud Bokhary. Tel.: +97338248021. E-mail: Mahmoud.bokhary@gmail.com

Introduction. Hematopoietic stem cell transplantation (HSCT) is currently considered the standard of care for many hematological disorders.[1] However, this treatment modality requires tremendous resources. Performing HSCT procedures in developing countries (where many patients have low socioeconomic standards) usually encounters financial, ethical, technological, administrative, and medico-legal challenges. There is a constant need to reach a compromise between requirements and available resources.[2]

Thalassemia and sickle cell disease/anemia constitute the most common inherited recessive disorders associated with consanguinity, which is a common phenomenon in Egypt.[3] Based on 30 years of experience and 4256 transplants, as shown in **table 1**, this article is an update of our previously reported results published in 2008 and focuses on the challenges and opportunities that continuously face our HSCT program and how we try to solve them.[4]

Challenges facing hematopoietic stem cell transplantation in Egypt:

A. Offering transplant to every indicated patient
B. Sources of stem cells
C. Availability of donors
D. Socio-economic challenges
E. Hepatitis
F. Genetic diseases
G. GVHD management
H. Minimal residual disease (MRD)
I. New drugs

A. Offering transplant to every indicated patient.

The population of Egypt in 2020 exceeded 100 million.

There are fifteen transplant centers, and the transplant rate/million is 8.4, which is considerably higher than the number we reported previously in 2008, where the transplant rate/million was 2.8.[4] We are still

Table 1. Patients underwent allogenic and autologous stem cell transplantation.

	ALLO	AUTO	TOTAL
YEAR 1997 (May)	36	11	47
YEAR 1998	78	10	88
YEAR 1999	80	26	106
YEAR 2000	86	3	89
YEAR 2001	94	6	100
YEAR 2002	97	23	120
YEAR 2003	103	27	130
YEAR 2004	128	23	151
YEAR 2005	142	19	161
YEAR 2006	131	33	164
YEAR 2007	113	53	166
YEAR 2008	110	47	157
YEAR 2009	124	105	229
YEAR 2010	131	115	246
YEAR 2011	144	72	216
YEAR 2012	165	137	302
YEAR 2013	158	174	332
YEAR 2014	146	184	330
YEAR 2015	161	198	359
YEAR 2016	175	213	388
YEAR 2017	170	205	375
TOTAL	**2572** (60%)	**1684** (40%)	**4256**

far away from western standards, where transplant rates are between 36-40 /million.[5]

B. Stem Cell Sources.

Stem cells obtained by bone marrow harvesting were the only source until the late-80s when peripheral blood stem cells (PBSCs) collection became available at our centers. We were one of the first teams who almost entirely changed the source of stem cells from BMSCs to PBSCs. In a paper published by our group in 1999 comparing PBSCT to BMSCs, PBSCT was found to be associated with faster hematopoietic recovery, and the incidence of aGVHD did not exceed that seen with BMSCs.[6] This change in stem cell source dramatically improved the motivation of donors by avoiding hospital stays and painful collection procedures.

C. Availability of donors.

Approximately 25–30% of patients who have siblings are expected to have an HLA identical donor. This figure approximates 40% among the Egyptian population owing to the larger size of the families. The probability of finding a matched donor depends on several factors, among which are the panel size, frequency of a specific HLA type in the population, and ethnic groups of both the donor and the recipient. Less than 3% of donors listed in the international registries are of oriental origin, which further complicates the process of finding matched donors for our patients.[7] Egypt does not possess a local donor registry. This obstacle has been mitigated with the initiation of haploidentical transplants at our centers.[8] Since June 2015, our team has performed 43 haploidentical transplants, as shown in **table 2**. Stem cell sources were either PBSCs or BMSCs. PTCy prophylaxis, together with cyclosporine, was administered to all patients in addition to mycophenolate mofetil in selected cases.[9,10]

Table 2. Number of patients underwent Haploidentical HSCT in our center.

Malignant	No=32	Benign	No=11
AML	12	SCID	3
ALL	12	OP	2
CML	4	SAA	1
NHL	2	PRCA	1
MDS	2	LAD	1
		FA	1
		BTM	1
		HLH	1

D. Socio-economic challenges.

Healthcare systems in Egypt: The Healthcare system in Egypt consists of both public parastatal and private sectors. Public health coverage is provided through the Ministry of Health, which operates a series of free health care facilities. There are two major parastatal organizations, the Health Insurance Organization (HIO), and the Curative Care Organization (CCO). Health Insurance Organization covers disabled individuals, graduates, employees, and widows. Curative Care Organization works in different governorates, and contracts for care delivery with other organizations. Private insurance plans are also available, as well as a network of private health care services and health facilities.

Financial Constraints: The cost of sophisticated molecular techniques and newer drugs is sometimes limiting. However, developing countries must have the expertise to offer "state of the art" treatment strategies, including HSCT. Such an approach will provide a potentially curative treatment locally at a much lower cost than in western countries. A stem cell transplantation (SCT) in Egypt cost ranges between 11,000 to 17,000 US dollars depending on the type of transplant (autologous, allogeneic, or haploidentical). The cost of SCT procedures in our centers is no more than 10% of the cost in western countries.[11] The post-transplant follow-up period further increases the socio-

economic burden on our patients. That is because strict hygienic conditions at home are paramount, and a considerable proportion of patients find it challenging to comply with hygiene recommendations, even if the treatment is provided for free.[12] Moreover, the follow-up dropout rate is relatively high among Egyptian patients (10%), and this is because most transplant units are located in the capital and major cities, while the vast majority of patients reside far away.

E. Hepatitis.

In Egypt, the prevalence of Hepatitis B virus (HBV) infection among adults aged 15-59 years is 1.4%.[13] More seriously, 15% of the population is seropositive for Hepatitis C virus (HCV). The incidence rate of HCV is 2.4 per 1000 person-year. Ten percent of our HCV patients are chronically infected, and 90% of them harbor genotype 4 of the virus.[14,15] HBV infection or reactivation in patients undergoing chemotherapy or HSCT may progress to hepatic failure, while this is much less in HCV infection.[16] Antiviral prophylaxis is beneficial to HBsAg and anti-HBc positive patients since the incidence of HBV reactivation in patients not receiving antiviral prophylaxis has been reported to be 4.1%.[17,18]

Lamivudine or third-generation antivirals (Entecavir or Tenofovir) are the most commonly used for HBV suppression. Entecavir and tenofovir are preferred over lamivudine due to the possibility of lamivudine resistance. Prophylaxis is started at least one week prior to or in concordance with the conditioning regimen of HSCT, and suppression continues to 12-24 months after the transplantation. The inability to detect HBV DNA and HBsAg negativity in addition to the appearance of anti-HBs antibodies is an indicator of HBV resolution and allows for discontinuation of antiviral therapy safely.[19]

Vaccination against HBV should be offered to patients undergoing auto- or allo-HSCT before starting the conditioning regimen.[17]

Currently, it is recommended to treat hepatitis C virus infection prior to HSCT. However, the treatment of HCV concurrently with HSCT may be a better alternative for selected patients when it is not safe to delay transplant.[20] The new direct-acting antivirals (DAAs) for suppression and treatment of active HCV infection are currently available in Egypt with acceptable prices and are covered by third-party payers.

In 2004, our team demonstrated that the high prevalence of HCV and HBV among our patients is strongly associated with hepatic GVHD and SOS. Hence, early antiviral therapy was advised in an attempt to delay and ameliorate liver disease progression.[21]

F. Genetic diseases.

Thalassemia: Thalassemia is the most common hereditary hemoglobinopathy in Egypt. There are 10,000 registered cases in addition to more than 20,000 non-registered cases, 95% of whom are beta-thalassemia major (BTM). The carrier state is between 9 and 11%.[22] Challenges with thalassemia are the lack of prenatal diagnosis, inadequate chelation therapy before transplant, and siblings are frequently affected by the disease. Consequently, patients present with high Pesaro risk scores, high prevalence of (HCV and HBV) (~75%), and the referral to HSCT clinics is usually delayed. As a sequel to the factors above, delayed engraftment frequently occurs.[21] Our team performed 201 cases of BTM, and after a median follow-up period of 12 years, the OS was 82.4% **(Figure 1)**.

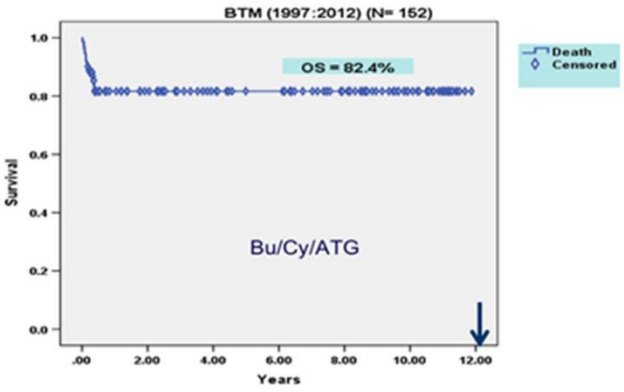

Figure 1. Overall survival of our 201 BTM cases after a median follow-up period of 12 years.

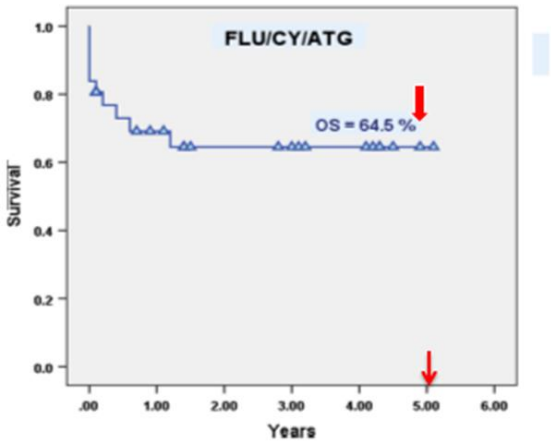

Figure 2. Overall survival of our 63 FA patients after six years of follow up.

Fanconi Anemia (FA): There is a strong association of parental consanguinity with Fanconi anemia. As a result, siblings are frequently affected by the disease.[23] As in other types of hereditary anemia, diagnosis of FA and detecting its associated mutations is usually late, and patients are referred to HSCT at older ages. FA is the third indication of allogeneic-HSCT for non-malignant hematological disorders in Egypt after hemoglobinopathies and idiopathic aplastic anemia. Our team performed 63 transplants for FA, and the overall survival of our patients was 64.5% (**Figure 2)**

after six years of follow up.[24,25]

G. Challenges facing GVHD management in Egypt.
Corticosteroids with or without a calcineurin inhibitor (CI) is the first line of treatment of acute and chronic GVHD. Less than half of patients respond to corticosteroids depending on the severity of the disease.[26,27] Different therapeutic options for steroid-refractory acute GVHD are available, including rabbit/equine antithymocyte globulin (ATG), alemtuzumab (Campath), interleukin-2 receptor antibodies as daclizumab and basiliximab, anti-TNFα drugs (such as infliximab), and extracorporeal photopheresis (ECP). At our centers, we started to use novel drugs for the management of cGVHD, including bortezomib, ruxolitinib, and ibrutinib.[28] However, many other drugs with reported efficacy in this setting are not readily available in Egypt, and the main challenge to the use of such novel approaches is the price, which is usually beyond the capability of many patients. Additionally, it is not yet covered by third-party payers. We started implementing PTCy as a graft-versus-host disease prophylaxis in HLA-matched HSCT in 52 cases. Pre-transplant conditioning regimens used were either FLU/BU (160 mg/m^2 of Fludarabine, and 16 mg/kg oral Busulfan both of which were divided over four days), or FLU/CY (120 mg/m^2 FLU divided over four days, and 25 mg/kg/d CY for four days).[29] Cyclophosphamide was administered at a dose of 50 mg/kg per day on days 3 and 4 post-transplantation, and cyclosporine was started on day 5. The cumulative 1-year incidence of cGVHD was 13.4%. Incidence of aGVHD grades I-II and III-IV were 3.8% and 11.5%, respectively. Overall survival (OS) for the total number of cases at one year was 73.1%, including both benign and malignant diseases. Disease-free survival (DFS) was 69.5%, as depicted in **Figure 3**. Considering our AML cases separately (29 cases), it is noteworthy that the relapse rate was not passively affected, as the OS was 70%, and the DFS was 66.7%, as shown in **Figure 4. O**ur results support the use of PTCy for HLA-matched sibling donor PBSCT due to the significant reduction in the cGVHD rate.[30]

H. Minimal residual disease (MRD).
Evaluation of morphologic remission only is not sufficient for risk stratification of a disease and cannot be relied upon for the determination of the risk of relapse.[31] The detection of minimal residual disease (MRD) after conventional chemotherapy is currently the most important tool in predicting the outcome and prognosis of patients with multiple hematological malignancies.[31,32] In Egypt, MRD is evaluated almost exclusively for acute lymphoblastic leukemia during and after induction therapy. The most common techniques utilized to detect MRD are the multicolor flow cytometry and quantitative polymerase chain reaction (PCR). Next-Generation Sequencing (NGS) is expected to improve risk stratification further using the MRD concept.[33] In our country, the MRD mentioned above tools are available. However, their cost is the main challenge facing their routine use. Multi-parametric flow and PCR are the most utilized tools with an acceptable cost, while NGS is still rarely ordered due to its high cost and non-availability in many of our centers.

I. New drugs.
Antifungals: The evolution of various diagnostic and therapeutic alternatives for invasive fungal infections led to better control of such a problem. However, in our country, the implementation of such strategies (either diagnostic or therapeutic) is limited due to

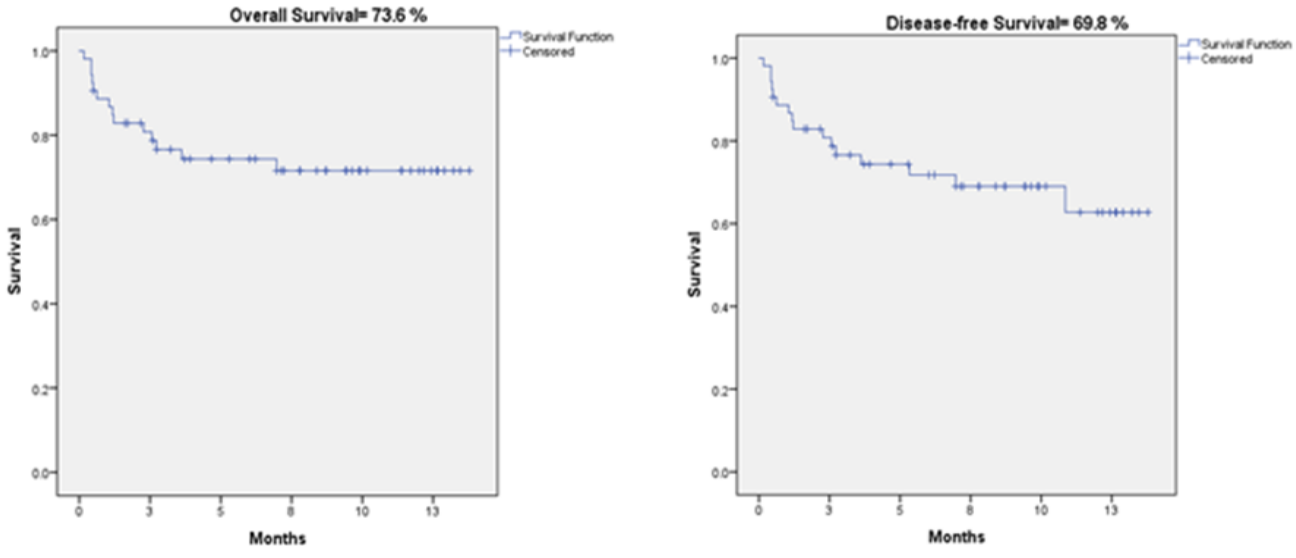

Figure 3. The use of PTCY in prophylaxis of malignant and non-malignant disorders receiving HLA-matched transplants.

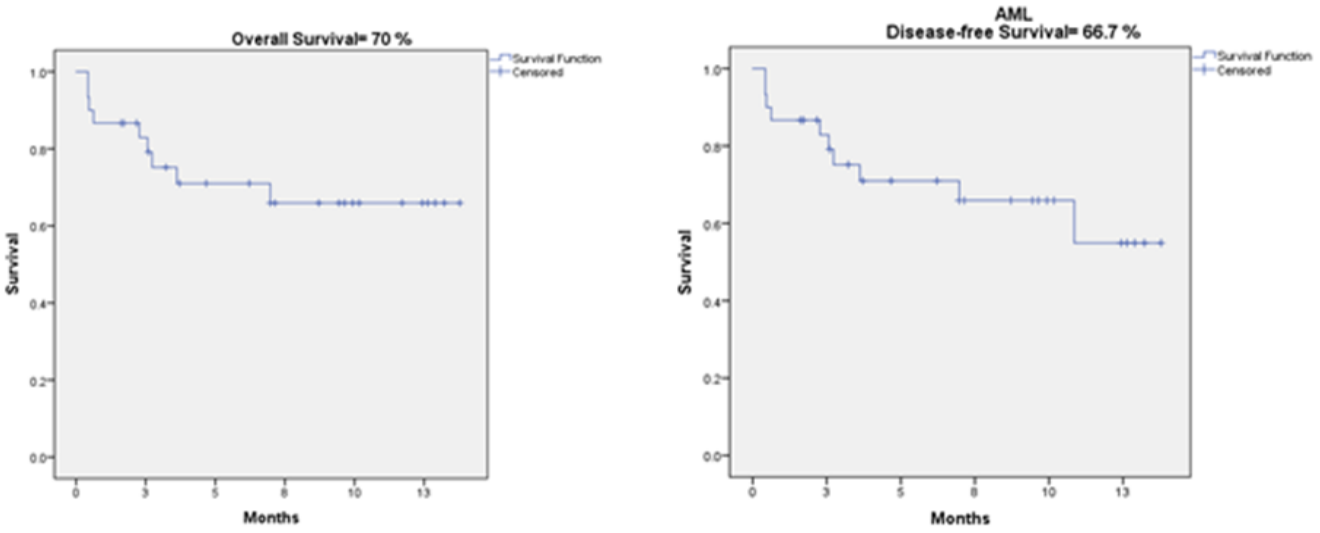

Figure 4. The use of PTCY in prophylaxis of 29 AML cases receiving HLA-matched transplants.

financial and logistic issues. Posaconazole is recommended for antifungal prophylaxis in HSCT patients suffering GVHD,[34] but due to its high cost, we usually use voriconazole. Our primary antifungal prophylaxis is still fluconazole.[35]

Diagnostic tools with considerable sensitivity and specificity for most of the commonly known invasive fungal infections are now available (Antigen detection, Beta-d-glucan, Galactomannan, and PCR). Such tools may potentially help to improve the prognosis of invasive fungal infections through earlier detection and commencing treatment early. However, the implementation of these new rapid diagnostic tests may be hindered by cost and infrastructure problems.

Eculizumab: Transplant- related thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are associated with transplant-related mortality in allogeneic HSCT patients. Previously, the majority of patients developed end-stage renal disease with low chances of survival. Eculizumab, a recombinant humanized monoclonal antibody against the complement protein C5, was found to improve the outcome of this condition, mainly if complement activation is the cause.[36] Unfortunately, Eculizumab is not yet available in Egypt. Supportive measures are the only interventions available for the treatment of TTP and HUS in our centers.

Defibrotide: Sinusoidal Obstruction Syndrome (SOS) is a life-threatening complication of HSCT.[37] Mortality in patients with SOS multi-organ dysfunction may exceed 80% even with supportive measures. Defibrotide, a polydisperse oligonucleotide with local antithrombotic, anti-ischemic, and anti-inflammatory activity when administered to patients with clinical SOS, is associated with improved survival rates of 41% in patients with multi-organ failure and 70% in patients without multi-organ failure.[38] The mean incidence of SOS in our patients with autologous and allogeneic HSCTs is 7% and 10%, respectively. Unfortunately, Defibrotide is not available in Egypt. Supportive measures (including fluid restriction, plasma expanders, and diuretics) are the only interventions available for the treatment of SOS in our centers.

Antivirals for CMV: Cytomegalovirus (CMV) viremia or disease is one of the most common complications of allogeneic HSCT. The first line of treatment for CMV viremia is gancyclovir or valganciclovir,[39,40] and both agents are available in Egypt. Their most commonly reported adverse event is myelosuppression, and in some cases, resistance may occur.[41] Second-line drugs such as foscarnet or cidofovir, as well as the newer antivirals, including terminase inhibitors (letermovir) and direct kinase inhibitors (maribavir), are not yet available in our country.[42] The use of CMV-specific T-cell therapy is also not available.

Immunization post-HSCT. Assuring that the patients' vaccination status is up to date per vaccination schedule is a significant challenge in our country, mainly due to cost and difficulties in counseling patients regarding the schedules, administration, adverse effects, and periodically monitoring titer levels. Post-HSCT, patients' humoral immunity is impaired, and a considerable decline in titers of vaccine-preventable diseases takes place.[43]

In our centers, it is standard practice to revaccinate patients after transplantation, usually starting after one year so that humoral immune reconstitution has fully taken place.

Anti-infectious Prophylaxis. The increasing incidence of multidrug-resistant gram-negative bacteria (MDRGN bacteria) is one of the most significant challenges we currently face in our centers. Antimicrobial options are becoming scarce, and success rates of eradicating infections are decreasing steadily over time.[44] In response to the heightened incidence of MDRGN isolates, our group started adopting institution-specific strategies based on local susceptibility data (biannual antibiogram). Implementing institution-specific strategies has improved response rates to MDRGN isolates and considerably decreased number of days on broad-spectrum antimicrobials and consequently opportunistic fungal infections, adverse events, drug interactions, and selection pressure.

Pneumocystis Jirovecii Pneumonia (PJP). Diagnosing PJP in our centers is complicated and highly based on clinical experience and imaging studies (chest CT scans). The definitive way to diagnose PJP is with sputum PCR. Other methods include sputum direct fluorescent antibody (DFA) and serum Beta-D-Glucan.[45] The tests mentioned above are not available in our country. Cotrimoxazole is used for PJP prophylaxis and treatment in our centers.

Conclusions. HSCT centers in Egypt face many challenges not only financial but also social and technical ones. There is an urgent need to improve techniques of genetic testing, new anti-GvHD medications as well as the availability of newer antimicrobial, antifungal, and antiviral drugs.

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