Stem cell transplantation in hematological disorders

A developing country experience-impact of cost considerations

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ABSTRACT

الأهداف: لوصف تجربتنا في برنامج زراعة نخاع العظم في وحدة زرع النخاع بكلية الطب – جامعة عين شمس.

الطريقة: تم نقل الخلايا الجذعية من الدم المحيطي لستة عشر مريضاً في وحدة زرع النخاع بكلية الطب – جامعة عين شمس – القاهرة – مصر، خلال الفترة مابين مارس 2005م وحتى يناير 2008م.

النتائج: تمت عملية الزراعة لـ 16 مريضاً متوسط أعمارهم كان 25 عاماً. كانت دواعي الزراعة هي: سرطان الدم النقوي المزمن، فشل النخاع العظمى، سرطان الدم الابيضاضي الحاد، سرطان الدم النقوي الحاد، والأورام الليمفاوية. سبع من المتبرعين و ستة من المرضى تبين سابق أصابتهم بفيروس سيتوميجالو (IgG)، الأجسام المضادة (Ab) قبل عملية الزرع. كما تبين أن أثنين من المتبرعين و أثنين من المرضى قد سبق وأن أصيبوا بالتهاب الكبد الوبائي – ب قبل الزرع، ولكن لم يكتشف الفيروس لديهم بالدم. لم تثبت إصابة أي من المتبرعين أو المرضى بالتهاب الكبد الوبائي – ج قبل الزرع. أصيب ثلاثة من المرضى يتفاعل الرقعة الحاد ضد المضيف (GVHD)، بينما أصيب خمسة بالنوع (GVHD) المزمن. كان السبب الرئيسي في وفاة أثنين من المرضى هو ارتجاع السرطان، وفشل النخاع العظمى في مريض واحد. مازال 13 مريض على قيد الحياة بدون ارتجاع المرض بعد متوسط متابعة 20 شهرا.

خاتمة: على الرغم من حداثة وحدة زرع النخاع في جامعة عين شمس، إلا أن نتائجنا تقارن بنتائج المراكز في الدول الغربية حيث تتكلف الزراعة هناك حوالى250,000 دولار.

Objectives: To describe the experience in setting up a bone marrow transplant program at Ain Shams University, Cairo, Egypt.

Methods: Sixteen patients were transplanted at Ain Shams University Bone Marrow Transplantation unit from March 2005 to January 2008.

Results: Sixteen patients were transplanted with a median age of 25 years. Indications for transplantation were chronic myeloid leukemia, acute myeloid leukemia, aplastic anemia, acute lymphoblastic leukemia, and aggressive lymphoma. Seven donors and 6 patients were positive for cytomegalovirus immunoglobulin G (IgG) antibody (Ab) pretransplant. Only one patient was positive for toxoplasma IgG Ab and another had a high titre for toxoplasma IgM Ab pretransplant. Two donors and 2 recipients were positive for hepatitis B antibody markers; however, none were positive for hepatitis B virus DNA by polymerase chain reaction (PCR). None of the patients or donors were positive for hepatitis C virus via PCR pre-transplant. Acute graft versus host disease (GVHD) was seen in 3 patients, while chronic GVHD was seen in 5 patients. Primary cause of death was recurrence in 2 patients and graft failure in one patient. Thirteen are alive and disease free with a median follow-up of 20 months.

Conclusion: Although our unit is a relatively new unit, these results are comparable to those achieved in the Western world and cost a mean of US$250,000.

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Human stem cell transplantation (HSCT) is undoubtedly one of the most important medical advances in the second half of the 20th century. Worldwide, approximately 30,000-40,000 transplants are performed yearly, and the number continues to increase by 10-20% each year. More than 20,000 people have now survived 5 years or longer after HSCT.[1] Currently, the major sources of stem cells for transplantation include bone marrow, peripheral blood, and cord blood.[2] Traditionally it has been used to treat hematological diseases as thalassemia, aplastic anemia, acute leukemia, and lymphoproliferative diseases.[3,4] Indications for transplantation continue to expand. Work that was carried out during the last few years suggests a possible role for transplantation in the treatment of non-hematological diseases as autoimmune diseases,[2] ischemic cardiomyopathy,[5,6] neurological diseases,[7] liver failure,[8,9] and other diseases. Although some of these trials were successful, results are still preliminary, and treatment is not yet standardized. Unfortunately, due to the multi-disciplinary team required for a successful bone marrow transplant (BMT) program, there are only a few centers in the developing world, which are performing bone marrow transplantation. In Egypt very few centers can perform bone marrow transplantation; thus, they cannot cover the need of the country. Here, we describe our efforts to develop a BMT program and the results achieved in a relatively short time period.

Methods. ***Inclusion criteria.*** Currently, patients with diseases amenable to HSCT who have the necessary resources whether own income, insurance, or governmental and a 6 antigen human leukocyte antigen (HLA) matched related donor are considered for HSCT in our unit. The HLA-matching for donor selection was based on serologic typing for HLA-A, B, and C antigens and on DNA typing for HLA-DR and B antigens.

Exclusion criteria. Patients with impaired liver or renal function were excluded from this study. In addition, patients with active hepatitis infection via high copies by polymerase chain reaction (PCR) were excluded from the study. Currently, we do not conduct mismatch related donor transplant or transplant from an unrelated donor.

Data for all patients transplanted at Ain Shams University, Cairo, Egypt, bone marrow transplantation unit since March 2005 to January 2008 were reviewed. Ethical committee approval for this retrospective study was obtained according to institutional guidelines. Consent form was taken from all patients before transplant. Our source of information included patients' charts, and our department prospectively updated electronic database. Seven single rooms with positive HEPA-filtered laminar airflow are available in the transplant unit and air quality is monitored monthly. Even though water in the rooms passes through a central filter first, all patients use bottled water for drinking. Only cooked food is allowed. We use dual lumen Hickman catheters size 36 and 28 for adults and pediatric patients respectively, which are inserted under local anesthesia by an expert vascular surgeon. Conditioning for chronic myeloid leukemia (CML) was with busulfan (Bu) 16 mg/kg over 4 days with cyclophosphamide (CTX) 120 mg/kg over 2 days. For acute lymphatic leukemia (ALL), conditioning was with 10 Gy total body irradiation (TBI) over 4 days, and CTX 120 mg/kg over 2 days. For acute myeloid leukemia (AML), conditioning was with Bu 16 mg/kg and fludarabine (F) 120 mg/m^2 over 4 days. For aplastic anemia, in one patient conditioning was with conventional CTX 200 mg/kg and anti-thymocyte globulin (ATG) 30 mg/kg/day for 3 days, whereas in the adult patient with aplastic anemia, equine ATG at a dose of 10 mg/kg/d for 4 days was used due to limited financial support. Thus, F 30 mg/m^2/day for 5 days was added to the CTX and ATG to enhance engraftment. As for autologous transplants, one patient with resistant non-Hodgkin lymphoma was mobilized by CTX 2 gm/m^2 with one dose of vincristine, while the other patient had Hodgkin disease with history of initial central nervous system (CNS) involvement; thus, the patient was mobilized with methotrexate (MTX) 3.5 gm/m^2 and cytosine arabinoside (Ara-C) 3 gm/m^2/day over 2 days. In the first patient, conditioning was carried out with Bu 16 mg/kg and CTX 120 mg/kg, whereas the patient with a history of CNS infiltration was conditioned with CTX 120 mg/kg and 10Gy TBI over 4 days. Prevention of graft versus host disease (GVHD) has generally been with cyclosporine (CsA) 3 mg/kg/day intravenously (IV) starting on day minus one, then patients were changed to oral CsA whenever they can tolerate oral intake, with MTX 10mg/m^2 on days 1, 3, 6 with or without day 11 depending on patients' tolerance. The target serum CsA level is 200-400 ng/ml. Staging of GVHD has been with the Glucksberg scale. The GVHD was treated with steroids. In one patient, he was switched to tacrolimus due to persistent high level of liver enzymes with use of CsA. However, he was later switched to a small oral dose of MTX every other week together with steroids due to persistent elevated liver enzymes with tacrolimus. All patients and donors are tested for cytomegalovirus (CMV) antibodies. Previously, patients received ganciclovir 5 mg/Kg IV every 12 hours day minus 8 to day minus one then patients' CMV PCR is checked weekly until patients are off immunosuppressives and treated preemptively accordingly. Recently, due to limited financial support, patients are given acyclovir 5 mg/kg IV every 8 hours

starting on day minus one, and CMV PCR is checked weekly and ganciclovir is only given as preemptive treatment. Post engraftment, patients received acyclovir 200 mg BD prophylactically for herpes zoster infection for the initial 6 months; however, patients who continue to receive immunosuppressives to combat GVHD were continued on acyclovir until they are off immunosuppressives. Patients received ciprofloxacin and fluconazole prophylactically against bacterial and fungal infection, respectively. They also received trimethoprim-sulfamethoxazole (TMP-SMX) twice weekly prophylactically against *Pneumocystis carinii* infection until they are off immunosuppressives. Our first line antimicrobial therapy for febrile neutropenia consists of aminoglycoside, third-generation cephalosporin, and a switch to a therapeutic dose of fluconazole. If the fever persists or the patient is toxic, vancomycin is added. However, if there is no response, cephalosporin is switched to carbapenems. If the fever persists or there is a pulmonary infiltrate, amphotericin is given instead of fluconazole. All patients used disposable incentive Spiro meter every 2 hours during waking hours during their period of admission. Patients receive blood if their hemoglobin falls below 8 g/dl and platelets if platelet counts were <20,000/ul, unless they are bleeding then they will receive platelets at a higher platelet count. All patients had dedicated donors available for platelet pheresis to provide single donor platelets when the blood bank supply is inadequate. All blood products are irradiated and packed red blood cells are received through leuco-filters. Serum CsA is measured weekly, serum electrolytes, liver and renal functions were performed 3 times weekly and complete blood count was carried out daily. In all patients, the stem cell source was peripheral blood with a target dose of $5x10^6$/kg CD34+ cells. Stem cells were collected by a CobeSpectra apheresis machine using a mononuclear cell (MNC) collection procedure. In patients receiving stem cells from a donor with a major ABO incompatibility, red cell contamination of the graft was reduced by collecting at a lower hematocrit value via adjustment of the plasma flow rate. For stem cell collection, normal donors received granulocyte colony-stimulating factor (G-CSF) at a dose of 10 µg/kg/ for 4 days. Stem cell harvesting was started on the fifth day and continued with G-CSF administration until the target CD34+ cell dose was obtained. In the autologous setting, patients were mobilized by chemotherapy and G-CSF; stem cell collections were initiated when the absolute CD34+ cell count in the peripheral blood was >20/µl. Flow cytometric identification of HSC was accomplished by determination of CD34+/CD45+ cells in an aliquot of the apheresis product or in peripheral blood using the 2-platform assay of the International Society for Hematotherapy and Graft Engineering.[10] Allogeneic peripheral blood stem cell grafts were infused without manipulation within 1-2 hours of harvesting. A cold mixture of equal volumes of dimethylsulfoxide and acid-citrate-dextrose were slowly added to autologous apheresis products to a final concentration of 10% for each. The cell suspension was transferred into the appropriate number of freezing bags and frozen to -100°C with a computer-controlled rate freezer. The frozen cells were transferred into liquid-phase nitrogen and stored. Handling of the stem cells was performed in a class 2 biological safety cabinet in the stem cell laboratory on the Ain Shams BMT Unit premises. Engraftment of leucocytes was recorded as the first day in 3 consecutive days with polymorph count >500/ul and for platelets as the first day in 7 consecutive days with a count of >20,000/ul without platelet transfusion. Chimerism was assessed by variable number tandem repeat on day 28 and at 2 months, 6 months, and one year post transplant, then yearly, unless otherwise indicated.

We used SPSS version 13 to calculate range and mean for absolute neutrophil count and platelet engraftment and estimate percentage of complications post-transplant. Kaplan Meier was used to estimate the survival rate.

Results. Peripheral blood stem cell harvesting was carried out from donors who were mobilized by G-CSF. Apart from slight bone pains and mild thrombocytopenia, no significant side effects were recorded during or immediately following mobilization and harvesting. A few donors complained of per oral parathesia due to hypocalcemia during the apheresis procedure, which was rapidly corrected with intravenous calcium gluconate.

Patient characteristics. Sixteen patients with an age range of 4-42 years (median 25) received stem cell transplant from March 2005 to January 2008 in Ain Shams Bone Marrow Transplantation Unit: 14 allogeneic matched related donor and 2 autologous transplants. Indications for allogeneic transplantation were: CML in 5 patients (4 patients in first chronic phase and one patient in second remission after blast crisis), acute myeloid leukemia in 6 patients, aplastic anemia in 2 patients, and one patient with T cell-ALL. Two patients underwent autologous transplantation for resistant non-Hodgkin lymphoma and Hodgkin's disease with initial CNS infiltration. Seven of the donors (44%) and 6 of the patients (37%) were positive for CMV IgG Ab pretransplant. Only one patient was positive for toxoplasma IgG Ab pretransplant and another had a high titre for toxoplasma IgM Ab for which he received a course of TMP-SMX pretransplant and was

transplanted successfully. Two donors were positive for HBcAb IgG, negative for HBsAb and negative for hepatitis B DNA by PCR, and 3 patients were positive for HBcAb and HBsAb, negative HBV DNA by PCR. None of the patients or donors were positive for HCV via PCR pre-transplant.

Stem cell dose. The mean stem cell dose infused was $6.4x10^6$/Kg CD+34 cells (range 5-8.3).

Engraftment. The white blood cells were engrafted at a mean of 13 days (range 11-18), whereas platelets were engrafted at a mean of 17days (range 15-25).

Complications. Acute graft versus host disease grade I was seen in 3 patients (18.7%), mainly affecting the skin, while chronic GVHD was seen in 5 patients; 5/16 (31%) suffered from limited skin GVHD and 3/16 (18.7%) had chronic liver GVHD affection, while ocular GVHD was seen in 4 patients (25%) and 5 patients (31%) had chronic oral GVHD with xerostomia. Four patients (25%) suffered from hemorrhagic cystitis 24, 45, 192, and 234 days post transplant and they were all treated by over-hydration except for one patient who suffered from CMV reactivation and was given ganciclovir. A 28-year-old patient with aplastic anemia developed secondary graft failure 4 months post transplant for which she received 2 doses of donor lymphocyte infusion. A stem cell booster dose was planned however, she died in failure before receiving it. The primary cause of death was recurrence (2 patients) 7 and 8 months post transplant and as mentioned previously one patient with aplastic anemia died of secondary graft failure 6 months post-transplant. **Table 1** demonstrates post-transplant complications.

Survival. Thirteen of these patients are alive and disease free (87.5%) with a median follow-up of 20 months (range 6-34). The survival curve by Kaplan Meier is presented in **Figure 1**.

Table 1 - Post-transplantation complications.

Complications	Number of patients	(%)
Acute skin GVHD	3	(18.7)
Chronic limited skin GVHD	5	(31)
Chronic oral GVHD	5	(31)
Chronic liver GVHD	4	(25)
Chronic ocular GVHD	4	(25)
Hemorrhagic cystitis	4	(25)
Graft failure	1	(6.25)

GVHD - human stem cell transplantation

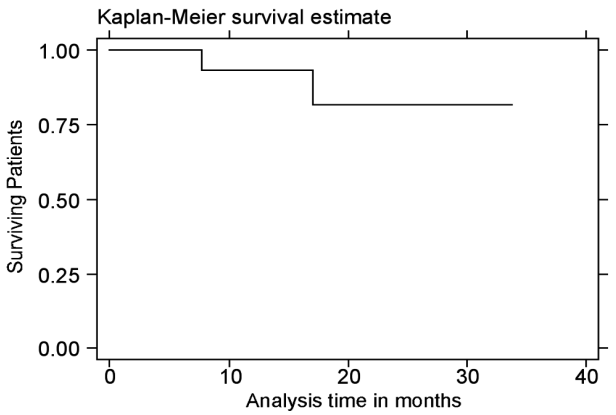

Figure 1 - Survival curve of bone marrow transplant patients overall.

Discussion. The BMT program at Ain Shams University Hospital started in January 2004; however, it was not until March 2005 that we transplanted our first patient who was a chronic myeloid leukemia case. The patient engrafted nicely; however, the patient suffered from acute and chronic GVHD. Since then we carried out several transplants, albeit, at a slow pace, mainly due to lack of sufficient financial support. Many protocols have been modified to suit local conditions. Tyrosine kinase inhibitors are internationally considered as the first line of therapy in CML and if patients develop resistance then they will be offered transplant.[11,12] In Egypt, most patients cannot afford financially to stay for years on tyrosine kinase inhibitors. Considering that it is known that results of transplant are better when they are carried out in the early chronic phase,[12] in under-developed countries with limited financial resources, it is more feasible and reasonable to transplant patients right away, if an HLA matched donor is available. Thus, bone marrow transplantation today offers an alternative to life-long treatment with tyrosine kinase inhibitors with its tremendous financial burden. To be noted, despite the small number transplanted in our unit, they significantly suffered from acute and chronic GVHD, mainly affecting the skin, eyes, and oral cavity. Whether these patients should receive more immunosuppressive treatment to inhibit GVHD or extend GVHD treatment beyond 6 months needs to be considered.

It has been shown in multi-center randomized trials that allogeneic HSCT is the most effective strategy for preventing relapse in patients in first complete remission (CR) of AML.[13,14] However, in adult patients, this benefit does not necessarily lead to a better disease-free survival, since allogeneic SCT is associated with significant transplant related mortality (TRM). In adults with good-risk AML, because chemotherapy alone or combined with differentiating agents can lead to sustained CR and cures, allogeneic SCT is usually indicated in second CR or first untreated relapse. In poor-risk AML, salvage

rates are less predictable and the probability of reaching a second CR is less certain; thus, allogeneic SCT is usually considered earlier, in first CR.[13,14] In our series, 6 patients with AML received allogeneic SCT. Except for chronic limited skin GVHD, ocular and oral GVHD, their transplant was uneventful with a follow-up range of 8-34 months (median 18 months). Approximately 50% of patients with malignant non-Hodgkin's lymphoma (NHL) and 20% of those with Hodgkin's lymphoma (HL) are not cured after anthracycline-based first-line chemotherapy.[15] High-dose chemotherapy (HD-CT) with autologous stem cell transplantation is considered to be the treatment of choice for relapsed high-grade NHL and HL patients, but the optimal treatment has not yet been defined.[16] As we had only undergone 2 autologous transplants, each using a different protocol, we cannot comment on the protocols, but both have been free of relapse for 10 and 8 months respectively.

Human stem cell transplantation is the first line of therapy in aplastic anemia.[17,18] The year 1972, recorded the first successful transplant of an aplastic anemia patient. The most commonly used conditioning regimen for aplastic anemia is CTX with ATG.[18] We only transplanted 2 cases, unfortunately, one suffered from graft failure 4 months post transplant and subsequently died. One of the reasons to be considered for this graft failure is the fact that the transplant was delayed as she did not have enough financial support for ATG coverage, and we could not use a large dose of ATG for the same reason. Even though we added F to our regimen, she still suffered from graft failure. Furthermore, the patient was positive for hepatitis B pretransplant, and on developing graft failure, the patient received frequent blood products and contracted also hepatitis C, which may have aggravated the bone marrow aplasia. Thus, it would be reasonable to sponsor a protocol that does not include very expensive drugs to avoid undue delay of transplant. Also, prompt treatment of sepsis and transfusion with only irradiated leukodepleted blood products to potential transplant candidates from the time of diagnosis will reduce rejection.[19] Bone marrow transplant in tropical countries poses a significant problem in terms of infections. Cytomegalovirus (CMV) infection is a significant cause of morbidity and mortality after allogeneic HSCT. The majority of cases of active CMV infection are considered to be due to reactivation of latent infection.[20,21] We encountered only 2 cases of CMV reactivation; one of them experienced more than one episode of CMV reactivation and in one this was associated with hemorrhagic cystitis. All episodes were treated successfully with ganciclovir. As only one patient was positive for toxoplasma IgG pretransplant and another had a high titre for toxoplasma IgM Ab, toxoplasma did not pose a serious problem, but as it is prevalent in Egypt, it is screened for routinely pre-transplant. A serious problem that we encounter in Egypt is hepatitis infection. Though 2 donors and 3 patients were positive for hepatitis markers, none were positive for hepatitis B DNA by PCR and none of the patients or donors were positive for HCV RNA via PCR pre-transplant. Patients positive for HBV markers received lamivudine during the peri-transplant period until they were off-immunosuppression and did not demonstrate viral re-activation. However, in a study carried on 35 transplanted patients in Nasser Institute in Egypt 3/8 (38%) of the HBV seropositive recipients developed HBV reactivation. Moreover, 5/13 (39%) of the HCV-seropositive recipients developed HCV reactivation.[22] Thus, a national multi-center trial is needed to develop the best strategy for managing hepatitis during HSCT. Acute GVHD was seen in only 3 patients (18.7%), mainly affecting skin grade I. Only one patient suffered from acute GVHD of gut post ingestion of contaminated food. Chronic GVHD was seen in 5 patients (31%); the 5 patients had limited skin GVHD; ocular GVHD was seen in 4 patients (25%) and 5 patients (31%) had chronic oral GVHD with xerostomia. It was not related to level of immunosuppression; however, it seems like a problem that needs to be addressed.

As this was a retrospective study and as we were just starting to recruit patients for transplantation, we acknowledge the limited number of patients in our study, which may affect our results. Since the writing of this article 7 more patients have been transplanted in our unit in a relatively shorter period. The average estimate cost of transplantation in the unit is around 75000 Egyptian pounds (60,000-120,000 Egyptian pounds). An average estimate of cost of transplant in western countries is at least USD250,000, if not more. As most patients, do not have the option to transplant in western countries, availability of good transplant units in Egypt is of utmost importance. This study demonstrates that in underdeveloped countries, HSCT protocols need to be modified to suit local conditions in each country, so that even with limited financial resources, results comparable to those obtained in western countries can be achieved.

References

1. Efiom-Ekaha D. Hematopoietic Stem Cell Transplantation. 2004 (cited on 26 September 2007). Available from: http://www.emedicine.com
2. Moore T. Bone Marrow Transplantation. 2005 (cited on March 28, 2008). Available from: http://www.emedicine.com
3. Braude P, Minger SL, Warwick RM. Stem cell therapy: hope or hype? ***BMJ*** 2005; 330: 1150-1160.
4. Samuel G, Kerridge I, Vowels M, Trickett A, Chapman J, Dobbins T. Ethnicity, equity and public benefit: a critical evaluation of public umbilical cord blood banking in Australia. ***Bone Marrow Transplant*** 2007; 40: 729-734.

5. Wolf D, Reinhard A, Krause U, Seckinger A, Katus H, Kuecherer H, et al. Stem Cell Therapy Improves Myocardial Perfusion and Cardiac Synchronicity: New Application for Echocardiography. ***J Am Soc Echocardiogr*** 2007; 20: 512-520.
6. Krause U, Harter C, Seckinger A, Wolf D, Reinhard A, Bea F, et al. Intravenous Delivery of Autologous Mesenchymal Stem Cells Limits Infarct Size and Improves Left Ventricular Function in the Infarcted Porcine Heart. ***Stem Cells Dev*** 2007; 16: 31-37.
7. Cova L, Ratti A, Volta M, Fogh I, Cardin V, Corbo M, et al. Stem cell therapy for neurodegenrative diseases: the issue of transdifferentation. ***Stem Cells Dev*** 2004; 13: 121-131.
8. Masson S, Harrison D, Plevris J and Newsome P. Potential of Hematopoietic Stem Cell Therapy in Hepatology: A Critical Review. ***Stem Cells*** 2004; 22; 897-907.
9. Yannaki E, Athanasiou E, Xagorari A, Constantinou V, Batsis I, Kaloyannidis P, et al. G-CSF–primed hematopoietic stem cells or G-CSF per se accelerate recovery and improve survival after liver injury, predominantly by promoting endogenous repair programs. ***Exp Hematol*** 2005; 33: 108-119.
10. Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I. The ISHAGE guidelines for CD34+ cell determination by flow cytometry. ***J Hematother*** 1996; 5: 213-226.
11. Passweg JR, Walker I, Sobocinski KA, Klein JP, Horowitz MM, Giralt SA. Validation and extension of the EBMT Risk Score for patients with chronic myeloid leukemia (CML) receiving allogeneic hematopoietic. ***Br J Haematol*** 2004; 125: 613-620.
12. Kantarjian H, Cortes J. BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia: using guidelines to make rational treatment choices. ***J Natl Compr Canc Netw*** 2008; Suppl 2: S37-S42.
13. Robin M, Guardiola P, Dombret H, Baruchel A, Esperou H, Ribaud P, et al. Allogeneic bone marrow transplantation for acute myeloblastic leukemia in remission: risk factors for long-term morbidity and mortality. ***Bone Marrow Transplant*** 2003; 31: 877-887.
14. Hamadani M, Awan F, Copelan E. Hematopoietic Stem Cell Transplantation in Adults with Acute Myeloid Leukemia. ***Biol Blood Marrow Transplant*** 2008; 14: 556-567.
15. Diehl V, Franklin J, Pfreundschuh M, Lathan B, Paulus U, Hasenclever D, et al. Standard and increased-dose Beacopp chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. ***N Engl J Med*** 2003; 348: 2386-2395.
16. Schütt P, Passon J, Ebeling P, Welt A, Müller S, Metz K, et al. Ifosfamide, etoposide, cy-tarabine, and dexamethasone as salvage treatment followed by high-dose cyclophosphamide, melphalan, and etoposide with autologous peripheral blood stem cell transplantation for re-lapsed or refractory lymphomas. ***Eur J Haematol*** 2007; 78: 93-101.
17. Abdelkefi A, Ben Othman T, Ladeb S, Torjman L, Ben Abdeladhim A. Rejection of the second allogeneic graft in a child with Fanconi anemia reversed by antilymphocyte globulin and donor lymphocyte infusion. ***Hematol J.*** 2003; 4: 452-453.
18. Muñoz Villa A, Díaz de Heredia C, Díaz González MA, Badell Serra I, Martínez Rubio A, González Valentín MA, et al. Severe acquired aplastic anemia: historical outcome of patients treated by allogeneic bone marrow transplantation from matched sibling donors. A study by the Spanish Group for Bone Marrow Transplantation in Children (GETMON). ***An Pediatr (Barc)*** 2008; 69: 5-9.
19. Bean MA, Graham T, Appelbaum FR. Gamma-irradiation of pretransplant blood transfusions from unrelated donors prevents sensitization to minor histocompatibility antigens on dog leukocyte antigen-identical canine marrow grafts. ***Transplantation*** 1994; 57: 423-426.
20. Pillay D, Webster A, Prentice HG, Griffiths PD. Risk factors for viral reactivation following bone marrow transplantation. ***Ann Hematol*** 1992; 64 (Suppl): A148-A151.
21. Angarone M, Ison MG. Prevention and early treatment of opportunistic viral infections in patients with leukemia and allogeneic stem cell transplantation recipients. ***J Natl Compr Canc Netw*** 2008; 6: 191-201.
22. Zekri AR, Mohamed WS, Samra MA, Sherif GM, El-Shehaby AM, El-Sayed MH. Risk factors for cytomegalovirus, hepatitis B and C virus reactivation after bone marrow transplantation. ***Transplant Immunol*** 2004; 13: 305-311.

Related topics

Beyzadeoglu M, Arpaci F, Surenkok S, Ozyigit G, Oysul K, Caglar K, Ataergin S, Yenicesu M, Kaya A. Acute renal toxicity of 2 conditioning regimens in patients undergoing autologous peripheral blood stem-cell transplantation. *Total body irradiation-cyclophosphamide versus ifosfamide, carboplatin, etoposide.* ***Saudi Med J*** 2008; 29: 832-836.

Maalouf WE. A novel method for reprogramming somatic cells into embryonic stem cells. ***Saudi Med J*** 2008; 29: 146-148.

Alshemmari SH, Ameen RM, Gyrafas J, Alqallaf DA, Sajnani KP. Factors influencing engraftment in autologous peripheral stem cell transplantation. *The experience of a local Kuwaiti transplantation center.* ***Saudi Med J*** 2007; 28: 1080-1085.