Basic Principles and Practice of Hematopoietic Cell Transplantation and Cell Therapy

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History of Hematopoietic Cell Transplantation and Cell Therapy

1. Experiments and observations in which of the following animal species encouraged further trials of marrow grafting between human leukocyte antigen (HLA)-matched human siblings?

   A. Mice
   B. Dogs
   C. Pigs
   D. Rabbits

Answer – B

Explanation: Studies of the dog leukocyte antigen (DLA) system proved that DLAs were crucial in determining the outcome of an allogeneic marrow graft. Dogs given irradiation and marrow from a DLA-mismatched littermate died of graft rejection or graft versus host disease (GvHD). Most recipient of DLA-matched marrow, especially those given some post-grafting methotrexate to suppress the graft versus host (GvH) reaction, became long-term healthy survivors. These observations encouraged further trials of marrow grafting between HLA-matched human siblings.

Biology of Hematopoietic Stem and Progenitor Cells

2. All of the following statements about hematopoietic stem cells (HSCs) are correct EXCEPT:

   A. HSCs are predominantly in G0 state in the marrow space
   B. Contrary to other types of stem cells, HSCs have limited ability of self-renewal
   C. HSCs can exit quiescence state and rapidly expand and differentiate
   D. Activated hematopoietic stem cells can return to dormancy

Answer - B

Explanation: HSCs are predominantly in a quiescent, non-dividing, G0 state and only a small number of cells enter the cell cycle in order to maintain a supply of mature hematopoietic cells (Choice A). By definition stem cells are undifferentiated and capable to divide for indefinite periods throughout the lifetime (Choice B is incorrect). HSCs do exit quiescence and rapidly expand and differentiate in order to regenerate hematopoiesis in response to certain conditions, such as blood loss, infections, or treatment-induced pancytopenias (Choice C). The quiescent state is thought to be an essential mechanism to protect HSCs from replication-associated mutations. Remarkably, the activated HSCs can return to dormancy upon re-establishment of homeostasis in the hematopoietic system, a powerful safeguard mechanism allowing repair without causing depletion of the HSC pool (Choice D).

Indications for Hematopoietic Cell Transplantation
3. Which statement from the Guidelines of American Society for Blood and Marrow Transplantation (ASBMT) on indication for autologous and allogeneic hematopoietic cell transplant (HCT) is CORRECT?

A. The guidelines were developed in response to a need identified by patients, providers, payers and policy makers
B. Indications for HCT are categorized into three groups in the ASBMT guidelines
C. The goal is to update these guidelines every 12 to 18 months
D. These guidelines answer whether HCT should be pursued as a treatment for an individual patient

Answer – A

Explanation: The American Society for Blood and Marrow Transplantation (ASBMT), in response to a need identified by patients, providers, payers and policy makers, established a Task Force to provide guidance on indications for hematopoietic cell transplantation (HCT), that is, which indications may be considered as routine care versus indications where evidence is emerging or insufficient (Choice A is correct). Indications for HCT were categorized into five groups (not three groups; choice B), as (1) Standard of care, where indication for HCT is well defined and supported by evidence, (2) Standard of care, clinical evidence available, where large clinical trials and observational studies are not available but HCT has been shown to be effective therapy, (3) Standard of care, rare indication, for rare diseases where HCT has demonstrated effectiveness but large clinical trials and observational studies are not feasible, (4) Developmental, for diseases where pre-clinical and/or early phase clinical studies show HCT to be a promising treatment option, and (5) Not generally recommended, where available evidence does not support the routine use of HCT. The goal is for ASBMT to periodically review these guidelines and update them as new evidence becomes available (not every 12-18 months; choice C). The Task Force emphasizes that the guidelines not be used to determine whether HCT should be pursued as a treatment for an individual patient (Choice D is incorrect). Whether or not to proceed with transplantation in an individual patient is a clinical decision that is best made between the patient and his/her provider after a careful consideration of the alternatives, risks and benefits of the procedure.

Current Trends of Hematopoietic Cell Transplantation –CIBMTR analysis till the year 2016

4. All of the following statements about current uses of allogeneic hematopoietic cell transplantation (allo-HCT) by donor type in U.S. are true EXCEPT:

A. The number of unrelated donor (URD) transplants has surpassed the number of allo-HCT from related donors after the year 2006
B. The numbers of URD and HLA-identical siblings has shown a downward trend in absolute numbers after the year 2012
C. There has been an increase in the numbers of HLA-haploidentical transplants from the year 2012 onwards
D. There has been steady increase in the numbers of transplants using cord blood grafts from the years, 2003 to 2015

Answer - D
Explanation: The number of unrelated donor (URD) transplants has surpassed the number of allo-HCT from related donors after the year 2006 (Choice A) and the gap between these two types of approaches peaked in the year 2012 (Figure 1). After the year 2012, the numbers of URD and HLA-identical siblings has shown a downward trend in absolute numbers (Choice B). Transplants performed with alternative donors are increasing. From 2003 to 2011 (not 2015; choice D), there were a steady increase in the numbers of transplants using cord blood grafts as a result of several published studies demonstrating its benefit in both children and adults. From the year 2012 onward, there has been an increase in the numbers of transplants from “other relatives”, which is likely due to the use of HLA-haploidentical donors with post-transplant cyclophosphamide strategy (Choice C). In the year 2014, the numbers of transplants using other relatives surpassed the total numbers of cord blood transplants (CBTs) performed in the U.S., accounting for 11% of all allo-HCT performed in the U.S. In the year 2015, HLA-haploidentical donor transplants are the only group of donor type that is increasing with all other donor types showing decline or stability in use (Choice C). See Figure 1.

Figure 1: Stratifying the number of allogeneic hematopoietic cell transplants recipients in the U.S. by donor type, recipients of unrelated donor transplants represent the largest group.10


Current Trends of Autologous Hematopoietic Cell Transplantation –CIBMTR analysis till the year 2016

5. Which statement about trends of autologous hematopoietic cell transplants (auto-HCT) in U.S. by recipient age is CORRECT?
A. The total number of auto-HCT for neoplastic diseases in older adults continues to decline
B. In the year 2015, 25% of the total auto-HCTs were performed in older adults with lymphomas and multiple myeloma
C. There is a trend towards increase use of auto-HCT in older (≥70 years of age) adults
D. There is a trend towards decrease use of auto-HCT in multiple myeloma in patients’ ≥70 years of age

Answer - C

Explanation: The total number of autologous hematopoietic cell transplants (auto-HCT) for neoplastic diseases continues to rise in older adults (not decline; choice A). In the year 2015, over 50% (not 25%; choice B) of auto-HCT in patients with lymphomas and multiple myeloma were performed in older adults (≥60 years old). There is a trend towards increase use of auto-HCT in lymphomas (Choice C) and multiple myeloma (Choice D is incorrect) in patients’ ≥70 years of age, representing 12% of auto-HCT activity in the year 2015. See Figure 2

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Pre-transplant Recipient Assessment for Allograft

1. Which statement about hematopoietic cell transplant comorbidity index (HCT-Cl) is INCORRECT?

   a. It was designed using data from patients treated with allogeneic hematopoietic cell transplantation (allo-HCT)
   b. It has been validated on numerous occasions
   c. It is an important decision making instrument to select intensity of conditioning regimen for allo-HCT
   d. It can be used alone to determine outcomes after allo-HCT.

   Answer - D

   Explanation: The hematopoietic cell transplant comorbidity index (HCT-Cl) was initially designed using clinical data from 1,055 consecutive patients treated with allo-HCT from 1997 to 2004 at Seattle Care Alliance (SCCA/Fred Hutchinson Cancer Research Center (FHCRC; choice A). The index was validated among patients transplanted at SCCA/FHCRC as well as other transplant institutions worldwide (Choice B). The HCT-Cl included 17 comorbidities acquiring scores from 1 to 3. The HCT-Cl scores of 0, 1–2, and ≥3 showed good discrimination of nonrelapse mortality (NRM; 14%, 21%, and 41%) and survival (71%, 60%, and 34%), respectively. HCT-Cl was deem to be an important decision making instrument for selection of appropriate conditioning regimen for patients with acute myeloid leukemia or myelodysplastic syndromes and those with lymphomas including chronic lymphocytic leukemia (Choice C). The HCT-Cl together with the degree of severity of blood cancer could be used to stratify outcomes of patients 60 years or older who were treated nonmyeloablative (NMA) conditioning regimens for allo-HCT (Choice D is incorrect). Recently, a combined HCT-Cl with age model was designed (by the same group) and validated that takes into account the burden of comorbidities (17 in total) as well as increasing age in risk assessment prior to allo-HCT. The HCT-Cl index can be easily accessed via ASBMT iPhone application.

Immunogenetics in Allogeneic Hematopoietic Cell Transplantation

2. Which statement accurately defines the concept of linkage disequilibrium within the human leukocyte antigen (HLA) system?

   A. Linkage disequilibrium implies that certain alleles occur together with a higher frequency than expected by chance.
   B. Linkage disequilibrium is less frequently observed between loci that are in close proximity with a gene
   C. Linkage disequilibrium implies that certain alleles do not occur together in a gene
   D. Linkage disequilibrium is not observed between loci that are in close proximity

   Answer - A

   Explanation: Linkage disequilibrium (LD) implies that certain alleles occur together with a greater frequency than expected by chance (nonrandom gametic association) (Choice A is correct and choice C
is incorrect). In general, LD is more frequently observed between loci that are in close proximity with a gene (Choices B and D are incorrect). Linkage disequilibrium is a hallmark of both HLA class I (in particular HLA-B and HLA-C) and HLA class II (in particular HLA-DR and DQ) loci. Although there is strong LD between the DPA1 and the DPB1 loci, due to a recombination hotspot telomeric to HLA-DP, the LD between HLA-DP and the other HLA class II loci is rather low. For this reason, matching for HLA-DR and DQ in two unrelated individuals is frequently not accompanied by matching for HLA-DP. On the other hand, LD is at the basis of the probability for an individual to identify a HLA-matched unrelated donor (MUD): In patients with frequent HLA-haplotypes such as HLA-A1, HLA-B8, and HLA-DR3, the probability is much higher than average, whereas in patients with unusual LD, for instance through recombination, the probability drops dramatically, and clinicians may be advised to immediately consider a HLA-mismatched unrelated or family donor. In certain cases, LD may also help to predict allelic resolution; however, this is not completely accurate, particularly in ethnic groups where HLA types have not yet been well studied. For instance, more than 95% of white individuals who carry HLA-B*07:02 will have HLA-C*07:02, whereas those who carry B*18:01 may have either C*07:01, C*12:03, or C*05:01.

Non-HLA Factors for Selection of Allografts

3. Peripheral blood versus marrow graft sources in unrelated donor setting: All of the following statements are true according to the study published in New England Journal of Medicine by Anasetti and colleagues (2012) EXCEPT:

   a. Peripheral-blood grafts may reduce the risk of graft failure
   b. Marrow grafts may reduce the risk of chronic GvHD
   c. Neutrophils engraftment was faster with marrow grafts
   d. Overall survival at 2 years did not differ significantly between the peripheral blood and the marrow graft sources

Answer – C

Explanation: This important phase III, multicenter, randomized trial of transplantation of peripheral blood versus marrow grafts in neoplastic hematologic diseases from unrelated donors compared 2 year survival probabilities with the use of an intention-to-treat analysis. Between March 2004 and September 2009, the investigators enrolled 551 patients (less than 66 years of age) at 48 centers. Patients were randomly assigned in a 1:1 ratio to peripheral blood or marrow graft sources, stratified according to transplantation center and disease risk. The median follow-up of surviving patients was 36 months (interquartile range, 30 to 37). The overall survival rate at 2 years in the peripheral blood graft group was 51% (95% confidence interval [CI], 45 to 57), as compared with 46% (95% CI, 40 to 52) in the marrow group (P=0.29), with an absolute difference of 5% points (95% CI, -3 to 14). Results were similar among HLA-mismatched pairs, recipients with advanced disease, and recipients older than 40 years of age, although this trial was not powered to detect potential differences within these subsets. The overall incidence of graft failure in the peripheral blood graft group was 3% (95% CI, 1 to 5), versus 9% (95% CI, 6 to 13) in the marrow group (P=0.002; Choice A). In addition, graft failure was more common after marrow transplantation from an HLA-mismatched donor than after marrow transplantation from an HLA-matched donor (16% versus 7%, P=0.04). Graft failure was rarely observed after transplantation from peripheral blood graft source from HLA-mismatched donors (2%) or HLA-matched donors (3%).

The incidence of chronic GvHD at 2 years in the peripheral blood graft group was 53% (95% CI, 45 to 61), as compared with 41% (95% CI, 34 to 48) in the marrow graft group (P=0.01; Choice B). There were no significant between-group differences in the incidence of acute GvHD or relapse. Among patients
randomly assigned to receive peripheral blood grafts, as compared with those randomly assigned to receive marrow grafts, the median time to neutrophil engraftment was 5 days shorter (P<0.001), and the median time to platelet engraftment was 7 days shorter (P<0.001). (Choice C is incorrect) The investigators did not detect significant survival differences between transplantation from peripheral blood and marrow graft sources from unrelated donors. Exploratory analyses of secondary end points indicated that peripheral blood grafts may reduce the risk of graft failure, whereas marrow grafts may reduce the risk of chronic GvHD.

**Handling and Processing of Hematopoietic Cell Therapy Products**

4. Which of the following is NOT a vital component of cryopreservation process for hematopoietic cell therapy product (CTP)?

   A. Infusion of acid-citrate-dextrose (ACD) into CTP
   B. Warming of CTP
   C. Post-thaw cell assessment of CTP
   D. Cooling protocol for CTP

   Answer - A

**Expert perspective:** Cryopreservation is essential practice for autologous hematopoietic cell therapy products (CTP), and is on occasions performed on allogeneic hematopoietic CTPs. The stability of fresh CTPs is time sensitive, and, if done properly, cryopreservation allows long-term storage of viable and potent hematopoietic progenitor cells (HPCs). The entire process of cryopreservation can be viewed or divided into five (5) major components following successful handling of fresh hematopoietic CTP. These components include 1) addition of cryopreservation solution, 2) cooling protocol, 3) storage, 4) warming prior to infusion of CTP (Choice B) and 5) post-thaw CTP assessment (Choice C). infusion of ACD is part of hematopoietic cell progenitor collection by apheresis [HPC (A)] in majority of cases. It’s an entirely separate process from cryopreservation. (Choice A)

**Outcomes of Hematopoietic Cell Transplantation – CIBMTR analysis till the year 2016**

5. What is the leading cause of reported deaths after autologous hematopoietic cell transplant (auto-HCT) in the years 2013 and 2014?

   a. Organ Failure
   b. Infection
   c. Primary disease
   d. Second malignancy

   Answer – C

**Explanation:** After autologous hematopoietic cell transplantation (auto-HCT), primary disease is the most commonly reported cause of death representing 69% of deaths (Choice C is correct). Infection and organ failure were reported in 3% and 2%, respectively as cause of death. Second malignancy and “Other” were reported as cause of death in 2% and 24%, respectively to CIBMTR. Figure 3.

References:

10. Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, Omel JL, Orchard PJ, Palmer J, Saber W, Savani BN, Veys PA, Bredeson CN, Giralt SA, LeMaistre CF. Indications for


1. Engineered therapeutic T cell therapies combine concepts from which of the following long-standing therapeutic strategies?

A. Engineered antibodies
B. Vaccination
C. Transplantation
D. All of the above are correct
E. Only A and B are correct

**Answer – D**

**Explanation:** The engineered T cell therapies represent the convergence of diverse areas of medicine and basic science.¹ This new therapeutic approach i.e. chimeric antigen receptor (CAR) T cells combine concepts from three long-standing therapeutic strategies namely engineered antibodies, vaccination and transplantation.¹ Engineered antibodies have become a standard platform for recognizing and targeting disease but are largely used to block target protein activity (e.g. anti-CD20) or to target a toxic payload (e.g. brentuximab vedotin). Vaccination, which uses various methods to awaken the native immune system, may have the therapeutic power of unleashing complex immune responses in favor of the recipient. Finally, transplantation has established the paradigm of using a living therapeutic platform (cells or organs), though usually for replacing a defective system.¹ Careful combination of such traditional therapeutic approaches has allowed an integrated smart sense-and-response agent, i.e. CAR T cells.

2. What was the most common indication of hematopoietic cell transplantation in the U.S in the year 2014?

A. Lymphoma
B. Acute myeloid leukemia
C. Multiple myeloma/plasma cell disorders
D. Myelodysplastic syndromes

**Answer – C**

**Explanation:** The most common indications for hematopoietic cell transplantation (autologous and allogeneic) in the US in 2014 were multiple myeloma/plasma cell disorders (1st) and lymphoma (2nd), accounting for 56% of all hematopoietic cell transplantations reported to CIBMTR. Acute leukemias (acute myeloid leukemia, acute lymphoblastic leukemia) and myelodysplastic syndromes (combined with myeloproliferative neoplasms) are the most common indications for allogeneic transplants accounting for 70% of allogeneic HCTs.²
3. **Which statement about chronic graft-versus-host disease is correct?**

   A. Unlike acute graft-versus-host disease, chronic graft-versus-host disease does not affect hepatobiliary system  
   B. It remains one of the major causes of late transplant-related mortality  
   C. It does not affect pancreatic tissue  
   D. Manifestations of chronic graft-versus-host disease are always widespread

**Answer – B**

**Explanation:** Chronic graft-versus-host disease can involve not only the epithelial target tissues affected in classic acute graft-versus-host disease (gastrointestinal tract, liver, skin, and lungs) but also any other organ system, including oral, esophageal, musculoskeletal, joint, fascial, ocular, and lymphohematopoietic systems; hair and nails; and genital tissues.\(^3\) (Choice A is incorrect) Also, chronic graft-versus-host disease may be associated with pancreatic atrophy and exocrine insufficiency leading to malabsorption that often improves with oral pancreatic enzyme supplementation.\(^4,5\) (Choice C is incorrect) Importantly, in all cases, drug reaction, infection, recurrent or new malignancy and other causes must be excluded before making a diagnosis of chronic graft-versus-host disease.\(^4\) Manifestations of chronic graft-versus-host disease may be restricted to a single organ or site (Choice D is incorrect) or may be widespread with profound impact on quality of life and it remains one of the major causes of late transplant-related mortality.\(^4\) (Choice B is correct)
4. Which statement about HLA-matched sibling transplants and hematopoietic graft type in adults (age ≥18 years) is correct?

A. The trend of using HLA-matched sibling bone marrow grafts has increased over the last 15 years in adult recipients
B. Peripheral blood remains the major graft source using HLA-matched sibling donors in adult recipients
C. Regardless of the graft type the transplant activity using HLA-matched sibling donors has increased since the year 2000
D. In 2015, use of peripheral blood grafts increased when compared to the activity of previous 3 years

Answer - B

Explanation: Among adult (age ≥18 years) recipients of HLA-matched sibling transplant, mobilized peripheral blood hematopoietic progenitor cells are the most common type of grafts. (Choice B is correct) The proportion use of bone marrow grafts for HLA matched sibling transplants has ranged from 11% to 14% since 2006 and remains lower compared to peripheral blood grafts. Compared to the year 2000, the use of bone marrow grafts has steadily declined. (Choice A is incorrect) Since the year 2002, overall transplant activity using HLA-matched sibling donors, regardless of the graft type, have declined. (Choice C is incorrect) In 2015, use of peripheral blood grafts declined when compared to the activity of previous 3 years. (Choice D is incorrect)

5. Which of the following are risk factors for chronic graft-versus-host-disease?

A. Prior episode of acute graft-versus-host disease
B. Transplantation of grafts from male donors in female recipients
C. Receipt of bone marrow grafts
D. All of the above
E. Choices B and C

Answer - A

Explanation: Risk factors for the development of chronic graft-versus-host disease include a prior episode of acute graft-versus-host disease (Choice A is correct), receipt of mobilized peripheral blood grafts (recipients of bone marrow grafts have less chronic graft-versus-host disease; choice C is incorrect), transplantation of grafts from female donors in male recipients (Choice B is incorrect), HLA disparity between recipient and donor, history of chronic myeloid leukemia and older age of the recipient and the donor.3,6 It is important to emphasize that establishing risk factors for any disease condition cannot be assumed as a static phenomenon but risk factors could change overtime with advances in the field of Medicine.

References:

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1. Which of the following is the most consistent risk factor associated with progression of upper respiratory syncytial virus (RSV) respiratory tract infection to lower respiratory tract infection (RSV pneumonia) after hematopoietic cell transplantation?
   
   A. Neutropenia  
   B. Lymphopenia  
   C. Cytomegalovirus seropositivity  
   D. Longer time to neutrophil engraftment

   **Answer - B**

   **Explanation:** Risk factors for the progression of upper respiratory syncytial virus (RSV) respiratory tract infection to lower respiratory tract infection and relating to fatal clinical disease have been evaluated in several hematopoietic cell transplant populations. The most common risk factor described using different methods remains presence of lymphopenia. (Choice B is correct). In prospective multicenter study, on behalf of European Bone Marrow Transplant (EBMT) Society, lymphopenia, not neutropenia (Choice A is incorrect), significantly increased the risk of lower RSV respiratory tract infection. Older age and donor status, were also significant risk factors in a study from Fred Hutchinson Cancer Research Center (FHCRC) whereas CMV serostatus (Choice C is incorrect), acute graft-versus-host-disease, time relative to neutrophil engraftment (Choice D is incorrect) and preemptive aerosolized ribavirin at low-dose 2 hour daily were not significant. The investigators from University of Texas M.D. Anderson Cancer Center (MDACC), have demonstrated that season of the year (e.g. during the winter), disease relapse, graft-versus-host-disease, increasing age, and lack of neutrophil engraftment are relevant risk factors for the development of RSV pneumonia.

2. Which of the following statements about respiratory syncytial virus (RSV) infection and its treatment is correct?
   
   A. A large randomized trial has shown clear benefit using ribavirin for the treatment of RSV infection  
   B. The addition of immune globulin to ribavirin is an approved therapy  
   C. Transplant candidates with upper respiratory RSV infection can safely proceed with conditioning regimen  
   D. Respiratory secretions of any hospitalized transplant recipient who experiences signs or symptoms of RSV infection should be tested promptly by viral culture and rapid diagnostic test.

   **Answer - D**

   **Explanation:** Respiratory syncytial virus (RSV) infection is an important complication after hematopoietic cell transplantation (HCT), and RSV lower respiratory tract disease results in substantial early mortality and late airflow obstruction among survivors. No controlled clinical study of sufficient size to allow conclusions regarding efficacy of any therapeutic intervention against RSV was performed. There have been several reports, mostly retrospective, on ribavirin therapy for RSV infection. The only existing controlled trial of aerosolized ribavirin in transplant recipients was able to
recruit just 14 patients. There was a trend for lower viral loads in the ribavirin-treated patients but no difference in outcome. A large recent study of 280 patients with upper respiratory tract infection showed that use of aerosolized ribavirin was the most important factor for reducing the risk for RSV lower respiratory tract disease, RSV associated, and for all-cause mortality. The use of ribavirin by any route is supported by a systematic review showing a reduction in the risk for lower respiratory tract disease when treatment is given at the upper respiratory virus stage and an improvement in outcome of RSV pneumonia by ribavirin therapy. On the basis of retrospective studies as well as a prospective trial with inadequate accrual, some researchers recommend preemptive aerosolized ribavirin for patients with RSV upper respiratory tract infection, especially those with lymphopenia (during the first 3 months after hematopoietic cell transplant) and preexisting obstructive lung disease (late after hematopoietic cell transplant). The addition of immune globulin or pavilizumab to ribavirin is also controversial but a systematic review suggested better outcome if immune globulin was given to patients with lower respiratory tract disease (Choice B is incorrect). Transplant candidates who present with upper respiratory disease due to RSV or other community-acquired respiratory viruses (e.g. influenza, human metapneumovirus, and parainfluenza virus) who have not yet received conditioning regimen are at significantly increased risk for developing life-threatening lower respiratory infection. Such individual’s should be postponed for transplant until symptoms resolve. (Choice C is incorrect) Respiratory secretions of any hospitalized hematopoietic cell transplant candidate or recipient who experiences signs or symptoms of community-acquired respiratory virus infection(s) should be tested promptly by viral culture and rapid diagnostic tests. (Choice D is correct) If two diagnostic samples taken approximately 2 days apart do not identify a respiratory pathogen despite persistence of lower respiratory symptoms, bronchoalveolar lavage and further testing are advised. This testing is critical because of the high morbidity and case fatality of RSV disease and the frequent presence of significant co-pathogens among hematopoietic cell transplant recipients when it occurs during the peri-transplant period.

7. **Clinical cytomegalovirus (CMV) disease can be associated with which of the following problem(s)?**

   A. Gastroenteritis  
   B. Pneumonia  
   C. Hepatitis  
   D. Retinitis  
   E. All of the above

**Answer - E**

**Explanation:** Cytomegalovirus (CMV) continues to be an important complication after allogeneic HCT. The direct effects which have been extensively described include the spectrum of CMV disease manifestations. CMV gastroenteritis is the most common clinical presentation in this population. While pneumonia is the most serious manifestation, it has become relatively infrequent with current preventative strategies for CMV disease in hematopoietic cell transplant recipients. Other rare manifestations of CMV disease include hepatitis, retinitis and encephalitis.
8. Which of the following statements about cytomegalovirus (CMV) seroconversion and infection is correct?

A. Letermovir prophylaxis can result in lower risk of clinically significant CMV infection
B. Preemptive therapy with letermovir is an approved approach to reduce clinical CMV disease
C. Ganciclovir prophylaxis is clinically acceptable approach in allotransplant recipients
D. All of the above

Answer - A

Explanation: Cytomegalovirus (CMV) infection remains most common clinically significant infection after allogeneic hematopoietic cell transplantation. The use of antiviral prophylaxis (e.g. to prevent CMV seroconversion by polymerase chain reaction based surveillance) is hampered by the lack of reasonably atoxic and effective drugs. High-dose acyclovir or valacyclovir has been used for this purpose but the antiviral efficacy is quite low. Administration of ganciclovir and valganciclovir, while effective, are limited by clinically unacceptable myelotoxicity after allotransplant; therefore these agents are reserved as preemptive therapy (e.g. to prevent clinical disease after CMV seroconversion detected by polymerase chain reaction–based surveillance). (Choice C is incorrect) While, this strategy has become standard and has been successful in reducing the incidence of CMV, the CMV seropositivity and early CMV reactivation after hematopoietic cell transplantation remains associated with increased mortality. More recently, letermovir prophylaxis to prevent clinically significant CMV infection in CMV-seropositive patients beginning a median of 9 days after hematopoietic cell transplantation and administered through week 14 (approximately day 100 after transplantation) was highly effective, led to minimal side effects, and was associated with lower all-cause mortality than placebo through week 24 after allotransplant. (Choice A is correct and choice B is incorrect). Patients who were considered to be at protocol defined high-risk for CMV reactivation and clinical disease benefited the most from letermovir prophylaxis. (Table-1)

Table 1: Protocol defined high-risk for cytomegalovirus (CMV) reactivation and clinical disease

| Subjects meeting any one of the following criteria at the time of randomization |
|---|---|
| 1. Related donor with at least one HLA-mismatch at one of the specified three HLA gene loci (HLA-A, -B, or -DR) |
| 2. Unrelated donor with at least one HLA-mismatch at one of the specified four HLA gene loci (HLA-A, -B, -C, and -DRB1) |
| 3. HLA-haploidentical matched donor |
| 4. Cord blood as graft source |
| 5. Ex vivo T cell–depleted graft |
| 6. Graft versus host disease of ≥grade 2 that led to the use of 1 mg or more of prednisone (or its equivalent) per kilogram of body weight per day |
9. Letermovir prophylaxis versus placebo for cytomegalovirus (CMV) in hematopoietic cell transplantation by Marty and colleagues published in New England Journal of Medicine\textsuperscript{11}: Which of the following adverse effects was NOT observed in letermovir cohort?

A. Atrial fibrillation/flutter
B. Edema
C. Vomiting
D. Myelosuppression

Answer - D

Explanation: The data presented at Bone Marrow Transplant Tandem meeting in February, 2017\textsuperscript{15} led to approval of letermovir by both United States Food and Drug Administration (FDA)\textsuperscript{16} and the European Medicines Agency (EMA).\textsuperscript{17} The data, detailed in manuscript form, was later published.\textsuperscript{11} Vomiting was reported in 18.5\% of the patients who received letermovir and in 13.5\% of those who were in placebo arm; edema in 14.5\% and 9.4\%, respectively; dyspnea in 8.0\% and 3.1\%; myalgia in 5.1\% and 1.6\%; atrial fibrillation or flutter in 4.6\% and 1.0\%; and alanine aminotransferase levels of more than 5 times the upper limit of the normal range in 3.5\% and 1.6\%. The investigators of the study claim, that “further analysis of atrial arrhythmias did not show a relationship with letermovir exposure.”\textsuperscript{11} (Choices A, B and C are correct) The time to engraftment among patients who started letermovir or placebo before engraftment was similar in the two groups without evidence of myelotoxicity.\textsuperscript{11} (Choice D is incorrect) No patient discontinued letermovir owing to these events, and only two events met the criteria for being a serious adverse event.\textsuperscript{11}

References


16. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209939orig1s000,209940orig1s000lbl.pdf Accessed on November 11, 2017

April 2018 – take the quiz by clicking here.

1. Which statement about hematopoietic cell transplants for acute myeloid leukemia is correct?

   A. The disease status at the time of transplant and the donor type are the major predictors of post-transplant survival
   B. Disease status at the time of transplant is the only predictor of post-transplant survival
   C. In pediatric population, the disease status at the time of transplant is the only predictor of post-transplant survival
   D. In adult population, donor type is the only predictor of post-transplant survival

**Answer - A**

**Explanation:** The CIBMTR has data for 33,130 patients receiving an HLA-matched sibling (n=13,118) or unrelated donor (n=20,012) transplant for acute myeloid leukemia between 2005 and 2015. The disease status at the time of transplant and the donor type are the major predictors of post-transplant survival. The 3-year probabilities of survival after HLA-matched sibling transplant in this cohort was 59% ± 1%, 52% ± 1%, and 27% ± 1% for patients with early, intermediate, and advanced disease, respectively (Figure-1). The probabilities of survival after an unrelated donor transplant were 52% ± 1%, 49%± 1%, and 25% ± 1% for patients with early, intermediate, and advanced disease, respectively (Figure-2). Among 1,312 pediatric patients with acute myeloid leukemia receiving HLA-matched sibling transplant between 2005 and 2015, the 3-year probabilities of survival following transplant for early, intermediate, and advanced disease were 69% ± 2%, 60% ± 4%, and 29% ± 4%, respectively (Figure-3).

Figure- 3: Overview of survival after HLA-matched sibling donor hematopoietic cell transplantation for acute myeloid leukemia in patient population less than 18 years of age during the period of 2005 to 2015. D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2016.
2. Which statement about hematopoietic progenitor cell collection by apheresis is correct?

A. The procedure is highly selective for procurement of CD34\(^+\) cells
B. The procedure involves collection of white blood cells from whole blood using centrifugation-based techniques
C. The procedure is limited to two type of apheresis machines
D. All of the above

Answer – B

Explanation: Hematopoietic progenitor cell collection by apheresis involves the extracorporeal separation and collection of white blood cells from whole blood using centrifugation-based techniques.\(^2\)\(^3\) The devices can collect these cells continuously, or intermittently through multiple cycles during the procedure. Separation and collection of white blood cells are optimized such that mononuclear cells (of which CD34\(^+\) cells are a subset) are enriched; however, such optimization is not completely selective and other cells, such as red blood cells and granulocytes may present at various concentrations in the final product.\(^2\)\(^3\)

Apheresis devices used for hematopoietic progenitor cell collection may differ in their hardware specifications, separation technologies and extracorporeal volume requirements; however all of them are considered having equivalent efficacy in their ability to collect CD34\(^+\) cells.\(^2\)\(^3\) Commonly used devices include the COBE Spectra (v.6.0 and 6.1; Terumo BCT, Lakewood,CO), Spectra Optia (Terumo BCT, Lakewood,CO), Amicus (Fresenius-Kabi, Lake Zurich, IL) and COM.TEC (Fresenius-Kabi, Lake Zurich, IL).\(^2\)\(^3\) The COBE Spectra and Spectra Optia have the capability to collect mononuclear cells continuously after separation in the centrifugation bowl.\(^2\) The Amicus and COM.TEC collects mononuclear cells intermittently (“cyclic mononuclear collection”) during multiple cycles over the duration of the procedure although flow of blood from the patient into the device and back to the patient is a continuous process.\(^2\)\(^3\) Refer to Table 1 for detailed listing of apheresis devices and their process.

Table 1: Devices for hematopoietic progenitor cell collection by apheresis and their process of collection\(^4\)

<table>
<thead>
<tr>
<th>HPC(A) Device</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. COBE Spectra – Manual (v.4.7) (Terumo BCT, Lakewood,CO)</td>
<td>Continuous blood flow; continuous MNC collection</td>
</tr>
<tr>
<td>2. COBE Spectra – Auto (v.6.0 and 6.1) (Terumo BCT, Lakewood,CO)</td>
<td>Continuous blood flow; cyclic MNC collection</td>
</tr>
<tr>
<td>3. Spectra Optia (Terumo BCT, Lakewood,CO)</td>
<td>Continuous blood flow; cyclic MNC collection</td>
</tr>
<tr>
<td>4. Amicus (Fresenius-Kabi, Lake Zurich, IL)</td>
<td>Continuous blood flow; cyclic MNC collection</td>
</tr>
<tr>
<td>5. COM.TEC (Fresenius-Kabi, Lake Zurich, IL)</td>
<td>Continuous blood flow; cyclic MNC collection</td>
</tr>
<tr>
<td>6. Haemonetics MCS (Haemonetics Corp)</td>
<td>Intermittent blood flow; cyclic buffy coat collection</td>
</tr>
</tbody>
</table>
Abbreviations: HPC(A), hematopoietic progenitor cell collection via apheresis; MNC, mononuclear cell
Adopted from [3]

3. **Which statement related to the use of citrate as an anticoagulant in acid-citrate dextrose-solution A during hematopoietic progenitor cell collection by apheresis is correct?**

   A. It is exclusively metabolized by the liver
   B. Mild hyperkalemia is a common occurrence
   C. Severe citrate toxicity is not uncommon complication
   D. Citrate toxicity is manageable in most cases

**Answer - D**

**Explanation:** The metabolism of citrate is mainly in kidney(s) and liver; therefore, patients with conditions affecting these organs are at increased risk of severe citrate toxicity. The most common adverse effect of hematopoietic progenitor cell collection by apheresis is symptomatic hypocalcemia caused by infusion of citrate related calcium chelation. Hypocalcemia is usually manifested by mild perioral and/or acral paresthesia requiring operator to slow the reinfusion rate. The benefit of oral calcium supplements in this setting is questionable, although the practice is widespread. Severe citrate toxicity is uncommon during apheresis procedure; signs may range from involuntary carpopedal spasms, nausea and vomiting to frank tetany with spasms in other muscle groups, including life threatening laryngospasms and grand-mall seizures. Acute severe hypocalcemia leading to fatal cardiac arrhythmia has been reported. Controlled infusion of 10% calcium gluconate or calcium chloride is effective in management of these complications. Studies performed with and without calcium gluconate or calcium chloride show the effectiveness of continuous calcium infusion for the prevention of mild to moderate citrate toxicity.

4. **Which test addresses the suitability of the donor/recipient?**

   A. Pregnancy test
   B. Recent travel to South Africa
   C. Anti-nuclear antibody test
   D. Hepatitis panel

**Answer: A**

**Explanation:** Issues that deal with the safety of the donor/recipient during and after hematopoietic cell collection process defines donor suitability. Strictly, suitable donor or recipient refers to issues that relate to the general health or medical fitness of the donor or recipient to undergo the collection procedure or therapy. Donor eligibility places emphasis on safety of the recipient and healthcare provider such as risk of transmitting of infectious, hematologic or immunological diseases. Issues related to determination of donor eligibility are covered in the “hematopoietic progenitor cell, apheresis and marrow donor history questionnaire form” (www.aabb.org/tm/questionnaire).
5. According to the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee of ISCT-EBMT (JACIE) International Standards for Hematopoietic Cellular Therapy, which statement regarding pregnancy testing is correct?

A. Serum pregnancy testing is required for all female donors
B. A pregnancy test shall be performed for all female donors with childbearing potential within seven days prior to starting the donor mobilization regimen
C. A pregnancy test shall be performed for all female donors with childbearing potential within 5 days prior to the initiation of the recipient’s preparative regimen
D. A pregnancy test shall be performed for all female donors within 10 days prior to the initiation of the recipient’s preparative regimen

Answer: B

Explanation: According to 6th edition of FACT-JACIE standards for hematopoietic cellular therapy, a pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to starting the donor mobilization regimen and, as applicable, within seven (7) days prior to the initiation of the recipient’s preparative regimen. The 7th edition of FACT-JACIE Standards are being developed and the draft may be viewed at http://www.factwebsite.org/Inner.aspx?id=1475&blogid=86.

References:

1. Which of the following Dynamic International Prognostic Scoring System (DIPSS) or DIPSS plus risk categories is widely accepted indication for allogeneic hematopoietic cell transplantation for primary myelofibrosis?

A. Low-risk DIPSS
B. Intermediate-1 risk DIPSS plus
C. Intermediate-2 risk DIPSS or DIPSS plus
D. None of the above

Answer - C

Explanation: The Dynamic International Prognostic Scoring System (DIPSS; which considers patient age, symptoms, anemia, leukocytosis, and the presence of circulating blasts)\(^1\)\(^-\)\(^3\) and the DIPSS- plus (adding adjusted DIPSS, cytogenetics, thrombocytopenia and red blood cell transfusion dependence as risk factors)\(^4\) are the current standard measures for prog nostication in patients with primary myelofibrosis (PMF) and are often also applied to patients with post-polycythemia or post-essential thrombocythemia myelofibrosis.\(^4\) Patients classified as intermediate-2 or high-risk by either of these scoring systems (Table 1) have median life expectancies of 3 to 4 and 1 to 2 years, respectively, whereas patients with low- or intermediate-1 risk may have life expectancies of 10 to 20 years and 8 to 10 years, respectively. On this basis, allogeneic hematopoietic cell transplantation is typically recommended for patients with intermediate-2 and high-risk disease but not for those in the lower risk categories (with few exceptions).\(^3\)\(^5\) Noteworthy, preliminary data indicate that the addition of somatic DNA mutations to DIPSS/DIPSS plus models will further improve risk stratification.\(^3\)\(^,\)\(^6\)\(^,\)\(^7\) Conceivably, different transplant strategies will variably affect the impact of different mutations on the outcome of allogeneic hematopoietic cell transplantation.\(^3\)

Table 1 – Primary Myelofibrosis Risk Categories Based on DIPSS and DIPSS plus

<table>
<thead>
<tr>
<th>DIPSS</th>
<th>Risk</th>
<th>DIPSS plus*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>1 to 2</td>
<td>Intermediate-1</td>
<td>1</td>
</tr>
<tr>
<td>3 to 4</td>
<td>Intermediate-2</td>
<td>2</td>
</tr>
<tr>
<td>5 to 6</td>
<td>High</td>
<td>≥3</td>
</tr>
</tbody>
</table>

* Add 1 if DIPSS intermediate-1, add 2 if DIPSS intermediate-2, add 3 if DIPSS high = adjusted for DIPSS

2. Which statement about chronic graft-versus-host disease (cGvHD) is correct?

A. The outcome with current therapies for cGvHD is unsatisfactory
B. The incidence of cGvHD has decreased
C. Approximately, 20% of allogeneic hematopoietic cell transplant recipients develop cGvHD
D. All of the above statements are true

Answer - A

Explanation: Chronic graft-versus-host disease (cGvHD) currently represents the leading cause of nonrelapse mortality and morbidity after allogeneic hematopoietic cell transplantation (allo-HCT). In parallel with an increased use of granulocyte colony-stimulating factor (G-CSF)-mobilized hematopoietic progenitor cell products as a graft source, the incidence of cGvHD has increased. Currently, up to 50% of allo-HCT recipients develop this multisystem inflammatory disease that occurs late after transplantation. The outcome with current therapies for cGvHD is unsatisfactory. Standard primary treatment is glucocorticoids with or without other immunosuppressive agents; however, nearly 50% of patients continue to have inadequate control of their cGvHD and require second-line systemic treatment. Moreover, systemic glucocorticoids are wrought with long term complications, thereby increasing morbidity and mortality in this patient population that are otherwise cured of their original malignancy.

3. Which statement about ABO group types is correct?

A. ABO antigen inheritance is dependent on HLA inheritance
B. ABO antigens are expressed exclusively on red blood cells
C. Antibodies directed against the ABO antigens appear during the first year of life
D. Genes determining ABO groups are located on chromosome 6

Answer - C

Explanation: The genes encoding ABO carbohydrate glycosyltransferases are located on chromosome 9q34, far from the genes encoding HLA (chromosome 6p21), and are, therefore, inherited independently. In general, HLA-matched allogeneic hematopoietic cell donors may have ABO incompatibility in approximately 25% to 50% of transplantations. The ABO blood group antigens are immunodominant sugars that are expressed throughout the body on the surface of red blood cells (RBCs), platelets, white blood cells, vascular and organ endothelium, and in plasma. Blood typing is determined by the presence of blood group antigens on the surface of RBCs (forward typing) as well as by the presence of blood group antibodies in the plasma (reverse typing). These antibodies, termed isohemagglutinins, are directed against the ABO antigens lacking on the patient’s cells, and are not present at birth but appear during the first year of life.

4. Which statement about refined Disease Risk Index (DRI) as developed by Armand and colleagues for allogeneic hematopoietic cell transplantation is correct?

A. It was developed following analysis of prospective data
B. It stratified patients into risk groups across all age groups
C. It stratified patients into 4 groups with very different overall survival
Correct Answer – C

Explanation: The outcome of allogeneic hematopoietic cell transplantation (allo-HCT) is predominantly influenced by disease type and status, it is essential to be able to stratify patients undergoing allo-HCT by disease risk. Armand and colleagues (2014)\textsuperscript{16} validated and refined the Disease Risk Index (DRI) after analyzing the outcomes of 13,131 adult (>18 years of age) patients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) who underwent allo-HCT (excluding syngeneic transplantations) between 2008 and 2010. Among the 17, 223 patients in this data set, investigators excluded 2,361 patients with missing disease type, disease subtype, or disease status information; patients transplanted for nonmalignant or rare disorders (e.g., histiocytic disorders, large granular lymphocyte or natural killer cell leukemias); and 1,731 pediatric (age <18 years) patients. The newer DRI stratified patients into four risk groups with 2 year overall survival ranging from 64 to 24% and is the strongest prognostic factor, regardless of pre-specified age, conditioning regimen intensity, graft source, or donor type.\textsuperscript{16-17} This tool should not be fixed but should instead be refined by the transplant community as new information becomes available.\textsuperscript{16}

5. Which statement about marrow microenvironment is correct?

A. Cellular composition of marrow niche is completely characterized
B. Activated hematopoietic stem cells function in hypoxic zones of the marrow
C. CXCL12 adventitial reticular cells are specialized mesenchymal stem cells
D. CXCL12 adventitial reticular cells are source of stromal derived factor-1

Correct Answer - D

Explanation: The fine-tuning of hematopoietic stem cells (HSCs) properties takes place in a specialized microenvironment in the marrow, termed the HSC niche. Cellular composition of stroma remains incompletely characterized, largely due to paucity of phenotypic markers that unambiguously discriminate between the distinct stromal cell sub-populations.\textsuperscript{18-20} In steady-state hematopoiesis, a complex interplay between the cell-extrinsic cues and the cell-intrinsic regulatory pathways regulate the fate of HSCs.\textsuperscript{18} Hypoxic zones (“metabolic niche”) in the marrow are close to the bone and far from the capillaries which harbor cells with a profound long-term (LT) repopulating potential. From the laboratory standpoint, hypoxia (in the hypoxic zones) favors low Hoechst dye uptake and slow metabolism, the hallmarks of quiescent HSCs. The CXCL12 adventitial reticular (CAR) cells release abundant CXCL12 (also known as stromal derived factor-1) chemokine for the CXCR4 receptor expressed on HSCs. CXCL12 are responsible for HSC homing into the niche. CAR cells are also major producers of stem cell factor (SCF), the ligand for c-kit receptor, thus providing the HSCs and progenitor cells with key regulatory factors. CAR cells are not mesenchymal stem cells (MSC).\textsuperscript{18}


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1. Which statement about parainfluenza virus infection after hematopoietic cell transplant is NOT correct?
   
   A. In several prospective studies, ribavirin had no impact on progression from upper to lower respiratory tract infection
   B. Data do not support treating patients with parainfluenza virus associated upper respiratory tract infection.
   C. The treatment with intravenous immunoglobulins remains controversial
   D. The treatment with ribavirin remains controversial

   **Answer - A**

   **Explanation:** In several retrospective studies (not prospective studies), ribavirin had no impact on viral shedding, symptom and hospitalization length, progression to lower respiratory tract infection (LRTI), or mortality in patients with parainfluenza virus (PIV). Experience from Fred Hutchinson Cancer Research Center with aerosolized ribavirin suggested a moderate reduction in overall mortality, but not in death due to respiratory failure. A recent systematic review evaluated aerosolized or systemic ribavirin in 10 retrospective studies of HCT recipients and hematologic malignancy patients and found no difference in PIV-associated mortality or in progression to LRTI. The impact of intravenous immunoglobulins (IVIG) alone remains to be determined, although IVIG in PIV-LRTI cases did not reduce mortality. Current treatment options are limited and data do not support treating patients with PIV-associated upper respiratory tract infection. However, some centers are using ribavirin and IVIG especially in treating LRTI. New promising drugs are in development.

2. Which statement about trends of autologous hematopoietic cell transplants in U.S is correct?
   
   A. In 2016, the number of transplants for lymphomas increased
   B. In 2016, the number of transplants for multiple myeloma decreased
   C. In 2016, the number of transplants for lymphomas decreased
   D. Choices A and B are correct

   **Answer – C**

   **Explanation:** In 2016, the number of transplants for lymphomas decreased after a steady increase since 2007, and may represent the increased availability of novel non-transplant therapeutic options for some lymphoma subsets. The annual number of autologous transplants for multiple myeloma is increasing steadily. In 2016, 8,776 myeloma autologous transplants were performed, up from 5621 in 2010.
3. Which allogeneic recipient with HLA-mismatch transplant is more likely to develop anti-HLA antibody or antibodies?

A. Child to mother HLA-mismatch haploidentical transplant  
B. History of allogeneic blood transfusion(s)  
C. Multiparous recipient  
D. All of the above

Answer - D

Explanation: The human major histocompatibility complex (MHC), also termed the human leukocyte antigen (HLA) complex, consists of more than 200 genes located close together on chromosome 6.\(^8\) The molecules encoded by genes within this region are of fundamental importance to the innate and antigen-specific immune systems.\(^8\) The high allelic variability represents a barrier against successful HLA-mismatch transplantation. Exposure to non-self HLA antigen can result in the development of anti-HLA antibodies in transplant recipients, which in certain circumstances are donor specific and can cause poor graft function and/or graft (transplant) failure. From the data in adults with hematological malignancies who underwent HLA-haploidentical transplants, pregnancy appears to be a powerful inducer of anti-HLA antibodies and donor specific antibody or antibodies especially the multiparous females.\(^10\) Besides pregnancy, transfusion of allogeneic blood products also has been identified as a common risk factor for developing anti-HLA antibodies, both in healthy individuals and transplant recipients.\(^11-14\)
4. Which statement about anti-HLA antibody or antibodies is NOT correct?

A. Not all anti-HLA antibodies are directed against donor’s mismatch HLA antigens
B. Evaluation of anti-HLA antibodies should be performed in all patients receiving HLA-mismatch transplants
C. The risk of transfusion-associated HLA alloimmunization is higher in patients receiving red blood cell transfusion compared to platelet transfusion
D. Anti-HLA antibodies may be unique to a specific allele or limited group, or recognize an epitope that is shared by more than one HLA molecules

Correct Answer - C

Explanation: In adult patients with hematologic malignancies referred for allogeneic hematopoietic cell transplantation, the reported total prevalence of anti-HLA antibodies can be up to 40%, especially in HLA-mismatched transplantation. However, not all of these anti-HLA antibodies are directed against donor’s mismatch HLA antigens. The risk of transfusion-associated HLA alloimmunization is higher in patients receiving leukocyte and platelet transfusions compared to erythrocytes, since leukocytes and platelets express large number of HLA antigens. These anti-HLA antibodies may be unique to a specific allele or limited group, or recognize an epitope that is shared by more than one HLA molecules resulting in cross-reactivity. Evaluation of anti-HLA antibodies should be performed in all patients receiving HLA-mismatch transplants to avoid graft failure and improve overall survival.

5. Which statement about genome editing approaches is correct?

A. They can mediate gene addition only
B. They rely on bacterial nucleases only
C. They can be performed only on cells ex vivo
D. Advancement in genome editing with programmable nucleases have revolutionized gene therapy

Answer - D

Explanation: Gene editing technologies are in their translational and clinical infancy but are expected to play an increasing role in the field of cell-based genetic therapies. Genome editing technologies have been developed that are based on engineered or bacterial nucleases. The advancement on genome editing with such programmable nucleases, including zinc-finger nuclease (ZFN), TAL effector nuclease (TALEN), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated RNA-guided endonuclease Cas9 (CRISPR/Cas9), have revolutionized gene therapy per se, and primarily hematopoietic stem cell gene therapy (HSC-GT). In contrast to viral vectors, which can mediate only gene addition, genome editing approaches offer a precise scalpel for gene addition, gene ablation, and gene “correction” and other highly targeted genome modifications in cells. Genome editing can be performed on cells ex vivo or the editing machinery can be delivered in vivo to effect in situ genome editing.
1. How I treat respiratory viral infections in the setting of intensive chemotherapy or hematopoietic cell transplantation


1. Which statement about engraftment syndrome is INCORRECT?

A. Spitzer criteria may be used to diagnose this clinical condition
B. It does not occur in the setting of allogeneic hematopoietic cell transplant
C. Maiolino criteria may be used to diagnose this clinical condition
D. G-CSF should be stopped immediately

Answer - B

Explanation: Engraftment syndrome is one of the early complications after hematopoietic cell transplantation (HCT) and is believed to be triggered by injury to the vascular endothelium. The presence of skin rash, hypoxemia, or diarrhea is frequently observed during the period of neutrophil recovery in HCT (autologous or allogeneic) settings. Most cases of engraftment syndrome have been described after the introduction of growth factors and transplants using peripheral blood grafts. Generally, Maiolino or Spitzer criteria are used to diagnose this clinical condition. G-CSF should be stopped immediately. Initiation of corticosteroids, in correct clinical setting (see Table-1), is also an important therapeutic intervention.

Table 1: Maiolino and Spitzer criteria for the diagnosis of engraftment syndrome

<table>
<thead>
<tr>
<th>Maiolino criteria (2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninfectious (without clinical or microbiologic documentation or without response to antimicrobial treatment) fever (&gt;38°C) 24 hours before or at any time after neutrophil engraftment</td>
</tr>
<tr>
<td><strong>PLUS</strong> any of the following</td>
</tr>
<tr>
<td>• Cutaneous rash (maculopapular exanthema &gt;25% body surface area)</td>
</tr>
<tr>
<td>• New pulmonary infiltrates (on chest x-ray or CT scan without other causes) from noncardiogenic pulmonary edema</td>
</tr>
<tr>
<td>• Noninfectious diarrhea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spitzer criteria (2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A diagnosis of is established by the presence of all three major criteria or two major criteria and one or more minor criteria. It should occur within 96 hours of engraftment (neutrophil count of &gt;500/ml for 2 consecutive days).</td>
</tr>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>• Temperature of &gt;38.3°C with no identifiable infectious etiology</td>
</tr>
<tr>
<td>• Erythrodermatous rash involving more than 25% of body surface area and not attributable to a medication</td>
</tr>
</tbody>
</table>
Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates consistent with this diagnosis, and hypoxia

Minors criteria

- Hepatic dysfunction with either total bilirubin >2 mg/dl or transaminase levels >two times normal
- Renal insufficiency (serum creatinine of >two times baseline)
- Weight gain >2.5% of baseline body weight
- Transient encephalopathy unexplainable by other causes

†In the setting of allogeneic hematopoietic cell transplant, additional clinical and pathologic symptoms and signs of graft-versus-host disease should at least initially be absent.⁸

2. According to data reported to CIBMTR, what is 3-year overall survival among auto-transplant recipients for multiple myeloma in the years since 2005?

   A. 50-60%
   B. 60-70%
   C. 70-80%
   D. 80-90%

Answer – C

Explanation: Outcomes after autologous hematopoietic cell transplant with the use of novel agents and treatment paradigms such as post-transplant maintenance in the treatment of multiple myeloma have led to significant impact in overall survival. The 3-year overall survival among auto-transplant recipients for multiple myeloma were 68% ± 1%, 73% ± 1% and 77% ± 1% of the transplants that were performed in 2001 to 2004, 2005 to 2008 and 2009 to 2012, respectively.⁹
3. Which statement about chimeric antigen receptor modified T cell (CAR T cell) therapy is INCORRECT?

A. CAR T cell therapy has the ability to harness a patient's immune system to target neoplastic cells
B. Mechanisms of reducing toxicities and preventing antigen escape with CAR T cell therapies are fully elucidated
C. CD19 antigen is not the only identified anti-tumor target for CAR T cell therapy.
D. Mechanisms of incomplete tumor elimination by CAR T cells are being further investigated

Answer - B

Explanation: The ability to harness a patient's immune system to target neoplastic cells is now transforming the treatment of many cancers, including hematologic malignancies. The adoptive transfer of T cells selected for tumor reactivity, or engineered with natural or synthetic receptors has emerged as an effective modality, even for patients with tumors that are refractory to conventional therapies. The most notable example of adoptive cell therapy is with T cells engineered to express synthetic chimeric antigen receptors (CARs) that reprogram their specificity to target tumor antigen (e.g. CD19). CD19 is an excellent target for CAR-T-cell therapy in B-cell malignancies since it is expressed across a broad range of B-cell differentiation stages, and is ubiquitously expressed. Additional potential CAR targets (e.g. BCMA, CD138, CD30, SLAM7 etc.) for patients with variety of hematological malignancies have been identified and are undergoing robust clinical investigation. Ongoing research in CAR T cell therapy is focused on understanding the mechanisms of incomplete tumor elimination, reducing toxicities, preventing antigen escape, and identifying suitable targets and strategies based on established and emerging principles of synthetic biology of this technique.
4. Which statement about Natural Killer (NK) cell receptors is CORRECT?

A. NK cell receptors are encoded by genes that undergo somatic rearrangements
B. NK cell exclusively have activating receptors
C. All NK cell receptors are referred to as, “immunoglobulin-like receptors”
D. NK cell inhibitory receptors recognize major histocompatibility complex (MHC) class I molecules

Answer - D

Explanation: NK cells are lymphocytes that belong to the innate immune system and constitute approximately 10% of the mononuclear cells in the blood. They have both, cytotoxic and regulatory properties. Unlike the receptors of B and T lymphocytes, NK cells do not undergo clonotypic gene rearrangements to express antigen receptors and may efficiently determine “non-self” from “self”. The NK cell receptors may be activating or inhibitory and are not limited to immunoglobulin-like receptors (KIRs). Inhibitory receptors on NK cells primarily recognize MHC class I molecules as “self”, which prevents NK cell mediated cytotoxic activity. The ability of NK cells to become activated by host cells that lack MHC class I is called “recognition of missing self”

5. Which statement best describes the term “adult stem cell plasticity”

A. Ability of tissue-specific stem cells to acquire the fate of cell types different from the tissue of origin
B. Ability of stem cells to migrate from bone marrow niche to bloodstream
C. Reprogramming of activated hematopoietic stem cells to G0 state
D. All of the above

Answer - A

Explanation: The term “adult stem cell plasticity” defines the ability of tissue-specific stem cells to acquire the fate of cell types different from the tissue of origin i.e. similar to the differentiation ability of embryonic stem cells. Studies show that pluripotent stem cells with properties similar to embryonic stem cells (called induced pluripotent stem cells) can be induced readily from differentiated somatic cells. This finding has led to great excitement regarding the potential of these cells for improving the understanding and treatment of disease and has highlighted the need for a better mechanistic understanding of the reprogramming process. The generation of induced pluripotent stem (iPS) cells in the laboratory of Shinya Yamanaka, has demonstrated that adult mammalian cells can be reprogrammed to a pluripotent state by the enforced expression of a four defined pluripotency factors referred to as “Yamanaka factors”: OCT4, SOX2, KLF4 and c-MYC. Specific somatic cells can be used to derive iPS cells, which can then be induced to undergo differentiation into various types of somatic cell, all with the same genetic information. For example, dopaminergic neurons could be generated from the cells of a patient with Parkinson's disease and then transplanted to replace those neurons that have been lost. These differentiated cells can also be used in disease models for studying the molecular basis of a broad range of human diseases that are otherwise difficult to study (for instance, those that affect brain cells) and for screening the efficacy and safety of drug candidates for treating these diseases. Despite numerous technical advances in the derivation of human iPS cells, relatively little is known about their molecular and functional equivalence to embryonic stem cells, which could affect their potential therapeutic utility. Addressing this question will require a careful analysis of the genomic and epigenomic integrity of human iPS cells, as well as the development of optimized differentiation
protocols and reliable assays to evaluate the functionality of iPS cell-derived specialized cells. For example, epigenetic changes might cause the unexpected immunogenicity of transplanted autologous iPS cells.

References
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1. In what time frame does delayed hemolysis after minor ABO incompatible hematopoietic cell transplant tend to occur?

A. 7-17 days  
B. 30-45 days  
C. 61-90 days  
D. After 100 days

Answer - A

Explanation: Delayed hemolysis following minor ABO incompatible hematopoietic cell transplant tend to occur between 7 to 17 days. This condition should be suspected in a patient with an unexplained acute drop in hemoglobin (specifically during the hematopoietic engraftment phase). The diagnosis is confirmed by positive hemolytic laboratory indices. The pathophysiology is explained by generation of blood group isohemagglutinins by donor’s B lymphocytes (“passenger lymphocytes”) in the graft.

2. Which is the predominant graft source among adults (age≥18 years) who receive unrelated donor transplants?

A. Cord blood  
B. Peripheral blood  
C. Bone marrow  
D. Cord blood combined with bone marrow

Answer - B

Explanation: Among adult recipients of unrelated donor transplants, mobilized peripheral blood stem cells is also the predominant graft source, accounting for 78% of unrelated donor transplants in 2016. This practice continues to remain high despite randomized clinical trial results demonstrating increased late complications such as chronic graft-versus-host disease with peripheral blood grafts. The number of umbilical cord transplants in adults peaked at 12% in 2010 but has since declined to <10% and accounted for 8% of unrelated donor grafts in 2016 among adult recipients.
3. What is the approximate 3-year probability of survival after HLA-matched sibling transplant in patients with chemosensitive diffuse large B cell lymphoma (DLBCL)?

A. 25-30%
B. 45-55%
C. 70-75%
D. 75-80%

Answer - B

Explanation: Allogeneic hematopoietic cell transplant (HCT) for treatment of DLBCL is generally used only in patients with aggressive disease that has been resistant to previous therapies, including autologous transplant. Among the 1,070 patients who underwent an HLA-matched sibling HCT for DLBCL from 2005 to 2015, the 3-year probabilities of survival were 51% ± 2% and 27% ± 3% for patients with chemosensitive and chemoresistant disease, respectively.³
4. Which statement about infusion of thawed hematopoietic cell therapy product is CORRECT?

A. It should be infused within 90 minutes
B. It should be infused within 180 minutes
C. It should be infused between 30 to 60 minutes
D. It should be infused as soon as possible.

Answer - D

Explanation: Delaying infusion of thawed cell therapy product can result in cell clumping plus dimethyl sulfoxide (DMSO) in liquid phase adversely affects cell viability. Therefore, thawed product administration should be completed as soon as possible. In the case of transplants using more than one cellular therapy product (e.g., double cord blood transplant), the program must wait to administer the second product until it is determined that the first unit was administered safely with no adverse events.

5. Which of the differentiation cascade correctly reflect step-wise hierarchy of human stem and progenitor hematopoietic cells

A. Pluripotent stem cells → totipotent stem cell → multipotent stem cells → oligopotent precursor cells → unipotent precursor cells
B. Totipotent stem cell → pluripotent stem cells → multipotent stem cells → oligopotent precursor cells → unipotent precursor cells
C. Totipotent stem cell → multipotent stem cells → pluripotent stem cells → oligopotent precursor cells → unipotent precursor cells
D. Totipotent stem cell → pluripotent stem cells → oligopotent precursor → multipotent stem cells cells → unipotent precursor cells
**Answer - B**

**Explanation:** A fertilized egg (zygote) represents a totipotent stem cell, a cell with unrestricted differentiation potential; the only cell with the capacity to give rise to all cells necessary for the development of fetal (including placenta) and adult organs. Embryonic cells, forming a cluster inside the blastocyst, are pluripotent stem cells, capable to generate a variety of specialized cell types, but are limited in their differentiation potential since it is unable to develop into a fetus (unable to develop placenta). Further, hematopoietic developmental processes lead to generation of multipotent stem cells residing in adult somatic tissues. Their physiological functions are to maintain tissue homeostasis by replenishing mature cell populations of the given tissue or organ, and to respond to stress by repairing damaged tissue. For example, multipotent stem cells from a mesodermal tissue like the blood can make all the cells of the blood, but cannot make cells of a different germ layer such as neural cells (ectoderm) or liver cells (endoderm). Unipotent cells make cells of a single cell type. An example is a germ cell stem cell that makes the cells that mature to become egg or sperm, but not other cell types.

**References:**

1. Which of the following statements about mechanism of action of granulocyte colony-stimulating factor (G-CSF) is CORRECT?

A. G-CSF upregulates CXCL12 synthesis  
B. G-CSF deactivates proteases in bone marrow  
C. G-CSF upregulates SDF-1 expression  
D. G-CSF might be involved in cleavage of CXCR4

**Answer - D**

**Explanation:** Granulocyte colony-stimulating factor (G-CSF) continues to be the most widely used agent for inducing egress of CD34+ cells. G-CSF is a recombinant cytokine that functions as a myeloid growth factor whose mechanism of action is incompletely understood. Ongoing research has uncovered initially unsuspected polyfunctionality for G-CSF. Biologic data suggest that G-CSF down-regulates CXCL12 (also known as, stromal derived factor-1[SDF-1]) and activates CD26 protease, thereby causing integrin-β1 dysfunction and ultimately disruption of hematopoietic stem cell niche interaction. Following G-CSF administration, the marrow microenvironment is rich in proteolytic enzymes released by neutrophils, including metalloproteinase-9, neutrophil elastase, and cathepsin G. The metalloproteinase-9, neutrophil elastase, and cathepsin G can cleave and functionally inactivate CXCL12 (SDF-1). Furthermore, there is evidence to suggest that CXCR4 (receptors expressed on CD34+ cells) may be proteolytically cleaved by G-CSF. This cleavage of CXCR4 on mobilized CD34+ cells results in the loss of chemotaxis in response to the CXCR4 ligand, the chemokine CXCL12 (SDF-1).

2. **AETHERA trial** aimed to assess whether brentuximab vedotin improves progression free survival when given as early consolidation after autologous hematopoietic cell transplantation in subjects (age ≥18 years) with high-risk relapsed and primary refractory classic Hodgkin’s lymphoma.

Which of the following statements is CORRECT?

A. It was a multicenter single-arm prospective trial  
B. Brentuximab vedotin improved progression free survival  
C. The trial was terminated early due to poor accrual  
D. Brentuximab vedotin was administered at a dose of 1.2 mg/kg every 3 weeks for 2 years

**Answer – B**

**Explanation:** AETHERA was a randomized double-blind, placebo-controlled, phase III trial at 78 sites in North America and Europe. Patients with high-risk relapsed or primary refractory classic Hodgkin’s lymphoma who had undergone autologous hematopoietic cell transplantation were randomly assigned, by fixed-block randomization with a computer-generated random number sequence, to receive 16 cycles of 1.8 mg/kg brentuximab vedotin or placebo intravenously every 3 weeks, starting 30-45 days after transplantation. Randomization was stratified by best clinical response after completion of salvage chemotherapy (complete response versus partial response.
versus stable disease) and primary refractory Hodgkin’s lymphoma versus relapsed disease less than 12 months after completion of frontline therapy versus relapse 12 months or more after treatment completion. Patients and study investigators were masked to treatment assignment. Analysis was by intention to treat. Between April 6, 2010, and Sept 21, 2012, patients were randomly assigned to the brentuximab vedotin group (n=165) or the placebo group (n=164). Progression-free survival by independent review was significantly improved in patients in the brentuximab vedotin group compared with those in the placebo group (hazard ratio 0.57, 95% CI 0.40-0.81; p=0.0013). Median progression-free survival by independent review was 42.9 months (95% CI 30.4-42.9) for patients in the brentuximab vedotin group compared with 24.1 months (11.5-not estimable) for those in the placebo group. The study reported consistent benefit (hazard ratio <1) of brentuximab vedotin consolidation across all analyzed (study defined high-risk and refractory) subgroups.5

3. Which statement about autologous transplant and post-transplant consolidation therapy in classic Hodgkin’s lymphoma is CORRECT?

A. Autologous hematopoietic cell transplantation is the standard of care for patients in whom frontline therapy has been ineffective and who are regarded as transplant eligible on the basis of disease status and ability to tolerate the treatment.

B. Roughly 30% of patients might be cured with autologous transplantation in relapsed or refractory settings

C. Consolidation therapy with brentuximab vedotin is the standard of care approach for all patients after autologous transplantation.

D. A and C

Answer - A

Explanation: High-dose therapy and autologous hematopoietic cell transplantation is the standard of care for patients in whom frontline therapy for classic Hodgkin’s lymphoma has been ineffective and who are regarded as transplant eligible on the basis of disease status and ability to tolerate the treatment.5-7 This treatment is based on findings from two studies6-7, which showed a decreased rate of disease progression and a pattern for improved overall survival. Roughly 50% of patients might be cured after autologous transplantation; however, most patients with unfavorable risk factors progress after transplantation.6-10 Risk factors that have been repeatedly associated with strong prognostic value in identification of patients who might benefit from additional therapy after autologous transplantation include (i) a history of Hodgkin’s lymphoma refractory to frontline therapy or (ii) a short time to first relapse, (iii) presence of extranodal disease before transplantation, (iv) absence of chemosensitivity to salvage therapy before transplantation, and (v) presence of residual disease at the time of transplantation.8-16 In AETHERA trial3, eligible patients had at least one of the following risk factors for progression after autologous transplantation: primary refractory Hodgkin’s lymphoma (failure to achieve complete remission, as determined by investigator), relapsed Hodgkin’s lymphoma with an initial remission duration of less than 12 months, or extranodal involvement at the start of pre-transplantation salvage chemotherapy.
4. Which of the following reflects distinct hematopoietic stem cell phenotypic signature (flow cytometry-based characterization)

A. Lin*, CD34+, CD38+  
B. Lin+, CD34+, CD38+  
C. Lin*, CD34*, CD38-  
D. Lin+, CD34*, CD38-

Answer - C

Explanation: Despite the availability of methods that greatly facilitate and enhance the precision of studies with well-defined cell populations, genuine human hematopoietic stem cells have not been either quantified or purified, and thus remain at present less well defined than murine hematopoietic stem cells. Therefore, one must always keep in mind that phenotypic labels assigned to defined populations (e.g. the most primitive long-term hematopoietic stem cells) signify, at best, heterogeneous fractions only enriched in the population of interest. Keeping these limitations in mind, the most primitive human hematopoietic stem cells seems to express CD34 and lack Lin (lineage surface markers) and CD38 cell surface antigens and have the capacity to reconstitute sublethally irradiated non-obese diabetic/severe combined immunodeficiency or Rag2⁻γc⁻ model.

5. Which statement about overall utilization of unrelated donors in pediatric allogeneic transplants is CORRECT?

A. Bone marrow remains the most common graft source  
B. Use of umbilical cord blood peaked in 2009  
C. Peripheral blood accounted for 21% of pediatric unrelated donor graft type in 2016.  
D. All of the above

Answer – D

Explanation: Bone marrow remains the most common graft source for unrelated donors accounting for 50% in 2016. The use of umbilical cord blood peaked in 2009 at 48% of unrelated donor transplants but has since shown a downward trend and is at 28% of pediatric unrelated donor transplant activity in 2016. Peripheral blood accounted for 21% of pediatric unrelated donor graft type in 2016.
Figure 1: Overall utilization of unrelated donors in pediatric allogeneic transplant. D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2017 (Accessed September 1, 2018)

References

October 2018 – take the quiz by clicking here.

1. Concerning the following pair of recipient and donor HLA typing, which is the true statement?
   (HLA mismatch indicated in bold)

   Recipient
   
   A*02:01  B*27:02  C*02:02  DRβ1*:04:01  DQβ1*:03:02  DPβ1*:01:01
   A*25:01  B*18:02  C*12:03  DRβ1*:14:54  DQβ1*:05:03  DPβ1*:02:02

   Donor
   
   A*02:01  B*18:02  C*02:02  DRβ1*:04:01  DQβ1*:03:02  DPβ1*:01:01
   A*25:01  B*18:02  C*12:03  DRβ1*:14:54  DQβ1*:05:03  DPβ1*:02:02

   A. Recipient is more likely to have graft-versus-host disease
   B. Recipient is more likely to have graft rejection
   C. Both A and B are correct

   Answer: A

   Explanation: The single HLA-B mismatch in the recipient with homozygosity for the matched HLA-B loci in the donor implies that the donor’s graft will most likely mount a graft-versus-host effect. However, when reviewing transplant data it is prudent to acknowledge transplant population, conditioning regimens and graft-versus-host disease prophylaxis differ and that this may impact the outcome of a mismatch in various ways.

2. Which of the following options reflect correct order of gene expression sequence?

   A. Translation→transcription→splicing
   B. Transcription→splicing→translation
   C. Transcription→translation→splicing
   D. Splicing→transcription→translation

   Answer – B

   Explanation: The first step of gene expression is transcription, where RNA polymerases decode the DNA using specific start and stop signals to synthesize RNA. In the subsequent step, splicing removes portions of the RNA that do not code for protein. Next, the spliced RNA is modified for export out of the nucleus and into the cytoplasm, where ribosomes translate the RNA into protein products.
3. Which statement about passenger lymphocyte syndrome is CORRECT?

A. It is characterized by severe lymphopenia
B. It is caused by engraftment of donor’s lymphocytes in the graft
C. It is a complication associated with major ABO mismatch allogeneic transplant
D. None of the above

Answer - D

Explanation: Passenger lymphocyte syndrome is an important cause of immune hemolysis (anemia not lymphopenia) after allogeneic transplantation. It mainly occurs in minor (not major) ABO and Rh mismatched transplants (hemolysis resulting from other blood group systems has been reported) with the onset of hemolysis occurring between 3 and 24 days after the transplant.\(^2,3\) It is observed after production of antibodies by viable donor “passenger” lymphocytes (not due to their engraftment), transplanted with the graft, against the recipient’s red blood cell antigens. The hemolysis is usually mild and self-limited. The direct antiglobulin test becomes positive in the recipient and antibodies against A, B or both RBC antigens are detectable in serum and eluate. The treatment includes transfusion of group O RBC or antigen-negative red blood cell units. In rare cases in which severe hemolysis occurs, additional treatments, such as stronger immunosuppression or plasma exchange, may be necessary.\(^2\) Once the donor CD34\(^+\) cells are engrafted and incompatible recipient red cells are removed, donor red cells will have normal survival in the recipient.\(^2\)

4. Which of the following statements about donor lymphocyte infusion is CORRECT?

A. There are randomized data which support its use in all patients with relapsed disease
B. It appears to be most beneficial for acute myeloid leukemia relapses
C. It can cause graft-versus-host disease
D. All of the above

Answer - C

Explanation: The ability of infusions of unmanipulated donor leukocytes to mediate antitumor responses was originally described in patients with chronic myeloid leukemia in hematologic relapse following allogeneic hematopoietic cell transplantation.\(^4,5\) Remission rates of up to 80% have been reported in chronic myeloid leukemia (not acute myeloid leukemia) patients who relapse after transplant. Moderate success has been achieved with use of donor lymphocyte infusion after relapse in other malignancies such as acute myeloid leukemia (15%–40%), low-grade lymphomas (≤60%), and multiple myeloma (40%–60%). Fewer than 5% of patients with relapsed acute lymphoblastic leukemia respond to donor lymphocyte infusion alone.\(^6\) Although the etiology is unclear, the reason could be lack of antigenic expression or overwhelming tumor burden at the time of treatment. Graft-versus-host disease is the major obstacle with donor lymphocyte infusion. As donor lymphocyte infusion is most often used to treat relapse, the situation in which any donor lymphocyte infusion is given is necessarily individualized to the disease and the patient. This inherent variability has led to inconsistent and widely disparate practices that tend to be institution and investigator specific.\(^7\) Randomized trials of donor lymphocyte infusion have been impeded by the lack of a defined standard of care.\(^7\)
5. Which of the following statements about mortality from allogeneic transplantation is CORRECT?

A. Among HLA-matched sibling transplant recipients, within the first 100 days, primary disease accounts for the majority of deaths
B. Among unrelated donor allogeneic hematopoietic cell transplantation, within 100 days, mortality related to infection, organ failure, graft-versus-host disease accounts for the majority of deaths
C. Among HLA-matched sibling transplant recipients, at or after 100 days, infection and organ failure represent the majority of deaths.
D. Among unrelated donor allogeneic hematopoietic cell transplantation, after 100 days, mortality related to infection, organ failure, and graft-versus-host disease accounts for the majority of deaths.

Answer – B

Explanation: Among HLA-matched sibling transplant recipients, within the first 100 days, primary disease accounts for 27% of deaths, while infection and organ failure represent 36% of deaths. At or after 100 days, 58% of deaths are attributed to primary disease. Among unrelated donor allogeneic hematopoietic cell transplantation, within 100 days, mortality related to infection, organ failure, graft-versus-host disease accounts for 45% of deaths; after 100 days, 47% of deaths are related to primary disease.

Figure 2: Causes of death after unrelated donor hematopoietic cell transplantation done in 2014-2015.

References:

1. Which of the following statements about hepatic sinusoidal obstructive syndrome (SOS) following hematopoietic cell transplantation is INCORRECT?

   A. It is characterized by jaundice, fluid retention and tender hepatomegaly
   B. The diagnostic criteria (Modified Seattle and Baltimore) for hepatic SOS has limitations
   C. The pathogenesis of SOS is believed to reside at the level of arterial hepatic endothelial cell
   D. Defibrotide is treatment of choice for severe SOS

Answer – C

Explanation: Hepatic sinusoidal obstructive syndrome (SOS) is an often fatal syndrome characterized by jaundice, fluid retention, and tender hepatomegaly. This condition may range in severity from mild and reversible to one associated with fatal multi-organ failure (MOF), hepato-renal syndrome, and mortality. The diagnostic criteria has limitations, often leading to misdiagnosis and at times, late diagnosis. In adults, as opposed to a pediatric population, the Baltimore criteria may be preferred over the Seattle criteria. Neither criterion considers the case of late-onset SOS typically appearing more than 21 days (“late-onset”) after hematopoietic cell transplantation. The pathogenesis of SOS is believed to reside at the level of venous hepatic endothelial cell. Histologically, development of hepatic SOS demonstrates damaged sinusoidal endothelial cells with venular obstruction and centrilobular hemorrhagic necrosis in zone 3 of the liver acinus. Continued injury causes deposition of collagen, sclerosis and fibrosis of hepatic venules and sinusoidal occlusion which ultimately lead to liver failure and death. Ursodeoxycholic acid appears to be useful as an agent to prevent hepatic SOS. Defibrotide, a single-stranded polydeoxyribonucleotide which possesses anti-ischemic, anti-thrombotic, and thrombolytic activity but without significant anticoagulant effects. Multiple studies have demonstrated 30–60% complete remission rates with defibrotide, even among patients with severe SOS and MOF. Defibrotide has been approved by the US Food and Drug Administration and European Medicines Agency for the treatment of adults and children affected by SOS with renal or pulmonary dysfunction after hematopoietic cell transplantation. The use of defibrotide sodium is contraindicated in patients being treated concurrently with anticoagulants or fibrinolytic therapies. Guidelines from the British Society for Blood and Marrow Transplantation, recommend its prophylactic use in children (IA recommendation) and adults (IIA recommendation) at high risk of SOS: pre-existing hepatic disease, second myeloablative conditioning transplant, allogeneic transplant for leukemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, or a diagnosis of primary hemophagocytic lymphohistiocytosis, adrenoleukodystrophy or osteopetrosis.
Table 1: Routinely employed hepatic sinusoidal obstructive syndrome diagnostic criteria\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Modified Seattle criteria\textsuperscript{1} (1984)</th>
<th>Presence of at least two of the following within 20 days of transplantation:</th>
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<tbody>
<tr>
<td></td>
<td>1. Serum total bilirubin concentration &gt;2 mg/dL</td>
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<tr>
<td></td>
<td>2. Hepatomegaly or right upper quadrant pain</td>
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<tr>
<td></td>
<td>3. Sudden weight gain (&gt;2% of baseline body weight) due to fluid accumulation</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Baltimore criteria\textsuperscript{2} (1987)</th>
<th>Serum bilirubin &gt;2 mg/dL within 21 days of transplantation plus at least two of the following,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Hepatomegaly</td>
</tr>
<tr>
<td></td>
<td>2. Ascites</td>
</tr>
<tr>
<td></td>
<td>3. Weight gain &gt;5% from pre-transplant weight</td>
</tr>
</tbody>
</table>

2. Which of the following statements about second malignancy after hematopoietic cell transplantation is INCORRECT?

A. The risk for non-squamous cell cancers is increased in patients younger than age 30 years who receive radiation therapy
B. The risk for squamous cell cancers is not increased in patients with chronic graft-versus-host disease
C. Children who receive cranial irradiation are at risk for developing brain tumors
D. The risk of post-transplant lymphoproliferative disorders is increased with T cell depletion platform

Answer – B

Explanation: In one of the largest studies, Rizzo and colleagues from the CIBMTR retrospectively studied 28,874 allogeneic transplant recipients and noted 189 solid tumor malignancies, twice the rate expected rate compared to general population.\textsuperscript{16} The risk for non-squamous cell cancers was increased substantially in patients younger than age 30 years who received radiation as part of conditioning while chronic graft-versus-host disease and male gender were the main determinants for risk of squamous cell carcinomas.\textsuperscript{16-17} Children who have received cranial irradiation are at risk for developing brain tumors.\textsuperscript{18} These data underscore the need to develop strategies to promote lifelong surveillance programs.\textsuperscript{5} Risk factors for secondary malignancy includes radiation therapy, length/severity of immunosuppression, and chronic graft-versus-host disease.\textsuperscript{16-18} Screening for breast cancer is recommended at an earlier age (25 years or
8 years after radiation, whichever occurs later) but no later than age 40 among recipients of total body radiation or chest irradiation. Early referral to a dermatologist should be considered in patients with skin lesions suspicious for cancer. Post-transplant lymphoproliferative disorders are a rare complication of allogeneic transplant associated with greater donor-recipient HLA disparity, T cell depletion and graft-versus-host disease. Overall incidence is 1% at 10 years after transplantation.

3. Which of the following statements about trends of allogeneic hematopoietic cell transplant for malignant diseases in older adults (defined here as >60 years of age) is CORRECT? (CIBMTR data)

A. The trends have increased in all malignant diseases except acute myeloid leukemia
B. The trends have decreased in all malignant diseases except acute myeloid leukemia
C. Overall the trends have increased in acute myeloid leukemia, acute lymphocytic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma
D. There has been no change in trends in acute myeloid leukemia, acute lymphocytic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma

Answer – C

Explanation: The number of allogeneic transplants for treatment of malignant diseases in older adults continues to increase. In 2016, 30% of allogeneic transplant recipients were older than 60 years of age. There is an increasing trend of ≥70 year of age transplant recipients which represented 4.6% of allogeneic transplants for acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma in 2016.
4. Which of the following factor(s) may influence toxicity associated with chimeric antigen receptor (CAR) T cell therapy?

A. Disease type  
B. CAR T cell construct  
C. Age of the subject  
D. All of the above  
E. A and B

Answer – D

Explanation: The magnitude and timing of the toxicities associated with chimeric antigen receptor (CAR) T cell therapy vary considerably between different CAR T cell constructs and disease type (B-acute lymphoblastic leukemia versus non-Hodgkin lymphoma).21 Other variable such as age, co-morbid condition(s) and prior therapies may also influence toxicity profile.21-24 For example, children might be less likely than adults to have short- or long- term cytokine release syndrome-related morbidity and/or mortality and the rates of grade III–IV cytokine release syndrome (using the Penn cytokine release syndrome grading scale22) are higher in patients with B-acute lymphoblastic leukemia than in those with non-Hodgkin lymphoma (48%23 versus 26%24, respectively).

5. Which of the following statements about survival after hematopoietic cell transplantation for myelodysplastic syndrome (MDS) is CORRECT? (CIBMTR data)

A. The 3-year probabilities of survival are 52% ± 2% for recipients of sibling donor transplants for early MDS  
B. The 3-year probabilities of survival are 49% ± 1% for recipients of unrelated donor transplants for early MDS  
C. The 3-year probabilities of survival are 45% ± 1% for recipients of sibling donor transplants for advance MDS  
D. The 3-year probabilities of survival are 41% ± 1% for recipients of unrelated donor transplants for advance MDS  
E. All of the above

Answer – E

Explanation: Allogeneic transplant is a potentially curative treatment for myelodysplastic syndrome (MDS). Outcomes differ according to disease status at the time of transplant. The CIBMTR has data on 7,611 patients receiving an allo-transplants for early (n=2,717) and advanced (n=4,894) MDS performed between 2005 and 2015. The 3-year probabilities of survival were 52% ± 2% and 49% ± 1% for recipients of sibling and unrelated donor transplants for early MDS, respectively. Among patients with advanced MDS, corresponding probabilities were 45% ± 1% and 41% ± 1%.

References:


December 2018 – take the quiz by clicking here.

1. At the time of U.S. Food and Drug Administration approval, what were the overall complete responses (complete remission plus complete response with incomplete hematologic recovery) of tisagenlecleucel for the treatment of patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that was refractory or in second or later relapse?

   A. 20%-35%
   B. 40%-55%
   C. 60%-65%
   D. 70%-95%

**Answer - D**

**Explanation:** On August 30, 2017, the U.S. Food and Drug Administration granted regular approval to tisagenlecleucel for the treatment of patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. Approval of tisagenlecleucel was based on a single-arm, ELIANA trial of 63 patients with relapsed or refractory pediatric precursor B-cell ALL, including 35 patients who had a prior hematopoietic cell transplantation. Patients received a single dose of tisagenlecleucel intravenously within 2 to 14 days following the completion of lymphodepleting chemotherapy. Of the 63 patients who were evaluable for efficacy, the confirmed overall remission rate as assessed by independent central review was 82.5% (95% CI 70.9, 91.0), consisting of 63% of patients with complete remission (CR) and 19% with complete remission with incomplete hematological recovery (CRi). All patients with a confirmed CR or CRi were minimal residual disease negative by flow cytometry. Median remission duration was not reached (range: 1.2 to 14.1+ months).¹

2. At the time of U.S. Food and Drug Administration approval, what were the complete response rates of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma who had failed two or more lines of systemic therapy?

   A. 30%-35%
   B. 40%-65%
   C. 70%-80%
   D. 81%-90%

**Answer - B**

**Explanation:** On October 18, 2017, the U.S. Food and Drug Administration granted regular approval to axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Approval was based on a single-arm multicenter, ZUMA-1 trial of 108 adult patients. Eligible patients had refractory disease to the most recent therapy or relapse within one year after autologous hematopoietic cell transplantation. Patients received a single infusion of axicabtagene ciloleucel following completion of lymphodepleting chemotherapy. Of the 101 patients
evaluated for efficacy, the objective response rate (ORR) as assessed by independent central review was 72%, with a CR rate of 51% (95% CI: 41, 62). The duration of response was longer in patients with a best overall response of CR, as compared to a best overall response of partial remission (PR). Among patients achieving CR, the estimated median duration of response was not reached (95% CI: 8.1 months, not estimable) after a median follow-up of 7.9 months. The estimated median duration of response among patients in PR was 2.1 months (95% CI: 1.3, 5.3).²

3. At the time of U.S. Food and Drug Administration approval, what were the complete response rates of tisagenlecleucel for adult patients with relapsed or refractory large B-cell lymphoma who had failed two or more lines of systemic therapy?

A. 20%-45%  
B. 50%-60%  
C. 70%-80%  
D. 81%-90%

Answer – A

Explanation: On May 1, 2018, the U.S. Food and Drug Administration approved tisagenlecleucel a CD19-directed genetically modified autologous T-cell immunotherapy, for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Approval was based on a single-arm, open-label, and multicenter, phase II, JULIET trial. Eligible patients must have been treated with at least two prior lines of therapy, including an anthracycline and rituximab, or relapsed following autologous hematopoietic cell transplantation. Patients received a single infusion of tisagenlecleucel following completion of lymphodepleting chemotherapy. The overall response rate as assessed by an independent review committee for the 68 evaluable patients was 50% (95% CI: 37.6, 62.4) with a complete response rate of 32% (95% CI: 21.5, 44.8). With a median follow-up time of 9.4 months, the duration of response was longer in patients with a best overall response of complete response, as compared to a best overall response of PR. Among patients achieving complete response, the estimated median duration of response was not reached (95% CI: 10.0 months, not estimable). The estimated median response duration among patients in PR was 3.4 months (95% CI: 1.0, not estimable).³

4. What is the recommended dose of axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy?

A. 0.2 to 5.0 x 10⁶ chimeric antigen receptor-positive viable T cells/kg body-weight  
B. 0.1 to 2.5 x 10⁸ total chimeric antigen receptor -positive viable T cells  
C. 0.6 to 6.0 x 10⁸ chimeric antigen receptor -positive viable T cells  
D. 2 x 10⁶ chimeric antigen receptor -positive viable T cells/kg body-weight (maximum 2 x 10⁸)

Answer – D

Explanation:

- The recommended dose of axicabtagene ciloleucel for adult patients with relapsed or refractory DLBCL who had failed two or more lines of systemic therapy is a single
intravenous infusion with a target of $2 \times 10^6$ chimeric antigen receptor (CAR)-positive viable T cells per kg body weight (maximum $2 \times 10^8$), preceded by fludarabine and cyclophosphamide lymphodepleting chemotherapy.\(^2\)

- The recommended dose of tisagenlecleucel for the treatment of patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse is one infusion of 0.2 to $5.0 \times 10^6$ (CAR)-positive viable T cells per kg body weight intravenously for patients who are ≤ 50 kg, and 0.1 to $2.5 \times 10^8$ total CAR-positive viable T cells intravenously for patients who are > 50 kg, administered 2 to 14 days after lymphodepleting chemotherapy.\(^1\)

- The recommended dose of tisagenlecleucel for relapsed or refractory adult DLBCL after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma is $0.6$ to $6.0 \times 10^8$ CAR-positive viable T cells.\(^3\)

5. Which of the following statements about axicabtagene ciloleucel and tisagenlecleucel is CORRECT?

A. Tisagenlecleucel is approved by U.S. Food and Drug Administration in the setting of relapsed/refractory primary central nervous system lymphoma
B. Axicabtagene ciloleucel is approved by U.S. Food and Drug Administration in the setting of relapsed/refractory primary mediastinal large B-cell lymphoma
C. Axicabtagene ciloleucel has 41-BB co-stimulatory domain
D. Tisagenlecleucel has CD28 co-stimulatory domain

Answer – B

Explanation: The U.S. Food and Drug Administration granted approval to axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. U.S. Food and Drug Administration approved tisagenlecleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma but not primary mediastinal large B-cell lymphoma. Tisagenlecleucel and axicabtagene ciloleucel are not indicated for the treatment of patients with primary central nervous system lymphoma. Compared to tisagenlecleucel, which has 41-BB co-stimulatory domain, axicabtagene ciloleucel utilizes a CD28 co-stimulatory domain. Clinically, CD28 based CARs typically display more robust early in vivo expansion,\(^4\)\(^-\)\(^6\) whereas 4-1BB CARs may have longer persistence,\(^6\) though the clinical relevance of expansion kinetics is still under investigation.\(^4\)
References: