Transplant Strategies for Hematologic Malignancies

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Disclosures

I have nothing to disclose.
Goals

- To review evolution of stem cell source and applications of stem cell transplant in the treatment of hematologic malignancy.
- To highlight some of the evolving treatment strategies to improve outcomes after transplant.
- Impact of novel therapies on transplant strategies
- To present clinical scenarios that confront hematologist–oncologists and transplant physicians in the care of such patients.
Indication for Transplants 1977

Acute Leukemia
Aplastic Anemia

Types of Marrow/Stem Cell Transplants 1977

Bone marrow from Sibling Donors
Indications for Transplant 2017

**Hematologic Malignancy:**
- Leukemia (ALL, AML, CML, CLL)
- Lymphoma
- Hodgkin Lymphoma
- Myeloma
- Myelodysplasia
- Myeloproliferative Disorder

**Solid Tumor Malignancy:**
- Testicular
- Sarcoma
- Brain
- Neuroblastoma
Indications for Transplant 2017 (Cont’d.)

- Acquired Non-Malignant Disease:
  - Aplastic Anemia
  - Amyloid
  - Autoimmune diseases

- Inherited Non-Malignant Disease:
  - Sickle Cell
  - Thalassemia
  - Severe Combined Immune Deficiency
  - Osteopetrosis
  - Granulocyte & Macrophage Disorder
  - Fanconi’s Anemia
# Types of Marrow/Stem Cell Transplants - 2017

1. Allogeneic sibling  
2. Matched donor  
3. Allogeneic parental matched donor  
4. Allogeneic unrelated matched donor  
5. Syngeneic (twins)  
6. Cord blood  
7. Autologous marrow  
8. Autologous peripheral blood stem cell  
9. Allogeneic peripheral blood stem cell  
10. Allogeneic donor leukocyte infusion  
11. Gene modified stem cells:  
   - ADA deficiency  
   - Gaucher  
   - AIDS  
12. Ex vivo expanded stem cells  
13. T cell depleted allogeneic or autologous graft
Likelihood of Finding an Unrelated Adult Donor

Growth of Registry: Increased Likelihood of Match for All Patients

% of recipients finding match

year


All Races
Black/African American
Caucasian
Hispanic/Latino
Asian or Pacific Islander
Native American

NATIONAL MARROW DONOR PROGRAM®
Transplantation for Hematologic Malignancy

- Age is no longer a barrier to either allogeneic or autologous transplant.

- Ability to find donors for nearly all patients: Matched sib, matched unrelated, Cord blood, Haplo identical family member.

- Results comparable.

- Molecular analysis to determine indications and timing of transplant.
Acute Myelogenous Leukemia

- HLA typing at the time of diagnosis to determine transplant options.

- Molecular and cytogenetic risk assessment at time of diagnosis.


- Varies with molecular subtype (IDH1/2, FLT3).

- Therapy would be bridge to transplant.
Transplant for Acute Myelogenous Leukemia

- Transplant in first remission depending on risk group: high risk cytogenetics, normal cytogenetics with poor risk molecular typing, (FLT$_3$) more than 1 cycle to achieve a remission.

- Secondary AML: breast cancer

- All patients in second remission: Good risk patients who relapse are no longer good risk

- Advanced AML in relapse on protocol designed for such patients
Transplant for Acute Lymphoblastic Leukemia

- HLA typing at time of diagnosis.
- Changes in natural history with use of pediatric based regimens: 60% cure rate. (AYA)
- Assessment of MRD after induction/consolidation to determine timing of transplant.
- Induction failure ALL: MRD + leukemia is a form of induction failure
- High risk patients in first remission: age, Ph+ disease, MRD + patients
- All patients in second remission (adults)
- Extramedullary relapse
- Secondary ALL
Myelodysplasia

- Transplant only curable option
- Issue is timing and assessment of risk/natural history
- Age not a barrier
- Response to hypomethylating therapy
- Transfusion dependency, iron overload
Lymphoma

- Auto transplant for high risk in first remission? (Double hit?)
- Relapsed diffuse large cell lymphoma.
- Induction failure
- Follicular lymphoma with less that 1 year response to initial R-CHOP chemotherapy.
- Anaplastic large cell lymphoma (ALK negative) in first remission.
- Relapsed ALK positive lymphoma.
- Cutaneous T cell lymphoma
Hodgkin disease

- Major indication is for treatment of patients who relapse and respond to subsequent therapy.
- No indication for transplant in first CR.
- Patients who do not achieve remission with ABVD.
- Brentuximab, ICE as bridge therapy to transplant.
- Brentuximab as bridge to allogeneic transplant for those patients who relapse after auto.
The patient is a 56 year old woman who presented with mild pancytopenia 4 years after receiving adjuvant chemotherapy (AC-T) for treatment of stage 2 ER+/PR+ breast cancer. As she had a lumpectomy and lymph node dissection, she also received breast irradiation following completion of chemotherapy treatment. A bone marrow examination showed Myelodysplasia, with 12% blasts in the marrow, and deletion 7 chromosome abnormality in 13/20 metaphases. Her white count was 2.3, with 70% neutrophils with no blasts, hemoglobin 9.6 and platelet count of 96,000. She has one sibling who was found to be an HLA match.

Questions:

Should she receive hypomethylating therapy as treatment?

Is transplant an option for her and if so, when?
Hypomethylating Therapy

- Phase III trial of azacitidine versus supportive care (CALGB)
- All subtypes
- Delayed transformation
- Hematologic improvement
- Phase III trial in higher risk patients (ARA-C, azacytidine, supportive care)
- 24 months median survival versus 15 months (.0001)
- 50% of patients do not respond
Outcome of Patients with MDS After Failure of Decitabine Therapy

- 87 Patients
- Median survival 4.3 months after progression
- 12 months survival rate: 12%

Similar for: High risk, intermediate 1 and 2

*Reference: Cancer, Volume 116, Issue 16, Pages 3830-3834*
Survival after Decitabine Failure
MDS Outcomes after Flu/Mel Allo

Overall Survival

Disease-free Survival
K–M for all patients (200 de novo and 64 t-MDS)
Strategy

- High risk: hypomethylating therapy as bridge to transplant
- Low risk: at time of progression
- Transfusion dependant, infections
The patient is a 26 year woman who developed stage 3B Hodgkin disease, was treated with ABVD chemotherapy and achieved a complete remission confirmed by CT PET at the end of 6 cycles of treatment. A repeat scan at 6 months showed recurrent disease, and she received ICE chemotherapy, followed by stem cell collection and an autologous transplant, and was in complete remission at the end of treatment. At the time of her one year anniversary, a repeat scan showed recurrent disease confirmed by biopsy.

Questions:

How should she be treated?

Is there a role for allogeneic transplant in the treatment of her disease?
Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma


PFS Following Treatment with Brentuximab Vedotin


©2015 by American Society of Hematology
Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma

Robert Chen, Joycelynne M. Palmer, Sandra H. Thomas, Ni-Chun Tsai, Len Farol, Auayporn Nademanee, Stephen J. Forman, and Ajay K. Gopal

1\textsuperscript{st} relapse

Best bridge to transplant: ICE, Brentuximab, Nivolumab

Post transplant therapy
The patient is a 63 year man with Stage 3 diffuse large B cell lymphoma, bulky in the abdomen, and an elevated LDH at the time of diagnosis. He received 6 cycles of R-CHOP and was in remission after 2 cycles, and this was confirmed again at the end of treatment. However he suffered a recurrence in the original area of bulky disease 8 months after completing treatment and was referred for consideration of autologous transplant.

**Questions:**

*What should be his next treatment?*

*What is the role of autologous transplant in the management of relapsed DLBCL?*
Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trneny, Andre Bosly, Nicolas Ketterer, Ofer Shpilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, and Norbert Schmitz

JCO Sep 20, 2010:4184-4190; published online on July 26, 2010; DOI:10.1200/JCO.2010.28.1618.
Strategies to Improve Outcome after Autologous Transplant for Diffused Large B Cell Lymphoma

- Post transplant therapies: Revlimid, Ibrutinib, anti PD1
- CAR T cells post transplant.
- CAR T cells as bridge to transplant?
HIV status does not affect the outcome of autologous stem cell transplantation (ASCT) for non-Hodgkin lymphoma (NHL).

Krishnan A, Palmer JM, Zaia JA, Tsai NC, Alvarnas J, Forman SJ

Survival Probability

Time (Years) from Transplant

HIV Status
Positive
Negative

p-value = 0.9287
The patient is a 67 year old healthy woman who presented with a high WBC count of 79,000 and the blasts were CD 19+, CD34+, TdT positive, and chromosome analysis showed the presence of the Philadelphia chromosome. She received treatment with HyperCVAD and desatinib and achieved a molecular remission after the first cycle, and then went on to receive cycle 2 with cytosine arabinoside/methotrexate. She has no sibling donors but did have a 12/12 match in the registry.

**Question:**

*Should she undergo allogeneic unrelated transplant while in first molecular remission?*
- Age not a barrier to transplant.
- Allogeneic transplant still better outcome for Ph+ disease.
- MRD analysis?
- If + MRD, what to do?
- Treat to MRD negative before transplant? Risk?
The patient is a 50 year old man with long standing MPD/ET who after became pancytopenic, with systemic symptoms of fever and weight loss and a bone marrow showed myelofibrosis. He had had treatment with hydrea and anagrelide, and the spleen was mildly enlarged. He was treated with transfusions and a Jak 2 inhibitor with systemic response (increased appetite, decreased fever) and about a 30% decrease in his spleen size. He had no siblings but does have a matched unrelated donor. His only other medical problem was multiple sclerosis required occasional use of a walker and self catheterization for bladder emptying.

Questions:

Is there a role for allogeneic transplant in the management of MPD, and is so, when?

What impact does the MS play in these decisions?
Allogeneic hematopoietic cell transplantation for advanced polycythemia vera and essential thrombocythemia.


Improved Outcomes Using Tacrolimus/Sirolimus for Graft-versus-Host Disease Prophylaxis with a Reduced-Intensity Conditioning Regimen for Allogeneic Hematopoietic Cell Transplant as treatment of Myelofibrosis

David S. Snyder, Joycelynne Palmer, Karl Gaal, Anthony S. Stein, Vinod Pullarkat, Firoozeh Sahebi, Nyana Vora, Ryotaro Nakamura, Stephen J. Forman

Biology of Blood and Marrow Transplantation, Volume 16, Issue 2, February 2010, Pages 281-286
Issues in Transplant for MPD/MF

- Long national history and evolution of disease from one form to another
- Transfusion/iron overload
- Spleen size
- Time to engraftment after transplant
- Disappearance of fibrosis over long period of time
The patient is a 50 year old woman who presented with MDS and a minus 7 abnormality. She underwent an allogeneic transplant from her healthy HLA matched brother, achieved a complete remission and full donor chimerism (100% donor, XY karyotype). Approximately 18 months after transplant she developed pancytopenia, and marrow was done to rule relapse of MDS. The marrow exam showed M4 acute leukemia and a chromosome analysis showed an XY karyotype in all the cells?

**Questions:**

*Is this recurrence of MDS with evolution to AML?*

*How should it be managed?*
Evidence of Donor-Derived Hematologic Malignancies after Hematopoietic Stem Cell Transplantation


Biology of Blood and Marrow Transplantation, Volume 12, Issue 5, May 2006, Pages 511-517
- Clonal hematopoiesis in donor (myeloid)
- MGUS → Myeloma
- Mono clonal B cell lymphocytosis
Post Transplant Treatment to Reduce Chances of Recurrence

- Transplant as an all or none therapy with the goal of cure of the disease.

- Historically no post transplant anti cancer therapy.

- Multiple myeloma: transplant not a curative therapy by itself.

- Post transplant treatment (imid or proteosome inhibitor based) improves progression free and overall survival.

- Principle of treating measurable or not measurable MRD post transplant for other diseases.
Post Transplant Therapy to Reduce Chances of Relapse

- Multiple Myeloma: Imids, PI, anti CS1 antibody, anti CD38 antibody.
- Hodgkin disease: Brentuximab, anti PD 1 antibody.
- ALL: CD 19 CAR T cells, anti CD 19 BiTE, TKI for Ph+ ALL.
- AML/MDS: hypomethylating therapy.
Role of Hematologist/Oncologist, PCP, Internet, NP’s/PA’s in Long Term Treatment of Transplant Patients

- Metabolic: BP, ASCVD, Diabetes, pre-diabetic, thyroid
- Secondary malignancies: screening, reduce risky behavior
- Musculoskeletal: bones, muscles, frailty
- Cognitive