New Directions in Aplastic Anemia: What is on the Horizon

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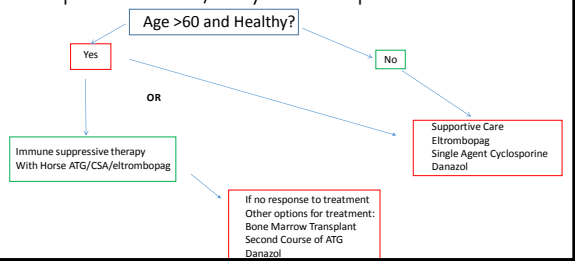
Case Presentation #1

- 62 y/o male, with hypertension, who presented to his PCP for evaluation of fatigue, shortness of breath with exertion and easy bruising.
- He has noted more fatigue and shortness of breath over the last 3-4 months. Not associated with cough, chest pain, fevers, weight loss.
- He has been on his current blood pressure medication for "years" and has not been taking any over the counter or herbal products.
- He has occasional alcohol use (3-4 drinks per month), but no tobacco use
- No family history of blood, liver, lung problems and no cancers.
- CBC performed by his PCP noted pancytopenia: WBC 2.1, hemoglobin 8.7, hematocrit 26.3%, platelet count 12K.

Case Presentation #1

- Work-up proceeded, including a bone marrow biopsy and peripheral blood testing.
- He was diagnosed with severe aplastic anemia
- Peripheral blood testing found a small PNH clone (white cell clone 1.2%)
- What is the best treatment course for this patient?

Treatment approach for older patients with acquired Severe/Very severe aplastic anemia



Patient Presentation

- Treatment was given with Atgam, cyclosporine and eltrombopag.
- He received transfusion support with red cells and platelets
- He was on levofloxacin, acyclovir and posaconazole for infection prevention
- At 6 months after Atgam was initiated he continued to need transfusions
- What is the next best treatment option for him?

Why do patients fail to respond after immune suppressive therapy?

- The cytotoxic T cells persist and the immune attack continues
- The marrow compartment is too damaged to recover
- A new defect is present (MDS) that makes the bone marrow stem cells dysfunctional and unable to recover
- The bone marrow stem cells are defective and unable to tolerate stress due to an unrecognized inherited marrow defect.

Work-up for patients who fail immune suppression

- I typically make sure there is not a component of nutritional defects, hormone deficiency.
- If not previously performed, I make sure testing for inherited defects is performed (telomere length and blood breakage testing).
- I make sure to repeat testing for PNH
- I will often repeat a bone marrow biopsy to make sure there isn't a new problem causing the pancytopenia, in particular MDS.

Treatment options for patients who fail initial immunosuppression

- Bone Marrow Transplant
- Eltrombopag
- Second Course of ATG
- Danazol
- Alemtuzumab (Campath)

Eltrombopag

- Eltrombopag (Promacta) is a thrombopoietin agonist (TPO agonist)
- TPO is present on both platelet forming cells and bone marrow stem cells
- Initial report in 2012 of benefit in AA patients who did not respond to initial immunosuppression (study performed at NIH)
- Response rate in that study was ~40%
- This drug is overall well tolerated, with GI complaints and potential for liver test abnormalities that need to be followed.

Second Course of ATG

- The use of rabbit ATG for those patients who failed initial course of horse ATG leads to ~30% response rate
- Problems associated with this treatment include an increase risk of viral infections (mononucleosis (EBV) and CMV in particular)

Alemtuzumab (Campath)

- Alemtuzumab is an antibody against CD52, a protein on the surface of many immune cells
- This drug is a potent immunosuppressant, and therefore the risk of a severe infection (mainly viral and fungal infections) is high

Danazol

- Danazol is a male hormone (androgen)
- Danazol can improve blood counts in patients with acquired aplastic anemia
  - Report found ~30% response in patients who failed immunosuppressive therapy (females higher response rate)
  - Report in patients who received Danazol as initial treatment ~45% response rate
- Danazol is most effective in patients with inherited marrow defects
  - NIH team reported the results of using Danazol in patients with telomere diseases, with good success
  - Fanconi Anemia patients can respond nicely to Danazol
- Overall well tolerated, with main side-effects stomach upset, liver function abnormalities, diabetes, elevated cholesterol.
- Liver tumors can form from Danazol, therefore ultrasounds are required for patients on long-term therapy.

Telomeres and telomere maintenance defects

- Telomeres are structures at the end of the chromosomes in cells that protect the chromosomes from deteriorating.
- Regulate the "age" of a cell-there is a natural shortening that happens through cell division
- The cell has machinery designed to prevent excess shortening, because if the telomeres get too short the cell will die off
- There are a group of disorders, called telomere diseases, where people have an inherited defect in this machinery
- People with telomere diseases will have telomeres that are much shorter than they should be.
- Short telomeres can not only make cells die to soon (which could cause aplastic anemia), but they can also make a cell more likely to turn into cancers.
- Short telomeres are also a cause of scar tissue development in the lung and liver

Telomeres and telomere maintenance defects

- In telomere disorders, people have a defect in the telomere repair machinery
- Their telomeres shorted too quickly, leading to early cell death and cancer risk
- NIH team studied the telomere length in patients before and after treatment with Danazol, finding that Danazol can lengthen telomeres
  - Blood counts improved significantly in almost all patients
- This has major implications for potentially "reversing" problems associated with short telomeres.
- In addition to improved blood counts, they found lung tests were better in some patients

Non-Transplant Options for AA

- Options exist to help the bone marrow compartment recover
- Major advance in the last few years for acquired aplastic anemia is the integration of eltrombopag as an agent to help improve response rates (initially in the setting of immune suppression failure, now in the upfront treatment with immune suppression)
- The finding that Danazol can increase telomere length in people with telomere diseases is a major finding as well. Questions I now have:
  - Can Danazol protect from the development of aplastic anemia?
  - Can Danazol protect the lungs and liver from developing scar tissue?
  - How do I integrate Danazol into post-transplant care of these patients?
  - Identification of those with unrecognized inherited defects is critical

Bone Marrow Transplant

- The basic goal behind a bone marrow transplant is to replace the bone marrow stem cells
- This involves a 2 step process:
  - Chemotherapy +/- radiation to prepare the host's body-what we call "conditioning"
  - Infusion of bone marrow stem cells from a donor
- Bone marrow stem cells have 2 major jobs:
  - They produce the blood cells-neutrophils, red blood cells, platelets
  - They produce the immune cells-lymphocytes
- The donor immune system builds up in the host's body
- Immune systems are particular-they attack what they don't recognize
  - Major problem with bone marrow transplant is the donor immune system attacking the host's body-what we call graft vs. host disease (GVHD)

Bone Marrow Transplant-Factors that Impact Outcome

- Conditioning Regimen
- Donor matching
- Donor source
- Health of the Host (Recipient)
- In aplastic anemia, you don't have cancerous cells to deal with, so we want to minimize the risks of the transplant
- These factors impact the major complications of a transplant
  - GVHD
  - Infection
  - Toxicity to the body

Outcome for BMT with a Matched Related Donor is Excellent

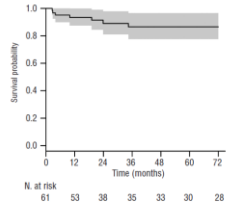
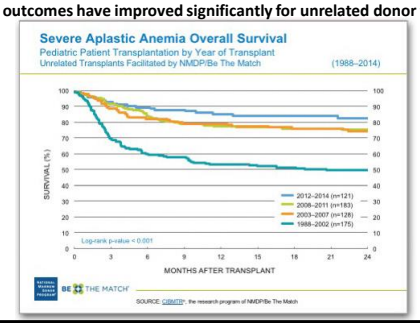


Figure 2. The 6-year probability of overall survival adjusted for waiting time to transplantation. The shaded area represents the pointwise 95% confidence interval.

Survival rates are ~90%

Transplant outcomes have improved significantly for unrelated donor transplants



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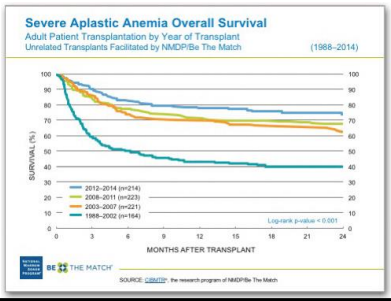


BMT for AA-Factors that Impact Outcome

- Donor Matching
- Immune markers (HLA-markers) are "flags" that mark your personal immune cells
- In looking for a donor we want to match these immune markers as best as we can
- Key immune markers-major HLA-markers (A,B,C, DRB1)
- Minor immune markers are investigated as well
- These are passed along from your parents
- Some of the HLA markers run along racial background
- Progress in donor matching: We now test the HLA markers based on the DNA of the markers (what we call high-resolution) so the quality of the match is better.

BMT for AA-Factors that Impact Outcome

- Donor Source (Product)
- Transplants can be performed using multiple different products:
  - Matched related donors-bone marrow or peripheral blood stem cells
  - Matched unrelated donors-bone marrow or peripheral blood stem cells
  - Mismatched unrelated donors-bone marrow or peripheral blood stem cells
  - Umbilical cord blood-1 or 2
  - Haploidentical (half-match-sibling, parent, child)
- Advantages and dysadvantages exist for each one:
  - Peripheral blood stem cells engraft better and faster than bone marrow cells
  - Bone marrow stem cells cause less GVHD
  - Umbilical blood=the matching is less strict, but the risk of infection and engraftment failure is higher
- Multiple studies have shown that the best product for transplant for aplastic anemia is bone marrow rather than peripheral blood stem cells.
- Cord Blood transplants can be performed with success in aplastic anemia
- Haploidentical (half-matched) transplants can be performed as well
- There is a continued need to broaden the population of volunteer donors

BMT for AA-Factors that Impact Outcome

- **Conditioning Regimen**
- Conditioning regimen is modified some based on host factors (age, presence of an inherited defect) and donor factors
- Challenge in aplastic anemia is that the immune system is already in "attack mode" against bone marrow stem cells
- Learned early on that conditioning is absolutely necessary for a transplant to be successful in AA
- If the conditioning regimen isn't intense enough, then the transplant won't take (what we call engraftment failure-no donor cells grow/produce)
- If the conditioning regimen is too intense, then early and late complications are higher
  - Lung problems, in particular, can be a chronic problem when high-dose radiation was used
- Main focus of conditioning is utilizing agents that suppress the host's immune system
  - ATG (both rabbit and horse), alemtuzumab, fludarabine, cyclophosphamide
- Sometimes these agents also suppress the donor immune system
  - This may provide some activity against GVHD, but may also impact engraftment

Conditioning Regimens for BMT in AA

- **Progress in Conditioning Regimens:** WE have made significant improvements in the conditioning regimens over the years, leading to a reduction in post-transplant complications and improvement in engraftment rates.
- Common Conditioning regimens:
  - Matched related donor: Cyclophosphamide and ATG or alemtuzumab for younger patients. Fludarabine, Cyclophosphamide, and ATG or alemtuzumab for older patients
  - Matched unrelated donor : Fludarabine, Cyclophosphamide, ATG and low dose radiation or Fludarabine, Cyclophosphamide, and alemtuzumab
  - Cord Blood: Fludarabine, Cyclophosphamide, ATG and low dose radiation
  - Haploidentical: Fludarabine, Cyclophosphamide, and low dose radiation plus post-transplant Cyclophosphamide

BMT for AA-Factors that Impact Outcome

- Health of the Host
- Optimal supportive care prior to transplant to reduce risk of infection is important
- Use of irradiated blood products to reduce the risk of antibody formation is important to reduce complication rate
- Older patients are healthier than previously, which allows us to consider transplanting patients >age 60 if needed
- Making sure inherited aplastic anemia has been ruled out (as we use a much different conditioning regimen and screening program in these patients).

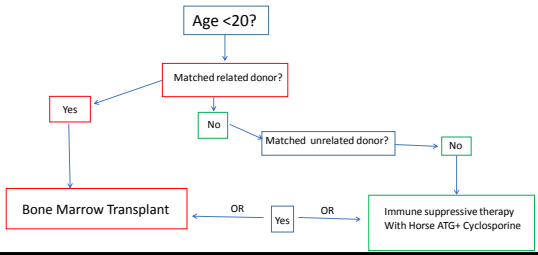
Case Presentation #1

- 62 y/o male with AA, who did not respond to his first cycle of horse ATG, cyclosporine, and eltrombopag
- Repeat bone marrow biopsy confirmed he had aplastic anemia, with no evidence of MDS
- Unrelated donors were investigated and he had 2100 potentially matched donors
- After discussing his options, he decided to proceed to a bone marrow transplant

Case Presentation #2

- 17 y/o female, very active and healthy, who was having new fatigue and bleeding problems
- She was diagnosed with acquired, severe aplastic anemia after a thorough work-up was performed.
- She does not have any sibling. She and her parents were HLA typed, with no match between them
- Review of her unrelated donor found 2 fully matched donors
- 1 donor is willing to give bone marrow product, 1 donor is not.
- What is the next best step for this patient?

Treatment approach for acquired Severe/Very severe aplastic anemia



Evolution of Management of Pediatric AA

- Patients under the age of 20 can do extremely well with both immunosuppressive therapy and bone marrow transplant
- With our current approaches for transplant, in particular the use of high-resolution typing, bone marrow source, conditioning regimens and supportive care, the outcomes of a fully matched unrelated donor transplant are comparable to transplant from a matched sibling
- Immunosuppression has it's long-term problems to consider, including the continued need for medications and the cumulative risk of MDS and PNH
- This has raised the question in the field-should we consider young patients with no sibling donor for upfront unrelated donor transplant rather than immune suppression?

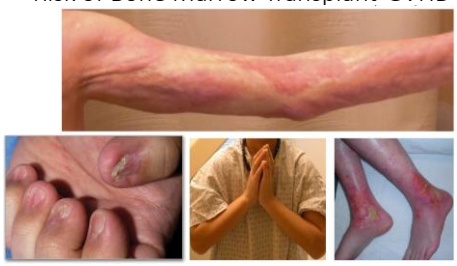
Risks of Bone Marrow Transplant

- Graft vs. Host Disease
- Infertility
- Endocrine problems
- Infections
- Bone problems
- Growth problems
- Medication side-effects

Risk of Bone Marrow Transplant-GVHD

- GVHD is when the new immune system attacks the body
- Main sites involved include skin, mouth, eyes, intestinal tract, liver, lungs
- This can be minor and easily controlled or it can be severe
- One of the reasons we choose bone marrow product is to reduce the risk of severe or long-acting GVHD
- Patients require prolonged treatment with immune suppression, thereby increasing their risk of infection
- The biggest impact on overall quality of life for patients with aplastic anemia receiving a bone marrow transplant is GVHD
- Progress is being made in controlling GVHD-big area of research in BMT

Risk of Bone Marrow Transplant-GVHD



Risk of Bone Marrow Transplant-GVHD

- All patients are given immune suppressive therapy as part of the transplant to help prevent GVHD.
- With aplastic anemia the taper of that immune suppression is slow (at least 1 year) to reduce the risk of GVHD
- Newer regimens/approaches are being studied in transplant to reduce GVHD but still maintain activity of the stem cells
- Managing later stage GVHD has improved, but also an area of active research.

Risks of Bone Marrow Transplant

- Infertility: the risk of being unable to have children (for both men and women) is dependent on the conditioning regimen (rates 50+%)
  - Discussion with fertility experts is important prior to proceeding with transplant
- Endocrine/Hormone Problems: Transplant can effect your normal hormone production (due to the chemotherapy) including:
  - Thyroid hormone production (regulates your metabolism) can be low-monitored with blood tests. This hormone can be replaced with a pill
  - Estrogen and testosterone production (sexual hormones)-impacting ability to have children, menstruation, sexual development. This is monitored with blood tests, and can be replaced with medications.
  - Bone Health-osteoporosis, or thinning of the bones, can happen from the transplant. Vitamin D, which is important in maintaining bone strength, can be low in patients.
- Growth Abnormalities
  - This is something we worry about in children who have gone through transplant.
  - Growth rates and hormone levels are followed, with some children benefitting from growth hormone supplementation.

Risks of Bone Marrow Transplant

- Increased risk of infection can last for decades after transplant
- Infections that are major concerns include viral reactivation and atypical infections (fungal infections).
- Patients that have infections prior to transplant are at higher risk of worsening infection with transplant
- We monitor for infection and use medications to try to prevent infections.

Decision between Transplant or Not?

- Factors that help decide include:
  - Neutrophil count-for those patients with a very low neutrophil count, they are at the highest risk of a life-threatening infection. The quickest way to get the neutrophil count better is with a transplant
  - Quality of the donor-matched vs. mismatched/alternative donors (cord blood, haploidentical). Immune suppression first-line is better than a higher risk transplant from mismatched/alternative donors
  - Support system requirements and financial burden of transplant is higher than that needed for immune suppression
  - Some patients like the idea of being "cured" with a transplant, although the counter to this is potentially living with GVHD

Questions?