New Directions in Aplastic Anemia: What’s on (and not on) the Horizon?

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Aplastic Anemia
Immunotherapy Results
Survival with good to excellent response is approximately 85-90% in children and 60-70% in adults. Relapse or clonal evolution usually 2-4 years. 15-30% require ongoing Cyclosporine A. The risk of clonal disease (MDS, AML or PNH) is real and justifies HLA-matched SCT as the treatment of choice at this time in patients < 40 years of age. The exact incidence of clonal disease in children is unknown.

Risk of Clonal Disease in Adults:
10-15% high risk clonal evolution (7-, high grade MDS, complex karyotype, leukemia)
Survival at 15 years: 95% with no event vs. 65% with an event
75% not high risk event vs. 25% with high risk event

Aplastic Anemia Immunotherapy
• Horse Anti-Thymocyte Globulin (100%) for 4 days (25% for 5 days)
• Methylprednisolone/Prednisone for 4-14 days followed by daily taper
• G-CSF until ANC ≥ 1000/µl (this is controversial – routine (37%), for infection (68.8%))
• Cyclosporine A until G-CSF discontinued and transfusion independent, then taper over 12 months

Aplastic Anemia Treatment
• Mild-Moderate Aplastic Anemia
  • Observation vs. Immunotherapy
• Severe Aplastic Anemia
  Matched Sibling Donor (<40 years of age)
  • HLA-matched transplant
  • Yes (or >40 years of age)
  • No (or >40 years of age)
  • Immunosuppressive therapy (IST)
  • if no response
  • High risk clone
  • Relapse – Reinitiate IST
  • Unrelated donor transplant
  • Experimental/Other therapy

Prospects for Better Management I
• HSCT
  • Recognition that bone marrow is the best stem cell source
  • Better matches
  • Better treatment
  • Larger more diverse registries
• Better immunosuppressive therapy (IST)
  • The addition of more potent or more agents has not proved beneficial
• We’re smarter
  • Do not support only in hopes of a spontaneous resolution of SAA
Prospects for Better Management II

- Better immunosuppressive therapy (IST)
  - The addition of more potent or more agents has not proved beneficial
  - High-Dose Cyclophosphamide remains controversial
    - Pro:
      - Response similar to ATG/CsA
      - Lower late event rate (relapse and clonal evolution were observed in NIH study)
    - Con –prolonged neutropenia:
      - High invasive fungal incidence (21 and 39% in treatment naïve and refractory patients, respectively)
      - Long hospitalization
      - Cost

Prospects for Better Management III

- Salvage Therapy
  - Rabbit ATG is more lymphocytotoxic and has been successful in salvaging some patients
  - Rabbit ATG is inferior to Horse ATG: 68% vs. 37% as frontline therapy – response 77% and complete remission 30%
  - Alemtuzumab (anti-CD52) has some value as salvage therapy but inferior to Horse ATG/CsA (only 19% response rate)

Prospects for Better Management IV

- Risk stratification to guide therapeutic choices
  - Pretreatment telomere length may correlate with:
    - Relapse
    - Clonal evolution
      - Short telomeres – 4 to 6 fold higher likelihood of clonal evolution (MDS or leukemia)
    - Survival
    - Patients with evidence of red cell production (reticulocytes) do better

Prospects for Better Management V

New Agents
- Eltrombopag (TPO-mimetic)
  - Responses
    - 9/12 no platelet transfusions
    - 6/12 improved hemoglobin (3 no longer needed transfusions of red blood cells)
    - 9/12 improved neutrophil count
- Daclizumab (Zenapax; anti-IL-2)
  - Response in moderate aplastic anemia (19/45)
- Alefacept (suppresses T-cell function)

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