New Directions in Aplastic Anemia Treatment: What’s on the Horizon?

Danielle Townsley, MD, MSc
Hematology Branch
National, Heart, Lung and Blood Institute
National Institutes of Health

Today’s agenda

Novel agents and active research
Novel transplants for aplastic anemia

NEW DIRECTIONS IN TREATMENT FOR APLASTIC ANEMIA

- Add to horse ATG + CsA platform
  - G-CSF (Neupogen)
  - Mycophenolate mofetil
  - Sirolimus
  - long course immunosuppression
- Augment initial lymphocytotoxicity
  - Horse ATG
  - Rabbit ATG
  - Campath

HEMATOPOIETIC GROWTH FACTORS AS THERAPY FOR SAA

Ganser A et al., Blood 1990; 76;1287: IL-3 pilots
Kojima S et al, Blood 2002;100:786: G-CSF-monosomy 7
Tichelli A et al, Blood 2011; 117:4434: G-CSF shows no survival benefit

ELTROMBOPAG

- 2nd generation small molecule thrombopoietin (TPO) agonist
- Orally administered non-peptide
- FDA accelerated approval in 2008 for treatment of chronic ITP

Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

Matthew J. Olsen, M.D., Ph.D., Philip Scheinberg, M.D., Katherine B. Callicott, M.D., Ronan Desmond, M.D., Yong Tang, M.D., Ph.D., Rodrigo Davila, M.D., Anker H. Parikh, M.D., Susan A. Bresnahan, M.D., Angelo Bacchetti, Ph.D., Xiaoyin Yang, M.D., Ph.D., Jay Lalezari, M.D., Ph.D., Cohn O. Wu, Ph.D., Minh T. Young, M.S., and Cynthia F. Butler, M.D.

- 44% (11/25) response rate
- Trilineage responses observed
- Transfusion independence
- Well-tolerated
CIRCULATING THROMBOPOIETIN LEVELS IN SAA

Feng X et al. Haematologica 2011; 96:602

Emmons R et al, Blood 1996; 87:4068

ELTROMBOPAG FOR REFRACTORY APLASTIC ANEMIA


Hematologic Response Criteria
- Platelets: >20K/uL increase, or transfusion-independence
- RBCs: >1.5 g/dL increase in Hb, or transfusion-independence
- ANC: >100% increase if severe neutropenia, or >500/uL increase

ELTROMBOPAG 50 mg daily
Dose escalation every 2 weeks to 150 mg daily
Hematologic response at 3-4 months
Responders followed monthly, on drug (extension study)

RESPONSE SUMMARY OF EXPANDED COHORT

Median follow up 9 months
(range 3-47 months)

17 responders (40%)
- 11 platelet responses
- 4 erythroid responses
- Additional 7 at >16wks
- 8 neutrophil responses
- Additional 3 at >16wks

44 patients enrolled
43 evaluable patients
1 patient ineligible not treated

26 non-responders
- 2 responded >16 weeks
- 1 died of progression
- 3 deaths from sepsis
- 6 clonal evolution

ROBUST RESPONDERS – CAN ELTROMBOPAG BE STOPPED?

- Platelets >50,000/uL
- Hb >10 g/dL
- Neutrophils >1,000
- > 8 weeks

Decrease dose by 50%
Counts remain > above limits for 8 weeks
Discontinue drug

- 4 patients tapered off drug after robust response attained
- 1 patient had drug stopped for cataract misdiagnosis
- Median time off drug 13 months (range 1-15m)
- No relapses or need to restart eltrombopag

CLONAL EVOLUTION IN REFRACTORY AA ON ELTROMBOPAG

Subject (Age) Baseline Clone Time on eltrombopag (months) Dysplasia Outcome
7 (60) NR 46,XY[20] -7[20] 3 N Died of progressive cytopenias
19 (60) NR 46,XY[20] -7[16][1-16] 3 N HSCT
26 (67) R 46,XY[20] +6/46,XY Y(1) 13 Yes (mild) HSCT
31 (41) NR 46,XY +5[1]/46,XY[17] 3 N Yes (mild) Cytogenetics normalized, awaiting HSCT
42 (17) NR No metaphases +1,der(1;7)/46,XY[16] 3 N HSCT

LINEAGE CHARACTERISTICS OF RESPONSES

12 Weeks-Primary Endpoint
Best Response at Follow-up

- Platelets
- Neutrophils
- Hemoglobin

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BONE MARROW CELLULARITY AT ONE YEAR

Pre-treatment | Post-treatment | Pre-treatment | Post-treatment

ELTROMBOPAG FOR TREATMENT NAÏVE AA

- Eltrombopag stimulation may expand the HSC pool in humans
- Given early may allow for increased response rate, accelerate count recovery, prevent HSC depletion, avoid clonal progression

ELTROMBOPAG ADDED TO IMMUNOSUPPRESSION 12-H-0150, NCT01623167

Eligibility
- SAA naïve to IST
- Age >2
- horse-ATG + CSA
- Eltrombopag

Primary Endpoints
- quality of response
- Toxicity

Phase III
- purpose is to determine whether eltrombopag improve the rate and quality of responses

RAPID HEMATOLOGIC RESPONSES IN PATIENTS AFTER IST WITH ELTROMBOPAG N = 25

CD34+ ENUMERATION OF BONE MARROW ASPIRATES

%CD34+ of CD45+ fraction

Fold Change From Baseline

ROBUST HEMATOLOGIC RESPONSES WITH ELTROMBOPAG COMPARED TO HISTORICAL IST

IST = Eltrombopag (n=25) IST(n=87)
TRANSMION INDEPENDENCE IS ACHIEVED FASTER WITH ELTROMBOPAG

ongoing NHLBI eltrombopag trials in bone marrow failure

- Newly diagnosed moderate and severe aplastic anemia
- Refractory aplastic anemia
- Moderate AA and unilineage bone marrow failure syndromes
- Low-int-1 risk MDS with any lineage cytopenias

Telomeres and bone marrow failure

- TELOMERE STRUCTURE AND BIOLOGY
  - Cap chromosome ends
  - Tandem TTAGGG repeats
  - Bound to array of proteins: telomerase complex
  - Forms higher order chromatin T loop
  - Shields 3' end to prevent recognition as a DNA “break” by non-homologous end joining machinery
  - TTAGGG loss with proliferation: “end replication problem”

Telemere repair complex

Dyskeratosis congenita

- Courtesy by B. Alter, NCI
HEMATOLOGY/HEMATOPOIESIS IN “NORMAL” FAMILY MEMBERS WITH TERC MUTATIONS

Hematology
- Normal peripheral blood counts
- Mild anemia with macrocytosis
- Mild thrombocytopenia

Hematopoiesis
- Severely hypoplastic
- ↓CD34 number
- Colony formation
- ↑erythropoietin, thrombopoietin

proband affected sister affected niece unaffected brother

TELOMERE LENGTH IN TERT MUTATION LEUCOCYTES

TELOMERE COMPLEX GENE MUTATIONS AND BONE MARROW FAILURE

SHORT TELOMERE DUE TO TELOMERE COMPLEX GENE MUTATIONS

SHORT TELOMERS OCCUR DUE TO ENVIRONMENTAL FACTORS – WITHOUT MUTATIONS

- Regenerative stress
- DNA damage
  - Neoplasm/radiation form inflammation
  - Telomere loss

Suggestive personal/family history:
- AK, AML, MDS
- Thrombocytopenia, macrocytosis +/- anemia
- Pulmonary fibrosis
- Cryptic cirrhosis, NHL, portal hypertension
- Premature greying of hair
- Mucocutaneous triad: leukoplakia, skin hypo/hyperpigmentation, nail dyskeratosis

If personal/family history is STRONGLY suggestive

- DEB or MMC chromosome breakage (PB)
- Flow FISH or qPCR (PB)
- IF/BMT, genetic screen of family donors

If personal/family history is HIGHLY suggestive

- Telomere disease unlikely
- Telomere disease possible
- Telomere disease unlikely

Measure leukocyte telomere content

Patient or family suspected BMT

Exclude Fanconi anemia if <40 Telomere disease likely

Consider genetic screening for telomere maintenance genes (patient and family)
SHORT TELOMERE LENGTH PREDICTS RELAPSE AND EVOLUTION IN SEVERE APLASTIC ANEMIA

N = 168 consecutive patients on NIH IST protocols
Mean age = 34 years (4-82 years)
no relationship to response to treatment (PR, CR)

RELAPSE RATE BY TELOMERE QUARTILES

SURVIVAL PROBABILITY BY TELOMERE LENGTH

SEX HORMONES INCREASE TELOMERASE ACTIVITY IN CULTURED HUMAN LYMPHOCYTES

Calado RT et al, Blood 2009
DANAZOL FOR TELOMERE DISEASES

11-H-0209: “Danazol for Genetic Bone Marrow and Lung Disorders”
ClinicalTrials.gov identifier: NCT01441037

Eligibility:
1. evidence of a telomerase disease (mutation or very short telomeres), and
2. aplastic anemia and/or pulmonary fibrosis

26 patients enrolled
No significant toxicity, good hematologic responses thus far

Exploring Alternative Graft Sources for Patients Lacking an HLA Matched Related or Unrelated Donor

• Up to 40% of pts with SAA refractory to IST lack an HLA matched donor
• These patients may be candidates for an HLA mismatched allogeneic transplant using either a cord blood or haplo-identical stem cell transplant
• Umbilical Cord Blood (UCB) is an alternative graft source for patients with hematological malignancies that lack an HLA-matched donor who require a transplant
  – UCB transplantation has lower rates of graft versus host disease (GVHD) despite HLA mismatching
  – UCB is associated with delayed neutrophil and platelet engraftment and an increased risk of graft failure

Umbilical Cord Blood Transplantation (UCBT)
Umbilical Cord Blood (UCB) transplants are a transplant option for patients lacking an HLA identical donor:
1. Cord blood is a rich source of Hematopoietic progenitor cells - more than human BM
2. Most cord transplants are mismatched for 1/6 or 2/6 HLA loci (HLA A, B, DR)
3. Less GVHD with MHC mismatching

UCB Transplantation for Aplastic Anemia: High Incidence of Graft Failure, Transplant Related Mortality, and Low Survival

Combined CD34+ Haploidentical and Cord Blood Transplantation for SAA

• Primary Investigator: Dr. Richard Childs (NHLBI)
• Hypotheses:
  – Co-transplantation of an UCB unit combined with CD34+ haplo-identical cells will
    • shorten time to neutrophil engraftment in patients with SAA
    • Transplanted haploidentical cells will provide a back up stem cell source if cord blood unit should fail to engraft
**Conceptual Study Design**

- Highly Immunosuppressive Conditioning
  - G-CSF 5μg/kg IV day +1 until engraftment (ANC > 500 x 3 days)

**NHLBI Protocol 08-H-0046: Combined Cord Blood and CD34+ Haploidentical Transplant for SAA**

- **Eligibility Criteria**
  - Severe aplastic anemia between ages 4-55
  - ANC < 500 cells/ul
  - Failure to respond to standard immunosuppressive therapy
  - No available HLA matched donor (related or unrelated)
  - Availability of at least one ≥ 4/6 HLA-matched cord blood unit with TNC ≥ 1.5 x 10^7 cells/kg
  - Availability of at least one HLA- haploidentical family donor

**OBJECTIVES**

- **Primary**
  - Potential to achieve engraftment (ANC > 500) of cord unit and/or haplo donor in >80% patients by day 42

- **Secondary**
  - Achieve an ANC > 500 by day 10 in >80% of pts
  - Safety of novel transplant regimen
  - Day 100 and 200 TRM
  - Incidence and severity of acute and chronic graft-versus-host disease (GVHD) following transplant

**Chimerism Patterns**

- **Myeloid Chimerism**
- **T-Cell Chimerism**

**Combined CD34+ Haploidentical and Cord Blood Transplantation for SAA**

- **Co-infusion of allogeneic haplo-identical CD34+ cells with allogeneic UCB is a feasible transplant option for patients with SAA**
  - Shortens the time to neutrophil recovery
  - Provides a backup stem cell source in the event of UCB graft failure
  - May improve the outcome of UCB transplantation in high-risk patients with SAA

- **Primary Investigator:** Dr. Richard Childs
- **Research Nurse:** Elena Cho, 301-594-8013
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OUR PATIENTS!!