ASCT0631
A Phase III Trial of G-CSF Bone Marrow Harvest

"A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation"

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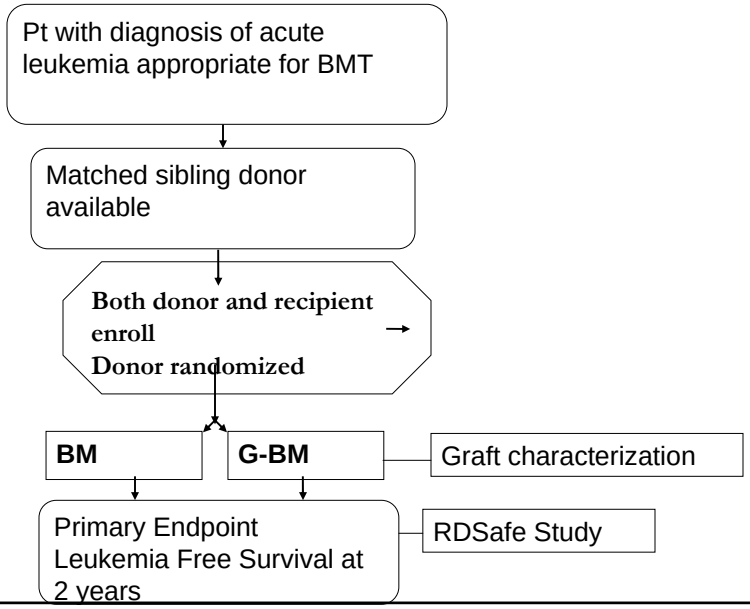
Sources of hematopoietic stem cells for transplant

- Bone Marrow (BM)
  - collected by needle aspiration under anaesthesia
  - Low T cell content
  - Lower stem/progenitor cell content
- Peripheral blood stem cells (PBSC)
  - Collected after 4-5 days of G-CSF treatment
  - Collected by apheresis (awake, on a machine for 4-5 hr/day for 1-3 days)
  - Much higher T cell content
  - Higher stem/progenitor cell content

Study Design



Ethical issues in G-CSF Rx in pediatric donors

- Bone marrow donation by minor sibling donors is standard of care for pediatric transplant in the US
- Are the sibling bone marrow donors in the ASCT0631 study research subjects?
- If so, is there potential for direct benefit?
- What are the risks of the experimental intervention?

Ethical issues in G-CSF Rx in pediatric donors

- Position of the pediatric BMT community is that bone marrow donation provides direct benefit to the sibling
- BMT is used to provide a curative option to patients with cancer and some non-cancer conditions
  - Often there is no other curative option, or
  - BMT increases the likelihood of cure over other treatments
- Impact of death in the family is devastating, directly to the sibling and indirectly via the effects on caretaking parents and others
- Thus, there is direct benefit to the sibling in bone marrow donation

Ethical issues in G-CSF Rx in pediatric donors

- Similarly, is there potential for direct benefit to the donor on ASCT0631?
  - Survival of the affected sibling is of direct benefit to healthy sibling donor
  - Study design which aims for improved EFS provides a chance to improve that benefit
- Position of the pediatric BMT community: ASCT0631 meets the 45 CFR 46.405 standard for both recipients and donors enrolled on the study

Ethical issues in G-CSF Rx in pediatric donors

- Are 5 shots of G-CSF risky for normal donors?
- The vast majority of adult transplants use G-CSF in the donors as a standard of care
- 20% of pediatric transplants used G-CSF in the donors in a 2004 report
- Most common short-term toxicity – bone pain
- Although not reported in children, there are at least 5 cases of splenic rupture reported in adults who have gotten G-CSF for some indication

Ethical issues in G-CSF Rx in pediatric donors

- G-CSF is a white cell stimulator. Does it increase the risk of leukemia?
- NMDP has followed 2408 unrelated donors since their donation, for a total of >9800 pt years of followup. No AML or MDS reported in this cohort (Pulsipher, Blood, in press)
- EBMT retrospective analysis:
  - Non G-CSF donors 9/28,134 (0.032%) w/a hematological malignancy vs.
  - G-CSF donors 5/16,432 (0.03%)

Ethical issues in G-CSF Rx in pediatric donors

- Pediatric Central IRB review:
  ASCT0631 meets the standard of minor increase over minimal risk for the donors (45 CFR 46.406)
- Approved by >30 IRBs at the time of referral

Standard consent form language

Normal individuals are at risk for developing cancer, including leukemia, lymphoma or other blood diseases throughout their lifetime. It is unknown whether filgrastim increases or decreases an individual's risk of developing cancer. The data being collected during follow-up will help establish if there are any positive or negative long-term effects from receiving filgrastim. Based on limited long-term data from healthy people who have received filgrastim, no long-term risks have been found so far.

Multilayered and interdisciplinary review of ASCT0631

- COG SCT Discipline
- PBMTC
- COG Disease Committees – AML and ALL
- COG BioEthics Committee
- COG Scientific Counsel
- CTEP/NCI
- Pediatric Central IRB

PBMTC STC0233 G-BM pilot study (Haydar Frangoul, Blood 2008)

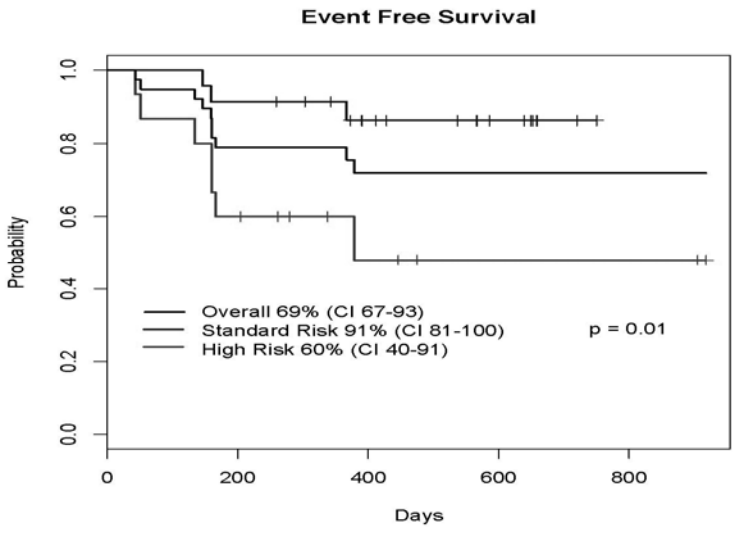
Matched sibling donors (N=42)

- Approved by 9 IRBs
- Median Age 9.2 y (range 1.1-22)
- All donors received all doses of G-CSF
- No donors experienced any significant pain related to G-CSF
- No reported donor complications

PBMTC G-BM Pilot

- All patients engrafted
- Median NC count 7 x10^8/kg (range 2.4-18.5)
- Median CD34 count 7.5 x10^6/kg (range 2-27.6)
- ANC>500 median 19 days (range 13-28, no G post BMT)
- Plts>20K median 20 days (range 9-44)

EFS (median follow up 24 months)



Why is this good science? How will we help children if the study is successful?

- PBSC collected after G-CSF mobilization is standard of care in adults, but used in a minority of children
- PBSC are superior to BM in adults

Why is this good science? How will we help children if the study is successful?

- Concern about the risk of chronic graft vs. host disease in kids caused by PBSC
- How can we provide the cell dose benefit to pediatric BMT recipients without the cGVHD risk?

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G-CSF BM collection

Primary Hypotheses of ASCT0631

- Larger cell dose in G-BM collections will improve leukemia-free survival
- G-BM will speed engraftment
- Lower rates of chronic GVHD
  - Compared to PBSC
  - ?Compared to conventional BM?

Secondary Objectives

- Impact of G-BM on hospital stay, Day 100 TRM and immune reconstitution
- Evaluate short- and long-term toxicities of G-BM vs. standard BM donation in collaboration with the RDSafe study.

Eligibility

- Recipients must be <22 years old
- Donors > 6 months old
- Acute leukemia in remission
- CML in first or second chronic phase
- Have completed reinduction therapy post-relapse, if applicable

Disease eligibility

- ALL CR2
- VHR ALL CR1: i) Ph+ ALL; ii) hypodiploidy (<44 chromosomes); iii) MLL rearrangement; iv) induction failure
- AML CR1 or CR2
- JMML
- CML in first or second chronic phase
- MDS

Donor eligibility

- SIZE: Donor must be of adequate size relative to the recipient – harvesting the maximum of 20cc/kg from the donor would result in a graft that will provide an adequate cell and volume dose to the recipient, in the opinion of the treating physician

<u>Donor Exclusion Criteria</u>

- HIV positive
- Sickle cell trait
- At high risk for donation due to pre-existing condition
- Pregnant or lactating
- Uncontrolled infection
- Auto-immune disease

Sample size

- 425 pts study has 80% power to detect a hazard ratio of 0.67
- Estimated 44 months of accrual

Why is this good science? How will we help children if the study is successful?

- A successful study result would improve the practice of pediatric bone marrow transplantation
- The higher cell doses could translate to less volume collected from donors – future benefit
- New standard of care in pediatric BMT

ASCT0631 Study Committee

- Haydar Frangoul, Vice-chair
- Bryan Langholz, statistician
- Donna Wall
- Kirk Schultz
- Sandeep Soni
- Mike Pulsipher
- Alan Gamis
- John Levine
- Cheryl Edens
- Anne Wohlschlaeger
- Jennifer Chan
- Julie Gastier-Foster
- Natia Esiashvili