

## **Nemours Oncology IRB Review of COG Protocol ASCT0631**

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

**Tim Wysocki, Ph.D., C.I.P., Chairperson  
Nemours Oncology IRB  
Nemours Children's Clinic  
Jacksonville, Florida**

### **Nemours Foundation**

- **Operates pediatric medical centers in Delaware and Florida with support from the Alfred I. du Pont Testamentary Trust.**
- **Nemours Office of Human Subjects Protection manages three IRB's under FWA # 000293.**
- **Nemours Oncology IRB reviews and oversees all Hematology-Oncology protocols at all Nemours sites.**
- **Members included three MDs, representatives of nursing, epidemiology, psychology, social work, and physical therapy and a parent of a child with cancer.**
- **IRB meetings are conducted monthly by video conference.**

## **Initial Review at IRB Meeting 7/2/08**

- **The IRB questioned both the risks and the potential direct benefit to healthy donors of receiving G-CSF.**
- **The IRB voted unanimously to defer approval of the protocol pending further information.**
- **Dr. Eric Sandler, the local PI, was asked to clarify possible risks and direct benefits to healthy donors and to forward the Pediatric CIRB rationale for approval of the protocol if it could be obtained.**

## **Reconsideration at 9-3-08 IRB Meeting**

- **Reviewed NCI Pediatric CIRB document detailing basis for approval under 45 CFR 46.406 and 21CFR 50.53.** *(No more than a minor increase over minimal risk.....but likely to yield generalizeable knowledge about the participant's condition or disorder)*
- **Reviewed pertinent journal articles submitted by Dr. Sandler** *(Pulsipher, et al, 2005, 2006; Grupp et al., 2006; and Frangoul, et al., 2007).*
- **Considered heavily the opinion of a physician IRB member about risks associated with G-CSF in siblings of children with cancer.**
- **Further evaluated other risks mentioned in the COG protocol and Pediatric CIRB summary.**

## **Points of Agreement with CIRB**

- **Sibling donors are research subjects.**
- **The protocol cannot be considered minimal risk and thus is not approvable under 404/52.**
- **Protocol holds no prospect of direct benefit to donors and is thus not approvable under 405/53.**
- **The study has the potential to yield information of substantial benefit to children with leukemia who receive bone marrow transplants via sibling donors.**

## **IRB Review of Journal Articles**

- **Few studies of G-CSF risks have been done in healthy children.**
- **Risk of leukemogenesis in donors after G-CSF administration (implicated in some laboratory studies) is unknown and difficult to disprove.**
- **Other rare but serious risks associated with G-CSF have been shown in studies with adults.**
- **The relevance of these findings to pediatrics is unclear due to the need for lengthy follow-up of large samples of participants.**

## **Nemours Oncology IRB Findings**

- The protocol offers no direct benefit to donors.
- Siblings of children with leukemia have elevated risk of developing leukemia themselves.
- G-CSF carries a theoretical risk of initiating onset of leukemia (leukemogenesis) in these healthy siblings, a risk that is difficult to confirm or disprove because of the required sample size and follow-up duration.
- G-CSF carries other risks, e.g. enlargement of the spleen (rarely rupture), bone pain, fever and others.
- Rare but serious risks of G-CSF have not been seen in pediatric donors, but sample sizes have been small.
- Determination that sibling donors have a “condition” per 45 CFR 46.406/21 CFR 50.53 was left undecided.

## **Nemours Oncology IRB Conclusions**

- G-CSF administration to healthy siblings of pediatric cancer patients constitutes more than a minor increase over minimal risk.
- Potential for improved outcomes of bone marrow transplant could benefit pediatric leukemia patients.
- COG Protocol ASCT0631 appears to be *“research not otherwise approvable that offers an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children”* (45 CFR 46.407 and 21 CFR 50.54).
- The IRB decided by unanimous vote that a request should be sent to OHRP & FDA to consider whether this protocol merits approval under these categories.