16 September 2011

Manuscript Number: BMT-2011-423R
Title: Osteonecrosis in Children after Allogeneic Hematopoietic Cell Transplantation: Study of Prevalence, Risk Factors, and Longitudinal Changes Using MR Imaging

Dr. Heslop:

We thank you and the reviewers for their comments and suggestions. We resubmit the above paper with revisions responding each of the comments and hope our work is now acceptable for publication in Bone Marrow Transplantation. Our detailed responses follow.

Should any additional questions arise, or information is needed, please do not hesitate to contact me.

All the best

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Reviewer #1 (Comments to the Author):
All my questions have been addressed.

Reviewer #2 (Comments to the Author):

I have only minor issues, which could slightly improve the manuscript.

Specific items:

1. The discussion reveals a very high presence of osteonecrosis in your sickle cell population. Please briefly describe for the readers, documenting with literature, why the sickle population is more susceptible to this issue and outline expected rates.

We have added a couple summary sentences to the Discussion on page 13 in response to your request as well as added supportive references.

Osteonecrosis is a well-known morbidity of sickle cell disease that has been positively associated with the frequency of vaso-occlusive pain crises and elevated hematocrit. This morbidity has been reported in 10-16% of symptomatic patients assessed radiographically and in up to 40% of patients radiographically examined regardless of symptoms. The high 50% prevalence of osteonecrosis we found in our sickle cell patients is similar to the MR-detected incidence of 65% reported after a follow-up period of 4 to 5 years.

2. In your discussion you state, "Unlike other investigators, we found no significant increase in risk for osteonecrosis among those who received TBI, probably because our patients received very small doses of radiation per fraction (150 cGy/ fraction twice daily)." This is speculation-where is the data to suggest that a large difference can occur with lowering of a TBI fraction from 200 to 150 that a large difference in osteonecrosis will occur? At most you could say "possibly" because (if other evidence supports).

We have revised the terminology to “possibly” as you suggested (page 13).

We agree that there is little data to support this hypothesis in the BMT population. However, radiobiologically, bone is a" late responding normal tissue ". Therefore, smaller doses per fraction will have a sparing effect on bone (this is one of the factors considered in radiation therapy planning where in normal tissues are to be spared the toxic effects of radiation. Cell survival curve characteristics of different types of normal tissues and the ability of these different tissues to repair themselves from radiation damage form the basis of different fractionation schedules. It has been shown by various radiobiological studies that smaller radiation doses per fraction do have sparing effect on late responding tissues but as we agree, little information is available relating this process to the development of osteonecrosis in the BMT population.

Smit BJ. Radiation related prognostic factors in radiation oncology. Eur J Gynaecol Oncol. 2000;21(1):7-12.

Ling CC, Gerweck LE, Zaider M, Yorke E. Dose-rate effects in external beam radiotherapy redux. Radiotherapy and Oncology 2010; 95:261-268.

Willers H, Beck-Bornholdt HP.Origins of radiotherapy and radiobiology: separation of the influence of dose per fraction and overall treatment time on normal tissue damage by Reisner and Miescher in the 1930s. Radiother Oncol. 1996 Feb;38(2):171-3.

3. You clarify somewhat why you don't have a strong association with GVHD because the percentage of patients you have getting steroids for >6m is very low. Can you also comment on other steps you take at your center that might mitigate skeletal morbidity? Do you give calcium/Vit D supplementation, bisphosphonates, or other therapies routinely, etc.?

We do not routinely administer calcium/Vit D supplementation, bisphosphonates, or other therapies to patients undergoing BMT. However, all patients do receive evaluation of nutritional intake and are advised regarding a healthy diet with early nutritional support implemented that may include calcium/Vitamin D supplementation. The use of nutritional supplementation and rarely bisphosphonates is on a case-by-case basis. Additional aspects that are included in patient care are good physical therapy support and encouragement of physical activity. All patients are monitored closely for endocrine function. Early replacement therapy is implemented when necessary in cases of hypothyroidism, growth hormone, hypogonadism, etc.

4. Finally, you qualify your speculation about mesenchymal stem cells, but I would be even more cautious. Not bad to hint at the possibility, but no solid evidence for this yet.

We agree with the need for caution at this point and hope we have effectively further tempered our comments (page 14); we have removed one sentence and the corresponding reference and “softened” the suggestion that alloHCT may contribute to osteonecrosis healing.