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Reply: Deferoxamine Restores Callus Size, Mineralization, and Mechanical Strength in Fracture Healing after Radiotherapy

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Sir:

We welcome the interesting commentary and questions raised by Dr. Hamid Namazi concerning our article regarding the use of deferoxamine in the prevention of radiation-induced pathologic fractures in the murine mandible. The referenced articles by Chan et al. do indeed show that the high doses of deferoxamine delivered systemically for thalassemia patients receiving transfusions and chelation therapy can cause undesirable side effects such as skeletal dysplasias.¹ In response to his concerns, we would like to address clinically relevant disparities in the duration of treatment, age of the patient population, and dosing between our intended clinical use and the development of skeletal dysplasias in thalassemia patients.

The articles by Chan et al. refer to a pediatric patient population with an average age of 12.1 years that are receiving high doses of systemic deferoxamine over an average period of 8.2 years. According to this dose information, the average pediatric patient received a total of 2,201,325 mg of deferoxamine over the course of their treatment before the development of skeletal dysplasias.¹ It should be noted that in this context, the more established (and rare) severe side effects of deferoxamine are visual and auditory symptoms of neurotoxicity and pulmonary syndrome.²⁻⁴

In stark contradistinction, our dosage of deferoxamine is a mere fraction of the dose delivered clinically for thalassemia. Furthermore, it is also injected locally into the fracture callus, thereby significantly reducing the possibility of untoward and widespread side effects, such as those reported in thalassemia patients. The clinical application we envision for deferoxamine in the head and neck cancer population would entail elderly patients with a mean age of 62 years, receiving five micromolar injections over a short period. Specifically, in our experiments, we delivered five injections of 200 μ M of deferoxamine over a course of 9 days, or 0.263 mg of deferoxamine total.^{5,6} Therefore, our dose is smaller than the systemic dose administered to thalassemia patients by a factor of 10^7 , or 10 million.

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DISCLOSURE

None of the authors has a financial interest in any of the drugs mentioned in this communication or the article being discussed.

In summary, we disagree with the reviewer's assertions that the consideration of skeletal dysplasia as a side effect of our intended use is a limitation to our study. The reviewer's concern regarding dysplasia is based on data obtained from pediatric patients receiving a high dose of deferoxamine over an extended period. This represents a drastically different patient population, dose amount and duration, and route of administration from what we are proposing in our work. There is no evidence to support skeletal dysplasias resulting from our intended use. Furthermore, deferoxamine has been in use clinically for over 50 years, and its side-effect profile is established and well known.⁷ These considerations are essential in the fair evaluation of our work.

We maintain that a more important consideration with this specific application is the tumorigenic safety of deferoxamine in the head and neck cancer patient population. Our findings in this animal model are encouraging and raise important questions about the potential investigation of the timing and dosing of this therapy in a clinical setting. As discussed in the article, the current literature is encouraging for the potential use of deferoxamine in these regards. However, even at these small doses, we still strongly encourage further investigation. We thank you for your commentary and hope to have clarified these concerns.

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