Amifostine Therapeutic Enhancement of Vascularity in an Irradiated Model of Mandibular Fracture Repair Model

Catherine N Tchanque-Fossuo, MD, MS; Behdod Poushanchi, BS; Deniz Sarhaddi, BA; Alexis Donneys, MD, MS; Sagar S Desphande, BS; Daniela A Weiss, BS; Steven R Buchman, MD

Abstract

Introduction: Radiation (XRT)-induced pathologic fractures (Fx) of the mandible can have devastating effects on patients. Delayed Fx healing is related to blood vessels obliteration and/or cell proliferation impairment. We have previously demonstrated the cyto-protective effect of the antioxidative drug Amifostine[1] (AMF) on bone osteoprogenitor cells[2]. Utilizing micro-computed tomography (µCT) after vessel perfusion, we intend to ascertain whether AMF can also preserve the vascularity of the highly cortical murine mandible after exposure to human equivalent dose of radiation (HEDR)[3] in a mandibular model of pathologic fracture repair[4].

Methods: Twenty-four male rats were randomized into 3 groups: Fx, XRT/Fx and AMF/XRT/Fx. XRT/Fx and AMF/XRT/Fx underwent 5-day fractionated HEDR over the left hemimandibles. AMF/XRT/Fx received AMF prior to XRT. After 14 days, all groups underwent unilateral left mandibular osteotomy with bilateral external fixation followed by distraction to a 2.1mm fracture gap. Forty days later, left ventricular catheterization and perfusion with Microfil was performed. Vascular radiomorphometrics were quantified via µCT.

Results: All radiated animals demonstrated clinical signs of radiation-induced mucositis and alopecia, but were less apparent in the AMF pre-treated group. We observed 84% rate of bony union in Fx compared to 67% in AMF/XRT/FX and 25% in the XRT/Fx. Further analysis revealed a substantial increase in Vessel Number (123%, $p<0.05$) and a corresponding decrease in Vessel Separation (55.5%, $p<0.05$) between AMF and non-AMF irradiated fractured mandibles (see Figures).

Conclusion: For the first time to our knowledge, we have established and quantified the effect of AMF prophylactic therapy on angiogenesis in the setting of radiotherapy. This important finding may further be optimized for an effective translation into the clinical arena of pathologic fracture treatment in HNC reconstruction. Our results set the stage for exploration of this targeted therapy alone and in combination with other therapies to mitigate radiation effects in the clinical setting.

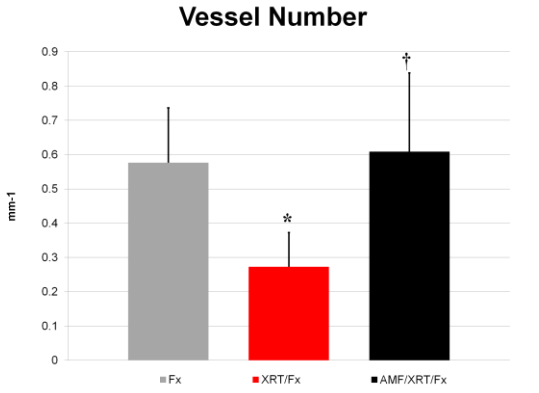

Figure 1. Vessel Number. Statistical significance at $p < 0.05$. (*) designates statistical difference between Fx and XRT/Fx and (†) designates statistical difference between XRT/Fx and AMF/XRT/Fx.

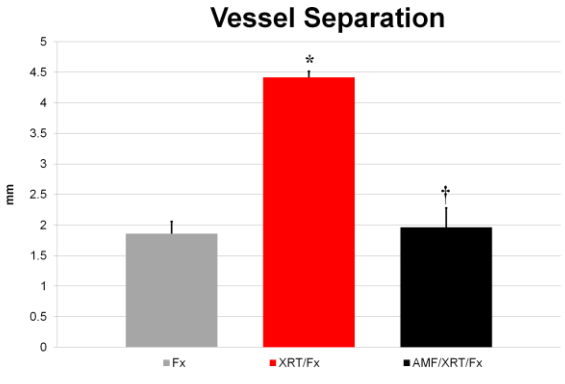

Figure 2. Vessel Separation. Statistical significance at $p < 0.05$. (*) designates statistical difference between Fx and XRT/Fx and (†) designates statistical difference between XRT/Fx and AMF/XRT/Fx.

References:

1. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol. 2000;18(19):3339-45.

2. Tchanque-Fossuo CN, Donneys A, Razdolsky ER et al. Quantitative Histologic Evidence of Amifostine Induced Cytoprotection in an Irradiated Murine Model of Mandibular Distraction Osteogenesis. Plast Reconstr Surg, 2012 in press.

3. Tchanque-Fossuo CN, Monson LA, Farberg AS et al. Dose-Response Effect of Human Equivalent Radiation in the Murine Mandible. Part I. A Histomorphometric Assessment. Plast Reconstr Surg. 2011;128(1):114-121.

4. Donneys A, Tchanque-Fossuo CN, Farberg AS et al. Quantitative Analysis of Vascular Response After Mandibular Fracture Repair Utilizing Micro-Computed Tomography with Vessel Perfusion. Plast Reconstr Surg. 2011; 127(4):1487-1493.

The authors have no financial interest and no disclosure regarding the content of this manuscript.