Journal of Plastic, Reconstructive & Aesthetic Surgery (2016) 69, 234—240

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Prophylactic amifostine prevents a pathologic vascular response in a murine model of expander-based breast reconstruction☆

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Received 18 June 2015; accepted 13 October 2015

KEYWORDS
Breast cancer;
Immediate breast reconstruction;
Amifostine;
Radiotherapy;
Expander-based reconstruction;
Vascularity

Summary *Background:* Although expander-based breast reconstruction is the most commonly used method of reconstruction worldwide, it continues to be plagued with complication rates as high as 60% when radiotherapy is implemented. We hypothesized that quantitative measures of radiotherapy-induced vascular injury can be mitigated by utilizing amifostine in a murine model of expander-based breast reconstruction.
Methods: 30 rats were divided into three groups: expander placement (Control), expander placement followed by radiotherapy (XRT), and expander placement followed by radiotherapy with amifostine (AMF/XRT). All groups underwent placement of a sub-latissimus tissue expander. After a 45 day recovery period, all groups underwent vascular perfusion and micro-CT analysis.
Results: Micro-CT analysis was used to calculate vessel volume fraction (VVF), vessel number (VN), and vessel separation (VSp). A significant increase in VN was seen in the XRT group as compared to the Control ($p = 0.021$) and the AMF/XRT ($p = 0.027$). There was no difference between Control and AMF/XRT ($p = 0.862$). VVF was significantly higher in XRT than either Control ($p = 0.043$) and AMF/XRT ($p = 0.040$), however no difference was seen between Control and AMF/XRT ($p = 0.980$). VSp of XRT was smaller when compared to both Control and AMF/XRT specimens ($p = 0.05$ and $p = 0.048$, respectively), and no difference was seen between Control and AMF/XRT ($p = 0.339$).

☆ This work was presented at the Plastic Surgery Research Council in Seattle, Washington on May 15, 2015.

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http://dx.doi.org/10.1016/j.bjps.2015.10.022

Conclusions: Amifostine administered prior to radiotherapy preserved vascular metrics similar to those of non-radiated specimens. Elevated vascularity demonstrated within the XRT group was not seen in either the Control or AMF/XRT groups. These results indicate that amifostine protects soft tissue in our model from a radiotherapy-induced pathologic vascular response.

Introduction

Breast cancer is one of the leading causes of cancer deaths in women worldwide, with nearly 1 out of every 8 women diagnosed during their lifetime.[1] A multidisciplinary approach to treatment remains the standard of care, with patients receiving various combinations of surgical extirpation, radiation, chemotherapy and hormonal therapy. Although advances in surgical care and earlier diagnoses have resulted in a greater number of women being candidates for breast conservation therapy, a substantial number of patients still are not candidates and require a mastectomy. Radiotherapy (XRT) has remained the cornerstone of the treatment plan for the majority of women with breast cancer as it has been shown to reduce loco-regional recurrence and increase disease-free survival. Despite the benefits of XRT, the injury to the surrounding soft tissue presents a significant clinical problem for breast reconstruction.

For women undergoing a mastectomy, reconstruction following surgery is a critical part in the overall road to recovery and the universal feeling of being whole. The number of women choosing to undergo reconstruction has increased significantly since the late 1990s, and continues to grow every year.[2] Given the increasing number of reconstructions, it would behoove the surgeon to have a set of strategic alternatives to consider when designing the optimal reconstructive plan. This individualized plan would be tailored for the patient so as to increase the quality of her life and enhance her self-image. Furthermore, in order to improve the current state of breast reconstruction following multimodal therapy, these methods would need to be both cost-effective and demonstrate low complication rates.

The current post-mastectomy breast reconstruction options include autologous tissue transfer and expander-based reconstruction. Autologous tissue reconstruction requires a more invasive operation than expander based reconstruction, with longer operative times and recovery periods, but the well-vascularized tissue that is introduced to the reconstruction site is able to withstand the scourge of XRT-induced side effects.[3,4] In comparison, expander-based reconstruction is a less invasive option, with shorter operative times and recovery periods; however, when combined with adjuvant XRT, it is associated with an unacceptably high complication rate and low patient satisfaction, and therefore rarely is utilized for patients undergoing XRT.[4,5] XRT-induced injury in soft tissue has been extensively studied, yet remains poorly understood. Despite the high complication rate reported for post-mastectomy expander-based reconstruction with adjuvant XRT, the mechanism of injury to skin and soft tissue has not previously been examined in a clinically relevant model. A better understanding of the mechanism of XRT injury could potentially lead to therapeutic interventions aimed at increasing the number of viable reconstructive options for breast reconstruction in the setting of XRT. Similarly, engineering novel therapeutic techniques that mitigate XRT-induced injury and ensure viable soft tissue post-radiation may re-introduce expander-based reconstruction as an option to women undergoing post-mastectomy XRT.

Amifostine (AMF) is a cytoprotectant that is currently used to reduce the incidence of xerostomia in patients undergoing radiotherapy for head and neck cancer and has also been shown to ameliorate the devastating effects of radiation on bone. The cytoprotective benefits of AMF and lack of protective effect on cancer cells has been extensively studied in many cancers including head and neck and lung cancer. However, its radio-protective benefits have never been studied in patients undergoing breast reconstruction after mastectomy.[6,7] This meliorism has been well illustrated and quantified in the ability of AMF to protect the vasculature of the mandible from the noxious effects of XRT. Prior work in our laboratory has demonstrated the extent by which XRT can induce injury to the skin. Further work in our lab has also demonstrated the ability of AMF prophylaxis to reduce the rate of complications from 69% to 30% in our model.[8]

We hypothesize that the pathological effects of XRT on skin and soft tissue are mediated through a mechanism of vascular degradation, direct cellular depletion, and diminished function of the cells responsible for the generation and maintenance of the soft tissue envelope required for expander-based breast reconstruction. We further posit that the cytoprotective properties of AMF will function to protect the vascularity of skin and soft tissue in a radiated expander-based breast reconstruction model. To test our hypotheses, this study utilizes a murine model to determine the degree by which XRT impairs vascularity and new blood vessel formation after tissue expansion. We subsequently exploit the novel radio-cyto-protective properties of AMF in order to gauge the extent by which this radioprotectant can prophylactically mitigate the deleterious effect of XRT on the vascular supply and angiogenic capacity of expanded soft tissue.

Methods

Animal experimentation was conducted in accordance with the guidelines published in the Guide for the Care and Use