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Phase-1 Clinical Studies of Wound Healing in Tolerated Dose Chemotherapy

Hala Ahmad*

Department of Oncology, University of Yonsei, Seoul, Korea

Opinion Article

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***For Correspondence:**
Hala Ahmad, Department of Oncology, University of Yonsei, Seoul, Korea

E-mail: halaahmad@gmail.com

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DESCRIPTION

Maximum Tolerated Dose (MTD) chemotherapy is designed to impact rapidly dividing cells, thus a practical concern exists for deleterious effects on wound healing. The timing of the chemotherapy (neoadjuvant versus adjuvant) and specific drug administered may also influence the effects. Various pre-clinical studies have documented delayed wound healing from chemotherapy; however, it appears transient, it is most apparent when drug is administered during the inflammatory phase of healing and may be ameliorated to a degree with the administration of granulocyte colony-stimulating factor.

Several clinical evaluations have documented limited impact of chemotherapy on wound healing. In one study patients with locally advanced mammary carcinoma treated with surgery and perioperative chemotherapy, there

were no negative effects on wound healing. In a separate study evaluating obstetric and gynaecologic patients, the incidence of wound complications was 11% and chemotherapy did not increase the risk of wound complications surgery.

It appears the most detrimental effects occur when chemotherapy is administered within two weeks pre-or-one week post-operative and the presence of low albumin or haemoglobin is associated with a greater risk of delayed wound healing. Nevertheless, in general, it is felt the benefit of promptly initiating chemotherapy outweigh any immediate complications associated with surgery. It is important to note that the majority of studies, experimental or clinical, that have evaluated the effects of chemotherapy on wound healing have looked at primary wound healing, which is arguably the most relevant for the surgeon. The effects of chemotherapy agents on second intention wound healing are for the most part unknown. In one experimental model, nitrogen mustard decreased granulation tissue and wound concentration.

In veterinary medicine, there are several factors that likely limit the impact of chemotherapy on wound healing; clearly, the dose intensity used in companion animals is significantly lower than that used in oncology in human patients, neoadjuvant/perioperative chemotherapy is relatively uncommon, and most patients start chemotherapy 10-14 days post-surgery. A paucity of information exists in the veterinary literature with most of the data limited to dogs with osteosarcoma treated with either cisplatin or doxorubicin either pre-operative for 2-3 cycles or 2-10 days post-surgery. Neither study reported an increase in post-operative morbidity. On the other hand, survival did not appear to improve with these protocols. Therefore, general recommendations are to wait 7-14 days after surgery to begin chemotherapy, especially for more high-risk prodices such as intestinal resection and anastomosis.

The use of metronomic chemotherapy is becoming more commonplace. As conventional chemotherapy typically involves the use of pulsatile cycles of chemotherapy given at the MTD with long breaks to allow recovery of normal cells from damage, metronomic chemotherapy instead utilizers continuous administration of chemotherapeutics at a dosage well below the MTD, without prolonged drug-free breaks. Unlike MTD chemotherapy, where the tumor cells are the primary targets of therapy, metronomic therapy appears to target cells of the tumor microenvironment including the endothelial cells that support and nourish the tumor. The mechanism of action includes direct apoptosis for dividing endothelial cells, suppression of the mobilization of Circulating Endothelial Progenitor Cells (CEPs) form the bone marrow. And increasing the production of the body's own natural angiogenesis inhibition and depletion of T-regulatory lymphocytes, thereby decreasing immune tolerance. Although metronomic therapy is often considered "antiangiogenic" to date there is no evidence on whether its use has a detrimental effect on wound healing, as the vast majority has reported its use either weeks post-surgery or in the treatment of bulk disease.