Results of GM-CSF treatment in chemotherapeutic extravasation ulcers

Dear Editor,

Extravasation injury is defined as the damage caused by leakage of a solution from a vein into the surrounding tissue spaces during intravenous (i.v.) administration. Although the leakage of non-toxic agents is usually (but not always) not a problem, extravasation of chemotherapeutics may lead to severe local tissue problems and even result in loss of full thickness of the skin and underlying structures. Patients undergoing chemotherapy have a 4.7% risk for extravasation [1]

Based on their potential to cause local tissue injury, drugs are classified as vesicant, irritant or non-vesicant, depending on their capability to induce the formation of blisters and/or cause tissue destruction [2]. Doxorubicin, as a potent vesicant drug, causes progressive indolent skin ulceration in case of extravasation. Local toxicity is characterized by pain, erythema and swelling at the extravasation site and can progress onto tissue necrosis of the skin and deeper anatomical structures such as the underlying tendons and bone, thereby leading to great pain and functional impairment.

The prevention or early effective treatment of chemotherapeutics' extravasation in the fragile cancer patients is of particular importance, not only because of the morbidity of surgical therapy of the extravasation-induced injury in these immunocompromised patients with slow wound healing rates, but also because of the indolent insidious nature of the developing ulcer which tends to progress and erode the deeper structures with the passing of time. Some general conservative measures include cessation of infusion, aspiration of some of the extravasated fluids from the same i.v. line before the needle is withdrawn and administration of the antidote (if there exists), resting and elevating the affected site for 48 hours [1,3]. Surgical management of these injuries mainly consists of debridement and skin grafting to the involved areas and flap repairs on occasions of accompanying large tissue necrosis. Unfortunately, once extravasation occurs, both surgical and supportive non-surgical therapies are far from being satisfactory, and thus more effective methods need to be developed.

Both experimental and clinical trials involving the application of exogenous recombinant growth factors to chronic wounds have been conducted over the past 10 years in an attempt to accelerate healing [4]. Granulocyte-macrophage colony stimulating factor (GM-CSF) increases neutrophil phagocytic activity, leading to the elimination of the doxorubicin-DNA complex released from the dead cells on the ulcer base before it is taken up by the surrounding viable cells at the extravasation site. GM-CSF appears to be a multipotent wound-healing cytokine in skin, and stimulates the growth of all cellular components in vitro that form the structural basis of human skin, i.e., keratinocytes, fibroblasts and endothelial cells. GM-CSF is shown to induce endothelial cells to express an activation and differentiation program, including proliferation and migration that relate to angiogenesis. It was also shown to induce the contraction of the wound. Since the breakdown of vascular integrity at the extravasation site and the reduced contraction rate of wound have particular importance in doxorubicin extravasation injury, GM-CSF must have beneficial effects by reversing these factors. The preventive roles of GM-CSF and granulocyte colony stimulating factor (G-CSF) in an established wound model were investigated and CSFs were found to be quite useful in the early treatment of lesions due to doxorubicin extravasation [5].

While extravasation-related injuries were well classified according to the extravasating agents, clinical grading of these ulcers in accordance with the outcome of the treatment method is still missing. In our study described below ulcers from chemotherapeutics extravasation were classified according to the depth of the lesions (grade I: lesions with hyperemia and swelling without any ulceration; grade II: lesions with ulcer development; grade III: lesions with eschar and full thickness skin loss) and treated with 3 doses of subcutaneous injection of 10 μg/kg (max. 150 μg in each injection) GM-CSF once a week, in which half of the dose is injected to the base of the lesion and the other half around the extravasation area. Twenty-five cases with 29 chemotherapeutic extravasation episodes are reported here in. Lesions graded as I or II were healed completely with this treatment. Progression in healing was not observed in any of the lesions classified as grade III at the first evaluation, which eventually needed debridement. The data from our series suggests that the proposed classification can be used for the grading of chemotherapeutic extravasation lesions, which will definitely help to compare results of different studies concerning the treatment of extravasation injuries. Although the proposed treatment may prevent the progression of grade I and II lesions to more severe ones, it is not efficient in the treatment of lesions with full thickness skin loss.

References

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