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Short Commentary Open access

A Role for Intralesional (Intratumoral) Therapy with Two Cytokines in the Management of Some High Risk Patients with Cutaneous Melanoma

E George Elias[1*] **and Bhuvnesh K Sharma**[2]

[1]*University of Maryland St. Joseph Medical Center, Towson, Maryland, USA*

[2]*ScyTek Laboratories, Logan, Utah, USA*

***Corresponding author**: Elias EG, MD, Phd, University of Maryland St. Joseph Medical Center, Towson, Maryland, USA, Tel: 1-410-337-1000; E-mail: egelias1@comcast.net

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Commentary

Despite all preventive measures, the incidence of cutaneous melanoma continues to rise. While surgery can induce potential cure in patients with low risk primary disease, adjuvant therapy is needed in addition to surgery in high risk patients with primary melanoma. High risk patients include those with invasive primary of over 0.75 mm depth of invasion, the presence of ulceration or mitosis at the primary site regardless to the depth of invasion. The objective of adjuvant therapy is to prevent disease recurrence and metastases and improve patients' survival. Several approaches and a variety of agents were administered *systemically* in the *postoperative* period, i.e., post resection of the primary site, with and without regional lymphadenectomy, and some resulted in limited success but far from having major impact on the disease. In the meantime, sentinel lymph node identification and excisional biopsy identified occult metastases that can be surgically eliminated, but more importantly is to initiate adjuvant therapy in relatively early stage of the disease. Again, this failed to show survival advantage.

Furthermore, patients with in-transit metastases, without any evidence of other metastases, have very guarded prognosis. Repeated local excisions, even with hyperthermic limb perfusion, and intralesional therapy with various drugs revealed very limited response rates without any survival benefits.

While melanoma is an immunogenic tumor, it seems to be very heterogeneous as it expresses various melanoma-specific antigens, peptides and has variable genetic profiles among different patients. Therefore, autoimmunization may overcome such heterogeneity.

In the meantime, it has been shown that intralesional administration of Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) in multiple small in-transit metastases at doses ranging from 400-500 microgram (μg) daily for 4-5 consecutive days and repeated every 21-28 days, gave high response rate but with some side effects such as leukocytosis and fatigue. In addition, intralesional administration of interleukin-2 (IL-2) at doses ranging from 0.6-18 million IU, 2-3 times per week, resulted in over 60% response rate but with 58% systemic side effects at the higher dosages.

On the other hand, to avoid the side effects and the development of immune tolerance, when GM-CSF was administered at low nontoxic dose of 500 μg once per week, it resulted in high response rate in small in-transit metastases that ranged in size from few mm up to 1 cm located in the skin and subcutaneous tissue. Of 127 lesions treated, 110 had complete response to GM-CSF therapy, and the other 17 lesions failed but were successfully treated with low dose IL-2 of 11 million IU weekly. There were no systemic side effects but only local skin reaction at the injection sites. Furthermore, preoperative sequential administration of 500 μg once at the primary site of invasive cutaneous melanoma followed the next day by IL-2 administration once, at the same site, of 11 million IU, one week before the definitive standard surgical procedure. The resected tissues showed complete tumor necrosis with massive histiocytosis. In addition, immunohistochemical studies on the resected tissue revealed overexpression of helper (CD4+) and cytotoxic T cells (CD8+) at the injection sites and in some regional lymph nodes. This clearly indicated a massive immune response at the injection sites that seemed to be transmitted via the lymphatics. The first treated patient had stage IIIC disease and is alive, free of disease, for over 4½ years.

It has been shown that intralesional administration of GM-CSF can activate and increase the number of dendritic cells at the injection site as well as at the regional lymph nodes, while intralesional administration of IL-2 can activate Tumor Infiltrating Lymphocyte (TIL). The function of these 2 cytokines can complement one another. Dendritic cells are very efficient Antigen Presenting Cells (APCs) that are capable of processing the tumor antigens and subsequently present the processed antigens to T lymphocytes, activated by IL-2 administration, creating tumor-specific cytotoxic T cells in vivo. This approach utilizes patient own tumor (before excision) as the source for tumor-specific antigens to any given patient. It also seems to improve patients' survival.

However, this approach is not effective in large size tumors of 2 cm or more. In addition, it should not be used in the presence of an infected melanoma lesion as it can result in immune deviation by recognizing the bacterial antigens rather than the tumor. Autoimmunization utilizing sequential intralesional administration of GM-CSF followed by IL-2 seems to be very effective approach that can overcome melanoma heterogeneity. It lends itself to be evaluated as adjuvant therapy in controlled clinical trials.