

The Preoperative Sequential Administration of GM-CSF and IL-2 at the Primary Site of Cutaneous Melanoma Can Induce Immense Specific Antitumor Response: A potential New Approach to Adjuvant Immunotherapy

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The outlook for patients with metastatic melanoma is very poor. Therefore, every effort should be made to control the disease at its initial stage and at the time of the diagnosis. Several adjuvant therapeutic approaches administered systemically after tumor resection failed to have any major impact on melanoma. This clearly indicates that new adjuvant therapeutic approaches are needed, administered at relatively early stages of the disease to prevent disease recurrence and metastases.

Cutaneous melanoma is considered to be chemotherapeutic resistant tumor. On the other hand, it is an immunogenic tumor but extremely heterogeneous as it expresses various melanoma-specific antigens, peptides with different genetic characteristics among different patients. In addition, we must realize that we do not know all the antigens and peptides of different melanomas. Therefore, the ideal tumor-specific antigens are to utilize patient's own tumor cells to achieve active immunization. The cytotoxic T lymphocyte is only as effective as the antigen that activates it.

To overcome such tumor heterogeneity, autologous whole cell vaccine was tried with some success. However, such an

approach has several limitations: The patient has to have large enough resectable tumor to supply enough tumor cells for the repeated vaccination. In such case, the patients may have been under staged as they may have occult distant metastases that were not detected by physical examination or laboratory investigations. Another major hindering factor is that these tumors need special sterile facilities to separate tumor cells gently from normal tissue, irradiate tumor cells and store in deep freeze until ready to be used. Such process may result in some tumor cells damage and dysfunction.

A new approach utilizes patient's own primary tumor site in vivo as the source for tumor-specific antigens to initiate an autologous active tumor-specific cell mediated immunotherapy without the need for special facilities. Preoperative injection of low nontoxic doses of 2 cytokines; Granulocyte- Macrophage Colony Stimulating Factor (GM-CSF) followed by Interleukin-2 (IL-2) at the primary melanoma lesion can induce a strong antitumor response. GM-CSF is administered once as 500 microgram, followed the next day by IL-2 at 11 million IU once at the same site, one week before the standard surgical excision. This can initiate an immense immunological reaction at the injection site of the tumor, characterized by complete tumor necrosis with massive histiocytosis and strong lymphocytic infiltrate (tumor infiltrating lymphocytes – TIL) with over expression of helper (CD4+) and cytotoxic T lymphocytes (CD8+) at the primary lesion which is transmitted systemically

via the lymphatics. This was noted to take place in one week. Furthermore, early data suggest that this approach, in addition to be nontoxic, it seems to prolong patients' survival.

The initial administration of GM-CSF can activate and increase the number of dendritic cells at the tumor site. These cells are antigen presenting cells capable of processing the tumor antigens and subsequently present to T lymphocytes which are activated by IL-2 administration. It should be noted that all the induced and activated cells are endogenous to the patient as well as the patient's own tumor. This approach can overcome tumor

heterogeneity and induces active immunization in vivo. The candidates are patients with highly invasive primary melanoma who have guarded prognosis if received surgical resection only. However, the presence of infection at the tumor site is a contraindication to this approach as it may cause immune deviation. The induced dendritic cells could recognize the bacterial antigens, which are stronger than the tumor antigens, and fail to recognize the tumor.

This approach is relatively cheaper than other adjuvant therapeutic approaches and it seems to be more beneficial.