PERGAMON

European Journal of Cancer 39 (2003) 1039–1040

European Journal of Cancer

www.ejconline.com

Editorial Comment

Extended neoadjuvant chemotherapy in locally advanced breast cancer combined with GM-CSF: effect on tumour-draining lymph node dendritic cells by Pinedo *et al.*

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Dendritic cells (DC) were first described by Steinmann and colleagues in the 1970s [1]. Their major function is to capture and process antigen within peripheral tissues and migrate to secondary lymphoid tissues where they interact with lymphocytes to initiate and direct primary immune responses. Over the last 5 years, there has been increasing interest in the potential of DC to stimulate an immune response against cancer.

There are now over 30 clinical trials of DC therapy published in a variety of different tumour types. Most of these involve the generation of DC *ex vivo* from either monocyte or CD34+ haematopoietic progenitors under the influence of the cytokines granulocyte-monocyte colony stimulating factor (GM-CSF) and interleukin-4 (IL-4). DC generated in this fashion have been re-administered to patients in a variety of different formulations, schedules and routes, usually after pulsing with tumour cells or defined antigens, in an attempt to initiate cancer-specific immune responses. Most trials involve patients in a follow-up schedule where an attempt is made to determine if there has been a specific immune response to the tumour cells. The majority of trials published to date have reported little in the way of systemic toxicity and, more recently, one has reported the correlation of immunological responses with clinical responses.

The paper by Pinedo and colleagues in the current issue of this journal [2] has taken a different approach by giving one of the cytokines needed for the generation of DC systemically. They have demonstrated an interesting effect of the administration of systemic GM-CSF on the numbers of DC in the tumour-draining lymph nodes of patients treated with moderately high dose chemotherapy for locally advanced breast cancer. They concluded that treatment with systemic GM-CSF was associated with a significant increase in the number of DC in the tumour-draining lymph nodes compared with a group of historical controls. In a subset of patients, they were able to demonstrate that there was a significant increase in the number of DC when comparing pre- and posttreatment lymph node samples. They suggest that this increase in the number of DC seen in the tumour-draining lymph nodes may be associated with an improved outcome for patients with locally advanced breast cancer. They propose a randomised study where patients will receive either six cycles of neoadjuvant chemotherapy or three cycles of neoadjuvant and three cycles of adjuvant chemotherapy combined with either GM-CSF or G-CSF. In the suggested study they propose to make an assessment of the lymph nodes, primary tumour and circulating peripheral blood for DC number, function and CTL responses.

The question of the effect of systemic GM-CSF in terms of DC number and function has been investigated by other authors [3]. In combination with another cytokine, tumour necrosis factor alpha (TNFα), they were able to show an increase in the circulating number of DC precursors in patients with cancer, as well as an increase in the number of DC within the skin, although they did not examine the lymph nodes. Other cytokines have been investigated, such as Flt-3 ligand which is known to have stimulatory effects on bone marrow progenitors [4] and has been demonstrated to have antitumour effects in murine models which were

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0959-8049/03/$ - see front matter
doi:10.1016/S0959-8049(03)00130-8

associated with increased numbers of DC and T cells at tumour sites, lymph nodes and peripheral blood [5]. Flt-3 has been administered pre-operatively to a group of patients with metastatic colorectal cancer prior to metastasectomy [6]. DC were mobilised into the peripheral blood in these patients and there was some evidence of an increased immune response, as measured by delayed type hypersensitivity testing.

Whilst the principle of immunotherapy involving DC is attractive, there remain many unresolved issues in this field. The dose of DC required, the route of administration and the effect of systemic cytokines is not yet clear. Many patients have now been involved in trials of DC therapy although there are subtle differences between the regimens used. Thorough assessment of immune function following therapy is necessary, but future studies need to focus on clinically relevant outcomes if these approaches are going to find a place in the therapeutic armamentarium.

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