

2.0 BACKGROUND AND RATIONALE

2.1 Overview

The management of metastatic cancer remains unsatisfactory. Of greater concern, is the fact that in recent years the incidence of certain cancers such as malignant melanoma have been doubling approximately every ten years (2). Although relatively low risk "thin" lesions have a higher rate of cure with limited surgical margins, the optimal surgical management for high risk "thick" melanomas remains unclear. Even with generous surgical margins and regional lymphadenectomy, many lesions will recur (3,4). Levamisole may be useful as a surgical adjuvant (5), however, this is not universally accepted. High dose interferon α can reduce recurrence in Stage I and II melanoma by about 40%, but it is associated with significant toxicity. There is continuing effort to identify other approaches, such as immunotherapy, that might lend themselves to adjuvant use.

Dimethyl triazeno imidazole carboxamide (DTIC) is the best single chemotherapy agent with a response rate in systemic metastatic disease of approximately 20% (6). Significantly increased response rates can be expected by newer combination programs such as tamoxifen, BCNU, cis-platinum and DTIC (7), but with increased toxicity. There is no consensus on second-line treatment. At this point, consideration is often given to the use of cytokines or other experimental approaches.

The role of the immune system in malignant melanoma has been an area of intense interest. Melanoma antigens have been well studied in the past, as has evidence of a host immune response (7-9). Agents that can stimulate non-HLA-restricted cellular cytotoxicity, such as interferons and interleukin-2, have produced sustained regressions in some patients.

It is now possible to trigger an immune response through gene transfer. Numerous models have been developed and have led to several clinical trials exploring the possibility of manipulating either tumor cells or host lymphocytes transfected with a variety of cytokine genes. Other specific gene therapy strategies have sought to directly influence the interaction between immunocyte and antigen presenting cell by enhancement of HLA-restricted immunity.