8. Immunotherapy for peritoneal ovarian carcinoma metastasis using ex vivo expanded tumor infiltrating lymphocytes

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Background to the standard treatment of ovarian cancer

Cancer of the ovary is responsible for the highest proportion of the mortality in patients with gynecologic malignancies. The overall survival for these patients at 5 years is 39% [1]. Epithelial ovarian carcinoma (EOC) represents 90% of the histologies and is thus the most frequent histologic group. Primary peritoneal carcinoma, also called extravarian mullerian carcinoma, has the same pattern of tumor spread and sensitivity to chemotherapy as EOC, although the ovaries are not primarily involved in the pathologic process. Other malignancies that originate from the ovaries include those of germ cell and stromal cell origin. These are considered separately and have a different clinical presentation and a different response to treatment.

The standard first-line treatment of EOC or peritoneal carcinomatosis includes an initial exploratory laparotomy. Abdominal surgery is performed to accomplish certain objectives: (1) to establish a histopathologic diagnosis, (2) to obtain intraoperative staging of the tumor, and (3) to achieve the maximum feasible removal of the tumor. Currently, surgical staging follows the 1985 recommendations of the Federation Internationale Gynecologie Obstetrique (FIGO). Surgical treatment is followed in most cases by platinum-based chemotherapy utilizing either carboplatinum or cisplatinum in combination with cyclophosphamide. Platinum-based chemotherapy is the treatment of choice in patients who have stage II–IV disease, which represents 90% of all patients with EOC. No single adjuvant treatment approach has been established for patients whose disease appears to be confined to the ovaries, although many of these patients will ultimately relapse, even after receiving chemotherapy. Combination chemotherapy regimens that include cisplatin or carboplatin produce overall response rates that are in the range of 60–80% [2,3]. The majority of these patients will ultimately progress, or will relapse after a complete pathologic response due to either primary or acquired drug resistance [4]. Recent phase II data have shown high response rates with taxoids, for example, taxol or taxotere [5,6], although there are few complete responses and treatment with these drugs may be both toxic and costly. In consideration of the overall low frequency
of complete pathologic responses as defined by a negative second-look operation and the modest survival that is achievable with current treatment modalities, it is important to develop novel strategies for EOC that involve mechanisms that are different from standard chemotherapy or radiation therapy.

Major advances in recombinant DNA approaches and in both cellular and humoral immunology have provided the means to develop novel treatment strategies against cancer of the ovary [7]. Examples of such advances include: (1) identification and molecular cloning of numerous cytokines such as recombinant (r) interleukin-2 (rIL-2) and recombinant interferons (rIFN-α, rIFN-β, and rIFN-γ) [8,9], (2) identification of cell surface molecules [10] on lymphoid and other hemopoietic cells that are important in the induction and in the effector phase of the immune response, (3) the development through hybridoma technology of a number of monoclonal antibodies (mAbs) that have reactivity against EOC cells [11,12], including a small number of human mAbs with reactivity to tumor associated surface antigens [13], and (4) the development of gene transfer protocols for introducing appropriate genes into cells [14].

**Lymphokine activated killer cells and tumor infiltrating lymphocytes**

Potentiation of an autologous tumor-specific immune response is a central goal of biologic therapy in cancer. In a variety of murine models, therapy with the cytokine interleukin-2 (rIL-2) alone can result in significant tumor regression [reviewed in 15]. Potential mechanisms involved in this antitumor effect include the activation of lymphokine activated killer (LAK) cells, the generation of cytotoxic T lymphocytes against the tumor, and the production of cytokines such as tumor necrosis factor-α (TNF-α) or IFN-γ.

Clinical responses, including durable complete remissions, were observed in cancer patients treated with ex vivo activated LAK cells and high doses of rIL-2. Complete plus partial response rates in initial clinical trials were approximately 20% in melanoma, 30% in renal cell carcinoma, 10% in colorectal carcinoma [16,17], and 20% in ovarian cancer [18,19]. However, these responses are comparable to those observed with rIL-2 alone in most of the trials, and LAK cells do not appear to add substantially to the clinical efficacy of rIL-2 alone [20]. Individual responses have been noted in patients with other malignancies, including lung carcinoma, Hodgkin’s, and non-Hodgkin’s lymphomas, but comparatively few patients have been treated with malignancies other than melanomas, renal cell carcinoma, or colon carcinoma. Rosenberg et al. [21] reported the treatment of 181 patients with metastatic cancer with either rIL-2 alone or with LAK cells plus rIL-2. Of these patients 97 had renal cell carcinoma and 54 had malignant melanoma. Ten complete responses among 85 assessable patients were found in the group who received LAK cells plus rIL-2. Four complete responses among