

Guest Editor

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## High-Dose Interleukin-2 in Metastatic Disease: Renal Cell Carcinoma and Melanoma

Despite significant advances in the treatment of a variety of malignancies, highly effective therapies for most patients with metastatic renal cell carcinoma or metastatic melanoma are rare. Traditional oncologic treatment methods, such as chemotherapy, surgery, and radiation therapy, are marginally effective in these diseases, except in special circumstances.[1-3] Systemic immunotherapy with cytokines, such as interferon alfa (IFN- $\alpha$ , Intron A, Roferon-A) and interleukin 2 (IL-2, Proleukin), produces the highest response rates (10% to 27% [renal cell carcinoma] and 15% to 20% [melanoma]), but the search for more effective therapies continues.[2,4,5]

### Efficacy of High-Dose IL-2

Since the first National Cancer Institute reports of the effectiveness of high-dose IL-2 (administered as an IV bolus) and lymphokine-activated killer (LAK) cells in patients with advanced malignancies, research has focused on establishing effective IL-2-based therapies, primarily for patients with metastatic renal cell carcinoma and metastatic melanoma.[6,7] The addition of LAK cells to high-dose IL-2 therapy was eventually abandoned, but high-dose IL-2 therapy remains the treatment of choice for these two advanced malignancies, producing overall response rates of approximately 15%. [1,7,8]

The use of high-dose IL-2 therapy for metastatic renal cell carcinoma and metastatic melanoma, however, is associated with significant toxicity, including hypotension requiring vasopressor support, oliguria, pulmonary congestion, arrhythmias, and neurologic toxicity. To reduce toxicity and maintain or improve efficacy, researchers have investigated several other regimens, such as those using lower IL-2 doses or alternative methods of administration (eg, continuous IV infusion, subcutaneous). Unfortunately, none of these alternative regimens have proven superior to high-dose IL-2 therapy in patients with metastatic renal cell carcinoma or metastatic

melanoma.[2,4] Additionally, combining IL-2 with IFN- $\alpha$ , chemotherapy agents, or both has not significantly improved the outcome in patients with metastatic renal cell carcinoma.[7] In metastatic melanoma patients, the use of IL-2-based biochemotherapy has been quite promising, producing overall response rates as high as 64%, but recent preliminary data from a large, randomized, multicenter study comparing biochemotherapy with chemotherapy alone suggest that biochemotherapy is not significantly better than chemotherapy (M.B. Atkins, oral communication, June 2002).[2] Therefore, high-dose IL-2 therapy is likely to remain one of the most logical therapies for patients with metastatic renal cell carcinoma and metastatic melanoma.

### Review of Clinical Trials

The first article in this supplement provides a comprehensive review of the available results of clinical trials evaluating IL-2-based therapy for metastatic renal cell carcinoma and melanoma.

### Managing Toxicities

The second article focuses on the safe administration of high-dose IL-2 and appropriate techniques for managing toxicities. My coauthors, Rowena Schwartz, PharmD, BCOP, and Lori Stover, RN, BSN, are both experienced health-care practitioners at the University of Pittsburgh Cancer Institute, which treats more than 400 new melanoma patients each year and is a cancer center with many years of experience in the administration of high-dose IL-2.

### Future Directions

Because high-dose IL-2 therapy in metastatic renal cell carcinoma and metastatic melanoma is effective but toxic, numerous clinical trials are currently evaluating IL-2 in combination with other agents, such as histamine and NG-monomethyl-L-arginine, to determine methods of enhancing efficacy and reducing toxicity.[4,9,10] The results of these trials are eagerly awaited.

I hope this supplement to *ONCOLOGY* provides useful information regarding the use of high-dose IL-2 as treatment of metastatic renal cell carcinoma and metastatic melanoma patients in your clinical practice. For patients with either of these diseases who are ineligible for high-dose IL-2 therapy and for whom the prognosis is dismal, ongoing clinical trials, such as trials evaluating low-dose IL-2 in patients with organ dysfunction and a new formulation of IL-2 associated with reduced toxicity, may produce promising results.[5]

—Janice Dutcher, MD

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