High-Dose Interleukin-2 Therapy for Metastatic Renal Cell Carcinoma and Metastatic Melanoma: Still the Standard

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My 2002 article provided an overview of the various interleukin-2 (IL-2)-based treatment regimens that had been explored over the preceding two decades—well as in ongoing trials—for the treatment of metastatic renal cell cancer and metastatic melanoma. The article discussed the critical role of immunotherapy with IL-2 in producing durable complete responses, despite formidable toxicity. At the time of publication, a number of ongoing clinical trials were evaluating the potential role of lower-dose regimens or other schedules to modulate toxicity. The hope was to make IL-2 a more generalizable therapy. Several of the then-ongoing studies cited in the article have since been reported. The results of these studies have been critical in defining the impact of these modifications on the known efficacy of high-dose IL-2 in terms of durable complete responses. The conclusions projected in the 2002 article remain correct.

2002 Conclusions Have Held Up

Interleukin-2 is still the only therapy that has the reproducible possibility of curing adults with stage IV solid tumors (excluding germ cell tumors and lymphomas). There are many patients with either renal cell cancer or melanoma who were treated with high-dose IL-2 and who are still alive, having had durable complete responses that are ongoing and that have lasted for decades. The two randomized trials comparing low-dose and high-dose IL-2 in metastatic renal cell cancer, which were in preliminary stages in 2002, have both been reported, with results favoring high-dose IL-2. The response rate in patients who were treated with high-dose IL-2 was double that seen in patients who were treated with regimens of low-dose intravenous IL-2 or subcutaneous administration of IL-2 alone[1]—and double that seen in patients treated with lower-dose IL-2 plus interferon.[2] In addition, many more durable complete responses were seen in the high-dose IL-2 arms, with many of these responses now surpassing a decade in duration.[1,2] The most recent study conducted by the Cytokine Working Group demonstrated an improved response rate of 28% with high-dose IL-2 in patients with metastatic renal cell cancer.[4] This study also attempted to prospectively evaluate patient selection criteria, and at first pass demonstrated that patients with clear cell renal cell cancer and those with an Eastern Cooperative Oncology Group performance status of zero were more likely to benefit from high-dose IL-2 therapy.[4]

In patients with melanoma also, high-dose IL-2 is much better able than low-dose regimens to produce durable responses and complete responses; this was the case in 2002 and has been a consistent observation since then. High-dose IL-2 continues to be an important immunotherapy regimen for beneficial long-term outcomes in metastatic melanoma, with durable (years-long) complete responses. An ongoing trial has just started, similar to the above-mentioned renal trial, in which features of disease will be prospectively collected in the hopes of “selecting” a profile in melanoma patients that predicts for response to IL-2. The randomized trial of biochemotherapy compared to chemotherapy alone (E3695) has been reported, and biochemotherapy did not show a significant additive effect on survival.[3] Others have been more enthusiastic in espousing biochemotherapy, however. Thus, the use of biochemotherapy for melanoma remains a work in progress and a subject of continued discussion and investigation. The bottom line is that the conclusions of my November 2002 paper still hold up! As new treatments for both renal cell cancer and melanoma enter the clinical arena, the standard to which these should be compared should continue to be the potential for durable long-term remission or even cure that is afforded to a small but real number of these patients who are treated with high-dose IL-2.

Recent and Future Directions
My 2002 article addressed important issues that confront the treating physician dealing with a complex treatment regimen—a regimen that has significant issues with toxicity, but that also has potential for outstanding outcomes. Since then, studies have evaluated dose levels, various schedules, and different routes of administration. These studies have concluded that the best use of IL-2, producing the best outcomes, remains high-dose treatment, administered by an experienced team in the appropriate setting.

How do we continue to incorporate high-dose IL-2 into the armamentarium for renal cell cancer and melanoma? It has not been and should not be supplanted by newer agents that, while perhaps more manageable and capable of producing positive results in larger numbers of patients, still have as their major benefit stabilization of disease, with some progression-free benefit and likely some additive survival benefit. The therapeutic goal for these patients should remain the achievement of durable complete responses, measured in terms of years. Our most promising strategy right now is the development of techniques for identifying those patients who are expected to have major responses and complete responses to high-dose IL-2.

Ongoing studies are continuing to evaluate ways of identifying those most likely to respond; this is being done through the evaluation of diagnostic approaches that are more complex than simply clinical selection. (In renal cell cancer, however, we have made progress even with clinical selection.[4]) Ongoing evaluation of molecular characteristics, immunological profiles, and gene expression profiles will hopefully yield the sought-after selection criteria.

Nevertheless, in the last decade we have learned more about the molecular biology of both renal cell cancer and melanoma, and this new knowledge may help us select more appropriate treatments for the various subtypes of these entities. In renal cell cancer, we now have identified molecular differences that distinguish between the pathologic phenotypes of clear-cell, papillary, chromophobe, Xp-translocation (and its partners), and collecting duct renal cancers—and even subtypes of these. In melanoma, we now know that there are molecular differences between melanomas that arise in sun-exposed tissues, and ocular melanoma and mucosal melanomas. These subtypes seem to predict sensitivity to immunotherapy and/or sensitivity to targeted therapies in both renal cell carcinoma and melanoma. Hopefully in the near future these subtypes will not only help guide treatment selection, but will also direct therapeutic agent development.

The goal for further development of IL-2 therapy has always been to enhance the overall response rate; this may be achieved with our increasing knowledge of the components of the immune system and the complex T-cell interactions that stimulate and regulate immune response. Our better understanding of co-stimulation and immune-cell inhibition may also lead to improved therapeutic strategies. Thus, we will learn to better select good candidate patients, and we will be able to optimize the ability of the immune system to function under the influence of IL-2. Again, the observation of decades-long durable responses—essentially cures—with high-dose IL-2 must continue to guide future development of therapy for metastatic renal cell cancer and melanoma.

References:
REFERENCES


