

# Interleukin-2 in the treatment of unresectable or metastatic renal cell cancer: Time to write the obituary?

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Until recently, the treatment of advanced renal cell cancer was frustrating. The disease was both unpredictable and resistant to all traditional cytotoxic approaches. The field was further complicated by the phenomenon of spontaneous remissions, which frequently led to phase II studies being mounted on the basis of a response seen in a phase I study. The exact frequency of the spontaneous remission rate is unclear, but in a study comparing gamma interferon with a matched placebo, the response rates were 4% and 7% to gamma interferon and placebo, respectively, and 1% of patients experienced a durable complete response rate.<sup>1</sup>

Immunotherapy and cytokines have been extensively investigated. Alpha-interferon at various doses has been considered a standard, based on numerous phase II studies and at least 2 phase III studies showing a survival benefit. The toxicity associated with interferon and the lack of consistency of effect led to questions regarding whether it was a useful palliative therapy. High-dose interleukin-2 (IL-2) first entered the scene in 1985, when Rosenberg and colleagues reported a high rate of durable remissions from the use of high-dose IL-2 with LAK (lymphokine-activated killer) cells.<sup>2</sup> A larger study demonstrated a lower response rate of 14%, with a median duration of response of over 18 months, and led to the approval of high-dose IL-2 in the United States.<sup>3</sup> The treatment-related death rates of 3%–5% and the impressive morbidity requiring vasopressor support and intensive care unit backup limited the use of high-dose IL-2 to selected specialized centres. In Canada, few centres adopted such an intensive palliative therapy, generally just under a short-term investigative protocol.

Since these initial observations 20 years ago, there has been a major investment in exploring the potential of IL-2 at varying doses, schedules and combinations. This was stimulated by the lack of alternatives and by the hope that we might find a way to achieve durable remissions in a select few, without putting most patients through an arduous and risky procedure that is ultimately not beneficial. Unfortunately, these efforts have been largely unsuccessful, as the review by Hotte and colleagues<sup>4</sup> clearly demonstrates.

The sea change in renal cell cancer has come from the introduction of therapies targeted against vascular endothelial growth factor (VEGF) and other signalling pathways, such as mammalian target of rapamycin (mTOR). We now have 2 approved anti-VEGF therapies (sunitinib and sorafenib), with several others showing promise in phase II studies and one positive phase III study of the mTOR inhibitor temsirolimus. The anti-VEGF therapies are oral and thus convenient for patients; the toxicities are generally manageable, and the rates of disease control are impressive. Both sunitinib and temsirolimus were compared to interferon in the first-line setting and demonstrated superior efficacy and a better toxicity profile. Sorafenib has demonstrated better survival and time to progression, compared with placebo, in patients who are refractory to cytokines. The main factor limiting the widespread use of these agents in Canada is economic.

Given the availability of new therapies to treat renal cell cancer, is there still a role for further investigation of the high-dose IL-2 approach? Probably yes, but investigations should be done in centres that have the appropriate experience and expertise. Investigation of lower intensity IL-2 has proven disappointing; studies should now focus on predictive markers to identify a subset of patients most likely to benefit.

Should we attempt to develop such expertise in Canada? The principle of distributive justice would argue that we should not. In Canada, we are struggling to provide therapies that do have a proven survival benefit but also a significant incremental cost. The new targeted therapies for renal cell cancer are some of many that fall into this category. In such a setting of resource restriction, it is difficult to justify the development of a highly expensive, highly toxic therapy that benefits only a small fraction of patients with renal cell cancer. The review by Hotte and colleagues is a useful and timely requiem for IL-2 in Canada.

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