THE ROLE OF HIGH-DOSE INTERLEUKIN-2 IN METASTATIC RENAL CELL CANCER IN THE ERA OF CHECKPOINT INHIBITION —AN EXPERT PERSPECTIVE

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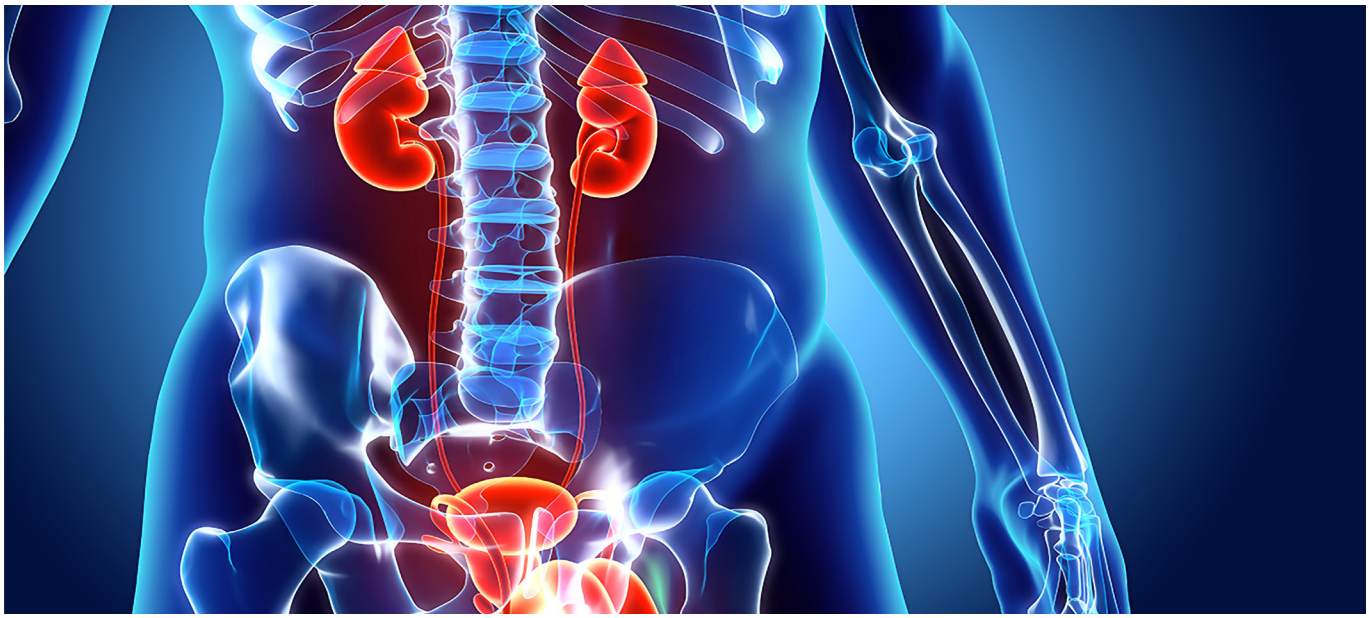

High-dose interleukin-2 (HD IL-2) therapy is one of the few treatments for adults with metastatic renal cell cancer (mRCC) that can produce complete responses that are often durable for decades without further therapy.[1,2] However, HD IL-2 is a rigorous treatment that some patients may be unable to tolerate. It is therefore generally reserved for patients who are younger (usually considered ≤65 years); have good performance status (Eastern Cooperative Oncology Group score of 0–1); normal organ function, particularly cardiac, pulmonary and renal function; normal clinical laboratory values (bilirubin, platelet, hemoglobin, thyroid function, transaminases); and a clear cell histology for mRCC.[1]

The depth of response that can be achieved still drives the use of HD IL-2 in specific patients with mRCC today (together with the decades of clinical observation and use that has led to improved management of potential immune-related side effects), despite the availability of new targeted and immunological therapies, such as the combination of nivolumab + ipilimumab.[3,4] In fact, over recent years, studies have indicated improved efficacy for HD IL-2 therapy, which may be due to improved salvage therapies for HD IL-2 refractory patients, but this has also been attributed to better patient selection and a greater understanding of the clinical features that predict treatment outcomes.[1] However, despite intense interest and investigation, there is still no clear molecular profiling or stratification to identify patients with mRCC who might have an excellent response to HD IL-2 therapy.

The prognosis of a patient with mRCC is typically categorized according to disease risk (favorable, intermediate and poor prognosis), based on the presence of specific clinical and laboratory risk factors.[4] Treatment guidelines, such as those produced by the National Comprehensive Cancer Network (NCCN), now use these risk categories to direct therapy.[5]

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Table 1: Efficacy of nivolumab + ipilimumab versus sunitinib in patients with advanced renal-cell carcinoma (CheckMate 214 study)[4]

Outcome*	Intermediate-/poor-risk disease		Favorable-risk disease	
	Nivolumab + ipilimumab (n=425)	Sunitinib (n=422)	Nivolumab + ipilimumab (n=125)	Sunitinib (n=124)
18-month OS, %	75 (70–78)	60 (55–65)	88 (80–92)	93 (87–97)
HR	**0.63** (99.8% CI: 0.44–0.89)		**1.45** (99.8% CI: 0.51–4.12)	
P-value	<0.001		0.27	
PFS, months	11.6 (8.7–15.5)	8.4 (7.0–10.8)	15.3 (9.7–20.3)	25.1 (20.9–NE)
HR	**0.82** (99.1% CI: 0.64–1.05)		**2.18** (99.1% CI: 1.29–3.68)	
P-value	0.03†		<0.001	

**All outcomes are presented as median (95% CI) unless otherwise stated; †The prespecified threshold for statistical significance was 0.009 for PFS.*
CI = confidence interval; HR = hazard ratio for nivolumab + ipilimumab vs sunitinib; NE = not evaluable; NR = not reached; OS = overall survival; PFS = progression-free survival.

One of the key prognostic models recommended in the current NCCN guidelines was developed by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), while the other prognostic model was developed by the Memorial Sloan Kettering Cancer Center (MSKCC).[5–8] The IMDC risk factors for poor survival consist of impaired performance status, <12 months from diagnosis to treatment, a low hemoglobin count and high serum calcium, neutrophil and platelet counts. The MSKCC risk factors for poor survival consist of a low Karnofsky performance status, high lactate dehydrogenase, low serum hemoglobin, high corrected serum calcium, and <12 months from diagnosis to treatment.[8] For both these models, patients with favorable-risk disease have none of these risk factors, patients with intermediate-risk disease have one or two risk factors, and patients with poor-risk disease have three or more risk factors.[6–8]

Recently, a phase III trial investigating the efficacy of nivolumab + ipilimumab compared with sunitinib, in patients with advanced renal-cell carcinoma (CheckMate 214), found that overall survival (OS) and objective response rates were significantly higher with nivolumab + ipilimumab in patients with intermediate- and poor-risk disease (IMDC criteria), but not in patients with favorable-risk disease (**Table 1**).[4] This somewhat surprising result led to the investigation of the efficacy of HD IL-2 treatment based on risk factors/categories, to assess whether differences in clinical outcomes were also present in patients with favorable-, intermediate- or poor-risk disease.[9]

The PROCLAIM[SM] database is a multi-institutional clinical registry of patients treated with HD IL-2 that began data collection in 2011, with retrospective data collected from 2006 and prospective data collected from 2011–2018.[9] Patients enrolled in the registry were treated with HD IL-2 as per standard-of-care for their center and the treating physician's clinical judgment. Generally, this involved administering an intravenous dose of 600,000 IU/kg or 720,000 IU/kg over 15 minutes every 8 hours for up to 14 consecutive doses over 5 days.[2] A second cycle of therapy was usually administered after a 9-day rest period, dependent on patient tolerance. Additional cycles could be recommended at the discretion of the treating physician.[2] In total, 356 patients with mRCC received HD IL-2 monotherapy.[9] Of these, 119 (33.4%) met favorable, 203 (57.0%) met intermediate, and 34 (9.6%) met poor IMDC risk criteria.[9] Across all IMDC risk categories, treatment with HD IL-2 resulted in median OS and 2-year survival rates consistent with recent reports of checkpoint inhibitor immunotherapies and anti-vascular endothelial growth factor therapies (**Table 2**).[4,9] All risk categories also showed improved survival compared with historical cytokine data, consistent with the results of the 2015 HD IL-2 SELECT study—a prospective, multicenter trial conducted by the Cytokine Working Group to investigate proposed predictive markers of response to HD IL-2 in 120 patients with mRCC.[9,10] Results from the SELECT study revealed an objective response rate of 25% (23% in 'good risk' and 30% in 'poor risk' patients [MSKCC criteria]) for patients with mRCC treated with HD IL-2 therapy, substantially greater than historical response rates for HD IL-2 (estimated to be 14% across seven phase II clinical trials).[10,11]

Table 2: Survival outcomes for 365 patients with metastatic renal cell cancer treated with high-dose interleukin-2 monotherapy (PROCLAIMSM registry)[9]

	Favorable risk	Intermediate risk	Poor risk
OS, months	64.5 (39.4–112)	57.6 (34.5–62)	14 (4–58)
2-year OS, %	73.8%	63.7%	39.8%

All outcomes are presented as median (95% CI) unless otherwise stated.
CI = confidence interval; OS = overall survival.

Separate analyses of data from the PROCLAIM[SM] database indicate improved OS with sequential HD IL-2 and anti-VEGF therapy in mRCC, and there is evidence to suggest that patients with metastatic melanoma or mRCC may benefit from HD IL-2 therapy following progression after checkpoint inhibitor treatment.[2,9,12] These data suggest that there may be a subset of patients who may respond to HD IL-2 therapy who do not respond to treatment with checkpoint or anti-VEGF inhibitors (and *vice versa*). There are several ongoing studies evaluating the concurrent or rapid sequential use of HD IL-2 and checkpoint inhibitor immunotherapies in patients with mRCC (e.g. Clinical.Trials.gov Identifiers: NCT02964078 and NCT03991130). The preliminary results appear promising and we await the final data with interest.

Overall, in patients with mRCC who meet the eligibility criteria, HD IL-2 remains an important part of the treatment paradigm, both as first-line and subsequent therapy.[2,9]

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