High-dose Interleukin-2 Can Produce a High Rate of Response and Durable Remissions in Appropriately Selected Patients With Metastatic Renal Cancer

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Summary: Metastatic renal cancer remains hard to treat and the treatment is generally palliative. However, high-dose interleukin-2 (HD IL-2) produced 5% to 10% complete remissions and most of these were durable. With the advent of newer treatments with less toxicity, the role of HD IL-2 is uncertain. We present here a case series of 72 patients with metastatic renal cancer given first-line treatment with HD IL-2. From 2003 to 2006, the patients were offered treatment with HD IL-2 irrespective of their histologic features (retrospective cohort). From 2006 to 2008, the treatment was only offered to patients after stratification into risk groups based on histologic criteria (prospective cohort). In the early series, the response rate to HD IL-2 was 27% (8/30), but with prospective stratification of patients by histology the response rate was 52% (21/40) in the group with favorable histologic features. Combining outcome for all patients with the favorable histology (including those identified retrospectively) 49% (28/57) responded with 25% (14/57) achieving a complete remission and these seem durable. Patients with metastatic renal cancer should be carefully assessed for their suitability to undergo treatment with first-line systemic therapy with HD IL-2 as in carefully selected patients it has a high-rate response and durable remissions.

Key Words: metastatic renal cell carcinoma, high-dose interleukin-2, histologic features

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Renal cell carcinoma (RCC) is a relatively common malignancy and it is estimated that 57,760 people were diagnosed with and 12,980 died of cancer of the kidney in the United States during 2009 (http://info.cancerresearchuk.org/cancerstats/types/kidney/index.htm). Nephrectomy can be curative for early stage disease, but most patients develop metastatic disease as approximately 30% of patients already have metastatic disease at diagnosis and up to 30% of patients will relapse after potentially curative resection.[1,2] Metastatic (M)RCC is resistant to cytotoxic drugs and for many years treatment with either interleukin-2[3] or interferon-α[4] was the standard of care. For most patients, there are limited gains from treatment and very few received long-term benefit. Recently, new agents targeting the Vascular Endothelial Growth Factor and mammalian Target of Rapamycin pathways have become the first line standard of care systemic therapy for most patients with MRCC.[5] The current first-line treatment of choice for many patients is sunitinib and in the United Kingdom this is the only drug recommended by NICE. Sunitinib has a response rate of around 47% and produces some survival benefit.[6] Despite these high response rates, there are very few complete remissions (3%) and it is rare that these are durable after stopping treatment.

In contrast to antiangiogenic therapy, HD IL-2 produces a relatively high proportion of responses that are complete and can be very durable. Overall, around 20% of HD IL-2 treated patients achieve an objective response with around 8% obtaining a complete response and these are mostly durable.[7,8] Despite the potential curative effects of HD IL-2, its use has been limited by significant toxicity. HD IL-2 toxicities mostly result from capillary leak syndrome that manifests as a hypovolemic state with fluid accumulation in the extravascular space resulting in hypotension, pulmonary congestion, and renal impairment. There have been many attempts to reduce the toxicity of HD IL-2 by reducing the dose or changing the schedule but randomized trials suggest that in terms of durable remissions HD IL-2 is the preferred regimen.[7,9] Although potentially serious and occasionally fatal toxicities can occur, clinical guidelines have been developed to ensure its safe administration.[10] Thus despite the toxicity, HD IL-2 remains the only potentially curative medical therapy for patients with MRCC and efforts to improve its effectiveness or select appropriate patients for treatment are clearly important.

Several studies have sought to evaluate the pretreatment characteristics of MRCC patients most likely to benefit from HD IL-2 so treatment can be targeted. The largest current series, reporting 20 years experience, suggest clinical factors such as good prognostic scores according to Memorial Sloan-Kettering Cancer Center (MSKCC) criteria,[1] no prior immunotherapy and higher baseline weight are good predictors of response.[8] Other potential predictors of response are the histologic type of tumor. RCC is classified into 6 main subtypes: clear cell (conventional), papillary, chromophobe, translocation-associated, collecting duct, and unclassified carcinomas. The histology of conventional clear cell carcinoma can be further described by architectural pattern (alveolar, solid, trabecular, tubular, cystic, and there may be focal areas with a papillary growth) and by cytoplasmic staining characteristics (percentage of clear versus granular cells).[11–13] Clear cell tumors were long considered the most IL-2 responsive and a

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retrospective analysis of 163 IL-2-treated patients conducted by Upton et al[14] suggested favorable histologic features to include a high proportion of alveolar pattern, a low proportion of granular cells and no papillary architecture. However, no details of complete response rates were given.

The current situation in the treatment of MRCC poses a dilemma for clinicians and patients. There are two very different treatments with very different outcomes. Targeted therapy (such as antiangiogenic drugs) provides good disease control and palliative benefit but little evidence of long-term benefit after treatment ceases. It is delivered as an outpatient and is generally reasonably well tolerated with mild/moderate but on-going toxicities. HD IL-2 by contrast is complex and produces severe acute toxicity requiring inpatient delivery but can produce long-term benefits, which are durable after cessation of treatment. Therefore, albeit in a small subgroup of patients, it is considered the only potentially curative medical therapy for MRCC.

Against this background and at a time of rapidly changing treatment for patients with MRCC, we present our case series using HD IL-2. Our use of HD IL-2 changed with the licensing of new treatments in 2006 and with the availability of data on the possibility of selecting patients for this type of treatment. We describe outcomes of patients in both retrospective and prospective cohorts (before and after assessment of histology before treatment) and detail response rate, complete response and survival (see Fig. 1 for overview of case series and its timing). Our data suggest substantial benefits for carefully selected patients and thus, a continued role for the use of HD IL-2 in the management of MRCC.

PATIENTS AND METHODS

Treatment

Treatment with HD IL-2 comprised Proleukin (Novartis) 600,000 units/kg given over 15 minutes 8 hourly as tolerated for a maximum of 14 doses over a 5-day period.

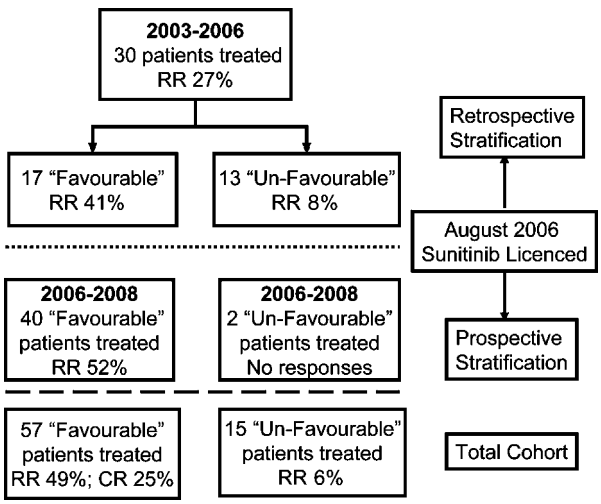

FIGURE 1. Overall schema of the patient series. The histology of patients treated was retrospectively classified in the initial series (2003 to 2006). In the prospective series, (2006 to 2008) the histology was assessed before commencing patients on treatment.

After a 10-day break, the patients were treated with another 5-day cycle. Treatment was delayed or interrupted according to standard guidelines[10] and full supportive measures were available as needed. Two 5-day cycles constitute 1 course of treatment and patient's response to the treatment was evaluated by CT scan approximately every 10 weeks using RECIST criteria.[15] In patients whose disease was controlled and had acceptable toxicity, the treatment was repeated at 10 to 12 week intervals to maximum response. Those achieving a complete remission were given 1 further cycle of treatment.

Patients

We report a case series of 72 patients with histologically confirmed RCC and measurable disease radiologically treated with HD IL-2. These are all patients commencing first-line systemic treatment with HD IL-2 at the Christie NHS Foundation Trust between July 2003 and December 2008. Patients were classified according to the MSKCC score that was developed to predict MRCC patients survival by assessing 5 pretreatment features or parameters that are associated with shorter survivals: low Karnofsky performance status (< 80%), high serum lactate dehydrogenase (> 1.5 times upper limit of normal), low hemoglobin (< lower limit of normal), high "corrected" serum calcium (> 2.5 mmol), and the absence of prior nephrectomy.[1] Only patients with good or intermediate prognostic scores were considered for this treatment in keeping with evidence that these are the most likely to benefit.[8] The patients were not eligible if they had an Eastern Cooperative Oncology Group performance status greater than 1, any current evidence of CNS involvement, any recent corticosteroid administration, or active autoimmune disease. Coronary artery disease was excluded by history and ECG with routine exercise ECG or stress Echocardiography was used to assess all patients older than 55 years.

Patients were treated on routine medical oncology wards using treatment principles described by Schwartzentruber.[10] During the initial period (July 2003 to August 2006), 30 patients (retrospective cohort) were considered for treatment with HD IL-2 based on general clinical fitness/MSKCC prognostic score and treated after discussion of other available options. Patients' tumors were retrospectively assessed using a modified histologic system based on that earlier described by Upton et al.[14] From August 2006 (when antiangiogenic therapy was licensed in the UK) until December 2008, in addition to clinical factors, histology was prospectively assessed and classified as "favorable" or "unfavorable" before a decision about treatment was made. Forty patients (prospective cohort) who opted for HD IL-2 therapy had "favorable" histology and a further 2 patients who did not fit these criteria were also treated after discussion of the available data. Follow-up was as of July 31, 2010.

Histologic Assessment

Retrospective histologic assessments were done by 2 of us (K.S./J.H.S.) who were blinded to the outcome of therapy. Histologic evaluation was done using standard H&E-stained sections. All cases were evaluated according to a protocol based on the consensus classification of carcinoma types[13] and the UICC staging and Fuhrman nuclear grading systems.[16] Conventional (clear cell) renal carcinoma may have variable amounts of clear or granular or eosinophilic components. Each case was assessed for architectural features (alveolar, solid tubular, cystic, and

papillary).[17] The presence or absence of sarcomatoid areas was also noted.[18] Cytoplasmic staining characteristics were noted (clear cells versus granular cells). It was noted whether these features represent greater than 50%, less than 50%, or < 10% of the carcinoma area.

Statistical Analysis

Survival was calculated from the date of initiation of HD IL-2 treatment until date of either death or last follow-up for the overall survival or until date of progression or discontinuation of treatment for the progression-free survival and analyzed by the Kaplan-Meier method. The significance of differences between variables to predict for progression-free and overall survival were analyzed by log rank test. Statistical analysis was conducted with Stats-Direct version 1.9.7.

RESULTS

Demographics, Response Rate, and General Findings of the First (Retrospective) Cohort

Out of 30 patients in the retrospective cohort, an objective clinical response was seen in 8 (26.6%) patients with 4 patients (13%) having complete resolution (CR) of their disease and 4 (13%) had partial response (PR). Of the complete response patients, only 1 had disease relapse after 18 months. Although these results are better than many series, the response rates are of similar magnitude and are consistent with the observation that patients with better MSKCC prognostic scores respond better to HD IL-2.[8]

The demographics for the patients are summarized in Table 1 (section 1). The majority of the treated patients (63%) had an MSKCC score of 0, but responses were also seen in MSKCC 1 score patients. Similarly, although most patients had only 1 site of metastasis and these seemed to have a higher response rate (40%), responses were also seen in patients with 2 and 3 sites of metastases.

Retrospective Assessment of Response Based on Histologic Features in Clear Cell RCC

The histologic review showed that out of the 30 patients in this cohort, 28 (93%) had clear cell (conventional) and 2 (6%) had papillary carcinomas. When reviewed as described in the article by Upton et al,[14] it was clear that predominance of an alveolar architectural pattern, a low proportion of granular cells and lack of papillary features were all associated with better responses (Table 2). The only apparent contradictions were in the patients whose tumor was predominantly solid pattern and those with small amounts of papillary features. The Upton series[14] contained only 2 patients with more than 50% "solid" features who both failed to respond but in our series 2 of the 4 patients with more than 50% solid features had an objective clinical response. The response rate in tumors that were predominantly alveolar or solid (more than 50% of each/both) was 44% (7 of 16 patients). Although only 1 of 10 patients (10%) with 10% to 50% of both features combined had a clinical response, no response was observed in the 2 patients with clear cell tumors that had < 10% of this combination. Similarly, we found that whereas responses were rare in those patients with more than 10% papillary features there were a significant number with a trace of papillary features (< 10%) and these had a good response rate.

The Response Rate and Survival Post HD IL-2 in Patients Whose Tumors Exhibit "Favorable" Histologic Features

Since August 2006, in addition to clinical assessment using MSKCC score, histologic assessment based on the criteria of Upton et al was carried out before making a decision about treatment. Forty patients prospectively identified as being in the "favorable" histology group (no significant (< 10%) papillary features and at least one other "good" feature; more than 50% alveolar and/or solid architecture and < 50% cells with granular rather than clear cytoplasm) were treated. The objective clinical response rate for this prospectively identified group of patients was 52·5% (21 of 40) compared with the 26·6% (8 of 30) response rate of the retrospective cohort. Importantly, the complete response rate was also excellent in this group. Out of the 40 histologically prospectively identified patients, 10 had achieved CR (25%) compared with 4 out 30 (13%) in the retrospective cohort patients.

TABLE 1. Summary of Response Rate by Sex, Age, MSKCC (Memorial Sloan Kettering Cancer Center) Score, and Number of Organs with Metastasis

	First (Retrospective) Cohort (All Patients)		Second (Prospective) Cohort (Favorable Histology Only)		All Favorable Histology Patients (17 From First Cohort and 40 of Cohort 2)	
	Number = 30	Response = 8	Number = 40	Response = 21	Number = 57	Response = 28
Sex						
Male	23 (77%)	6/23 (26%)	29 (72.5%)	15/29 (52%)	41 (72%)	20/41 (49%)
Female	7 (23%)	2/7 (28.5%)	11 (27.5%)	6/11 (54.5%)	16 (28%)	8/16 (50%)
Age						
< 55	15 (50%)	4/15 (27%)	17 (42.5%)	11/17 (64.7%)	24 (42%)	14/24 (58%)
> 55	15 (50%)	4/15 (27%)	23 (57.5%)	10/23 (43%)	33 (58%)	14/33 (42%)
MSKCC score						
0	19 (63%)	5/19 (26%)	33 (82.5%)	19/33 (57%)	42 (73.6%)	23/42 (55%)
1	9 (30%)	3/9 (33%)	6 (15%)	2/6 (33%)	13 (23%)	5/13 (38%)
2	2 (7%)	0	1 (2.5%)	0	2 (3.4%)	0
Number of organs with metastasis						
1	10 (33%)	4/10 (40%)	18 (45%)	10/18 (55.5%)	25 (44%)	14/25 (56%)
2	7 (23%)	1/7 (14%)	14 (35%)	9/14 (64%)	18 (31.5%)	11/18 (61%)
3	12 (40%)	2/12 (16%)	6 (15%)	1/6 (16.6%)	12 (21%)	2/12 (16.6%)
4	1 (4%)	0	2 (5%)	1/2 (50%)	2 (3.5%)	1/2 (50%)

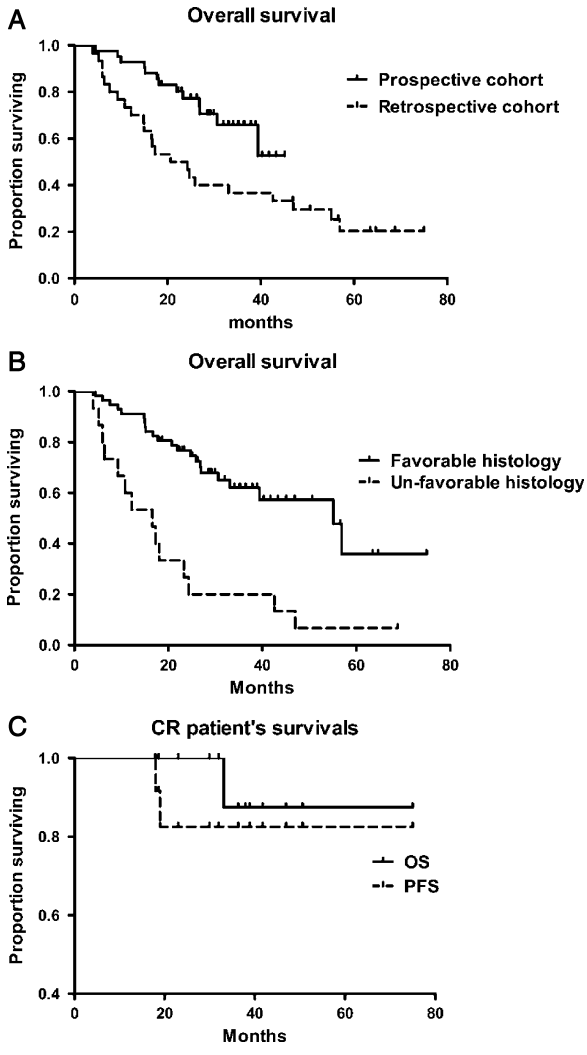

FIGURE 2. Kaplan-Meir Survival plots. A, Illustrates the overall survival in the prospective cohort (identified as having favorable histology) compared with the retrospective one ($P = 0.0062$). B, Shows the difference in overall survival between the "favorable" and "non favorable" histologic groups in response to IL-2 therapy ($P = 0.0002$). The median overall survival is estimated to be 55 months in the patients with favorable histology and is only 13 months in the other group. C, Plots for progression free and overall survival for all 14 patients who achieved CR posttreatment with HD IL-2. Remissions are durable and median survival is not yet reached. OS, overall survival; PFS, progression-free survival.

Only 2 patients who were assessed as having "unfavorable" histology opted for treatment with HD IL-2 after 2006 and neither of these responded to treatment. The overall survival was also assessed (Fig. 2A) and there was a clear improvement in survival between the 2 cohorts. The apparent improvement is likely to be in part owing to the treatment of patients more likely to benefit from HD IL-2, but other factors may also account for these differences including the widespread availability of Sunitinib (which was generally given to those who did not respond to HD IL-2) and the differences in MSKCC prognostic scores (Table 1).

TABLE 2. Response Rate by Specific Features of Clear Cell Carcinoma as Stratified From the Retrospective Patient Cohort

	> 50%	10-50%	< 10%
Alveolar	5/12 (41.6%)	3/14 (21%)	0/2 (0%)
Solid	2/4 (50%)	0/1 (0%)	5/22 (22.7%)
Alveolar and solid combined	7/16 (44%)	1/10 (10%)	0/2 (0%)
Granular	2/17 (11.7%)	3/7 (43%)	3/4 (75%)
Papillary	0/5 (0%)	0/1 (0%)	8/22 (36%)

Overall Assessment of HD IL-2 as a Treatment Option for MRCC; Objective Response, Survival, and Durability of Complete Response

In this series, a total of 72 MRCC patients were treated with HD IL-2. Of these, 57 had "favorable" histology of whom 28 (49%) responded with a 25% (14/57) complete remission rate. Of the patients with "unfavorable" histology only 1 (6%) responded and this was not a complete response. The survival data are currently relatively immature but also seem very good for the "favorable" histology group with median survival estimated to be 55 months (Fig. 2B).

To date only 2 of the patients who have achieved complete remission on medical therapy have relapsed. One has subsequently died but the other is in complete remission after resection of a solitary recurrence. Thus, the durability of complete remissions seems very good (Fig. 2C) as is generally the case with patients achieving complete remission on HD IL-2.[8] In addition to those achieving a CR as a result of HD IL-2 treatment, 5 patients who responded were subsequently able to have their disease surgically resected to a CR. The value of surgery in this situation is unclear and the CRs may be less durable with the longest duration currently being 17 months postsalvage surgery (6, 13, 15+, 17, and 17+ months for individual patients).

Treatment Duration and Toxicity

Many patients stopped treatment after 1 cycle in view of absence of objective radiologic response. For those who responded, the treatment was continued to maximum response unless limited by toxicity. Those who achieved CR received an average of 3.3 cycles (range 2–5 cycles).

HD IL-2 is a toxic treatment and grade 1 to 2 toxicities were very common affecting all patients with various severities. They were managed in accordance with published guidelines[10] and generally resolved rapidly at the completion of treatment. Management of the complications of vascular leak was routinely achieved through the use of a sliding scale of intravenous fluid infusion based on recorded blood pressure. Most patients were managed on routine medical wards, however, 4 patients required admission to the intensive care unit with 2 of them requiring inotropic support for significant hypotension but none of them needed ventilation. In 4 patients, complications were sufficient to require stopping the treatment. These included 1 patient who suffered a cerebral vascular accident confirmed by MR scan and whose clinical signs took several weeks to fully resolve. The others were an acute confusional state, immune thrombocytopenic purpura, and severe allergic reaction.

DISCUSSION

MRCC remains a difficult cancer to treat despite the wide and increasing range of drug treatments. Although vascular endothelial growth factor and mammalian Target of Rapamycin inhibitors are currently the standard of care for most patients, these drugs are rarely curative. In contrast, it is intriguing that HD IL-2 can induce complete remission in a small number of patients with MRCC and these remissions are durable in most patients. However, in view of the uncertain overall benefit and the significant toxicities, HD IL-2 has diminished in popularity recently. Importantly, with a wide range of treatments available the potential exists to select the most appropriate treatment for individual patients using a variety of clinical, histologic, immunohistochemical, or genetic features to aid treatment choice.[19] Here, we provide further retrospective data to support the use of selection by clinical[8] and histologic features.[14] Notably, we also provide data on the first prospective series of patients selected by clinical and histologic criteria and this confirms that the overall response rate in this selected group is very high with a high rate of complete remissions. This is the key attraction of HD IL-2 for cancer patients and this high frequency of complete remissions has not been earlier reported. Critically, the durability of such medical complete remissions seems comparable with that earlier reported although follow-up is relatively short compared with the long follow-up at the NCI.[8] Furthermore, patients can be converted to complete remission by salvage surgery (around 10%) but the durability of these remissions is less clear. Importantly, all patients reported here were treated as "first line medical therapy" and the role of treatment after failure of antiangiogenic therapy is speculative and should be used with caution.[20]

Significantly, in this series we have treated very few patients with nonalveolar or solid clear cell cancer and we cannot exclude substantial benefit in other subgroups of patients. There are other potential methods of selecting patients for treatment with HD IL-2 and these include the expression of carbonic anhydrase IX (CAIX)[21] or assessment of CAIX polymorphisms[22] (reviewed in 19), all of which have been suggested to predict good response to IL-2. Moreover, the independence of various factors must be assessed as there may be links between several predictive factors-for example, CAIX expression is inversely correlated with numbers of granular cells.[23] Such issues along with validation of other markers are also being assessed in the "SELECT" study[24] and initial results were reported at ASCO 2010.[25] It is interesting to note that these results[25] do not confirm to the selection criteria proposed by Upton et al[14] or the value of CAIX to select patients for HD IL2.[21] The reason for the apparent discrepancy with our series is unclear but one possible reason is that we adapted the Upton criteria based on our retrospective cohort rather than using them as reported. The SELECT trial reported response rates of 36%, 26%, and 33% in the "Good," "Intermediate," and "Poor" Histology groups, respectively, and thus, could not show the value of selection by histologic criteria. Importantly, when we analyze our data by the original criteria we find 60%, 44%, and 36% in the "Good," "Intermediate," and "Poor" Histology groups respond, respectively, and hence also agree that the Upton criteria should not be used in an unmodified way (Table 3) – it would clearly be of great interest to analyze the results from the SELECT trial using the histologic criteria as modified by us. Overall, the prospective series reported here identifies a group of patients who it seems should receive HD IL2 as initial therapy because of both the high rate of response and the high complete remission rates. Ideally, the potential benefits of HD IL2 in this group should be confirmed in a randomized trial compared with the current effective standard of care which for many patients is Sunitinib.[6] For the other groups, work should continue to refine the selection criteria. Certainly, this series does not prove that patients with unfavorable histology should not be treated with HD IL2 as in the prospective part of this series only 2 patients who had unfavorable histology elected to have HD IL2. It therefore remains possible that other groups will also derive considerable benefit from HD IL2.

Apart from selecting patients with favorable features predictive of response to HD IL-2, it is also important to try to improve outcomes still further. It is clear that certain subsets of patients with MRCC have disease that is responsive to immunotherapy and it is attractive to try to build on this to produce even more frequent durable remissions. Certainly, there is the potential to combine HD

TABLE 3. Comparison of Different Approaches to Histologic Classification of Patients in This Series

	Upton Good (More Than 50% Alveolar Features and no Granular or Papillary) Intermediate (Less Than 50% Alveolar and Granular and no Papillary) Poor (Papillary Features or More Than 50% Granular Features or Without Alveolar Features)			Current Series Favorable Group (< 10% Papillary Features and At Least One Other "Good" Feature; > 50% Alveolar and/or Solid Architecture or < 50% Cells With Granular Rather Than Clear Cytoplasm)	
	Good	**Intermediate**	**Poor**	**Favorable**	**Unfavorable**
Preselection (n = 30)	2/2 (100%) (PR 2/2)	2/5 (40%) (CR 2/5)	4/23 (17%) (CR 2/23) (PR 2/23)	7/17 (41%) (CR 4/17) (PR 3/17)	1/13 (PR 1/13)
Postselection (n = 42)	1/3 (33%) (PR 1/3)	9/20 (45%) (CR 5/20) (PR 4/20)	11/19 (58%) (CR 5/19) (PR 6/19)	21/40 (52.5%) (CR 10/40) (PR 11/40)	0/2 (0%)
All (n = 72)	3/5 (60%) (PR 3/5)	11/25 (44%) (CR 7/25) (PR 4/25)	15/42 (36%) (CR 7/42) (PR 8/42)	28/57 (49%) (CR 14/57) (PR 14/57)	1/15 (6%) (PR 1/15)

The outcomes are analyzed by the original Upton criteria[15] or the modified criteria used here.

IL-2 with other therapeutic approaches in the hope that these may prove synergistic. The recent report of apparent survival benefit in patients treated with (low dose) IL-2 in combination with a vaccine[26] is encouraging. Other approaches include the use of cell therapy (reviewed in 27) as the combination of cell therapy and HD IL-2 seems very effective in melanoma.[28]

In summary, this case series shows an ongoing role for MRCC treatment with HD IL-2 and is the first series of patients prospectively selected by defined histologic and clinical criteria. It is not possible to achieve such a high complete remission rate (around 25%) with any other therapy and the toxicity of this treatment is acceptable in suitably experienced centers. Thus, the option of HD IL-2 should be considered for all patients with MRCC and this option should be discussed with all the patients who have clinical and histologic features that make them likely to benefit. Future trials should aim to prospectively confirm benefits compared with other standards of care, to identify further groups of patients who may benefit, and to further harness the power of immunotherapy to deliver even more frequent durable responses in renal cancer patients.

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