Immunotherapy for metastatic renal cell carcinoma: is it a therapeutic option yet?

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Until 1 year ago, immunotherapy was considered the standard treatment of metastatic renal cell carcinoma (MRCC) producing objective response of 10%–20% and an overall survival of ~1 year. Recently, some multitarget-oriented drugs have shown an impressive activity in MRCC with a high percentage of partial response and/or stable disease with a significant impact on survival. Nevertheless, immunotherapy remains another important therapeutic option for these patients. The value of immunotherapy is its curative potential in some patients and its capability to obtain very durable responses as demonstrated by long-term follow-up. Interesting results seem obtained also when immunotherapy is used in combination with some chemotherapeutic agents. Gemcitabine demonstrated be a good drug to combine with immunotherapy because of its little detrimental effects on cellular immunity. In phase II studies, interesting results have been reported. We treated 41 patients with MRCC using a biweekly schedule including s.c. interleukin 2 (IL-2), gemcitabine and vinorelbine. The overall response was 40% and the median survival was 24 months. Treatment was well tolerated and easily manageable. Vaccines are another promising treatment of RCC intended to stimulate a specific antineoplastic response. Vaccines have been explored both in an adjuvant and in a metastatic setting. We started a pilot study with dendritic cells vaccine loaded with autologous tumor in MRCC. The treatment has resulted feasible, well tolerated and effective in a minority of patients. In the future, combination immunotherapy with multitarget-oriented drugs may be one way forward. Also advances in cellular therapies and new immunomodulatory molecules as monoclonal antibodies are producing new therapeutic options. Finally, the identification of a panel of prognostic factors could provide an important tool to guide the choice of treatment of patients with a different risk profile. Therefore, the increasing therapeutic options for RCC should be seen not as a competition among the different treatments but as an expanding armamentarium available for these patients.

Key words: chemoimmunotherapy, metastatic renal cell carcinoma, vaccine

Introduction

The management of metastatic renal cell cancer (MRCC) constituted a therapeutic challenge and no standard therapy has been established until few years ago. As known, RCC is a chemoresistant neoplasm with antiblastic agents inducing objective response only in a minority of patients.

Recently, some multitarget-oriented drugs have shown an impressive activity in MRCC with a high percentage of partial response (PR) and/or stable disease (SD) and with a significant impact on survival [1, 2].

As known, RCC is one of the most immunoresponsive of human malignancies. Thus, immunotherapy remains one of the most important therapeutic options for these patients. The value of immunotherapy is its curative potential in some patients and its capability to obtain very durable responses as demonstrated by long-term follow-up [3, 4].

Cytokines

Interleukin 2 (IL-2), with or without lymphokine-activated killer cells, has demonstrated an important antitumoral activity in RCC. As single agent, IL-2 has been evaluated in various dose and treatment schedules yielding a response rate of ~10%–23% [5, 6]. As the initial i.v. use of this cytokine was associated with severe toxicity requiring even intensive care support, several studies were initiated to evaluate the efficacy of IL-2 given s.c. This IL-2 administration modality seems to provide therapeutic efficacy similar to that reported for i.v. IL-2 while drastically reducing treatment-related toxicity to the point of even permitting outpatient care and self-administration [7]. However, the response rate and duration seem to be longer with high-dose IL-2 with respect to low dose [8]. Some authors recently have also reported a better survival for high-dose IL-2 [9].

When IL-2 was used in association with interferon (IFN), the results were quite similar, while toxicity was significantly enhanced [9].
chemoimmunotherapy

Preclinical studies showed synergetic-additive effects when immunotherapy is used in combination with some chemotherapeutic agents. Initially, improved results were reported with an association of chemotherapy plus IFN. However, randomized studies demonstrated only a small increase in overall response with no difference in survival [10, 11].

More recently, Atzpodien et al. [12] reported in a large randomized trial high percentage of responses (31%) and a very long survival (25 months) with the combination of s.c. IL-2 plus IFN-α and 5-fluorouracil (5-FU) with respect to vinblastine and IFN-α. On the contrary, the addition of 13-cis-retinoic acid does not increase the results. Although encouraging, these results need further confirmatory studies.

In our first experience with low-dose s.c. IL-2, IFN-α and vinblastine, we reported in 23 patients with MRCC 21.6% of overall response and a 65% of SD. The median overall survival was 11 months, with 27 months for responders, 11 months for patients with SD and 8 months for patients with rapid progression [13].

experiences with gemcitabine plus immunotherapy

Preclinical data showed that gemcitabine (GEM) could be a good drug to combine with immunotherapy. In fact, it has been demonstrated that IFN-α increases the cytotoxicity of GEM and the tumor responses of human RCC in xenografts [14]. Moreover, GEM seems to exert a selective detrimental effect on the humoral immune response but not on specific antitumor cellular immunity. It has also been reported that weekly short infusions of GEM are not associated with reduction of CD4/CD8 ratio and natural killer cell in patients with solid tumors [15].

In Table 1 are reported the principal experiences with GEM used without and in association with immunotherapy in MRCC. The efficacy of GEM alone [16] in chemotherapy-naive MRCC has been explored in a phase II study and a response rate of 8% has been reported with a survival >12 months. Better results have been obtained when GEM was associated with other chemotherapeutic agents [17, 22, 23].

The association of GEM plus immunotherapy has been minimally explored. Rohde et al. [18] reported the results on nine patients pretreated with immunotherapy using GEM and IFN-γ. The response was 15% and the overall survival was 13.5 months. Ryan et al. [19] in 41 patients, treated with GEM plus 5-FU continuous infusion, IFN-α and low dose of IL-2 given s.c., reported an overall response of 14.6% and an overall survival of 20.6 months. Neri et al. [20] using GEM in association with s.c. IL-2 and IFN-α in 15 untreated patients reported an overall response of 28%, with a time to progression and survival lasting 14 and 20 months, respectively.

We explored the efficacy and tolerability of a schedule including low-dose s.c. IL-2 in association with GEM and vinorelbine (VRB) in a phase II trial using a biweekly schedule in patients with MRCC [21]. Forty-five patients were included in the study. The following schedule was used: IL-2 4.5 million IU daily from day 1 to day 4; GEM 1200 mg/m² on day 1 and VRB 25 mg/m² on day 1. Therapy was recycled every 14 days. The overall response was 40% with three patients (6.6%) obtaining a complete response (CR) and 15 (33.3%) PR. 13 (29%) experienced a SD and 14 (31%) progressed. Response occurred not only in soft tissue/lymph nodes (35%) and lung/pleural (30%) disease but also in bone/visceral (35%) disease. Median response duration was 20 months, 34+ for CR and 24 for PR. Median survival was 24 months, 27 for CR/PR/SD and 8 for progressive patients. Treatment was well tolerated and easily manageable. IL-2 was mainly administered as outpatient care. Most relevant toxicity was chemotherapy related with grade 1–2 neutropenia being most common. IL-2-related toxicity was as expected and completely reversible with stopping therapy.

In summary, we demonstrated that biweekly GEM–VRB plus low-dose IL-2 is a feasible and effective regimen in MRCC with a good toxic profile. On the basis of the present

Table 1. Principal studies with gemcitabine in metastatic renal cell carcinoma

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>OR/CR (%)</th>
<th>TtP/OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Mulder et al. [16]</td>
<td>39</td>
<td>GEM 800 mg/m², g 1, 8, 15</td>
<td>8.1/2.5</td>
<td>OS 12.3</td>
</tr>
<tr>
<td>Rini et al. [17]</td>
<td>39*</td>
<td>GEM 600 mg/m², g 1, 8, 15</td>
<td>17/0</td>
<td>TtP 7</td>
</tr>
<tr>
<td>Rohde et al. [18]</td>
<td>9**</td>
<td>GEM 5-FU c.i. 150 mg/m²/days 1–21</td>
<td>15/0</td>
<td>OS 13.5</td>
</tr>
<tr>
<td>Ryan et al. [19]</td>
<td>41</td>
<td>GEM IFN-α</td>
<td>14.6</td>
<td>6.6/20.6</td>
</tr>
<tr>
<td>Neri et al. [20]</td>
<td>15</td>
<td>GEM IL-2 s.c. + IFN-α</td>
<td>28</td>
<td>14/20</td>
</tr>
<tr>
<td>Guida et al. [21]</td>
<td>45</td>
<td>GEM IL-2 s.c. + IFN-α</td>
<td>40/6.6</td>
<td>OS 24</td>
</tr>
</tbody>
</table>

OR, overall response; TtP, time to progression; CR, complete response; OS, overall survival; GEM, gemcitabine; 5-FU, 5-fluorouracil; IL-2, interleukin 2; c.i., continuous infusion; IFN, interferon.
data, we are carrying out a large phase III trial comparing this schedule versus IL-2 immunotherapy alone.

**vaccinotherapy**

Vaccines are a promising but still experimental treatment of RCC. This approach theoretically should permit the selective and safe destruction of the neoplastic cells because they are intended to stimulate a specific tumor-protective immune response against neoplastic cells that share some antigens contained in the administered vaccine [3, 24, 25].

Vaccines can stimulate both antibody and cellular response against tumor. The type of response induced, its frequency and its magnitude depend on vaccine construct and on the adjuvant used. Cancer vaccines can be grouped in cellular, anti-idiotypic, peptide/protein based, glycolipid, and nucleic acid based. Immunological adjuvants can include not only the more classical ones (incomplete Freund’s adjuvant, alum, bacille Calmette–Guerin, QS-21) but also new molecules as cytokines [IL-2, IL-12 and granulocyte–macrophage colony-stimulating factor (GM-CSF)] or high purified immunogenic proteins cocktail (heat shock proteins) or dendritic cells (DCs).

To date, it is unclear what is the best number of antigens required to induce a more effective and clinically relevant immune response. For these reasons, several authors prefer to use vaccines containing a broad array of antigens rather than single, highly purified antigen. The stimulation of immune response against multiple targets should increase the chances of killing neoplastic cells and minimize the chances that tumor cells will be able to down-modulate the expression of all the targeted antigens to avoid immune attack [24].

Clinical trials are shown that vaccines are safe to use and have much less toxicity than other current therapies. Moreover, a growing body of evidence indicates that vaccines can be clinically effective although in a minority of patients. The recent use of DCs loaded ex vivo with a wide variety of tumor antigens has increased the frequency of tumor-specific immune responses and clinical regressions [25]. Though clinical trials conducted so far remains unsatisfactory, numerous new findings and knowledge in basic immunology and molecular biology indicate that these results could be significantly improved in the next future [24].

In RCC, vaccine has been explored both in an adjuvant and in a metastatic setting. A randomized phase III trial using an autologous tumor cell vaccine versus no treatment has showed a significant advantage for patients treated versus the control arm in terms of both disease-free and overall survival [25]. Another large phase III trial using heat shock protein versus observation in patients with high-risk recurrence after surgical treatment is ongoing.

In MRC, several experiences have been made using different types of vaccine (neoplastic cell, heat shock protein, DC) with an overall response resulting in ~10% [3].

We started a pilot study with DC generated from peripheral blood mononuclear cells obtained from leukapheresis procedure. After 6 days culture with IL-4 and GM-CSF, DCs were pulsed with autologous tumor lysate and matured with a cocktail of cytokines. Vaccine was administered i.d. at a dose of $10^6$ cells every 2 weeks for four times, followed by monthly administration in responding/SD patients until progression or vaccine availability. Low-dose IL-2 was also administered for 4 days after each vaccination. Until now, 17 patients have been treated (12 melanoma and 5 RCC). It was possible to prepare vaccine for all patients. The procedure, even though feasible, was elaborate and expensive. Compliance and tolerability were very high. No side-effects were registered, except IL-2-related side-effects. With regard to efficacy, we observed two PR (one MM and one MRCC; duration 12 and 3+ months, respectively), six SD (OS 8–4 months), one no evidence of disease for 14 months (MM with hepatic disease removed surgically), six PD and two not valuable (early).

Although significant progress has been made in vaccine therapy, it is still a long way to go.

**conclusions**

RCC is one of the most immunoresponsive of human malignancies; thus, immunotherapy remains one of the most important therapeutic options for this neoplasm. Moreover, despite exciting results obtained with the advent of the new tyrosine kinase inhibitors, the value of immunotherapy is its curative potential in some patients and its capability to obtain very durable responses.

Combination immunotherapy with multitarget-oriented drugs may be one way forward. Also the identification of a panel of prognostic factors could provide an important tool to guide the choice of treatment of patients with a different risk profile. Moreover, advances in cellular therapies, vaccines and new immunomodulatory molecules as monoclonal antibodies are producing new therapeutic options. Thus, the increasing choices available at present should be considered not as a competition among the different treatments but as an expanding armamentarium for the patients with MRCC.

**references**