Emerging immunotherapies for renal cell carcinoma

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In recent years, an improved understanding of renal cell carcinoma (RCC) tumour biology has resulted in major advances in the treatment of patients with metastatic RCC (mRCC). Although immunotherapy with interleukin-2 and interferon-α was once the standard of care for mRCC, the introduction of novel agents targeting angiogenesis and signal transduction pathways has markedly improved patient outcomes. However, targeted agents rarely induce complete responses, and patients eventually develop resistance to therapy, prompting consideration of novel therapeutic approaches and a resurgence of interest in immunotherapy for RCC. Phase I/II trials of vaccination with allogeneic dendritic cell/tumour fusions in patients with mRCC have demonstrated immunological and clinical responses in some patients, and T-cell modulating agents (e.g. antibodies against programmed death 1 and cytotoxic T lymphocyte-associated antigen-4, or soluble lymphocyte activation gene-3) and dendritic cell-activating toll-like receptor agonists have also shown encouraging evidence of efficacy in early-phase clinical trials. These early studies suggest that immunotherapy may continue to be an effective approach for patients with mRCC. As such, a number of other strategies are currently under investigation, including adoptive cell transfer (ACT) with T cells modified to target proteins expressed by renal tumours such as MAGE-A3/12, DR4 and TRAIL, and ACT with autologous natural killer cells. Results from trials of novel immunotherapies are encouraging, with data from other indications helping to facilitate development. To realise the full benefit for patients, it is likely that immunotherapy will need to be combined with targeted agents or other agents. Novel therapies used in combination or sequentially have the potential to improve outcomes in mRCC, and results from ongoing/planned trials will shape future therapy.

Key words: adoptive cell therapy, cancer vaccines, combination, immunotherapy, renal cell carcinoma, T-cell modulation

introduction

Renal cell carcinoma (RCC) is the most common form of kidney cancer and comprises ~3% of all malignant tumours in adults [1]. After the introduction of high-dose interleukin-2 (IL-2) as therapy for RCC over two decades ago [2], systemic IL-2 or interferon-α (IFN-α) remained the standard of care for patients with metastatic RCC (mRCC). In recent years, however, an improved understanding of tumour biology has resulted in significant advances in therapy [3]. The development of novel agents targeting angiogenesis and signal transduction pathways has markedly improved patient outcomes. Before their introduction, the median overall survival for patients with RCC was around 1 year, and only 10% of patients with metastatic disease survived past 5 years [1]. By contrast, the sequential use of targeted therapies can result in a progression-free survival of up to 27 months, and an overall survival of 40 months [4]. As a result, agents such as sorafenib, sunitinib, bevacizumab, everolimus and temsirolimus are now considered standard treatments for RCC [1, 3, 5].

Despite this substantial improvement in outcomes, treatment with these targeted agents rarely achieves complete responses and most patients ultimately develop resistance to therapy. These observations prompted a resurgence of interest in novel immunotherapeutic approaches for RCC [6]. The objective of this review is to discuss immunotherapies in development for RCC that may alter the treatment paradigm for RCC in the medium to long term.

rationale for immunotherapy in the treatment of RCC

Before the advent of targeted therapy for RCC, the mainstay of treatment for patients with metastatic disease was immunotherapy with IL-2 or IFN-α. There is a strong rationale for using immunotherapy in patients with RCC. The anecdotal observations of spontaneous remissions of advanced RCC (Figure 1) and infiltration of cancer tissue by tumour-specific immune cells, for example, suggest that immune mechanisms play a role in the natural disease course of RCC [7]. In addition, some patients treated with high-dose IL-2 experience durable complete responses of up to 2 years. However, because of toxicity concerns, high-dose IL-2 should only be considered in young and fit patients who can tolerate therapy. Biomarkers of response that might allow those patients who have the
capacity to respond to be selected and those who do not to avoid exposure to toxicity are yet to be identified. Furthermore, high-dose IL-2 has not been shown to significantly improve survival in patients with RCC [3].

The use of immunotherapeutic agents in patients with other tumour types, however, has been associated with substantial improvements in survival. For example, in a phase III trial, 676 patients with unresectable (advanced or metastatic) melanoma were randomly assigned to receive one of three treatments: single-agent ipilimumab, an antibody against cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), ipilimumab plus a glycoprotein 100 peptide (gp100) vaccine, or gp100 alone [8]. The median overall survival, in months, was 10.1 versus 10.0 versus 6.4 months in the ipilimumab alone, ipilimumab plus gp100 and gp100 groups, respectively [hazard ratios (HRs) for death compared with gp100 alone were 0.66, \( P = 0.003 \) for ipilimumab alone and 0.68; \( P < 0.001 \) for ipilimumab plus gp100]. Similarly, in a placebo-controlled phase III trial in 512 patients with castration-resistant prostate cancer, treatment with sipuleucel-T improved median survival by 4.1 months compared with placebo (HR for death: 0.78; \( P = 0.03 \)) [9]. These data provide proof-of-principle that immunotherapies have the potential to improve outcomes in patients with advanced cancer and, taken together with the fact that targeted agents have limited capacity to produce durable complete responses [10], support the use of novel immunotherapies for patients with RCC.

Indeed, evidence emerging from phase I/II clinical trials suggest new immunotherapies have the potential to improve outcomes when used either as single agents or in combination with targeted therapies [11–19]. There are three different approaches to immunotherapy currently being investigated in patients with RCC, comprising vaccines, adoptive cell therapy (ACT) and T-cell modulation, which are discussed in this review.

**vaccines**

Numerous vaccine approaches are currently being investigated for the treatment of RCC (Table 1) [11, 12, 15, 18, 20–26].

**AGS-003**

Findings of a phase II study evaluating AGS-003, a dendritic cell-based vaccine, administered in combination with sunitinib demonstrated improvement in median overall progression-free survival in newly diagnosed patients with mRCC (11.9 months for combination therapy versus 8 months for historical data with sunitinib alone) [12, 15]. No additive toxicity of the two agents was observed; the majority of AGS-003-related adverse events (AEs) were mild injection site reactions. A phase III study to evaluate AGS-003 plus sunitinib in patients with newly diagnosed advanced RCC undergoing nephrectomy is planned.

**IMA901**

IMA901 was developed based on the selection of nine human leukocyte antigen (HLA)-class I- and one HLA-class II-binding tumour-associated peptides. A phase II clinical study evaluated disease control rate, overall survival and safety of IMA901 intradermal vaccinations administered with or without low-dose cyclophosamide 300 mg/m\(^2\) [18]. Disease control rate at 6 months was 31% in the post-cytokine group (\( n = 40 \)), and overall survival rates were 87%, 79% and 68% at 6, 12 and 18 months, respectively. The majority of AEs...
reported were local injection-site reactions. A multicentre, open-label, randomised, phase III study is planned to determine whether IMA901 can prolong overall survival in patients with metastatic or locally advanced RCC when added to first-line therapy with sunitinib.

**MVA5T4**

MVA5T4 was engineered to stimulate the immune system to destroy cells expressing the 5T4 antigen, which is expressed on most solid tumours. A phase III study assessed overall survival and safety in patients with metastatic clear-cell RCC administered MVA-5T4 \((n = 365)\) or placebo \((n = 368)\) in combination with sunitinib, IL-2 or IFN-\(\alpha\) [11]. No significant differences in median overall survival were observed for MVA-5T4 \((20.1\) months) versus placebo \((19.2\) months; \(P = 0.55)\), and no differences in the incidence of AEs were observed. Antibody responses were quantified, and the immune response surrogate for 5T4 antibody response was used in a survival analysis to determine treatment benefit [21]. Results of this analysis demonstrated that a greater 5T4 antibody response was associated with longer patient survival in the MVA-5T4 treatment group.

**autologous tumour cell lysate**

Autologous tumour cell lysate vaccination therapy has demonstrated improvements in progression-free survival in a phase III study of patients with organ-confined RCC. An overall survival analysis including a follow-up period of 10 years showed that overall survival at 5 and 10 years for patients who received the vaccine was 80.6% and 68.9%, respectively, versus control patients who did not receive any adjuvant treatment \((79.2\%\) and 62.1%, respectively; \(P = 0.066)\) [16]. After 10 years, 53.6% of patients in the vaccine group versus 36.2% in the control group were still alive \((P = 0.022)\). An analysis of patient subgroups showed a significant benefit of the vaccine for patients with pT3 tumours \((P = 0.001)\).

**adoptive cell therapy**

The introduction of an immunodepleting preconditioning regimen before adoptive transfer led to substantial improvements in the efficacy of ACT for cancer treatment [27]. However, lymphocyte-activated killer cells have demonstrated variable objective response rates and no overall survival benefit in phase I/II randomised clinical studies in RCC [23, 24, 26, 28, 29]. Few clinical trials of tumour-infiltrating lymphocytes (TILs) have been conducted in RCC, and all have demonstrated poor objective response rates [20, 22, 25, 30–33]. However, genetic programming of T cells for RCC is associated with promising preclinical data [34, 35].

### T-cell modulation

**anti-CTLA-4 antibody**

CTLA-4 \((CD152)\) is an inhibitory receptor expressed by T cells, which upon ligand binding to CD80 and CD86, initiates T-cell proliferation and function, and maintenance of peripheral tolerance [36]. A phase II study of the anti-CTLA-4 antibody ipilimumab was conducted in patients with mRCC [19]. Five of 40 patients who received ipilimumab 3 mg/kg every 3 weeks achieved partial responses with a duration of 7 to 21 months, and the longest responses were among patients who had no prior treatment with IL-2. Immune-related AEs (irAEs) of grade 3/4 were reported in 17 of 40 patients; the most common irAE was enteritis. There was a highly significant association between autoimmune events and tumour regression \((\text{response rate} = 30\%\) with autoimmune event; 0% without autoimmune event; \(P = 0.009)\).

**anti-programmed death 1 antibody**

Programmed death 1 (PD1), a member of the B7-CD28 family, is a cell-surface co-inhibitory receptor that plays a critical role in the negative regulation of T-cell activation [37]. Patients with RCC characterised by PD1-positive TILs are significantly more likely to have larger tumours \((P = 0.001)\), tumours of higher nuclear grade \((P = 0.001)\), advanced tumour-node metastasis stage \((P = 0.005)\), coagulative tumour necrosis \((P = 0.027)\) and sarcomatoid differentiation \((P = 0.008)\) than patients without PD1-positive TILs (Figure 2) [38]. In preliminary results in 16 assessable patients with RCC from an ongoing phase I trial, treatment with the anti-PD1 antibody BMS-936558 resulted in partial tumour responses in five patients and stable disease lasting \(\geq 6\) months in three patients [17].

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**Table 1. Vaccines in development for renal cell carcinoma**

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Efficacy data</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>AGS-003</td>
<td>RNA-loaded dendritic cell-based vaccine</td>
<td>In phase II trial, median PFS was 11.9 months in patients with poor-risk mRCC [24, 26]</td>
<td>In phase III</td>
</tr>
<tr>
<td>IMA901</td>
<td>Developed from 10 naturally presented tumour-associated peptides</td>
<td>In phase II trial, post-cytokine arm overall survival rate was 87%, 79% and 68% for 6, 12 and 18 months, respectively [23]</td>
<td>In phase III</td>
</tr>
<tr>
<td>MVAST4</td>
<td>Antigen coded by modified vaccinia virus</td>
<td>In phase III trial, no difference in median overall survival versus placebo ((20.1) versus 19.2 months) [25]</td>
<td>Stopped development</td>
</tr>
<tr>
<td>Reniale®</td>
<td>Autologous tumour cell lysate</td>
<td>High 5T4 antibody response was associated with longer survival within the MVAST4-treatment group [22]</td>
<td>Data pending</td>
</tr>
</tbody>
</table>
relationship between drug dose and AE frequency has been observed, and drug-related, grade 3/4 AEs have been reported in 3 of 18 patients. This trial is ongoing, with the enrolment of additional RCC patients into an expansion cohort to further characterise efficacy and safety at the selected dose. Numerous phase I/II clinical trials targeting PD1, or its ligand PD-L1, are planned or enrolling patients with mRCC.

denileukin difitox

Denileukin difitox (DD) is a fusion protein of diphtheria toxin and human IL-2 that functions to deplete cells expressing the CD25 component of the IL-2 receptor [39]. In a phase I study evaluating combination therapy with DD plus high-dose IL-2, patients with mRCC received 9 mg/kg DD before high-dose IL-2 (group B; n = 9) or 9 mg/kg DD between IL-2 courses (group C; n = 6) [13]. Group A included three patients to assess safety only. The overall response rate was three of nine (33%) in group B and two of six (33%) in group C, including two patients with sarcomatoid RCC and one previously treated with sunitinib. One complete response was observed in groups B and C each. No unusual AEs were noted for DD in combination with IL-2 versus IL-2 alone; 33% of patients in groups A and B, respectively, had grade 3/4 vascular leak syndrome, similar to the control group.

soluble LAG-3

Soluble LAG-3 is an agonist of MHC class II-driven dendritic cell activation and enhances expansion of tumour-specific CTLs in vitro [40]. IMP321, a soluble LAG-3 fusion protein, was evaluated in a phase I, escalating-dose trial in 21 patients with advanced RCC [14]. A total of 21 patients received IMP321 0.5 to 30 mg per injection biweekly for six injections. Seven of 8 assessable patients who received the high-dose IMP321 experienced stable disease at 3 month versus 3 of 11 patients who received low-dose IMP321 (P = 0.015). No clinically important AEs were observed and good systemic exposure was achieved with doses above 6 mg.

combination strategies

For patients with RCC to achieve full benefits of treatment, it is likely that immunotherapies will need to be combined with targeted agents or included in other combination strategies. Based on the potential synergistic antitumour effects, a phase I study assessed treatment with the anti-CTLA-4 antibody tremelimumab in combination with sunitinib in patients with mRCC (Figure 3) [41]. Nine of 21 (43%) assessable patients achieved a partial tumour response; however, the combination therapy was associated with acute renal toxicity and one of seven patients who received tremelimumab 10 mg/kg plus sunitinib experienced sudden death. The investigators concluded that further evaluation of tremelimumab doses >6 mg/kg in combination with sunitinib was not recommended. Ongoing clinical trials are assessing the potential therapeutic benefit of various combination strategies, including vaccines in combination with the targeted agents sunitinib and bevacizumab, cytokine-induced killer cells, or immunostimulatory agents. However, careful attention must be given to the potential toxicity of combination regimens and to optimising the timing of treatments. For example, in a recent phase II trial of ipilimumab plus carboplatin and paclitaxel (CP) in patients with advanced non-small cell lung cancer, a phased regimen, whereby ipilimumab was provided after two courses of CP, appeared to have greater efficacy than a concurrent regimen [42], highlighting the importance of treatment scheduling in optimising outcome.

summary

Prior experience with IL-2 and recent clinical observations with novel immunotherapies in other tumour types provide the rationale for clinical trials to investigate the potential benefits of immunotherapy in patients with RCC, with emerging evidence from early-phase clinical trials supporting the use of vaccines and T-cell modulating agents in this indication. Effective immunotherapies with novel, potentially complementary mechanisms of action from targeted therapies, used in combination or sequentially with targeted therapies, or other combination partners, have the potential to improve outcomes in mRCC. In addition, more clearly defined
treatment strategies for patients with poor-risk disease or non-clear-cell histologies are required. It is hoped that results from ongoing/planned trials will shape future therapy and confirm the importance of this disease in the field of immuno-oncology.

disclosures
BE has received honoraria from Bayer, Roche, Pfizer, Novartis, GlaxoSmithKline and Aveo.

references

