Chapter 22
Immune Therapies for Metastatic Kidney Cancer

Kassem S. Faraj, Thai H. Ho, Mark D. Tyson, and Erik P. Castle

Background

One of the earliest reports demonstrating the potential application of immunomodulation for tumor regression was when administration of interleukin-2 (IL-2) led to a reduction of tumor burden in a patient with melanoma in 1984 [1]. This has since led to significant interest in the field of immunology and its role in managing various malignancies. The earliest studies evaluating the efficacy of immune system modulation in cancer demonstrated responses in advanced melanoma, lung cancer, colorectal cancer, bladder cancer, and renal cell carcinoma (RCC). The specific modulators that have been studied and used for therapy in advanced RCC include drugs involved in the pathways of IL-2, interferon alfa, cytotoxic T-lymphocyte antigen-4 (CTLA-4), and programmed cell death protein-1 (PD-1). This chapter will discuss the clinical use of agents that modulate the above pathways.

Interleukin-2

Interleukin-2 is a cytokine created by antigen-stimulated CD4 cells, CD8 cells, natural killers cells, and activated dendritic cells during the immune response. In early in vitro studies, this cytokine was found to be a potent stimulator of the immune system, facilitating and inducing various components of the immune

K. S. Faraj (✉) · M. D. Tyson · E. P. Castle
Department of Urology, Mayo Clinic, Phoenix, AZ, USA
e-mail: faraj.kassem@mayo.edu; Tyson.mark@mayo.edu; castle.erik@mayo.edu

T. H. Ho
Department of Hematology and Oncology, Mayo Clinic, Phoenix, AZ, USA
e-mail: ho.thai@mayo.edu

E. J. Trabulsi et al. (eds.), *Chemotherapy and Immunotherapy in Urologic Oncology*, https://doi.org/10.1007/978-3-030-52021-2_22

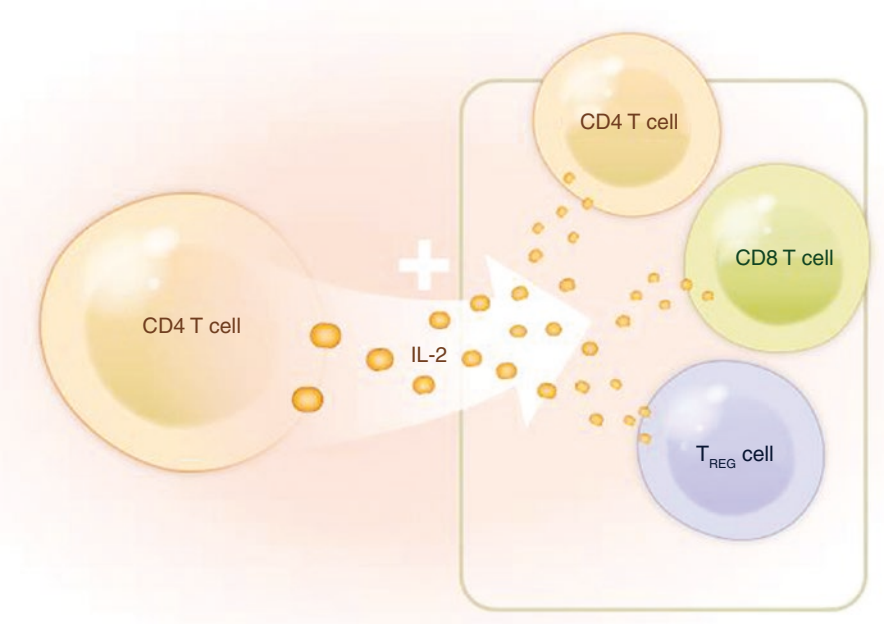

Fig. 22.1 Interleukin-2 release from CD4 cell permitting activation of various T cells

system (Fig. 22.1) [2]. Specifically, studies in mice found that administration of IL-2 permits the induction of T-helper cells, cytotoxic T cells, and antibody production [3].

One the earliest studies in humans that evaluated the effect of IL-2 on cancer was published by Lotze et al. This study involved ten patients with melanoma, colon cancer, and ovarian cancer. Patients were administered intravenously or intraperitoneally with high-dose IL-2 (30,000 U/kg) three times a day. Half of the melanoma patients exhibited an objective response that was sustained up to 6 months after conclusion of therapy. This study discussed that at the time of preparation of the manuscript, one patient with metastatic renal cell carcinoma (RCC) with pulmonary metastasis demonstrated a complete response with IL-2 [4]. One report by Rosenberg et al. in 1989 described the use of IL-2 in 652 cancer patients. IL-2 was administered alone or in conjunction with various adjunctive immunomodulators, cytokines, monoclonal antibodies, or chemotherapeutic agents [5]. The report revealed that objective regression was appreciated in 20–35% of patients and was durable. As a result of the encouraging potential effectiveness of this therapy, numerous trials at that time were performed [4, 6–9]. Metastatic RCC was one of the cancers that was found to be favorably responsive to this treatment.

A study in 1994 that enrolled 283 consecutive patients with both metastatic melanoma and RCC evaluated its efficacy in oncological outcomes. Seven percent of the RCC patients experienced complete regression, and 13% experienced partial regression [10]. At a 4-year update, the study reported a 19% overall response rate

and 9% complete response rate in the metastatic RCC patients. As result of the encouraging data, the US Food and Drug Administration (FDA) approved the use of high-dose IL-2 for patients with metastatic renal cell carcinoma. Further studies confirmed both the efficacy and durability of this treatment. One study that reviewed seven phase 2 clinical trials involved 255 patients with metastatic renal cell carcinoma and reported objective response rates of 15% of patients, with 7% complete responses and 8% partial responses. The responses were durable in many patients, as some experienced complete and partial responses for up to 80 and 131 months, respectively [11]. Although early studies suggested that administration of lymphokine-activated killer (LAK) cells with IL-2 facilitated tumor regression, this was found to be an ineffective adjunct to the IL-2 regimens in patients with metastatic RCC [6].

IL-2 was one of the first-line therapies for metastatic RCC for years but was not without its risks. Its use had been associated with significant toxicity and costs and its limitation to only be used at specialized centers. The toxicity of IL-2 was recognized in early studies, as Margolin et al. reported on toxicities in 93 patients who received high-dose IL-2 [12]. The most frequent toxicities observed were a capillary leak syndrome, which resulted in significant fluid shifts, hypotension, and vasopressor support. Nearly all patients experienced hepatic and kidney dysfunction. These adverse effects were found to be highly dose dependent and reversible after stopping treatment [7].

In an attempt to reduce the incidence and severity of adverse events, various therapy modifications were attempted. Reduced doses of IL-2 were studied in comparison to the standard high-dose regimen and were found to be less clinically active than the higher dose [13]. High-dose IL-2 was also compared to a combination of subcutaneous IL-2 with interferon in metastatic RCC, and the high-dose IL-2 was superior in regards to response rate. This study also suggested that patients with liver or bone metastasis may specially benefit from the high-dose regimen [14]. It was maintained as one of the first-line treatments for patients with metastatic RCC until recent years, when some of the less toxic, more efficacious therapies were described. Some of these therapies will be discussed later in this chapter.

Dose

The therapeutic dose and regimen of IL-2 varies in the literature. It has been found to be effective when used via an intravenous or subcutaneous route. The intravenous cycle typically consists of administration of a range of doses (7×10^4 to 18×10^6 U/kg). Various treatment regimens have been described using the intravenous route. One of the examples of an effective regimen described using an induction cycle of 18×10^6 IU/m^2 body surface area per day for 5 days for two courses, separated by at least 6 days. This is followed by a maintenance cycle consisting of one 5-day course of treatment. It was recommended that patients undergo two induction cycles and two maintenance cycles, with each cycle separated by 3 weeks

of no therapy [15]. Additional effective regimens have been described in the literature [9, 13, 16, 17].

The subcutaneous regimen also varies. Some have described daily treatments (Monday–Friday) for a given cycle, usually involving 250,000 U/kg/dose in the first week and then 125,000 U/kg/dose in subsequent weeks [13]. Another report that combined the subcutaneous route with interferon described using an initial dose of 5×10^6 every 8 hours for the first day, followed by daily treatments (Monday–Friday) for 4 weeks for each 6-week cycle [14].

Adverse Events

High-dose IL-2 is associated with many adverse events. Some are discussed above, but to summarize, patients can experience a range of adverse effects. Some of the low-grade complications include nausea, diarrhea, mild hematologic toxicities, elevation in liver enzymes, fevers, chills, fatigue, and rash. The high-grade complications can be related to a capillary leak syndrome that can result in significant vasodilation, severe fluid overload, and hypotension. Other side effects include confusion, depressed level of consciousness, renal dysfunction leading to oliguria, neurotoxicities, and cardiac toxicities. Patients can also experience severe infections due to neutrophil dysfunction [9, 16]. Patients commonly require intensive care unit admission and vasopressor support [16].

Interferon Alfa-2a

Interferon alfa-2a (IFN α2a) is a protein with immunomodulatory effects, including tumor regression. It is thought to increase the expression of HLA molecules, as well as facilitate activation of CD8 cells, which can have cytotoxic effects on tumor cells (Fig. 22.2) [18]. In some of the earliest reports, this drug was found to be effective as an antitumor agent in malignancies such as Kaposi's sarcoma, hairy cell leukemia, and cutaneous T-cell lymphoma [19]. As a result, it was eventually studied in metastatic RCC.

In a retrospective study by Quesada et al., 19 patients with metastatic RCC were given 3×10^6 units of daily IFN α2a or doses of 18×10^6 or 36×10^6 units twice weekly. Twenty-six percent of patients showed a partial response, 10.5% experienced an objective minor response, 16% of patients experienced mixed effects (i.e., progression in some sites and regression in other sites), 10.5% had disease stabilization, and 37% progressed [20]. In a prospective study that looked at various doses of IFN α2a in 159 patients with metastatic RCC, a 10% overall response rate was observed, and median overall survival was 11.4 months, with only 3% of patients

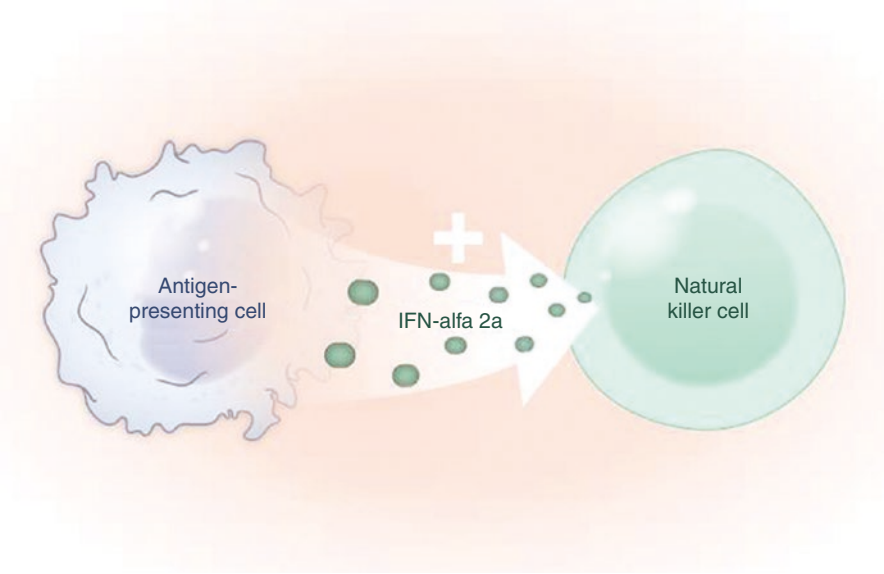

Fig. 22.2 IFN-alfa-2a release from antigen-presenting cells leading to activation of natural killer cell

being alive at 5 years or more [21]. A later randomized trial that looked at IL-2, IFN α2a, or both in patients with metastatic RCC revealed response rates of 6.5%, 7.5%, and 18.6% for the three groups, respectively. Event-free survival rates were 15%, 12%, and 20%, respectively. The combination group experienced a greater incidence of adverse events. Overall survival was similar in the three groups [15]. The overall median survival between the three groups was 12, 13, and 17 months, respectively. These differences were not statistically significant. Several other studies revealed similar survival benefit with interferon monotherapy [22, 23]. As a result of its efficacy, though limited in nature, it was considered one of the first-line therapeutic options in patients with metastatic RCC.

IFN α2a was commonly used until it was found to be inferior to some of the newer agents that were introduced for metastatic RCC around 10 years ago. In a multicenter, phase 3, randomized trial of 626 patients with previously untreated, poor prognostic metastatic RCC, patients were stratified to receive the mTOR (mammalian target of rapamycin) kinase inhibitor (temsirolimus), IFN α2a, or combination therapy. The patients who received temsirolimus alone had a significantly longer overall survival compared to the other two groups. Median overall survival times were 10.9, 7.3, and 8.4 months, respectively. Fewer patient experienced adverse events in the temsirolimus group than the interferon group. As newer agents such as mTOR inhibitors and checkpoint inhibitors became better understood and studied more, the use of both interferon and IL-2 significantly decreased due to decreased comparative efficacy and/or increased toxicity.

Dose

There are various doses and regimens that have been described for IFN α2a use in metastatic RCC. One of the regimens described for IFN α2a has been a subcutaneous route of 18×10^6 IU per day three times a week for 10 weeks as an induction treatment and then an additional 13 weeks as maintenance [15]. Another regimen includes subcutaneous injection of 5×10^6 IU of IFN α2a three times per week for 4 weeks as a 6-week cycle, with a maximum of six cycles [14]. The Medical Research Council Renal Cancer Collaborators described a regimen that consisted of a first week of IFN α2a with three treatments of 5, 5, and $\times 10^6$ IU, followed by three treatments per week of 10×10^6 IU, for a total of 12 weeks [23].

Adverse Events

Some of the side effects that have been described for interferon treatment include lack of appetite, anorexia, fatigue, nausea, dry mouth, shivering, heartburn, and hepatotoxicity [21, 23, 24].

Immunomodulators and Checkpoint Inhibitors

Mechanism and Biology

There are various factors that regulate T-cell homeostasis in the immune system. For a T cell to be activated, the T-cell receptor must bind the antigen of interest. This interaction alone is insufficient to activate a T cell. As a result, if only this interaction occurs, without an additional costimulatory stimulus, the T cells will become unresponsive (i.e., anergy) [25]. A second signal is required to permit T-cell activation (i.e., costimulation). This second signal typically involves the protein CD28, which is on the T cells. Upon stimulation by ligands on antigen-presenting cells (B7-1 or B7-2), activation of the T cell ensues [26]. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a protein that is a competitive inhibitor for B7-1/B7-2 that has a much greater affinity for these proteins than CD28. This protein functions as an inhibitor for T-cell activation [25, 26]. Consequently, increased activity of CTLA-4 can result in T-cell inhibition.

Another important pathway involves programmed cell death protein (PD-1) and the related ligand (PD-L1). PD-L1 is expressed by the various tumor cells and helps facilitate continued growth of the tumor cells by negatively regulating the immune system. When PD-L1 on tumor cells binds PD-1 on T cells, there is an inhibition of cytokine release and cytotoxic activity of antitumor T cells, permitting tumor growth [27]. Therapies involved in the above pathways (Table 22.1) will be discussed below in the form of CTLA-4 and PD-1 inhibitors.

Table 22.1 Key trials involving checkpoint inhibitors in metastatic renal cell carcinoma

Drug	Trial	Agents	Patients	PFS, mo	*P*	OS, mo	*P*	ORR (%)
PD-1 inhibitors								
Nivolumab	CheckMate 025	Nivolumab vs everolimus	821	4.6 vs 4.4	0.11	25.0 vs 19.6	0.002	25.0 vs 5.0
	CheckMate 214	Nivolumab + ipilimumab vs sunitinib	1096	11.6 vs 8.4	0.03	NR vs 26.0	<0.001	42.0 vs 27.0
	NCT03141177	Nivolumab + cabozantinib vs sunitinib (ongoing)	630	N/A	N/A	N/A	N/A	N/A
Pembrolizumab	KEYNOTE-427	Pembrolizumab	110	8.7	NR	NR	NR	33.6
	NCT02501096	Lenvatinib + pembrolizumab	30	13.8	NR	NR	NR	63.3
	NCT02133742	Pembrolizumab + axitinib	52	20.9	N/A	Not reached	N/A	73.0
	NCT02853331	Pembrolizumab + axitinib vs sunitinib (ongoing)	862	N/A	N/A	N/A	N/A	N/A
	NCT02811861	Pembrolizumab + lenvatinib vs Everolimus +lenvatinib vs sunitinib (ongoing)	1050	N/A	N/A	N/A	N/A	N/A
PD-L1 inhibitors								
Atezolizumab	IMmotion151[a]	Atezolizumab + bevacizumab vs sunitinib	915	11.2 vs 8.4	0.002	NR	NR	37.0 vs 33.0
Durvalumab	NCT03308396	Durvalumab + guadecitabine (ongoing)	58	N/A	N/A	N/A	N/A	N/A
Avelumab	JAVELIN Renal 101	Avelumab + axitinib vs sunitinib	888	13.8 vs 7.2	<0.001	NR	NR	55.2 vs 25.5
CTLA-4 inhibitors								
Ipilimumab	Yang et al	Ipilimumab 3 mg/kg followed by 1 mg/kg vs 3 mg/kg	21	NR	NR	NR	NR	4.8 vs 12.5 PR
	CheckMate 214 (see above)							
Tremelimumab	NCT00372853[b]	Dose escalation of tremelimumab + sunitinib	28	NR	N/A	NR	NA	43% PR

Abbreviations: *ORR* objective response rate, *PR* partial response, *OS* overall survival, *PFS* progression-free survival, *NR* not reported, *N/A* not applicable, *mo* months

[a]IMmotion151 primarily evaluated PFS in PD-L1+ patients. Secondary endpoints were PFS in ITT patient, ORR, and DOR. This table reports the results of the ITT analysis that included the entire cohort of the study

[b]NCT00372853 led to grade 3 or 4 adverse events in 61% of patients

Cytotoxic T-lymphocyte Antigen-4

One of the early reports that studied the antitumor effects of inhibiting CTLA-4 involved a study in mice that were injected with transfected tumor cells. These mice were then treated with anti-CTLA-4 or anti-CD28. Mice injected with anti-CTLA-4 exhibited inhibited tumor growth as compared with the anti-CD28-treated mice and the controls. The study concluded that removing inhibitory signals in the costimulatory pathway can enhance antitumor immunity (Fig. 22.3a and b) [28]. As a result of the encouraging preclinical studies, this therapy was investigated in clinical trials.

Ipilimumab is a CTLA-4 antibody that was found to be initially effective in achieving durable tumor regression in patients with melanoma [29]. Because RCC has previously been found to be immunoresponsive, a phase II trial was performed to evaluate the efficacy of ipilimumab in metastatic RCC. The trial consisted of 61 patients with metastatic RCC who were given two different regimens of ipilimumab. One group received 3 mg/kg for the first treatment followed by 1 mg/kg every 3 weeks, while the other received 3 mg/kg every 3 weeks. Partial responses were experienced 5/40 (12.5%) and 1/21 (4.8%) of the high- and low-dose groups, respectively [30]. The higher-dose cohort experienced a greater incidence of high-grade adverse reactions compared to the lower-dose group (42.5% vs 14%, respectively). Interestingly, in the aforementioned study, the incidence of autoimmune adverse events was associated positively with tumor regression. Despite the encouraging data related to tumor regression, the high adverse effect profile was concerning. As a result, the lower dose was used in trials as an adjunctive therapy option and will be discussed more in the section on PD-1 inhibition [31].

Dose

Two doses have been described for ipilimumab monotherapy in the use of metastatic RCC, 3 mg/kg and 1 mg/kg, as described in the previous section [30]. In modern studies, it is most effectively used as an adjunctive regimen. When used with nivolumab, it can be given at a dose of 1 mg/kg every 3 weeks for four doses during the induction regimen of therapy [32].

Toxicity

Some of the toxicities experienced by patients receiving ipilimumab therapy include autoimmune toxicity (enteritis, hypophysitis), adrenal insufficiency, gastrointestinal toxicity, colonic perforation, diarrhea, or aseptic meningitis [30].

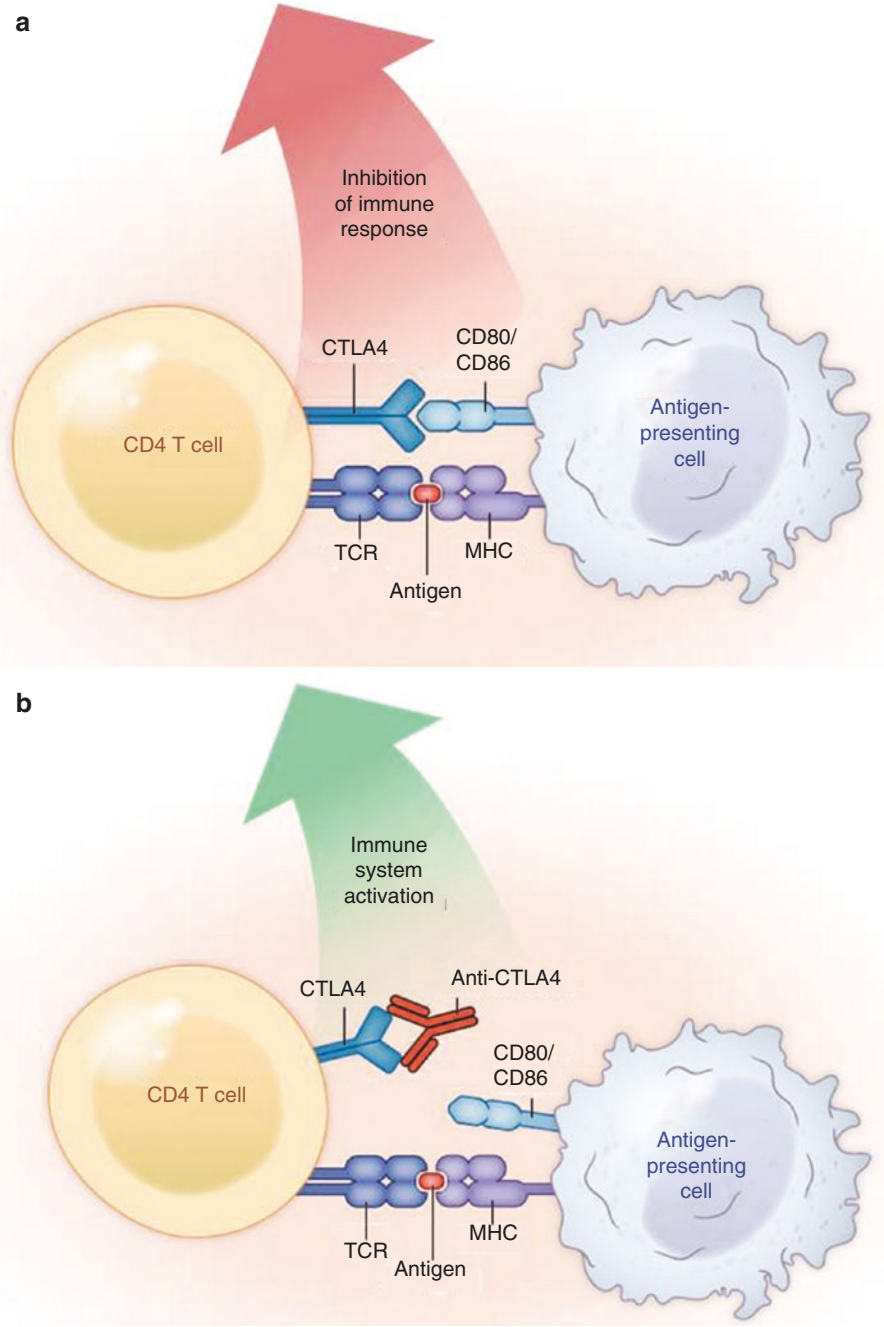

Fig. 22.3 (**a**) Binding of CTLA4 to CD80/CD86 leads to inhibition of immune response. (**b**) Binding of anti CTLA4 molecule to CTLA4 leads to activation of immune response

Programmed Cell Death Protein-1

An early study that evaluated the safety and activity of anti-PD-1 antibodies in patients with advanced malignancies was a phase 1 trial that included 296 patients with various malignancies, including metastatic RCC. Patients in each malignancy cohort were stratified into three groups that received different doses of the antibody (1, 3, 10 mg/kg). Fourteen percent of patients had grade 3 or higher adverse events. Metastatic RCC patients experienced a 27% response rate with therapy. Responses were durable, as about 65% of responses lasted in patients with greater than 1-year follow-up [33]. As a result, it was widely believed that blocking of the PD-1 receptor can help facilitate an immune response against tumor cells (Fig. 22.4a and b).

One of the most well-studied drugs in the class of PD-1 inhibitors is nivolumab. An early phase 2 trial revealed that this drug demonstrated antitumor activity in patients with metastatic RCC who were previously treated with agents targeting the vascular endothelial growth factor pathway. Three different doses were used (0.3, 2, 10 mg/kg) in a total of 168 patients. No dose-response relationship in progression-free survival (2.7, 4.0, 4.2 months), objective response rate (20%, 22%, 20%), overall survival (18.2, 25.5, 24.7 months), and adverse events (24%, 22%, 35%) was observed between the three groups [34]. Due to the encouraging antitumor activities of PD-1 inhibitors, they have been increasingly studied in the management of metastatic RCC.

In a randomized study of 821 patients, nivolumab was compared to everolimus, a mammalian target of rapamycin (mTOR) inhibitor in patients who were previously treated with antiangiogenic therapy. The median overall survival was 25 and 20 months, respectively. Nivolumab was also associated with a lower risk of death (HR 0.73) and a greater objective response rate (25% vs 5%), when compared to everolimus. High-grade adverse events were also less common in the nivolumab cohort (19% vs 37%) [35].

Another recent study was a phase 3 randomized trial that evaluated the efficacy of nivolumab plus ipilimumab versus sunitinib (vascular endothelial growth factor tyrosine kinase inhibitor) in 1096 patients with previously untreated metastatic RCC. The first group received nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) every 3 weeks for four doses (induction), followed by nivolumab monotherapy (3 mg/kg) every 2 weeks. The second group received sunitinib (50 mg) daily for 4 weeks for each cycle. In the intermediate- and poor-risk groups, as characterized by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), the overall survival at 18 months was 75% and 60% in the two groups, respectively. The objective response rate was 42% versus 27%, and complete response rate was 9% versus 1%. The nivolumab plus ipilimumab group experienced a 3.2-month longer progression-free survival than the sunitinib cohort. The overall adverse event rates were high in both groups (93% and 97%), with a grade 3 or 4 event occurring in 46% and 63% of patients, respectively [32].

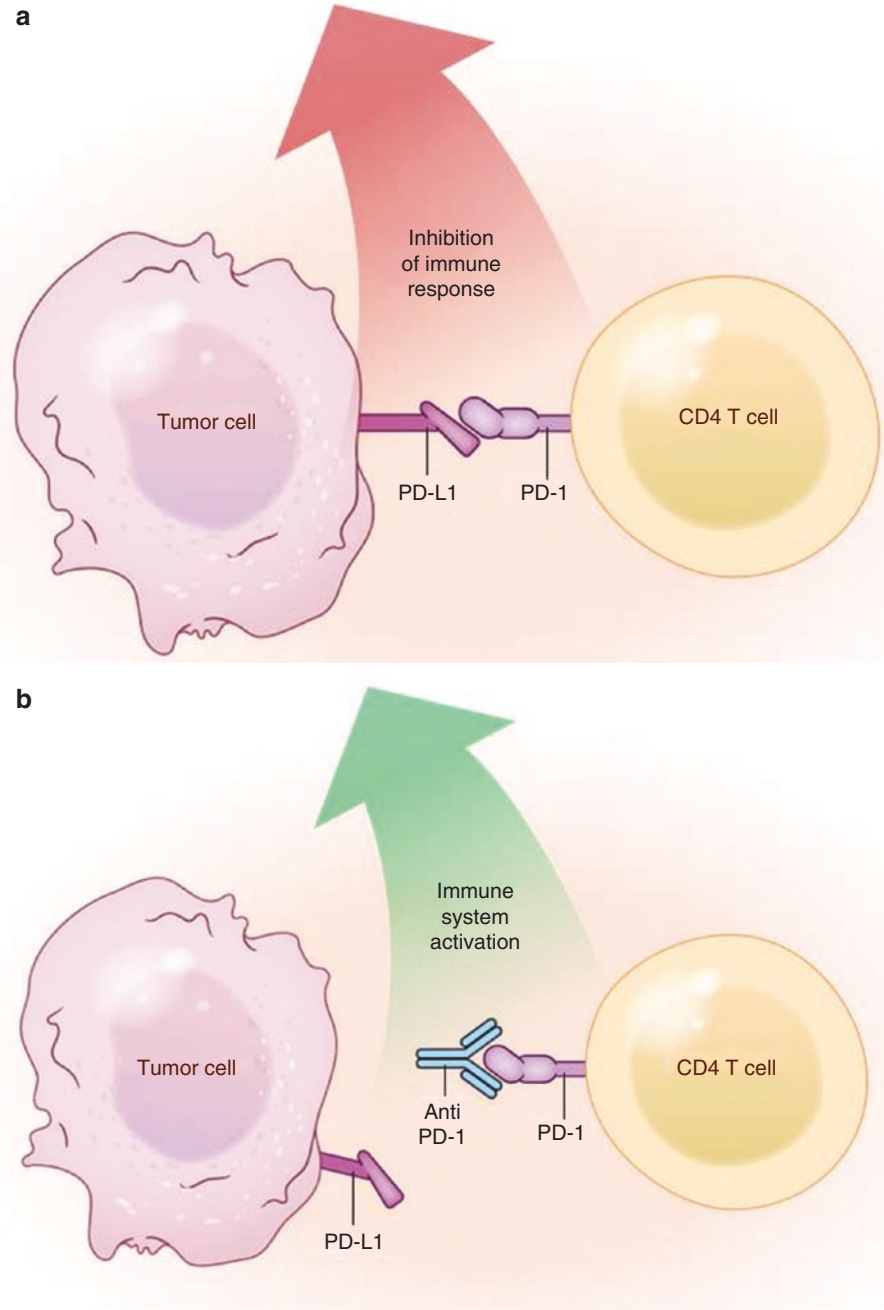

Fig. 22.4 (**a**) Binding of PD-1 and PD-L1 leads to inhibition of immune response. (**b**) Binding of anti PD-1 molecule to PD-1 leads to activation of immune response

An aspect that can be related to the PD-1 inhibitor therapy effectiveness is the extent of PD-L1 expression on tumor cells. Patients who have tumors that are PD-L1 negative may potentially have poor responses to anti PD-1 therapy [33]. When comparing tumors that have >1% vs <1% PD-L1 expression in patients undergoing anti-PD1 therapy, the former experiences significantly better objective response, progression-free survival, and overall survival compared with the latter. On the other hand, some studies have found that patients who are PD-L1 negative can still exhibit favorable responses from anti PD-1 therapy; thus PD-L1 expression may not adequately predict response to these agents [32].

Dose

The dose that has been described for nivolumab is 3 mg/kg, but the regimen has varied in described studies. When used as a monotherapy, a regimen of 3 mg/kg every 2 weeks for median treatment duration of 5.5 months was used in one study [35]. When used in conjunction with ipilimumab, nivolumab is given at a dose of 3 mg/kg every 3 weeks for four doses with ipilimumab (1 mg/kg), followed by monotherapy with nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks. Though CHECKMATE 214 described a maintenance dose of Nivolumab at 3mg/kg every 2 weeks, the flat dosage is approved by the FDA in this setting. Both dosages have demonstrated similar pharmacokinetic properties, with the flat dosage potentially providing a convenient option for patients and physicians.

Adverse Events

Some of the more common treatment adverse effects related to nivolumab include fatigue, pruritus, nausea, diarrhea, and decreased appetite. Patients can also experience rash, anemia, dyspnea, peripheral edema, mucosal inflammation, distortion of taste, stomatitis, hypertriglyceridemia, or epistaxis [35].

Conclusions

Immunomodulation is effective in managing patients with metastatic RCC. PD-1 in combination with CTLA-4 inhibitors should be considered as first-line therapies in these patients, particularly the patients classified as IMDC intermediate/poor risk. IL-2 and IFN α2a are historic options that are increasingly being replaced by checkpoint inhibitors. Additional studies with novel checkpoint inhibitors as well as novel regimens and combinations are needed to further increase the armamentarium for the treatment of patients with metastatic renal cell carcinoma.

Clinical Pearls

- Immunomodulation can be very effective in the metastatic renal cell cancer patient.
- Historically, IL-2 was used for metastatic renal cell cancer but is associated with significant toxicity, cost, and limitations.
- Interferon alfa-2a has been used for metastatic renal cell cancer but is viewed as inferior to some of the newer agents.
- PD-1 inhibitors and CTLA-4 inhibitors have shown improved outcomes and fewer adverse events in this patient population and should be considered as first-line treatments.

References

1. Rosenberg SA, Lotze MT, Muul LM, Leitman S, Chang AE, Ettinghausen SE, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. New Engl J Med. 1985;313(23):1485–92, Rosenberg SA. IL-2: The first effective immunotherapy for human cancer. J Immunol. 2014;192(12):5451–8.
2. Rosenberg SA, Grimm EA, McGrogan M, Doyle M, Kawasaki E, Koths K, et al. Biological activity of recombinant human interleukin-2 produced in Escherichia coli. Science. 1984;223(4643):1412–4.
3. Farrar WL, Johnson HM, Farrar JJ. Regulation of the production of immune interferon and cytotoxic T lymphocytes by interleukin 2. J Immunol. 1981;126(3):1120–5.
4. Lotze MT, Chang AE, Seipp CA, Simpson C, Vetto JT, Rosenberg SA. High-dose recombinant Interleukin-2 in the treatment of patients with disseminated cancer – responses, treatment-related morbidity, and histologic-findings. JAMA J Am Med Assoc. 1986;256(22):3117–24.
5. Rosenberg SA, Lotze MT, Yang JC, Aebersold PM, Linehan WM, Seipp CA, et al. Experience with the use of high-dose Interleukin-2 in the treatment of 652 cancer-patients. Ann Surg. 1989;210(4):474–85.
6. Rosenberg SA. Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer-cells for the treatment of patients with advanced cancer (Vol 85, Pg 622, 1993). J Natl Cancer Inst. 1993;85(13):1091.
7. Rosenberg SA, Lotze MT, Muul LM, Chang AE, Avis FP, Leitman S, et al. A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer-cells and interleukin-2 or high-dose interleukin-2 alone. New Engl J Med. 1987;316(15):889–97.
8. Law TM, Motzer RJ, Mazumdar M, Sell KW, Walther PJ, O'Connell M, et al. Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in the treatment of patients with advanced renal cell carcinoma. Cancer. 1995;76(5):824–32.
9. Klapper JA, Downey SG, Smith FO, Yang JC, Hughes MS, Kammula US, et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma – a retrospective analysis of response and survival in patients treated in the Surgery Branch at the National Cancer Institute between 1986 and 2006. Cancer. 2008;113(2):293–301.
10. Rosenberg SA, Yang JC, Topalian SL, Schwartzentruber DJ, Weber JS, Parkinson DR, et al. Treatment of 283 consecutive patients with metastatic melanoma or renal-cell cancer using high-dose bolus interleukin-2. JAMA J Am Med Assoc. 1994;271(12):907–13.

11. Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer J Sci Am. 2000;6:S55–S7.
12. Margolin KA, Rayner AA, Hawkins MJ, Atkins MB, Dutcher JP, Fisher RI, et al. Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors – analysis of toxicity and management guidelines. J Clin Oncol. 1989;7(4):486–98.
13. Yang JC, Sherry RM, Steinberg SM, Topalian SL, Schwartzentruber DJ, Hwu P, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol. 2003;21(16):3127–32.
14. McDermott DF, Regan MM, Clark JI, Flaherty LE, Weiss GR, Logan TF, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol. 2005;23(1):133–41.
15. Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. New Engl J Med. 1998;338(18):1272–8.
16. Allard CB, Gelpi-Hammerschmidt F, Harshman LC, Choueiri TK, Faiena I, Modi P, et al. Contemporary trends in high-dose interleukin-2 use for metastatic renal cell carcinoma in the United States. Urol Oncol. 2015;33(11):496 e11–6.
17. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol. 1995;13(3):688–96.
18. Hiroishi K, Tuting T, Lotze MT. IFN-alpha-expressing tumor cells enhance generation and promote survival of tumor-specific CTLs. J Immunol. 2000;164(2):567–72.
19. Krown SE, Real FX, Cunningham-Rundles S, Myskowski PL, Koziner B, Fein S, et al. Preliminary observations on the effect of recombinant leukocyte A interferon in homosexual men with Kaposi's sarcoma. N Engl J Med. 1983;308(18):1071–6, Golomb HM, Jacobs A, Fefer A, Ozer H, Thompson J, Portlock C, et al. Alpha-2 interferon therapy of hairy-cell leukemia: a multicenter study of 64 patients. J Clin Oncol. 1986;4(6):900–5, Foon KA, Sherwin SA, Abrams PG, Longo DL, Fer MF, Stevenson HC, et al. Treatment of advanced non-Hodgkin's lymphoma with recombinant leukocyte A interferon. N Engl J Med. 1984;311(18):1148–52.
20. Quesada JR, Swanson DA, Trindade A, Gutterman JU. Renal cell carcinoma: antitumor effects of leukocyte interferon. Cancer Res. 1983;43(2):940–7.
21. Minasian LM, Motzer RJ, Gluck L, Mazumdar M, Vlamis V, Krown SE. Interferon alfa-2a in advanced renal cell carcinoma: treatment results and survival in 159 patients with long-term follow-up. J Clin Oncol. 1993;11(7):1368–75.
22. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002;20(1):289–96, Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. New Engl J Med. 2001;345(23):1655–9.
23. Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Lancet. 1999;353(9146):14–7.
24. Quesada JR, Rios A, Swanson D, Trown P, Gutterman JU. Antitumor activity of recombinant-derived interferon alpha in metastatic renal cell carcinoma. J Clin Oncol. 1985;3(11):1522–8.
25. Chambers CA, Kuhns MS, Egen JG, Allison JP. CTLA-4-mediated inhibition in regulation of T cell responses: mechanisms and manipulation in tumor immunotherapy. Annu Rev Immunol. 2001;19:565–94.
26. Wolchok JD, Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist. 2008;13(Suppl 4):2–9.
27. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med. 2017;376(4):354–66.
28. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science. 1996;271(5256):1734–6.

29. Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci U S A. 2003;100(14):8372–7.
30. Yang JC, Hughes M, Kammula U, Royal R, Sherry RM, Topalian SL, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother. 2007;30(8):825–30.
31. Hammers HJ, Plimack ER, Infante JR, Rini BI, McDermott DF, Lewis LD, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. J Clin Oncol. 2017;35(34):3851–8.
32. Motzer RJ, Tannir NM, McDermott DF, Frontera OA, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. New Engl J Med. 2018;378(14):1277–90.
33. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. New Engl J Med. 2012;366(26):2443–54.
34. Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. J Clin Oncol. 2015;33(13):1430–7.
35. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. New Engl J Med. 2015;373(19):1803–13.