Molecular Pathways: Immune Checkpoint Antibodies and their Toxicities
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Abstract

The emergence of immune checkpoint inhibitors for solid tumor treatments represents a major oncologic advance. Since the approval of ipilimumab, a cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) antibody, for the treatment of metastatic melanoma, many drugs, especially those targeting PD-1/PD-L1, have demonstrated promising antitumor effects in many types of cancer. By reactivating the immune system, these immunotherapies have led to the development of new toxicity profiles, also called immune-related adverse events (irAE). IrAEs can involve many organ systems, and their management is radically different from that of cytotoxic drugs; irAEs require immunosuppressive treatments, such as corticoids or TNFα antibody. In addition, the occurrence of irAEs has raised significant questions. Here, we summarize progress that has been made toward answering these questions, focusing on (i) the impact of immunotherapy dose on irAE occurrence, (ii) the correlation between irAE and patient outcome, (iii) the safety of immune checkpoint inhibitors in patients already treated for autoimmune disease, and (iv) the suspected effect on tumor growth of steroids used for the management of irAEs. Clin Cancer Res; 22(18): 4550–5. © 2016 AACR.

Background
Immunotherapies soaring
Immunotherapy has recently led to a paradigm shift in cancer treatment, in which the main target is the immune system instead of the cancer cells. Indeed, cancer cells are known to bypass host immunosurveillance (i.e., the ability of the immune system to recognize and destroy cancer cells), leading to tumor growth (1). One mechanism by which cancer cells escape the immune system is by overexpressing immunosuppressive surface ligands that interact with T-cell molecules, such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) or programmed cell death protein (PD-1), leading to T-cell exhaustion (Fig. 1; ref. 2). This knowledge led to the development of immune checkpoint inhibitors, which can antagonize these immune inhibitory pathways. The anti–CTLA-4 monoclonal antibody ipilimumab was an early inhibitor to appear in this area and has been approved for the treatment of metastatic melanoma (3). Since then, many new agents, especially those targeting the PD-1/programmed cell death ligand 1 (PD-1/PD-L1) complex, such as the anti–PD-1 antibodies pembrolizumab and nivolumab, or the PD-L1 antibodies atezolizumab and durvalumab, have demonstrated promising effects in many different tumor types (4–10). In addition, pembrolizumab and nivolumab have recently been approved for the treatment of metastatic melanoma and non–small cell lung cancer (NSCLC) patients. Another escape mechanism involves tumor-associated macrophages (TAM; Fig. 1) and the colony-stimulating factor-1 receptor (CSF-1R). CSF-1R is a tyrosine kinase receptor involved in the differentiation and survival of macrophages and their precursors. TAMs can suppress antitumor immunity and have been associated with poorer patient outcomes (11). On the basis of these data, CSF-1R antibodies are under clinical development (12). By reactivating the IS, these immunomodulatory antibodies have led to the emergence of unusual autoimmune toxicities, also called immune-related adverse events (irAE; ref. 13). IrAEs management is challenging because they may concern many organ systems, including the skin, hepatic, gastrointestinal, endocrine, and pulmonary systems (14). As irAEs often require steroid treatments, which are thought to affect antitumor treatment efficacy, physicians require training to manage these irAEs and achieve the best patient care.

General safety profiles
IrAEs affect generally the tracts involved in common autoimmune diseases. They are here reported according to the NCI-CTCAE version 4.0. Anti–CTLA-4 antibodies mostly affect the skin and the gastrointestinal tract, as observed in 44% and 35% of cases, respectively, whereas the endocrine (6%) and hepatic (5%) systems are rarely affected (15). Skin adverse events (AE) are usually the first to appear (e.g., after 3 weeks), whereas gastrointestinal AEs can be expected at approximately 5 to 10 weeks, and liver AEs and hypophysitis appear later. Unlike endocrine events, most AEs can be reversed within a few weeks (16). Although AEs are frequent, they are usually low grade; low-grade AEs were observed in 85% of patients treated with ipilimumab for metastatic melanoma, but grade 3 to 4 AEs were observed in 24% of patients, mainly in the gastrointestinal tract (11%; ref. 15). The most common skin AEs are popular rashes associated with pruritus (skin itching), whereas alopecia (hair loss) and vitiligo (skin hypopigmentation) are rarely described. Being reported in 13% of clinical trials, hypophysitis is the most frequent endocrine AE. Hypo- or hyperthyroidism are
very uncommon (<6%). Colitis, indicated by diarrhea, abdominal pain and rectal bleeding, is the main gastrointestinal AE and the most severe irAE associated with anti–CTLA-4 (15). Although rare, cases of fatal bowel perforation have been described (<0.5%; ref. 17). Finally, the death rate due to CTLA-4 antibodies (ipilimumab or tremelimumab) is less than 1% (11/1,265 patients; ref.15). Few data exist about long-term toxicities related to ipilimumab. Most of the chronic side effects concern endocrine toxicities with the need of long-term hormone replacement. Chronic neurologic complications raise questions about the role of whole-brain radiotherapy in patients treated with ipilimumab (18).

The AE profiles of PD-1 or PD-L1 antibodies are very similar; however, the side effects of PD-1 and PD-L1 antibodies are less frequent and less severe than those of CTLA-4 antibodies. The main AE is asthenia (16%–34%), followed by decreased appetite (5%–19%), rash (16%), diarrhea (14%), and nausea (15%), which are mainly low grade. High-grade AEs occur in only 7% to 12% of patients (7, 19–23). Interestingly, those AEs considered irAEs are very uncommon and arise later; these include hypothyroidism (8%), hyperthyroidism (5%), and pneumonitis (4%), and very rarely, colitis or hepatitis. Deaths related to the treatment rate accounted for less than 1%, mostly due to pneumonitis (7, 19–22).

The AE profile of CSF-1R inhibitors is well characterized. Whether the disease is benign (e.g., pigmented villonodular synovitis) or malignant (e.g., solid tumors), asthenia affects 56% to 70% of patients; facial edema, pruritus, rash, and peripheral edema affect 64%, 56%, 40%, and up to 44% of patients, respectively (24, 25). Interestingly, autoimmune disorders such as lupus have been described with such agents but only in patients with a benign condition (pigmented villonodular synovitis) suggesting a role of the patient’s immune status in their occurrence (24).

Rare adverse events

As immune checkpoint inhibitors have recently entered clinical practice, they are thought to be involved in many rare AEs, the most relevant of which are briefly described here.

Several neurologic events have been observed in patients treated with ipilimumab, including Guillain-Barré syndrome, encephalopathy, aseptic meningitis, myasthenia (characterized by muscle weakness), and myopathy. Three deaths due to neurologic AEs have been linked to ipilimumab (26–30). Other rare side effects are mostly controlled with appropriate steroid-based treatments. Several hematologic side effects have also been attributed to ipilimumab, including one case each of neutropenia, thrombopenia, red cell aplasia, and hemophilia A.
Hypertension was more frequent with (N patients had at least one AE, irrespective of the treatment. Most rare AEs due to PD-1/PD-L1 antibodies are manageable with dedicated treatment. One death was attributable to multifocal central nervous system demyelination occurring under nivolumab treatment (39). Two case reports have described nivolumab involvement in myasthenia occurring in melanoma patients: In one case, nivolumab was associated with ipilimumab treatment; in the other case, both myasthenia and rhadomyolysis occurred when nivolumab was used alone (40, 41). In addition, one case of myositis occurred during nivolumab treatment, and the main symptom was respiratory discomfort (42). Regarding skin AEs, nivolumab treatment has been associated with several cases of psoriasis exacerbation, all occurring in patients with melanoma (43, 44). Lichenoid dermatitis occurred in 3 patients treated with pembrolizumab for melanoma (45). Pembrolizumab has also been associated with one case of acute autoimmune myocarditis. Fortunately, the symptoms rapidly improved after appropriate corticosteroid and heart-failure treatments (46). Cases of pancreatitis, retinal vasculitis, fasciitis, and arthritis have also been attributed to pembrolizumab treatment (47–50). Recently, 3 cases of sarcoidosis in sarcoma patients receiving pembrolizumab treatment have been described (51).

Similar cases were previously reported in melanoma patients treated with ipilimumab, Shahabi and colleagues (57) found that the neutrophil-activation markers CD177 and CEACAM1 were associated with gastrointestinal irAE occurrence. These data suggest a possible role of neutrophils in ipilimumab-associated gastrointestinal irAEs.

There are no data about the potential dose effects of PD-1/PD-L1 antibodies on toxicity. Only one study has suggested that there are no AE profile differences between NSCLC patients treated with different doses of pembrolizumab, i.e., 10 mg/kg every 2 or 3 weeks (58).

**Correlation between irAE occurrence and outcome**

Data are inconsistent about the impact of irAE occurrence on the outcomes of melanoma patients treated with ipilimumab. In 56 patients treated with both ipilimumab and gp100 melanoma-associated antigen, Attia and colleagues (59) showed a significant improvement in the overall response rate (ORR) of patients who experienced high-grade irAEs, at 36% versus 5% (P = 0.008). Some case series have brought better ORRs in renal cell carcinoma patients treated with anti-pd-1 antibodies. Vitiligo has been described in 11% of melanoma patients treated with pembrolizumab (63). Interestingly, this AE has recently been associated with favorable outcomes. In 67 melanoma patients treated with pembrolizumab, 17 patients (25%) developed vitiligo, and the ORRs were 71% and 28% in patients with and without vitiligo, respectively (64). Another study evaluated the incidence of skin AEs and outcome. Eighty-three patients were treated for lung cancer, melanoma, or prostate cancer with different schedules of pembrolizumab (10 mg/kg every 3 weeks; 10 mg/kg every 2 weeks; 2 mg/kg/3 per week). Thirty-five (42%) developed cutaneous irAEs, with the most frequent being maculopapular eruption, pruritus, and hypopigmentation. Regardless of pembrolizumab notransferase. Other combinations are currently being evaluated, including bevacizumab ± MPDL3280A (NCT019384242), pazopanib + pembrolizumab (NCT02014636), and axitinib + pembrolizumab (NCT02133742; ref. 56).

**Clinical-Translational Advances**

**A dose effect?**

As several irAEs occur after long delays, determining the most effective immunotherapy dose associated with the least toxicity is challenging.

Three studies have examined irAE occurrence versus ipilimumab dose. When comparing 10 mg/kg to 3 mg/kg, the risk ratios of global irAE incidence were not different [RR, 1.16; 95% confidence interval (CI) 0.97–1.38]. The difference was only statistically significant for high-grade (i.e., grade 3–4) irAEs (RR, 3.1; 95% CI, 1.59–6.03), which affect mostly the gastrointestinal tract (15). Using whole-blood gene-expression profiling in melanoma patients treated with ipilimumab, Shahabi and colleagues found that the neutrophil-activation markers CD177 and CEACAM1 were associated with gastrointestinal irAE occurrence. These data suggest a possible role of neutrophils in ipilimumab-associated gastrointestinal irAEs.

**Combination toxicities: immune checkpoint inhibitors with or without tyrosine kinase inhibitors**

The combination of ipilimumab and nivolumab was recently approved for treating advanced or metastatic melanoma (21). Compared with monotherapies, combination treatments [nivolumab, 1 mg/kg, plus ipilimumab, 3 mg/kg every 3 weeks for 4 doses] needed to be discontinued more frequently, with rates of 36.4% versus 14.8% and 7.7% for ipilimumab and nivolumab combined and for each drug individually, respectively. Discontinuation was mostly due to diarrhea and colitis. Grade 3–4 side effects were more frequent than in monotherapy arms [nivolumab, 3 mg/kg every 2 weeks, or ipilimumab, 3 mg/kg every 3 weeks]: 55% versus 16.3% and 27.3% respectively. No deaths were related to the combination. On the contrary, in NSCLC patients, the association of nivolumab, 3 mg/kg, plus ipilimumab, 3 mg/kg, was responsible for 2 deaths: One was due to myasthenia gravis and one due to renal failure. In the group, nivolumab, 3 mg/mg, plus ipilimumab, 1 mg/mg, every 3 weeks, one death was due to pneumonitis related to the treatment (55).

Immune checkpoint and tyrosine kinase inhibitor combinations are now being tested. Combinations of nivolumab plus sunitinib (N+S) or pazopanib (N+P) were evaluated in patients with metastatic renal cell carcinoma. One hundred percent of patients had at least one AE, irrespective of the treatment. Hypertension was more frequent with (N+S) than with (N+P), at rates of 48% and 25%, respectively. Similar results were observed for treatment discontinuation, at 36.4% and 25%, respectively, mostly due to increased alanine or aspartate aminotransferase. Other combinations are currently being evaluated, including bevacizumab ± MPDL3280A (NCT019384242), pazopanib + pembrolizumab (NCT02014636), and axitinib + pembrolizumab (NCT02133742; ref. 56).
schedule, time to progression was significantly better in patients who experienced skin irAEs than in those who did not (65). Similarly, in patients (n = 112) treated with nivolumab for advanced or metastatic melanoma, vitiligo and rash were associated with a significant improvement in OS: HR, 0.22; 95% CI, 0.03–0.81 and HR, 0.45; 95% CI, 0.25–0.77, respectively (66). Taken together, these data suggest a predictive role of skin irAE occurrence in patients receiving a PD-1 inhibitor.

Is it dangerous to treat patients having underlying autoimmune disease or chronic immunosuppression with immune checkpoint inhibitors?

By antagonizing immune inhibitory pathways, immune checkpoint inhibitor treatments were thought to potentially worsen autoimmune disease. A report on the largest group of patients with autoimmune disease who underwent ipilimumab treatment for metastatic melanoma was recently published (67). The autoimmune diseases included rheumatoid arthritis, psoriasis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, and autoimmune thyroiditis. Of the 30 patients, 50% experienced neither an irAE nor autoimmune disease exacerbation. Twenty-seven percent experienced autoimmune disease exacerbation, and 33% experienced high-grade irAEs. One death was associated with immune-related colitis. Few case reports have contributed other data; ipilimumab treatment appeared to be safe, especially in 2 kidney transplant patients, and only one patient with ulcerative colitis experienced autoimmune disease exacerbation during ipilimumab treatment (68–70).

No data are currently available about the effects of pembrolizumab treatment in patients with autoimmune disease. Two case reports have described the safety profile of pembrolizumab in patients with HCV alone or with HCV/HIV coinfection (71). Few data have shown thyroiditis aggravation in patients treated with nivolumab (72). Recently, a case report highlighted renal allograft rejection after 2 months of pembrolizumab treatment in a patient treated for metastatic cutaneous squamous cell carcinoma (73).

Of note, most of the patients in these cases were, at the time of the checkpoint inhibitor treatment, actively treated for their autoimmune or viral disease (by corticoid or immunosuppressive agents such as tacrolimus, mycophenolate, or antiviral therapies). The paucity of these data supports the necessity of additional investigations of checkpoint inhibitors in patients with immunodeficiencies or autoimmune disease. Currently, immune checkpoint inhibitors should be used with caution in these patients.

Does corticosteroid use really decrease the efficacy of immune checkpoint inhibitors?

Although steroids are thought to potentially reverse the antitumor effects of immunotherapies via their immunosuppressive effect, no data support this idea. In a pooled analysis of 139 metastatic melanoma patients treated with CTLA-4 blockade in a phase II trial, irAE management via high-dose steroids did not affect ORR (74). Of 298 melanoma patients treated with ipilimumab included in a study by Yang and colleagues, 103 patients (35%) required systemic corticosteroid (mostly 1 week or longer) treatments for irAEs. Twenty-nine (10%) patients required anti-TNFα therapy. No differences in OS and TTF were found (60) between patients who did and did not receive steroids. The impact of anti-TNFα on outcomes was not evaluable in this study with regard to the few patients who received this treatment. However, recent data have shown no worse outcomes in patients with diarrhea related to ipilimumab treated with infliximab (n = 7) compared with the other drug (n = 12; ref. 75). Similar results concerning the use of steroids were documented in two case reports of severe irAEs in melanoma treated with ipilimumab; corticosteroid treatments did not affect outcomes (76). No data are available about PD-1/PD-L1 or CSF-1R inhibitors in this context. However, regarding the effect of checkpoint inhibitors on the immune system, corticosteroids and other immunosuppressive treatments clearly need to be used according to their recommendations to treat irAEs (77). Guidelines recommend a short course of oral or i.v. steroids, at a dose of 1 to 4 mg/kg, associated with oral antihistamines in the presence of pruritus, with a rapid indication for treatment with infliximab or other immunosuppressive therapies if there is no improvement after 48 to 72 hours or if symptoms worsen (78).

Conclusions

Immune checkpoint inhibition is typically associated with transient irAEs, the majority of which resolve within a few weeks, excluding endocrine side effects. The rapid identification of these irAEs and the initiation of systemic immunosuppression can improve patients’ outcomes without compromising antitumor treatment efficacy. The development and implementation of immune checkpoint inhibitors, along with the presence of delayed toxicities, have raised questions and altered conventional anticancer drug development; these treatments have more of an on/off effect (79) than a dose effect, and no MTD has been defined. There is no rationale for dose repetition (58), and the optimal treatment duration is unknown because long responders have been observed, raising the question of whether to stop treatment or administer maintenance treatments (80). More important than an MTD is, the challenge for these new immunotherapies to identify minimum active doses, thereby achieving better tumor control and minimizing irAEs for optimal patient care, especially now with the arrival of the checkpoint inhibitors in earlier settings than metastatic disease (81).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: A. Italiano
Development of methodology: S. Cousin, A. Italiano
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Italiano
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Cousin, A. Italiano
Writing, review, and/or revision of the manuscript: S. Cousin, A. Italiano
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Italiano
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