Ipilimumab for the treatment of melanoma

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Practice points

- Ipilimumab is an anticytotoxic T-lymphocyte-associated antigen 4 monoclonal antibody approved by the EMA and the US FDA in 2011 for the treatment of unresectable or metastatic melanoma.
- It was the first therapy approved for metastatic or unresectable melanoma based on an improvement in overall survival.
- Ipilimumab is administered intravenously every 3 weeks for four doses total.
- Because of ipilimumab's mechanism of action, a significant concern can be the development of immune-mediated adverse reactions and patients should be monitored closely so any potential immune-related adverse effects are diagnosed and treated early. Some patients may require steroid therapy.

SUMMARY Melanoma is the sixth most common cancer in the US. Metastatic melanoma has increased in incidence over the past 30 years. In the US approximately 8600 people died from melanoma in 2009. It is an aggressive tumor; the prognosis of stage IV is poor. Before 2011, only dacarbazine and IL-2 were approved for metastatic melanoma. Major advances have been made in understanding the genetic profile, molecular factors that drive malignant transformation and the role of T cells in melanoma patients. Immune regulatory pathways affecting immune responses to cancer are becoming better defined. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) downregulates the pathways of T-cell activation. Ipilimumab is an anti CTLA-4 monoclonal antibody approved in 2011 to treat metastatic or unresectable melanoma.

Background

The incidence of metastatic melanoma is on the rise, and melanoma is currently the sixth most common malignancy in the US. Metastatic melanoma has been described as one of the most aggressive forms of human malignancy. Untreated, the median survival time is less than 1 year, with an estimated 5-year survival rate for stage IV of less than 15%. Despite accounting for less than 5% of skin cancer cases, melanoma accounts for almost 80% of skin cancer deaths [1]. It was estimated by the American Cancer Society that in 2014 approximately 76,100 new cases of melanoma would be diagnosed and approximately 9710 individuals would die of the disease [2]. Prior to 2011, the only drugs approved for metastatic melanoma were high-dose IL-2 and dacarbazine. The US FDA approved dacarbazine in 1975. Twenty-three years later, the approval of IL-2 was a significant breakthrough in cancer care in that it was proof that an agent targeting the immune system could lead to a significant response. IL-2 was the first treatment shown to improve the overall outcome in some metastatic melanoma patients. Response rates ranged from 10 to 20% with approximately 4–6% of patients obtaining a durable complete

KEYWORDS

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remission (CR) [3–5]. These results were the foundation for its approval by the FDA in 1998. Since then, major advances have been made in understanding the genetic profiles of melanoma cells, the molecular factors that drive malignant transformation and the role of T cells in patients with melanoma. These advances led to the approval in 2011 of ipilimumab (Yervoy™), a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody. The targeted agent vemurafenib, a BRAF inhibitor, was also approved in 2011. Both ipilimumab and vemurafenib have been shown in Phase III trials of patients with metastatic melanoma to improve survival [6–8]. In 2013, the number of options for the treatment of metastatic or unresectable melanoma increased again with the approval of the targeted agent dabrafenib for patients harboring the *BRAF* V600E mutation, as well as the approval of the MEK inhibitor trametinib.

Indications & usage

The FDA approved ipilimumab in March 2011 in an intravenous form for the treatment of metastatic or unresectable melanoma.

Dosage & administration

The standard dose of ipilimumab is 3 mg/kg intravenously (iv.) every 3 weeks for a total of four doses. It should be infused intravenously over 90 min.

Clinical pharmacology

Ipilimumab is an IgG1 kappa immunoglobulin produced in mammalian (Chinese hamster ovary) cell culture and has an approximate molecular weight of 148 kDA.

• Mechanism of action

Ipilimumab is a recombinant, human monoclonal antibody that binds to the CTLA-4. CTLA-4 is a critical negative checkpoint molecule that controls the activation and proliferation of T cells. In order to understand ipilimumab's mechanism of action, it is important to first understand the mechanism of T-cell activation. In order for T-cell activation and proliferation to occur, two signals are required. The first signal occurs when the T-cell receptor binds to its associated antigen that is presented on an MHC-I molecule on an antigen-presenting cell. Activation and proliferation can only occur after CD28 on the cell simultaneously binds with its costimulatory B7 (CD80/CD86) receptor family member on

the antigen-presenting cell, which results in the second signal. After both of these interactions are complete, CTLA-4 is upregulated, which will then produce an inhibitory signal and thus regulate T-cell activation. It completes this in two ways. First, it binds to the costimulatory B7 family members with a greater avidity than CD28. It also generates a negative signal to the activated T cell, which then inhibits activation and proliferation. Thus once CTLA-4 is bound to its costimulatory molecule, it acts as an inhibitory checkpoint receptor that blocks T-cell activation, preventing further immune activation. By doing so, in a normal immune system, CTLA-4's function is to regulate the balance between immune activation and tolerance as well as preventing uncontrolled T-cell activation and autoimmunity. However, in patients with melanoma, the early inactivation of T-cell function by CTLA-4 may also hinder the ability for the immune system to properly complete its function of tumor clearance. Thus ipilimumab was developed to specifically block the interaction of CTLA-4 with its ligands, allowing CD28 to bind to more costimulatory B7 receptor family members, thus stopping the intrinsic suppression of T cells. This potentiates the antitumor T-cell response by blocking the CTLA-4 inhibitory blockade of T-cell activation and proliferation and results in an augmented T-cell response. Ipilimumab's effect is indirect, most likely through T-cell mediated antitumor immune responses [9].

• Pharmacokinetics

The terminal half-life of ipilimumab has been determined to be 15.4 days. The clearance of ipilimumab has been found to increase with body weight; however, no dose adjustment is recommended for body weight after administration on an mg/kg basis. Age, performance status, gender, mild hepatic impairment (total bilirubin 1.0× to 1.5× upper limit of normal – ULN – or AST greater than ULN as defined using NCI criteria), renal impairment, previous cancer therapy and baseline lactate dehydrogenase levels had no clinically important effect on the clearance of ipilimumab. Ipilimumab has not been studied in patients with moderate or severe hepatic impairment [10].

Clinical evidence

• Overview of clinical trials

Ipilimumab was initially approved based on a Phase III randomized (3:1:1) double-blind

double-dummy clinical trial (MDX010-20) in patients with a diagnosis of metastatic or unresectable melanoma. These patients had received at least one prior systemic therapy. The trial's primary end point was overall survival (OS). Best overall response rate and progression-free survival (PFS) were also assessed. Six hundred and seventy six patients with *HLA-A2*0201* positive genotype were enrolled. This genotype facilitated the immune presentation of the investigational tumor peptide vaccine. Patients were randomly assigned to receive either the tumor vaccine with ipilimumab at a dose of 3 mg/kg iv. (n = 403), or vaccine placebo with ipilimumab (n = 137), or placebo with tumor vaccine (n = 136). Patients receiving systemic immunosuppression for organ transplantation, or those with active autoimmune disease were excluded. The results showed that patients receiving ipilimumab alone had a longer OS when compared with tumor vaccine with a median OS of 10.1 months in the ipilimumab-alone group versus 6.4 months in the gp100 vaccine group (p = 0.0026). The rates of OS in the ipilimumab-alone group and the gp100 group respectively were 45.6 and 25.3% at 1 year and 23.5 and 13.7% at 2 years. There was also an improvement in OS for patients treated with the combination of tumor vaccine plus ipilimumab when compared with patients treated with vaccine alone that was found to be statistically significant (p = 0.0004). Patients treated with ipilimumab had an overall response rate of 10.9%, which was better than the overall response rate seen in the ipilimumab plus vaccine group, 5.7%, and the vaccine alone group with a rate of 1.5%. When compared with the gp100-alone group, the risk of death for patients who received ipilimumab plus vaccine and those who received ipilimumab alone was reduced by 32% (p < 0.001) and 34% (p = 0.003), respectively. In each treatment group, over 95% of patients developed at least one adverse event (AE) during the trial. When compared with the vaccine groups the incidence of grade 3 or 4 drug-related AEs was higher in the two ipilimumab groups. Tissue-specific inflammation was the most common immune-related AE, and the majority were dermatological and gastrointestinal. Deaths associated with immune-related AEs were reported at 1.3% in the combination group, 1.5% in the ipilimumab-alone group and 0% in the gp100 treatment group. This was the first agent approved in 13 years for melanoma, and the first ever approved based on a positive impact on OS [7].

A subsequent randomized control trial published in 2011 looked at 502 previously untreated stage IIIC or stage IV melanoma patients. The primary end point was OS. These patients received ipilimumab at a dose of 10 mg/kg with dacarbazine versus dacarbazine plus placebo. This study also showed a significantly prolonged OS in the ipilimumab group of 11.2 versus 9.1 months (p < 0.001), a better 1-year survival of 47.3% versus 36.3% and a 28% reduction in the risk of death. They also found that the survival effect persisted with prolonged 3-year survival (20.8% versus 12.2%) with a hazard ratio for death of 0.7 (p < 0.01). The durability of the response was also higher in the ipilimumab plus dacarbazine group (19.3 months) when compared with the dacarbazine group (8.1 months). The overall AE rates were similar in both groups, although the rate of grade 3 or 4 AEs and grade 3 or 4 immune-related AEs was higher in the ipilimumab plus dacarbazine group. There were no deaths reported in the combination group, and one death in the dacarbazine-alone group due to gastrointestinal (GI) hemorrhage [8].

Various studies have shown objective tumor response rates range from 10 to 15% in those who receive ipilimumab [7]. The reduction in the likelihood of death when compared with dacarbazine or gp100 vaccine has been found to be 34 and 28%, respectively [7,11].

Newer agents, such as the anti-PD-1 receptor monoclonal antibody nivolumab, have been found to produce durable, objective responses in patients with melanoma, and it is thought these anti-PD-1 receptor agents will work in synthesis with ipilimumab. Preclinical data suggest that CTLA-4 and PD-1 may have complementary roles in regulating adaptive immunity. CTLA-4 and PD-1 are both inhibitory immunologic checkpoints and PD-1 blockade has been found to upregulate CTLA-4 expression, and CTLA-4 blockade upregulates PD-1 expression on tumor-infiltrating cells [12,13]. In a Phase I study, 86 patients with advanced melanoma who had received three or less prior therapies were found to have objective response rates higher than published monotherapy values when they received concurrent nivolumab and ipilimumab. The nature of the response was rapid and deep, with regression at the time of first imaging >80% reduction of tumor burden in most responding patients. All of the patients who had a response achieved a deep or complete response [14]. More long-term follow-up and Phase III trials are

needed, but these initial results are encouraging for the future direction of combination immunotherapy in the treatment of a very aggressive and often fatal disease.

No formal prospective data exist presently for the efficacy of ipilimumab in metastatic melanoma of the uvea; however, one multicenter retrospective analysis of 39 patients at four hospitals in the US and Europe of patients with uveal melanoma did show similar responses as those observed in cutaneous melanoma with manageable toxicities [15].

• Adverse reactions

The most common adverse reactions (>5%) include fatigue, diarrhea, pruritis, rash and colitis. Because of ipilimumab's mechanism of action, immune-mediated adverse reactions can become a significant concern and patients should be monitored closely so any potential immune-related AEs are diagnosed and treated early. Guidelines to manage common AEs were developed during the clinical development of ipilimumab. These guidelines recommend that low-grade immune-related AEs should be managed symptomatically.

For severe, persistent, or recurring immune-mediated reactions it is recommended to administer systemic high-dose corticosteroids. If the patient is refractory to this treatment, they may require treatment with other immunosuppressant therapies such as or mycophenolate mofetil for hepatic events or infliximab for enterocolitis. It is important to evaluate liver function tests before each dose to monitor for immune-mediated hepatitis. For immune-mediated endocrinopathies, thyroid function tests and clinical chemistries should be checked prior to each dose. It is also important to evaluate at each visit for signs and symptoms of endocrinopathy, perform hormonal testing or imaging of the brain if indicated, and institute hormone replacement therapy as needed [16].

Dose modification

It is important to withhold scheduled doses of ipilimumab for symptomatic endocrinopathy or any moderate immune-mediated adverse reactions. For patients receiving less than 7.5 mg of prednisone or equivalent per day who have a complete or partial resolution of adverse reactions (grade 0–1), ipilimumab dose can be restarted at its original dose of 3 mg/kg every 3 weeks until the administration of all four planned doses is

completed, or 16 weeks from the initial dose, whichever occurs first. Ipilimumab should be permanently discontinued if the patient has persistent moderate adverse reactions, or if it is not possible to reduce the patient's corticosteroid dose to 7.5 mg prednisone or equivalent per day. If the patient develops severe or life-threatening adverse reactions, ipilimumab should be discontinued and the patient should be evaluated immediately. If diarrhea develops, antidiarrheal agents can be attempted initially while other etiologies are ruled out. However, if the patient progresses to symptoms of colitis with abdominal pain, fever, ileus or peritoneal signs, an increase in stool frequency of seven or more over baseline, stool incontinence, the need for iv. hydration for more than 24 h, GI hemorrhage, or GI perforation, ipilimumab should be permanently discontinued and the patient should be evaluated urgently. Significant hepatic impairment including AST or ALT >5-times the ULN or total bilirubin >3-times the ULN would be another reason to permanently stop therapy. Less common side effects include Stevens–Johnson syndrome, toxic epidermal necrolysis, a rash complicated by full thickness dermal ulceration, necrotic, bullous or hemorrhagic manifestations, severe motor or sensory neuropathies, Guillain–Barre syndrome or myasthenia gravis, all of which would require permanently halting the therapy. Severe immune-mediated reactions may involve other organ systems resulting in nephritis, pancreatitis, pneumonitis, or noninfectious myocarditis. Immune-mediated ocular disease unresponsive to topical immunosuppressive therapy would also require permanent discontinuation of therapy [16,17].

• Assessments of response

Ipilimumab is an immunotherapeutic agent, thus it is associated with novel patterns of clinical response, distinct from those seen with conventional chemotherapy. The Response Evaluation Criteria in Solid Tumors (RECIST) were developed to standardize the assessment of responses to chemotherapy in clinical trials and cytotoxic chemotherapy is typically characterized by prompt responses. With immunotherapeutic agents, patients may experience varied patterns of response, and it is possible to see disease progression prior to observing a response. It is also possible to see new lesions develop while original lesions are decreasing in size. Because of these varying responses, the immune-related response criteria (irRC) was proposed to assess

a patient's response to ipilimumab. It was developed from the existing WHO and RECIST criteria but with some significant modifications. In general, the irRC considers the patient's 'total tumor burden' and requires confirmation of any suspected disease progression with a subsequent radiographic test 4 weeks later. More specifically, new measurable lesions ($\geq 5 \times 5$ mm) are incorporated into tumor burden, unlike WHO criteria in which these lesions always represent disease progression. New nonmeasurable lesions (i.e., $< 5 \times 5$ mm) also do not define progression, but do preclude immune-related complete response (irCR). The complete disappearance of nonindex lesions is required for an irCR. A CR is defined as a disappearance of all lesions in two consecutive observations not less than 4 weeks apart. A partial response is defined as $\geq 50\%$ decrease in tumor burden when compared with baseline in two observations at least 4 weeks apart. Thus a patient with new or progressive lesions can still be categorized as having a partial response as response is not based on the increasing size of index lesions, or the presence or absence of new lesions. The patient is deemed to have stable disease if when, compared with baseline, a 50% decrease in tumor burden cannot be established, nor a 25% increase when compared with nadir. Progressive disease is established when, in two consecutive observations at least 4 weeks apart, there is at least a 25% increase in tumor burden when compared with nadir (at any single time point) [10,18,19].

• Drug interactions

There has been no formal pharmacokinetic drug interaction studies conducted with ipilimumab.

• Use in specific populations

Ipilimumab is in pregnancy category C. There are no well-controlled studies of ipilimumab in pregnant women; however, based on animal data, ipilimumab may cause fetal harm in pregnancy. Human IgG1 is known to cross the placental barrier, therefore ipilimumab has the potential to be transmitted from the mother to the developing fetus [17].

It is unknown if ipilimumab is secreted in human milk. Animal models in monkeys treated with ipilimumab did find the drug present in milk [17]. In mothers who are nursing, it is recommended to discontinue nursing or discontinue ipilimumab.

Ipilimumab has not been evaluated for safety or effectiveness in the pediatric population. In geriatric patients, no overall difference has been seen in safety or efficacy in those over 65 years of age when compared with those younger than 65 [17].

There is no dosage adjustment needed for patients with renal impairment, or those with mild hepatic impairment defined as total bilirubin $>1.0\times$ to $1.5\times$ the ULN or AST $>$ ULN. Ipilimumab has not been studied in patients with moderate or severe hepatic impairment [17].

When determining therapy for patients harboring the *BRAF* mutation, immunotherapeutic agents and targeted therapy have distinct clinical profiles and attributes that must be considered. The onset of activity of targeted agents is rapid with a relatively high response rate of approximately 50% [20]. However, the number of patients with a complete responses is relatively low and estimated median PFS is short, approximately five and a half months for patients receiving single-agent *BRAF* therapy [21–23]. Ongoing trials investigating the combination of *BRAF* inhibitors and MEK inhibitors indicate the response rate is higher than with *BRAF* inhibition alone, and it is anticipated that they will replace *BRAF* inhibitor monotherapy in the future [24]. In contrast, responses to ipilimumab take time to develop, but have been found to be more durable with the potential for long-term survival benefits of therapy [6,20,25]. Long-term survival of up to 10 years in approximately 20% of patients who received ipilimumab was reported in a pooled analysis of long-term survival data from 12 clinical trials (eight Phase II, two Phase III and two observational studies) [26]. Limited data exist on sequential therapy with ipilimumab and vemurafenib. Preliminary results from the Italian cohort of ipilimumab expanded access programme suggest that in *BRAF*-mutation patients, initiating sequential therapy with ipilimumab can provide a better survival than the reverse [27]. However, in patients with *BRAF* mutations and high tumor load or rapid progression of disease, initiation with a *BRAF* inhibitor would provide a faster but possibly less durable response. In those with *BRAF* mutation and low tumor load or a slowly progressive disease, ipilimumab would be an appropriate initial therapy [6,28].

Conclusion

The research that led to the development and approval of ipilimumab brought to the forefront

the importance of both immunoregulatory circuits and immunomodulatory antibodies in the field of cancer therapy. Ipilimumab has had a significant impact on the landscape of melanoma therapy, and has been shown to create durable, long-lasting responses in these patients. However, there is a need to increase the number of patients who benefit from this therapy, further studies including those on combination therapies are needed. There have been reports, such as the dacarbazine ipilimumab study, that show a higher response rate with combination therapy [8]. Phase I trials looking at ipilimumab with newer agents such as nivolumab have also been promising; however, more long-term follow-up and Phase III trials are needed [14]. Presently, no biomarkers have been identified to predict responses to immunotherapy. The development of ipilimumab has changed the way patients with melanoma are treated and our further understanding

of these immunoregulatory pathways and checkpoints will be imperative in guiding the future direction of immunotherapy in the treatment of a very aggressive and often fatal disease.

Financial & competing interests disclosure

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