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REVIEW

Use of ipilimumab in the treatment of melanoma

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Utkarsh H Acharya
Joanne M Jeter

Department of Medicine, Division of Hematology-Oncology, University of Arizona Cancer Center, Tucson, AZ, USA

Abstract: Ipilimumab is a monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 that has been approved by the US Food and Drug Administration for the treatment of metastatic melanoma. Phase III trials have demonstrated an overall survival benefit with its use when compared with standard treatments and other investigational therapies. However, the drug poses a notable challenge, given its propensity for toxicity, and requires close surveillance when administered in clinical practice. This review discusses the mechanism of action for ipilimumab, its preclinical data, and the clinical trials that led to its approval by the Food and Drug Administration in 2011.

Keywords: melanoma, immunotherapy, ipilimumab

Introduction

The immune system plays a critical role in the defense against tumor cells, and discovery of this phenomenon has pointed to immunologic therapy as a viable therapeutic modality in the management of metastatic melanoma. Recognition of cancer cells by the immune system as foreign entities and the ensuing proliferation of cytotoxic T cells to eradicate these cells allows for the use of immunologic therapies, including interleukin (IL)-2, interferon, and novel agents such as ipilimumab, in treatment of metastatic melanoma.[1] Melanoma cells express various proteins, such as gp100, MART-1, and tyrosinase, which can serve as functional antigens and potentially drive an immune-mediated antineoplastic response.[1] The complex interplay of signals between antigen-presenting cells and T cells prior to cell activation is necessary before the T cell can perform its designated effector function. Before T cell activation, an antigen-presenting cell expresses an antigen via a major histocompatibility complex 1 molecule that is bound to the T cell receptor specific for that antigen (the CD8 receptor). Subsequently, additional costimulatory molecules on antigen-presenting cells are necessary for full activation of the T cell. This process takes place via a B7-1 (CD80) molecule on antigen-presenting cells, which binds to the CD28 receptor on T cells. Once completely stimulated, these activated T cells express IL-2, which further promotes the proliferation of additional cytotoxic T cells and directed activity to sites of antigen production.

Cytotoxic T-lymphocyte antigen-4 (CTLA-4, also known as CD152) is considered a homolog of the CD28 ligand and a costimulatory receptor with inhibitory signals to T cells.[2] In the early phases of T cell activation, upregulation of CTLA-4 by T cells results in competition with the CD28 receptor for binding to B7-1. Increased binding

Correspondence: Joanne Jeter
Department of Medicine, Division of Hematology-Oncology, University of Arizona Cancer Center, 1515 N Campbell Ave, PO Box 245024, Tucson, AZ 85724, USA
Email jjeter@azcc.arizona.edu

to CTLA-4 rather than CD28 results in downregulation of the T cell response in an effort to mitigate or prevent a presumably exaggerated immunologic response. Therefore, CTLA-4 expression may play a role in allowing tumor evasion, given its suppressive effects on T cell function. Conversely, CTLA-4 blockade allows T cell proliferation and ensuing antitumor activity.[3] Additionally, CTLA-4 activation has been shown to downregulate IL-2 production, decrease IL-2 receptor expression, and decrease cell cycle progression.[4] CTLA-4 knockout mice developed excessive accumulation of activated T cells and died of lymphoproliferative disorders within weeks of birth, which demonstrates that CTLA-4 blockade could augment immunologic activity against evolving tumors.[5] This finding was corroborated by a seminal study conducted by Leach et al in which in vivo administration of antibodies directed to CTLA-4 resulted in suppression of tumor cell activity and immunity to a secondary exposure to tumor cells.[6] Additional studies conducted on murine models have implicated the role of CLTA-4 inhibition in colon cancer, fibrosarcoma, and prostate cancer.[7] In particular, CLTA-4 blockade used in murine models of prostate cancer demonstrated pronounced antineoplastic activity by attenuating tumor growth and rejection as well as in the adjuvant setting after surgical excision.[8,9] These findings of CTLA-4 activity on immunologic function against tumorigenic diseases has paved the way for therapeutic use of monoclonal antibodies against CTLA-4.

Preclinical development in melanoma

Initial investigations evaluating the antineoplastic effects of CTLA-4 blockade were performed in conjunction with other immune-based therapies in murine melanoma models. The effectiveness of CTLA-4 blockade, singly or in combination with a granulocyte macrophage colony-stimulating factor (GM-CSF)-expressing tumor cell vaccine, was tested on rejection of the highly tumorigenic and poorly immunogenic murine melanoma B16-BL6.[10] Tumor eradication was noted in 80% of cases with combination treatment, and the same treatment regimen was found to be therapeutically effective against outgrowth of pre-established B16-F10 melanoma metastases in the lung.[10] CTLA-4 inhibition by itself was not noted to be as efficacious due to the poor intrinsic immunogenic capacity to express antigens to cytotoxic T cells; however, GM-CSF vaccination augmented this effect.[10]

Subsequently, additional studies evaluated the role of synergistic vaccination therapy with CTLA-4 blockade to augment T cell responses and tumor immunity elicited by DNA vaccines against the melanoma differentiation antigens, tyrosinase-related protein 2 and gp100.[11] Blocking CTLA-4 activity enhanced B16 tumor rejection, particularly in mice that received sequential therapy of vaccine followed by CTLA-4 antibody and subsequent boost vaccination. Interestingly, CTLA-4 blockade also increased the T cell responses to prostate-specific membrane antigen when given with the second or third vaccination.[11]

Ipilimumab

Human applications of these findings were made possible after a series of monoclonal antibodies were developed by Medarex Inc (Princeton, NJ, USA), by knocking out endogenous murine immunoglobulin genes and replacing them with human loci.[12] Ensuing immunization of these mice resulted in fully human monoclonal antibodies that alleviated the potential for infusion reactions as a consequence of murine sequences. Initially, two anti-CTLA-4 antibodies underwent clinical development, ie, ipilimumab and tremelimumab. Initially known as MDX-010, ipilimumab is an IgG1 monoclonal antibody against the extracellular domain of CTLA-4. Recognized by the pharmaceutical name of Yervoy™ (Bristol-Myers Squibb, New York, NY, USA), it was approved by the US Food and Drug Administration (FDA) for use in the treatment of metastatic melanoma in March 2011. Ipilimumab is commercially available in liquid form; for administration, it is diluted in normal saline or D5W to a concentration of 1–2 mg/mL and given intravenously over 90 minutes via an inline filter. While tremelimumab has similar effects and is a second-generation monoclonal antibody against CTLA-4, it failed to demonstrate significant survival in a Phase III trial compared with dacarbazine or temozolomide.[13]

Phase I and II studies

As previously noted, CTLA-4 blockade attenuates the growth of moderately immunogenic tumors and improves the rejection of nonimmunogenic to poorly immunogenic tumors in murine models.[14] To assess the biologic activity of CTLA-4 blockade in humans, Hodi et al performed the first Phase I trial utilizing MDX-010 in nine previously vaccinated patients with metastatic melanoma or ovarian carcinoma in 2003.[14] All patients received a single dose of MDX-010 at 3 mg/kg. MDX-010 was noted to stimulate extensive tumor necrosis in three patients with melanoma and to stabilize CA-125 levels in two patients with ovarian cancer previously vaccinated with irradiated autologous GM-CSF tumor cells. However, tumor necrosis was not observed in four patients

with a vaccination history, with cells not secreting GM-CSF. Notable toxicity included reversible acute hypersensitivity (one patient), grade III hepatotoxicity (one patient), and a grade I rash in all patients with melanoma. No patients experienced hypopigmentation.

Also in 2003, a Phase I trial at the National Cancer Institute investigated the role of CTLA-4 blockade in enhancing the effectiveness of two modified gp100 peptide vaccines in patients with metastatic melanoma.[15] The trial included 14 patients with metastatic melanoma who received ipilimumab at 3 mg/kg followed by serial vaccine injections every three weeks, with most patients receiving two cycles of therapy. Three of these patients achieved a response. Two patients with limited disease demonstrated complete responses, and a partial response was reported in a patient with complete resolution of a subcentimeter brain metastasis. Of note, eight patients developed immune-related adverse events on combined therapy. Common grade III/IV manifestations included dermatitis, enterocolitis, hepatitis, and hypophysitis. Vitiligo and antinuclear antibody-positive seroconversion were also noted. Given the relative success of this trial, it was extended to include a total of 56 patients with stage IV melanoma.[16] In this cohort, 29 patients received ipilimumab 3 mg/kg every three weeks and 27 patients received 3 mg/kg as their initial dose with subsequent doses reduced to 1 mg/kg every three weeks. Both groups received concomitant gp100 peptide vaccines with anti-CTLA-4 therapy. There was a 13% rate of sustained responses (more than two years) in several patients. Clinical response was more frequent among patients with higher grade immune-related adverse events, and plasma levels of ipilimumab were not correlated with disease response or toxicity.

In another early phase trial, Sanderson et al randomized 19 patients with stage III or IV resected melanoma to receive one of three dosing regimens of ipilimumab in addition to vaccination with three peptides directed at gp100, MART-1, and tyrosinase.[17] Concomitant ipilimumab at escalating doses of 0.3 mg/kg, 1 mg/kg, and 3 mg/kg was administered to each cohort in order to assess adverse effects and determine the maximum tolerated dose. Gastrointestinal toxicity was found to be dose-related, with grade III and IV diarrhea, abdominal cramping, and melena occurring more frequently in the higher-dose cohorts but found to be reversible. The maximum tolerated dose was defined as 1 mg/kg. Similar to the results published by Phan et al,[15] development of autoimmunity correlated with disease response: nine of 11 patients without autoimmune symptoms relapsed by 28 months, whereas relapse rates were lower among those patients with immune-related adverse events at that time. Relapse rates were similar regardless of the dose of ipilimumab.

Additional analysis of the trials performed by Phan et al[15] and Attia et al[16] were combined with a dose-escalation study of ipilimumab and gp100 peptide vaccines by Downey et al.[18] The composite data, which included 139 patients, failed to demonstrate a correlation between a higher dose and projected toxicities, response rates, overall survival, or progression-free survival in patients with metastatic melanoma.[18] However, analysis of this population did shed light on the impact of prior immunotherapies on patients who received ipilimumab. This study demonstrated that prior therapy with interferon alpha 2b was a negative indicator, but prior therapies with other immunologics, including IL-2, did not affect response. Further, high-dose IL-2 prior to ipilimumab therapy did not affect the response to treatment, although it did pose a risk of bowel perforation if given subsequent to ipilimumab.

In 2012, Prieto et al published a long-term follow-up on 177 patients treated with ipilimumab at various doses with or without gp100 or IL-2.[19] Complete remission rates ranged from 6% in the vaccination group to 17% for those receiving IL-2, with durable responses ranging from 54 to 99 months in this same group for a majority of patients. It should be noted that the best results in this study were in those who received ipilimumab in conjunction with IL-2. This study provides the longest prospective follow-up in melanoma patients treated with ipilimumab, with a five-year overall survival ranging from 13% to 25%. Therefore, despite the improvements seen with the use of ipilimumab, the long-term prognosis for those with metastatic melanoma remains poor.

An early Phase I/II study performed by Maker et al in 2005 was designed to assess the antineoplastic effects and toxicity profile of ipilimumab combined with IL-2 in patients with metastatic melanoma.[20] The study highlighted 36 patients who received ipilimumab every three weeks at different doses per cohort, with a majority of patients receiving a dose of 3 mg/kg and concomitant high-dose IL-2 therapy for a maximum of 15 doses at eight-hour intervals. Fourteen percent of patients developed grade III/IV toxicities, including enteritis, uveitis, and arthritis. Further, the trial failed to demonstrate any evidence supporting a synergistic effect of CTLA-4 blockade and IL-2 administration, although durable cancer responses were noted in patients who did respond to this combination.

An important combination Phase I/II trial was conducted by Weber et al, the primary objective of which was to study the pharmacokinetic profile of transfectoma-derived or hybridoma-derived ipilimumab in 88 patients with

unresectable stage III/IV melanoma.[21] Secondary endpoints of the trial were the clinical activity and tolerability of the drug. A majority of patients had prior systemic therapy with either chemotherapy or immunotherapy. Patients received ipilimumab as single doses escalating to 20 mg/kg, multiple doses up to 5 mg/kg, or multiple doses up to 10 mg/kg every three weeks. In the latter group, there was one complete response and one partial response, with stable disease noted in seven patients. While the study was not powered to compare efficacy between the groups, patients in the 10 mg/kg group appeared to demonstrate the best median progression-free survival at 95 days. However, patients in the same group also had significant toxicities, including grade IV colitis and ensuing colonic perforation requiring colostomy. Accompanying toxicities included rash, diarrhea, and hepatic dysfunction in a majority of patients. Further, all patients with a disease response experienced immune-related adverse events, suggesting that autoimmune toxicity was correlated with a favorable disease response.

Subsequent to these results, another Phase II trial enrolled 217 patients with previously treated stage III/IV melanoma in a randomized, multicenter, double blind, dose-escalation study.[22] Patients were randomized to receive ipilimumab at doses of 0.3 mg/kg, 3 mg/kg, or 10 mg/kg every three weeks for four cycles. Patients without disease at six months were then scheduled to receive maintenance doses every three months thereafter. The overall response rate was 11% in the 10 mg/kg group, 4% in the 3 mg/kg group, and 0% in the 0.3 mg/kg group. Overall survival was also noted to be superior in the 10 mg/kg cohort, with 30% of patients reported to be alive at 24 months. Toxicity profiles were found to be dose-dependent as reported in previous trials, with the most common adverse events including colitis and diarrhea. These findings added to the growing data on the efficacy of ipilimumab and supported further studies of ipilimumab scheduled at three-week intervals at a dose of 10 mg/kg.

Phase II and III studies

The first Phase III trial reporting on the survival benefit of ipilimumab in the treatment of metastatic melanoma was published in 2010 and led to the fast tracked approval of ipilimumab in March 2011.[25] A total of 676 HLA-A*0201-positive patients with previously treated unresectable stage III–IV melanoma were randomly assigned in a ratio of 3:1:1 to receive ipilimumab 3 mg/kg every three weeks for four doses with concomitant gp100 1 mg every three weeks (n = 403), single-agent ipilimumab at 3 mg/kg (n = 137), or gp100 alone (n = 136). Median overall survival was significantly improved at 10.0 months and 10.1 months among patients receiving ipilimumab alone and in the combination group, respectively, as compared with 6.4 months in the single-agent vaccine cohort (hazards ratio 0.68, $P < 0.003$). Overall survival was also superior, with 44% of patients receiving ipilimumab being alive at 12 months compared with just 25% of the vaccination patients being alive at that point. At two years, 22% of the patients who received ipilimumab alone were alive versus 14% of those who received the vaccine alone. Grade III/IV immune-related adverse events were reported up to 15% in the groups receiving ipilimumab compared with 3% in the vaccination group. Gastrointestinal toxicities, including diarrhea, colitis, nausea, vomiting, constipation, and abdominal pain, were commonly reported. A small percentage of patients experienced hypophysitis. Fourteen patients died for reasons related to therapy, and seven of these deaths were associated with immune-related adverse events. This study was the first to demonstrate a superior survival advantage of ipilimumab alone or in conjunction with gp100 vaccination when compared with a single-agent vaccine in patients with previously treated metastatic melanoma. However, the trial also illustrated that addition of gp100 to ipilimumab did not yield any synergistic survival benefit in patients with previously treated metastatic melanoma.

Ipilimumab and Dacarbazine

Prior trials leading to the approval of ipilimumab for the treatment of metastatic melanoma opened the debate of its efficacy when combined with conventional chemotherapy.[24] In 2011, a combination Phase II trial randomized 72 chemotherapy-naïve patients with metastatic melanoma to receive single-agent ipilimumab 3 mg/kg every four weeks or ipilimumab with dacarbazine 250 mg/m^2/day for five days at three-week intervals for a total of six cycles.[24] The objective response rate was 14.3% in the ipilimumab + dacarbazine group compared with 5.4% in the ipilimumab alone group, and median survival was longer in the combination group compared with the single-agent ipilimumab group (14.3 months versus 11.4 months). Grade III/IV toxicity in the combination therapy group was reported to be 22.9% versus 12.8% in the single-agent ipilimumab group, and most toxicity was reversible. This study was the first to examine the potential role of ipilimumab when combined with conventional chemotherapy, and demonstrated relative efficacy compared with single-agent ipilimumab.

In another randomized Phase III trial published in 2011, 502 patients with previously untreated metastatic melanoma were

randomized 1:1 to dacarbazine 850 mg/m^2 plus ipilimumab 10 mg/kg versus dacarbazine plus placebo on weeks 1, 4, 7, and 10, followed by single-agent dacarbazine every three weeks up to week 22.[25] Patients with an objective response or stable disease were continued on maintenance therapy with ipilimumab or placebo every 12 weeks. At 12 months, overall survival was 47% in the combination group compared with 36% in the placebo group. With regard to toxicity, patients receiving combined therapy demonstrated a greater frequency of grade III/IV adverse events compared with the single-agent arm (56% versus 28%, respectively); however, colitis was markedly less frequent than previously reported (2%). Further, there was a higher frequency of hepatotoxicity (20%) in this trial than that reported previously, which was felt to be attributable to the use of dacarbazine. Overall, this trial demonstrated the potential role of ipilimumab as first-line therapy in the treatment of metastatic melanoma as well as supporting an acceptable toxicity profile at a dose of 10 mg/kg.[21]

Practical considerations

Ipilimumab was ultimately approved for the treatment of unresectable metastatic melanoma at a regimen of 3 mg/kg intravenously every three weeks for four doses in March 2011. Given the paucity of effective treatment strategies in the setting of advanced melanoma, approval of ipilimumab by the FDA in this setting was ubiquitously celebrated because it allowed therapeutic inclusion for a wider population of patients when compared with alternate immunologic therapies. Thus, the National Comprehensive Cancer Network included ipilimumab in its guidelines as an option in the treatment of metastatic melanoma.[26]

Sequence of therapy

Given the potential toxicity profile of immunologic therapies, the sequence of treatment may be of significance in clinical practice. As noted above, treatment with high dose IL-2 prior to treatment with ipilimumab did not have an adverse impact on the response to ipilimumab therapy; however, bowel perforations have been associated with high-dose IL-2 given subsequent to ipilimumab.[18] Further, the eligibility criteria for treatment with ipilimumab are more lenient than those for high-dose IL-2. Thus, from the practical standpoint, it may behoove the clinician to use IL-2 for primary induction prior to using ipilimumab for those eligible for both treatment modalities.

Duration of therapy

The FDA approval for ipilimumab does not comment on maintenance dosing. However, previously conducted clinical trials included scheduled maintenance therapy every 12 weeks for patients with stable disease or an objective response at a dose of 3 mg/kg.[23,24] Therefore, the role of maintenance therapy using ipilimumab has yet to be clarified.

Toxicity profile and management

Colitis

The gastrointestinal side effects of ipilimumab can manifest as diarrhea, abdominal pain, and melena; complications include acute blood loss, refractory diarrhea, and bowel perforation with potential need for colectomy (and a risk of death). The prevalence of colitis among those treated with ipilimumab can be up to 35%. A randomized study assessing the tolerability and efficacy of CLTA-4 blockade with and without prophylactic budesonide was conducted in patients treated for metastatic melanoma.[27] Prophylactic budesonide did not affect the incidence of diarrhea, and patients receiving treatment with budesonide still required additional steroid treatment due to diarrheal complaints when compared with placebo. Thus, prophylactic use of steroids is not indicated or recommended, and corticosteroids are used only when necessary among those showing immune-related gastrointestinal effects.

Recommendations for management of autoimmune diarrhea include antimotility agents, with the addition of budesonide for grade II diarrhea and high-dose steroids for grade III + diarrhea. For high-dose therapy, one regimen recommends 125 mg of intravenous methylprednisolone, followed by oral prednisone 1–2 mg/kg/day with a four-week taper.[28] Treatment with ipilimumab may continue for grade I toxicity, but is conventionally withheld until symptoms improve for higher-grade toxicities. Infliximab may be indicated for those with refractory diarrhea, with surgical intervention reserved for profoundly refractory cases.

Hepatitis

Hepatitis conventionally manifests as right upper quadrant discomfort, nausea, vomiting, and serologic evidence of transaminitis with or without hyperbilirubinemia. For elevations of aspartate aminotransferase/alanine aminotransferase within five times the upper limit of normal, it may be reasonable to skip the next dose of ipilimumab until serologic resolution of transaminitis.[29] However, higher-grade transaminitis necessitates a four-week course of steroids and cessation of therapy. Immunosuppressive therapy with mycophenolate mofetil 500 mg every 12 hours may be instituted for steroid-refractory cases.[28]

Hypophysitis

Hypophysitis is diagnosed by serologic hormonal studies and magnetic resonance neuroimaging. Management consists of methylprednisolone 1–2 mg/kg/day followed by prednisone 1–2 mg/kg/day with a gradual four-week taper.[28] Additional endocrinopathies may also occur. The package insert recommends baseline thyroid function and serum biochemistry, although some experts recommend a comprehensive endocrine panel assessing anterior pituitary function.[28]

Dermatologic toxicity

Dermatologic toxicity typically manifests as a maculopapular rash with diffuse pruritus. Management of low-grade toxicity can be achieved with the use of topical steroids, whereas toxicity that is grade III or higher requires an initial prednisone dose of 1 mg/kg/day with a four-week taper. For grade IV skin toxicity, ipilimumab should be withheld.[28]

Neurotoxicity

Neuropathy can manifest as motor weakness or sensory neuropathy. Treatment with corticosteroids over four weeks and cessation of therapy is indicated for grade III+ neuropathy, but lower-grade neuropathy can be managed by holding the next dose of ipilimumab.[28]

Uveitis

Patients with uveitis may present with ocular pain, redness, and photosensitivity. Treatment of this complication consists of topical prednisolone acetate 1% for grade I–II toxicity. However, higher-grade toxicity necessitates discontinuation of ipilimumab therapy and use of systemic steroids tapered over four weeks.[28]

Immune-related adverse events associated with ipilimumab can be significant and require close surveillance and careful patient selection prior to instituting therapy. Effective management relies on early identification and prompt intervention. While the majority of immune-related adverse events are reversible, resolution is contingent on prompt intervention with corticosteroid therapy and cessation of therapy as described above.

Future directions

Although ipilimumab represents a significant advance in the treatment of melanoma, many questions remain regarding its optimal use. At the time of writing, 72 trials using ipilimumab are currently open and listed on the National Institutes of Health clinical trials website (www.clinicaltrials.gov). The majority of these studies are investigating its use in melanoma, but trials of prostate, cervical, ovarian, breast, lung, pancreatic, and kidney cancer are also in progress, as are studies in hematologic malignancies. In addition to the issues of duration and dosing of ipilimumab mentioned previously, use of this drug in combination with other chemotherapeutic and immunologic agents is an area of intense interest. The potential for ipilimumab to act as a sensitizer to radiation is also under investigation by several groups. In other trials, ipilimumab is being compared with interferon, which is the current standard of care in the adjuvant setting for individuals who have had completely resected melanoma. Lastly, investigations are continuing to define biomarkers predictive of response to this agent.

Disclosure

The authors report no conflicts of interest in this work.

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