Ipilimumab: Developmental History, Clinical Considerations, and Future Perspectives

Michael A. Postow, MD1,2
Medical Oncology Fellow
Melanoma/Sarcoma Service
Memorial Sloan-Kettering Cancer Center

Jedd D. Wolchok, MD, PhD1,2,3,4
Melanoma/Sarcoma Service
Memorial Sloan-Kettering Cancer Center

1Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, NY

2Weill Medical College of Cornell
University, New York, NY

3Associate Director
Ludwig Center for Cancer Immunotherapy
Memorial Sloan-Kettering Cancer Center
New York, NY

4Ludwig Institute for Cancer Research
New York Branch, New York, NY

Development of a Novel Immune-Modulating Therapy

Ipilimumab (commercial name Yervoy™, Bristol-Myers Squibb, Princeton, NJ) was approved on March 25, 2011 by the US Food and Drug Administration (FDA) for the treatment of advanced melanoma. Its approval was a landmark event in the history of melanoma treatment, as it was the first therapy ever to demonstrate improved overall survival in a randomized phase III trial for patients with metastatic melanoma. Ipilimumab is a monoclonal antibody that blocks cytoxic T-lymphocyte antigen 4 (CTLA-4). Since CTLA-4 is normally expressed on the surface of T-cells as a negative regulator of T-cell function, ipilimumab releases T-cells from this inhibitory mechanism, enabling the uninhibited T-cells to exert their full potential in creating antitumor immunity (Figure 1).

Over 15 years of research have established the foundations for the therapeutic potential of ipilimumab. Preclinical development was led by Dr. James Allison, who initially demonstrated that antibodies directed at CTLA-4 could result in tumor regressions in mice. Pilot clinical studies of ipilimumab followed, with the
first human phase I study of ipilimumab reported in 2002, demonstrating tolerability with early hints of clinical activity. Subsequent phase II studies focused on establishing appropriate dosing (0.3mg/kg vs. 3mg/kg vs. 10mg/kg) and schedule, suggesting that the dose of ipilimumab was relevant. The highest administered dose, 10mg/kg, resulted in a higher response rate compared to the 3mg/kg dose, albeit with increased side effects.

Ultimately, FDA approval at the 3mg/kg dose was based upon an overall survival benefit seen in a randomized phase III trial comparing ipilimumab (3mg/kg) with or without the gp100 peptide vaccine compared to gp100 alone for patients with previously treated, unresectable stage III or stage IV melanoma. More recently, the benefit of ipilimumab was also established for treatment-naïve patients through a second randomized phase III trial. Patients who received a higher dose of ipilimumab (10mg/kg) with dacarbazine had improved overall survival compared to those receiving dacarbazine alone.

**Unique Spectrum of Side Effects: Immune-Related Adverse Events**

Ipilimumab is generally well tolerated but can be associated with a host of novel side effects, presumably due to the immune system activation by CTLA-4 blockade. Collectively the spectrum of side effects is described as immune-related adverse events (irAEs). Though rates of irAEs differ in various trials, in the large, phase III trial reported by Hodi, et al (2010), irAEs most commonly affected the skin (rash/vitiligo/pruritis; 43.5% any grade, 1.5% grade 3-4); the liver (hepatitis/rise in liver enzymes; 3.8% any grade, 0% grade 3-4); the bowel (diarrhea/colitis; 29.0% any grade, 7.6% grade 3-4), and the endocrine system (hypophysitis, thyroiditis, adrenal insufficiency; 7.6% any grade, 3.8% grade 3-4).

More rarely, uveitis, conjunctivitis, neuropathy, myopathy, and nephritis have been known to occur. IrAEs are typically responsive to interruption or discontinuation of CTLA-4 blockade in combination with immunosuppressive drugs such as steroids or occasionally tumor necrosis factor-blocking antibodies. At present, there is no clear preventive strategy to avoid irAEs. A randomized, double-blind, placebo-controlled trial assessing the role of prophylactic budesonide in reducing ipilimumab-associated diarrhea showed no benefit.

"Patients who experience irAEs may be more likely to benefit. Serious irAEs, however, are not required for an anti-tumor response, nor do they guarantee clinical benefit."

Patients with underlying autoimmune diseases, particularly inflammatory bowel diseases and autoimmune hepatitis. Patients with underlying autoimmune conditions were excluded from clinical trials in the development of ipilimumab, and its safety has not been assessed in this patient population.

Retrospective analysis suggests that patients who experience irAEs may be more likely to benefit from anti-CTLA-4 therapy. Serious irAEs, however, are not required for an anti-tumor response, nor does the development of irAEs guarantee clinical benefit. Monitoring for predisposition to irAEs and attempting to separate the therapeutic benefits of anti-CTLA-4 therapy from irAEs are areas of ongoing investigation.

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**Figure 1.**

Panel "A" shows that T-cell activation involves binding of the T-Cell Receptor (TCR) to a peptide antigen bound to the major histocompatibility complex (MHC) on the surface of an antigen-presenting cell (APC). This process also involves the interaction of CD28 on T-cells with the B7 molecules on APC. Following T-cell activation, panel "B" shows that CTLA-4 is up-regulated and expressed on the cell surface of effector T-cells and functions as an inhibitory molecule, outcompeting CD28 in the binding to B7, and causing inhibition of T-cell activation and function. Ipilimumab binds to and inhibits the function of CTLA-4, thus enhancing T-cell function as shown in panel "C".
In addition to the unique side effect profile, ipilimumab is associated with novel patterns of clinical response, distinct from those observed with traditional cytotoxic chemotherapy. Cytotoxic chemotherapy typically is characterized by prompt responses. The "Response Evaluation Criteria in Solid Tumors" (RECIST) criteria were developed to standardize assessment of responses to chemotherapy in clinical trials. Patients treated with ipilimumab, however, experience alternative patterns and kinetics of response. In some cases, patients may have a period of early apparent disease progression before a profound disease response, or regression of initial lesions despite development of additional, smaller lesions.

A study evaluating the novel patterns of disease responses to ipilimumab across three phase II studies determined that improved survival was associated with a variety of radiographic response patterns.7 Consequently, the immune-related response criteria (irRC) were proposed to evaluate the benefits of ipilimumab and other related immunotherapeutic approaches. In general, the irRC considers the patient’s “total tumor burden” and requires confirmation of suspected disease progression with a subsequent radiographic test, approximately four weeks later. IrRC are already being used in tandem with traditional response criteria, such as RECIST, in current clinical protocols for prospective validation of immunotherapeutic agents such as ipilimumab.

**Patient Selection: Biomarker Analyses**

Considerable efforts have been directed towards understanding immunologic biomarkers associated with disease response to ipilimumab, to help determine which patients might be the best candidates for therapy. Monitoring of immunological parameters of patients undergoing therapy with ipilimumab has therefore been an integral component of completed and ongoing clinical trials. In one retrospective study of 51 patients treated with ipilimumab (10mg/kg), an absolute lymphocyte count (ALC) that exceeded 1000/µL at the time of the third ipilimumab dose (week 7 of therapy) was associated with an overall survival benefit.8

Additional work has investigated antigen-specific immune responses to a number of cancer-related antigens. Specifically, immune responses to the cancer-testis antigen NY-ESO-1 before or during ipilimumab therapy have been the most extensively characterized to correlate with clinical activity following therapy. In one recent study of 144 patients, those with detectable serum antibodies to NY-ESO-1 by ELISA prior to or during the course of ipilimumab therapy were more likely to achieve disease control (stable disease or disease response) from ipilimumab than those who did not have the serum antibodies.9 Seropositive patients treated at Memorial Sloan-Kettering Cancer Center who also had a detectable NY-ESO-1-specific CD8+ T-cell response showed a significant survival advantage compared to seronegative patients without a detectable CD8+ T-cell response. Though immunity to NY-ESO-1 was correlated with clinical benefit from ipilimumab, NY-ESO-1-specific immunity is likely a surrogate marker for the broader mechanisms of ipilimumab’s antitumor effects, rather than a direct mediator. Studies of ALC
and NY-ESO-1 have identified them as potential biomarkers in retrospective analyses, and prospective validation is an area of active research.

Future Directions: Combination Strategies To Increase the Number of Patients Who Benefit

Research leading to the approval of ipilimumab highlighted the importance of immune regulatory circuits and provided insights into how immunomodulatory antibodies that manipulate these mechanisms can dramatically improve clinical outcomes. Ipilimumab has fundamentally changed the landscape of melanoma treatment, with a substantial subset of patients now achieving long-term disease control and survival. Current research into understanding the pathophysiology of ipilimumab’s unique side effect profile and analyzing biomarkers predictive of response will ultimately lead to improved patient selection and clinical care.

Despite the therapy’s ability to create durable, long-lasting responses, there is a clear need to increase the number of patients who benefit. One study in treatment-naïve patients showed a trend towards a higher response rate when ipilimumab was combined with dacarbazine compared to ipilimumab alone. Despite the possibility of an additive effect in this study, further studies are necessary. Current and planned clinical trials are combining ipilimumab with chemotherapy, other immunotherapy, radiotherapy, and targeted therapy, such as BRAF inhibition (Table 1). Ipilimumab is also being investigated in the adjuvant setting after surgical resection of high-risk disease. We believe therapeutic strategies combining ipilimumab with other immunotherapeutic agents such as vaccines or other immunomodulatory antibodies that enhance T-cell responses may add to the benefit of ipilimumab, and we are conducting clinical trials to assess this promising possibility.

References

Ipilimumab and Radiotherapy

One promising combination therapeutic approach deserving of further investigation involves administering ipilimumab with radiotherapy. We recently reported on a patient treated with ipilimumab who had slowly progressive disease. After she received localized palliative radiotherapy, disease outside of the irradiated area remarkably regressed, possibly related to enhancement of the immune system by the radiation. This rare phenomenon has been described in the medical literature as the “abscopal effect” and refers to tumor regression outside of the irradiated field. Since we believe the immune system may be activated by radiotherapy, we are excited about the prospect of combining it with ipilimumab. We are actively designing a multi-institutional clinical trial to test this hypothesis.
PV-10, aka Rose Bengal: Intralesional Therapy For Metastatic Melanoma

Sanjiv S. Agarwala, MD
Professor of Medicine
Temple University School of Medicine
Chief, Oncology & Hematology
St. Luke’s Cancer Center
Bethlehem, PA

Intralesional therapy (direct therapeutic injection into a lesion) for metastatic melanoma was put on the map by a 1975 story in Cancer1 that reported the case of a 77-year-old male with 64 intracutaneous metastases and a pulmonary metastatic deposit. Over an eight-month period of inoculations with Bacille Calmette-Guérin (BCG), 17/17 of the treated lesions resolved and the pulmonary metastasis regressed more than 50 percent. The report suggested not only locally ablative effectiveness, but induction of host immune anti-tumor activity in regional and distant un.injected metastases through a systemic adjuvant response. Interest receded, however, when anaphylactic reactions and death due to disseminated BCG were reported in a subsequent trial. Randomized trials of BCG also failed to confirm a significant clinical benefit, and this approach ceased to be used in practice.2

Melanoma has remained a major clinical problem, however, and a significant percentage of patients have locally advanced disease at high risk for recurrence, progression, and metastasis despite locoregional therapy such as surgery and radiation. Patients with unresectable, multiple, or locoregionally advanced metastatic stage IIIIB/C or stage IV M1a/b melanoma in the subgroup with tumors accessible for direct injection are candidates for new incarnations of intralesional therapy.

Intralesional Therapy Revisited

Further research into intralesional therapy3 has been conducted since the BCG trials, in conjunction with a variety of treatment methods, such as carbon dioxide lasers, cryotherapy, electroporation (ECT), and cytokines (IL-2 and IFN-alpha and beta). Interest has especially been heightened recently by three investigational agents that appear to ablate tumors locally and produce systemic “bystander” effects: Allovectin-7, OncoVEXGM-CSF and PV-10. Given that melanoma is considered to become a systemic disease early in its course, the potential systemic effects of these newer agents could prove important.

Allovectin-7 is a plasmid/lipid complex with the DNA sequences encoding HLA-B7 and β2 microglobulin, both components of major histocompatibility complex class I (MHC-I). The reduced expression of MHC-I in melanoma cells is thought to enable them to evade recognition by T-cells. Researchers believe that Allovectin-7 will increase the immune system’s ability to recognize and target melanoma cells. The drug induces a fivefold increase in the frequency of HLA-B27 cytotoxic T cells, upregulates/restores MHC-I molecules, and induces a proinflammatory response. In a phase 2 trial of Allovectin-72 including 133 patients with stage IIIIB/C and stage IV M1a/b injectable cutaneous, subcutaneous or nodal melanoma lesions, the objective response rate (ORR) was 12 percent. There were no grade 3 or higher toxicities. A phase 3 trial of Allovectin-7 versus dacarbazine (DTIC)/temozolomide in recurrent stage III or IV melanoma with ORR (Complete Response + Partial Response, or CR + PR) at or >24 weeks as the primary endpoint is fully enrolled and awaiting analysis.

OncoVEXGM-CSF is a 2nd generation oncolytic herpes simplex virus encoding GM-CSF. It is thought to replicate only in tumor cells with subsequent lysis of injected tumors. Lysed cells are then taken up by antigen-presenting cells (APCs). There may also be an adaptive antimelanoma response enhanced by local expression of GM-CSF. In a phase 2 trial of OncoVEXGM-CSF, 20 percent of patients ultimately achieved a CR and 28 percent achieved an ORR. Ninety-two percent of the responses were durable (lasting at least 6 months), and the majority are ongoing, with a range of 18 to 40 months. Responses, observed in patients with all stages of disease, included complete resolution of visceral deposits.

The phase 3 OPTim trial of OncoVEXGM-CSF has enrolled 360 stage IIIIB/IV melanoma patients randomized 2:1 to OncoVEXGM-CSF versus subcutaneous GM-CSF alone. The endpoints are durable response at 6 months and overall survival.

PV-10 contains a small molecule fluorescein derivative. It is a non-pyrolytic solution of Rose Bengal disodium (10% RB) which is not metabolized, has about a 30-minute circulatory half-life and is excreted via bile. While PV-10 is excluded from normal cells, it transits through the plasmalemma (cell membrane) of cancer cells (including liver, breast, and other cancers in addition to melanoma) and accumulates in the lysosomes,7 triggering lysosomal release. It enters cancer cells and not normal cells because the cancer cells have a much higher fluidity (higher lipid content) in their cell membranes than normal cells do; even so, it requires a significant amount of PV-10 to ablate even the cancer cells, which helps explain why no hair loss or stomach lining problems have been observed to date in clinical studies. Autolysis is complete within 30-60 minutes. Acute exposure of antigenic tumor fragments to APCs is believed to produce the “bystander” effect in uninjected tumors. This mechanism is unique in that it leads to immediate reduction in tumor burden concomitant with immunologic activation.

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PV-10, aka Rose Bengal, from page 5

Rose Bengal's Non-Medical Origins

According to Provectus Pharmaceuticals senior vice president Eric Wachter, PhD, the name Rose Bengal was inspired by its color, which is like that of the deep rose-colored middle-of-the-forehead dot indicating marriage in Bengali and other women in India. A German patent #32584 was granted in Basel, Switzerland on February 1, 1885 to a man named Gnehm for a new family of wool dyes combining halogens with fluorescein, and one of them that ultimately included four iodines took the name Rose Bengal. Rose Bengal has been employed as a food dye as well. The first report of clinical use, in 1914, has Römer adding Rose Bengal to Safranin Victoria Yellow to treat ocular pneumococcal infection. Applications as a biological staining agent, mostly ocular, but also as an intravenous assay for impaired liver function, remained the primary medical use for nearly a century. The “eureka” moment for Rose Bengal as therapy came through this latter function, when a 1980s Japanese test of “Food Red no. 105,” intended to identify possible tumorigenicity, found instead dose-dependent survival increases, and left an unremarkable three-line trace in the literature. That trace was destined to have little impact until the late 1990s and the advent of high-powered computer searches. Provectus scientists looking for a laser-activated photodynamic therapy agent with antineoplastic activity identified Rose Bengal as a candidate. After subsequent animal and human study and reformulation, the laser activation aspect proved unnecessary and PV-10 was born.

Encouraging Phase 2 Response Rates

Following promising phase 1 results in 2008, we conducted a multicenter, international phase 2 trial in 80 patients with measurable stage III-IV melanoma. Intralesional injections of PV-10 were administered to as many as 10 target and 10 non-target cutaneous, subcutaneous, or nodal lesions. New or incompletely responsive lesions were retreated at weeks 8, 12, or 16, with follow-up to 52 weeks. Target lesions were ≥ 0.2 cm diameter, with at least one confirmed per patient by biopsy. Investigators observed up to 1-2 untreated, biopsy-confirmed bystander lesions that were typically small or difficult to access (including visceral lesions). The primary endpoint was objective response rate (ORR) for injected lesions. (Table 1.)

<table>
<thead>
<tr>
<th>Objective Response of Study Lesions, All Subjects (N = 80)</th>
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<tr>
<td>Best Response (RECIST, N=80 Subjects through Week 52)</td>
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<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>N (Subjects)</td>
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<tr>
<td>CR (complete responses)</td>
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<td>PR (partial responses)</td>
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<td>ND (not done)</td>
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<tr>
<td>CR + PR</td>
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<td>(Locoregional Disease Control)</td>
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Table 1. Phase 2: Preliminary Efficacy

Among the subjects treated (49 male/31 female, median age 70.0 years [range 33-97]), the median number of PV-10 treatments was 2 (1-4), with a median dose per treatment of 1.6 mL (0.1-15).

Twenty-four percent of patients had complete responses (CR) in target lesions and 25 percent had partial responses (PR) for an ORR of 49 percent. The locoregional disease control (CR+PR+stable disease [SD]) rate was 71 percent. Among the 38 subjects with bystander lesions, CR of their untreated lesions was reported in 24 percent, ORR in 37 percent, and locoregional control in 55 percent. Regression of bystander lesions strongly correlated with response in target lesions.

In a further analysis of the first 40 patients, those with CRs achieved significantly longer progression-free survival (11.1 months) than those with stable disease or progressive disease (PD) – 2.8 and 2.7 months, respectively. Responses in injected lesions appeared to be unrelated to disease stage or prior treatment.

No grade 4 or 5 adverse events (AEs) were attributed to PV-10, and over all, AEs were locoregional and predominantly mild-to-moderate.

Coming Next

The planned international phase 3 trial of PV-10 is expected to include up to 300 subjects with stage III-IIIIC melanoma. PV-10 will be compared with a control arm of chemotherapy with either dacarbazine (DTIC) or temozolomide, with progression-free survival as a primary endpoint. Enrollment in the 30-month trial is scheduled to begin in the second half of 2012.

The potential for combinations of systemic therapy with intralesional agents is now apparent, and preliminary trials of some intralesional agents in combination with prior therapies have already been initiated.

The bystander effect, which is postulated to occur as a result of an immunologic response to PV-10 and the other intralesional therapies, is
especially intriguing. A Phase 2B study is ongoing to examine the immunologic processes whereby PV-10 produces systemic response.

Recently, Provectus announced it had received guidance from the U.S. Food and Drug Administration (FDA) to submit its Phase 3 protocol for review. Provectus is seeking consensus on a design that will qualify for Special Protocol Assessment (SPA) and will support approval of PV-10 for its melanoma indication. The company intends to pursue the SPA path, which would represent an agreement with the FDA that the Phase 3 study design endpoints, statistical analyses, and other components of the planned clinical trials are acceptable to support approval of the product, depending, of course, on the outcomes.

If these intralesional therapies prove to be successful and gain FDA approval, the next logical step would be combination trials with recently approved systemic therapies such as ipilimumab and vemurafenib. Truly, the future for melanoma patients has never been brighter.

References


From the Editors, from page 1

would lead to landmark treatments. In 1996, Kirkwood, et al reported to us on the FDA’s approval of interferon alfa-2b, the first ever FDA-approved adjuvant biological therapy for high-risk melanoma patients. In 1998, Michael Atkins described the newly FDA-approved high-dose interleukin-2 regimen, the first ever for stage IV patients. Until this past year, these were the only immunotherapies approved for melanoma.

While these therapies were bonafide ‘breakthroughs,’ they resulted in cures for only a tiny fraction of patients. Now, immunotherapy has taken another quantum leap with last year’s approval of ipilimumab (Yervoy™). In our lead article, Drs. Michael Postow and Jedd Wolchok explore the great promise ipilimumab holds for so many patients with advanced melanoma. They describe the relative rapidity with which immune checkpoint blockade was developed and brought to the clinic with ipilimumab, and expertly summarize the clinical considerations with this drug and its limitless potential, especially in combination with other agents.

In our second story, Dr. Sanjiv Agarwala reviews the gradual evolution of intralesional therapy for cutaneous melanoma metastases and describes the recent resurgence of Rose Bengal (PV-10) as an intralesional agent. Although systemic therapies harnessing the immune system’s ability to combat and potentially cure melanoma have rightfully generated tremendous excitement, we need to remember that palliative treatments such as intralesional therapy still hold a vital place in our armamentarium. While we work toward cures, a significant subset of melanoma patients benefit greatly from the varied approaches to management of what can be devastating and incapacitating cutaneous metastases.

Over the past 30 years, if anything, we have observed that not all new scientific knowledge, including ‘breakthrough’ research, translates into dramatic patient gains. But even the smallest advances can, in their aggregate, improve and sometimes save the lives of patients, or at the very least, pave the way for advances that will improve or save the lives of patients. For three decades now, we have tried to keep our ever-growing readership abreast of these never-ending developments, large and small, in an accessible and timely way.

Allan C. Halpern, MD
Editor-in-Chief

Ashfaq A. Marghoob, MD
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