Melanoma treatment: where are we now and what's on the horizon?

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"Why can we trigger immune mechanisms in some patients so that they can overcome tumor tolerance, yet totally miss the mark in others? We are so close, but yet so far."

After years of frustrating clinical trials of toxic chemotherapy combined with just as toxic immunotherapy and no impact on overall survival, we have now been able to identify relatively nontoxic, impactful therapies. Of course, these therapies are not without issues. We have effectively identified genetic targets to treat certain types of melanomas and have also harnessed the power of the patient's immune system to assist in disease control. Although they both sound ideal, the targets, despite being effective, have limited efficacy before tumor progression; and with regard to immunotherapy, while some may derive long-term durable responses, the overall response rate to this therapy is low.

In this article, these major accomplishments are reviewed, so that we can incorporate them as building blocks to future therapies.

Targeted therapies

There has been an increasing interest in the RAF/MEK/ERK pathway since 2002, when Davies *et al.* first reported that 66% of melanomas harbor activating somatic missense mutations in the *BRAF* gene (*V600E*), leading to constitutive activation of this pathway [1]. Several other tumor suppressor genes and oncogenes are known to be involved in melanoma pathogenesis, likely leading to functional redundancy of different signaling pathways.

Vemurafenib (Zelboraf®, Genentech/Roche Pharmaceuticals; formerly PLX4032, Plexxikon) is an oral, highly selective inhibitor of the oncogenic *V600E* mutant BRAF kinase. The Phase II trial of vemurafenib in previously treated melanoma patients (BRIM 2) demonstrated an overall survival of 16.9 months, which is unprecedented in melanoma trials [2]. The Phase III trial (BRIM 3) comparing vemurafenib to dacarbazine in untreated patients with *BRAF V600E*-mutant metastatic melanoma demonstrated improvement in progression-free survival (PFS) and overall survival (OS) for patients receiving vemurafenib. The trial was closed early due to the significant benefit of vemurafenib and patients randomized

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to dacarbazine were then crossed over to the vemurafenib arm so that they could obtain the benefit of that therapy [3]. The robust data generated in this Phase III trial was the basis for US FDA approval of vemurafenib in patients with *V600E*-mutated metastatic melanoma.

Dabrafenib (GSK 2118436) is another oral, highly potent and selective inhibitor of the V600E/K/D mutant BRAF. A Phase II study of dabrafenib as salvage therapy, and a Phase III study of dabrafenib versus dacarbazine as front-line therapy for mutant *BRAF* metastatic melanoma patients demonstrated similar response rates and improvement in overall survival similar to vemurafenib [4]. This agent was also examined in a small trial for patients with *BRAF*-mutated melanoma and brain metastases. Intracranial disease control with dabrafenib, either before or after radiotherapy, was 81% in this small series, but invokes the question of how to best sequence treatment for *BRAF*-mutated melanoma patients with brain metastases [5].

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Trametenib (GSK1120212) is a potent and selective inhibitor of the MEK1/2 enzymes in advanced melanoma patients with known *BRAF* mutations. The randomized Phase III trial comparing trametenib to dacarbazine in *BRAF*-mutated melanoma in a crossover design looked at PFS as the primary end point. PFS in the trametenib arm was 4.8 months compared with 1.5 months in the dacarbazine arm (hazard ratio [HR]: 0.45) [6].

Although aiming at single targets within the MAPK pathway is a promising new therapeutic approach for the treatment of melanoma, and treatment with selective BRAF and MEK inhibitors can induce high response rates, the duration of these responses is limited. Emerging resistance to these inhibitors represents a significant clinical challenge, in part due to the existence of RAF isoforms and signaling through alternative oncogenic pathways, such as the PI3K/AKT/MTOR pathway [7,8], receptor tyrosine kinase (PDGFR-β)-dependent pathway [9] and COT (MAP3K8) [10] may provide the melanoma cells escape mechanisms to specific pathway inhibitors and underscore their ability to adapt to pharmacological challenges [7,8].

With this concept in mind, several trials are being conducted with multiple targeted agents. The only published combination trial to date is the dabrafenib/trametenib Phase I/II trial. Dabrafenib monotherapy demonstrated a 5.8-month PFS compared with dabrafenib plus full dose trametenib with a PFS of 9.4 months (HR: 0.39) in treatment-naive patients who harbored a *BRAF* mutation [11].

Mucosal, acral and cutaneous melanoma with chronic sun damage were found to harbor a mutation in the juxtamembranous domain of c-Kit (exon 11) that provided a rationale for the use of imatinib in this melanoma type. Results of a Phase II trial evaluating the effect of imatinib in patients with metastatic melanoma with c-kit aberrations demonstrated that over 30% of patients achieved a response (complete and partial response), whereas 50% had disease stability [12].

Immunotherapy

The interaction between antigen-presenting cells (APCs) and T lymphocytes is crucial for inducing melanoma-specific T-cell responses. In addition to the antigen specific interaction between the HLA peptide complex on the APC and the T-cell receptor (TCR), several different costimulatory and co-inhibitory molecules modulate the T-cell response. For instance, the T-cell surface molecule CD28 interacts with the B7 receptor on the APC to mediate a co-stimulatory signal (which is necessary in addition to the HLA peptide–TCR interaction for efficient priming of the T cell), whereas the T cell CTLA-4 interacts with B7 to downregulate T-cell activation, acting as a natural 'checkpoint' on the T cell-mediated immunologic response. Blocking interaction between CTLA-4 and B7 can overcome this checkpoint and enhance T cell-mediated antitumor activity. This can be achieved by an anti-CTLA-4 monoclonal antibody.

Ipilimumab, in a randomized Phase III clinical trial comparing ipilimumab alone versus gp100 vaccine alone with a combination of ipilimumab and gp100 vaccine, resulted in an improved OS of nearly 4 months (median survival duration of 10.1 and 10.0 months in the ipilimumab arm and the combined arm, respectively, in comparison to 6.4 months in the vaccination alone [HR: 0.66; 95% CI: 0.51–0.87; p = 0.033 and HR: 0.68; 95% CI: 0.55–0.85; p < 0.001, respectively]). This was the first randomized clinical trial that showed a statistically significant improvement in OS for metastatic melanoma [13]. Based on these data,

the FDA granted its approval for metastatic melanoma.

The activity and side-effect profile of anti-CTLA-4 antibodies have several characteristics that reflect their immune-mediated mechanism of action. Objective responses observed in patients with metastatic melanoma with ipilimumab were seen in approximately 7–10% of patients. Remarkably, as much as 70% of responses were durable [13,14]. The unique pattern of response to CTLA-4 monoclonal antibodies such as initial apparent progression of disease, even with emergence of new lesions, followed by regression and responses over the course of several months to years, has been demonstrated with these agents [15].

The PD-1 receptor is a negative regulator of antigen-activated T cells [16]. It bears homology to CTLA-4, but provides distinct co-inhibitory signals. The cytoplasmic domain of PD-1 contains two tyrosine signaling motifs that can attenuate the TCR/CD28 signal [17]. There are two known ligands for PD1: B7-H1/PD-L1 (hereafter termed PD-L1), the predominant mediator of PD-1-dependent immunosuppression, and B7-DC/PD-L2. PD-L1 is expressed by many tumors including melanoma, and its interaction with PD-1 resulted in tumor escape in experimental models [18].

MDX-1106 (BMS-936558/ONO-4538) is a fully human IgG4 monoclonal antibody specific for PD-1. The drug binds PD-1 with high affinity and blocks its interaction with both PD-L1 and PD-L2. A Phase I study of single-agent MDX-1106 in refractory solid tumors was conducted in 39 patients with advanced metastatic non-small-cell lung carcinoma, melanoma, castrate-resistant prostate cancer, renal cell carcinoma or colorectal carcinoma. Although efficacy was not the primary end point of this Phase I study, of the 39 treated patients, one durable complete response (colorectal carcinoma) and two partial responses (melanoma and renal cell carcinoma) were seen. Two additional patients (melanoma and non-small-cell lung carcinoma) had significant tumor regressions that did not meet criteria for partial response. This study suggested a more benign immune-related toxicity profile for anti-PD-1 than the one seen associated with anti-CTLA-4 [19]. Another Phase I trial was conducted on 16 patients with metastatic disease including melanoma. Objective responses were documented in 37.5% of patients lasting 3–13+ months; half of the patients had melanoma and there were few immune-related adverse events [20].

Future perspective

We must take what we have learned and build on it. We are combining immunotherapies and targeted therapies, immunotherapies with other immunotherapies and immunotherapies with radiation therapy. These are all attempts to enhance the patient's immune system to assist in tumor control but, to date, we do not understand the mechanism involved in this process. Why can we trigger immune mechanisms in some patients so that they can overcome tumor tolerance, yet totally miss the mark in others? We are so close, but yet so far. We need to develop better immune monitoring and analysis of accessible tumors in future clinical trials, so that we can develop a basic understanding of how we are manipulating this intricate system with our therapies.

We are combining multiple targeted therapies in an attempt to preserve a more durable response. However, when patients progress, we are requesting that they allow us to biopsy their tumors at the time of progression, so we can try to determine what went wrong. Herein lies the key to our future success: tumor biopsies and patient serum. I will argue however, that although it is important to examine blood and tumors of patients who progress during therapy, it is even more important to look at the blood and harvested tumors of our responders. What makes them so different and sensitive to treatment? Why are they the long-term responders? What went right? We need to examine their gene arrays, tumor antigens and tumor lymphocyte subtype populations. We need to learn from our successes as well as our failures, since our successes may hold the key to prognostic indicators of response and possibly even therapy selection, which will lead to durable disease control.

We need to continue to conduct research targeted at brain metastases, since more than half of our patients will succumb to this problem. Although the BRAF inhibitors clearly impact brain metastases, over time, these too progress. And what of those patients who do not harbor a *BRAF* mutation? Ipilimumab may help to control a limited amount of these patients, but many times the inflammatory response only worsens the CNS edema, making it difficult, if not impossible, to continue treatment. Since

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these tumors are not easily accessible for biopsy, it is difficult to evaluate progressing tumors; however, if patients require a craniotomy, this may provide a rare opportunity to harvest these brain metastases for research. I have no bright answers for where to go with this problem, but I do believe that by obtaining resected tumors, it may allow us to identify unique characteristics, creating an opportunity to design novel therapeutic developments.

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