MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

Section Editor: John M. Kirkwood, MD

Is There a Role for Single-Agent BRAF Inhibition in Melanoma?

Bartosz Chmielowski, MD, PhD
Associate Professor of Medicine
UCLA Jonsson Comprehensive Cancer Center
Division of Hematology and Oncology
David Geffen School of Medicine at UCLA
Los Angeles, California

H&O What makes BRAF inhibition a good approach to the treatment of melanoma?

BC BRAF inhibitors, especially when combined with MEK inhibitors, are an excellent treatment choice for the 40% to 50% of patients who have metastatic or unresectable melanoma that harbors the V600 *BRAF* mutation. These agents should not be used in patients with tumors that lack a *BRAF* mutation or whose BRAF status is unknown. In vitro, it has been shown that BRAF inhibitors can promote the growth of *BRAF* wild-type melanoma cell lines. In addition, sporadic cases of *RAS*-mutated malignancies have been described in patients treated with a BRAF inhibitor. Therefore, testing for the presence of the V600 *BRAF* mutation is extremely important. When eligible patients do receive a BRAF inhibitor, some tumor shrinkage occurs in nearly 80%, and a response occurs in more than 50%. Patients with highly symptomatic disease generally experience a rapid and significant decrease in their symptoms.

H&O Could you briefly describe the 2 BRAF inhibitors that have been approved for use in the treatment of melanoma?

BC The 2 approved agents are dabrafenib (Tafinlar, Novartis) and vemurafenib (Zelboraf, Genentech/Daiichi Sankyo). The response rate and duration of response with these 2 agents appear to be the same, but we must remember that no clinical trials have compared the agents head to head. We had 1 clinical trial that compared the dabrafenib/trametinib (Mekinist, Novartis) combination with vemurafenib. However, because dabrafenib was used in combination, it is impossible to use the data from this trial to compare the efficacy of single-agent dabrafenib with that of single-agent vemurafenib. Therefore, we must rely on cross-trial comparisons and personal clinical experiences.

Although these drugs do not differ in efficacy, they do differ in side effect profiles. The possible adverse events are similar because the 2 drugs have the same mechanism of action, but the side effects occur at different frequencies. Dabrafenib is more likely to cause fever, whereas vemurafenib is more likely to cause skin sensitivity to sunlight and cutaneous squamous cell carcinoma (cSCC) or keratoacanthoma.

Another difference relates to dosing. The dosage for dabrafenib is 150 mg twice a day; each capsule contains 75 mg of the drug, so patients take 2 pills twice a day. The dosage for vemurafenib is 960 mg twice a day; each tablet contains 240 mg, so patients take 4 pills twice a day. Taking dabrafenib may be easier for patients because they take fewer pills. However, should a patient require a dose reduction, dosing becomes more complicated. The next dosage level is 100 mg twice a day, so the same capsules cannot be used. The prescription must be cancelled and rewritten for 50-mg capsules. A new authorization from the insurance company is usually required, and this leads to a delay in dosing. With vemurafenib, patients take more pills, but it is much simpler to reduce the dose because we can simply instruct patients to take 3 instead of 4 pills twice a day.

H&O Could you talk more about the side effects of BRAF inhibitors?

BC The most common side effects of dabrafenib as a single agent are hyperkeratosis, headache, fever, arthralgia, cutaneous papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. The most common side effects of vemurafenib as a single agent are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and cutaneous papilloma.

Some adverse events require special attention. Both BRAF inhibitors can cause clinically significant cutaneous side effects. Treatment with vemurafenib may result in increased photosensitivity. Therefore, I always advise my patients on BRAF inhibitors to avoid sun exposure, wear protective clothing, and use a broad-spectrum ultraviolet (UV) A/UVB sunscreen and lip balm with a sun protection factor of at least 30 when they are outdoors. Both dabrafenib and trametinib can induce the development of cSCCs and keratoacanthomas; these have been seen in 11% of patients treated with dabrafenib and in 24% of patients treated with vemurafenib. When cSCC occurs, it usually develops soon after the initiation of therapy (on average, within 7-9 weeks), and more than 1 cSCC develops in approximately one-third of patients. Fortunately, these cSCCs are almost always well-differentiated, keratoacanthoma-like lesions. They can be successfully treated with a simple excision and rarely cause significant morbidity, although some patients with recurrent lesions must undergo multiple surgeries. The incidence of cSCC is reduced dramatically when BRAF inhibitors are used in combination with MEK inhibitors. In addition, we often see quite a significant number of cases of papillomas (wartlike lesions) and hyperkeratosis (the skin may feel like sandpaper). I also warn my patients that they will probably experience some degree of hair loss—never complete—and that the structure of their hair may change, such as from straight to curly. A new primary melanoma develops in up to 2% of patients. Because of the frequency of cutaneous side effects, it is prudent to perform a careful dermatologic evaluation before the initiation of therapy, every 2 months while the patient is on therapy, and for 6 months after the therapy has been stopped. All suspicious lesions should be excised and sent for a pathologic evaluation.

Fever is another common side effect of BRAF inhibitors, especially dabrafenib, although it is also seen with vemurafenib. Most of the time, the temperature is simply elevated, but rigors and chills also occur in some patients. In rare cases, fever may be complicated by hypotension, dehydration, and acute renal failure. Fever usually occurs within the first 2 weeks of therapy and rarely recurs after patients are rechallenged with the drugs. I always warn my patients about fever, which can be frightening for both them and their treating physicians.

Vemurafenib can cause electrocardiogram (EKG) changes—namely, QT prolongation. No clinical consequences have been seen, but we know that QT prolongation has the potential to cause ventricular arrhythmias, including torsades de pointes. I always obtain a baseline EKG, correct any electrolyte abnormalities, and try to discontinue other medications that can cause QT prolongation before a patient starts vemurafenib. I repeat the EKG and electrolyte measurements after 15 days of therapy, then monthly for 3 months, and finally every 3 months for the duration of treatment.

BRAF inhibitors also can cause fatigue, which is occasionally debilitating. Fatigue decreases quickly after the dose has been reduced. Approximately one-third of patients require a dose adjustment because of side effects.

Some less common side effects should be mentioned. One of the rare side effects of BRAF inhibitors is ocular toxicity, which may manifest as uveitis, iritis, dry eye, or conjunctivitis. Vemurafenib has also been linked to cases of Bell's palsy (peripheral facial nerve palsy). Increased glucose levels have been seen with BRAF inhibitors, especially dabrafenib. Cases of pancreatitis have been described in patients treated with dabrafenib, and cases of interstitial nephritis in those treated with either drug. Liver function should be monitored to detect possible hepatotoxicity early.

Clinicians should be aware that dabrafenib contains a sulfonamide moiety, so there is a potential risk for hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and for a hypersensitivity reaction in patients with sulfonamide allergy.

H&O What are the most important studies of single-agent BRAF inhibition in melanoma?

BC The most important studies are the phase 3 trials of dabrafenib vs dacarbazine (reported by Chapman and colleagues) and vemurafenib vs dacarbazine (reported by Hauschild and colleagues), which led to US Food and Drug Administration (FDA) approval of both drugs. The vemurafenib study was open to accrual sooner than the dabrafenib trial, and therefore crossover to a BRAF inhibitor was not allowed at the time of progression on dacarbazine. This approach was somewhat controversial. Later, the FDA mandated that crossover be permitted in this trial, but unfortunately most of the patients who would have been eligible had died. When the dabrafenib trial started accruing patients, it was considered unethical not to offer a BRAF inhibitor to patients whose disease had progressed on chemotherapy, and therefore crossover was a part of the original trial design.

The vemurafenib study, in which patients received 960 mg of vemurafenib twice a day, enrolled patients

with either metastatic or unresectable stage 3 melanoma. The primary endpoints were overall survival (OS) and progression-free survival (PFS). This study found that OS was significantly better with vemurafenib (13.6 months) than with dacarbazine (9.7 months). PFS also was better with vemurafenib (6.9 months) than with dacarbazine (1.9 months).

In the dabrafenib study, which was not designed to measure OS, PFS was better with dabrafenib (5.1 months) than with dacarbazine (2.7 months). A trend toward improved OS also was seen but was not statistically significant. This lack of significance can be easily explained by the previously mentioned crossover.

H&O What are the main limitations of BRAF inhibitors?

BC The average duration of response to a single BRAF inhibitor is just 6 months; only a minority of patients experience a long-lived response.

H&O Is there still a role for single-agent BRAF inhibition in melanoma?

BC There is nearly no role; therapy with a single BRAF inhibitor has been replaced with the combination of a BRAF inhibitor and a MEK inhibitor. I could imagine that a BRAF inhibitor might on rare occasion be used without a MEK inhibitor in a patient with a comorbidity precluding the use of a MEK inhibitor. MEK inhibitors have the potential to decrease the cardiac ejection fraction and to cause ocular toxicity, so they should be used with caution in patients with very advanced heart failure or severe retinal problems, for example.

Dual therapy not only increases the duration and rate of response but has been shown to decrease the frequency of side effects. This occurs because toxicity often is caused by the bypass activation of MEK in the presence of a BRAF inhibitor. The main exception to this observation is fever, which is more likely with BRAF inhibitor/MEK inhibitor combination therapy than with single-agent therapy.

H&O What are the mechanisms of resistance to BRAF inhibitors?

BC Multiple mechanisms of resistance have been identified. As we know, BRAF inhibitors by definition inhibit BRAF, which is one of the tyrosine kinases in the MAP kinase pathway. Extensive research has shown that mechanisms of resistance can be divided into 2 general groups: MEK-dependent and MEK-independent. The key MEK-dependent mechanisms include the emergence of mutant *BRAF*–concurrent *RAS* or *MEK* mutations and mutant *BRAF* amplification or splicing. MEK-independent mechanisms include mutations in the AKT/PI3K pathway and reactivation through insulin-like growth factor 1 receptor (IGF-1R) or platelet-derived growth factor receptor beta (PDGFR-ß).

H&O What experimental BRAF inhibitors are being studied?

BC The most advanced is encorafenib, also known as LGX818, which Array BioPharma is studying for the treatment of melanoma, mainly in combination with the MEK inhibitor binimetinib. We already have some data from the phase 3 COLUMBUS trial (NCT01909453) showing that the degree of response is the same as with the other BRAF inhibitor/MEK inhibitor combinations

I am especially interested in seeing the results of the LOGIC-2 trial (NCT02159066), in which patients initially receive a combination of encorafenib and binimetinib. At the time of progression, a third targeted agent is added on the basis of the results of genetic testing of the progressing melanoma.

H&O What other emerging combination approaches are being studied now?

BC GlaxoSmithKline was studying the combination of a BRAF inhibitor, a MEK inhibitor, and an AKT inhibitor, but now that Novartis owns the BRAF inhibitor and the MEK inhibitor but not the AKT inhibitor, the study is unlikely to continue.

Researchers continue to look at BRAF inhibitor/MEK inhibitor combinations with anti–programmed death 1 antibodies. We are waiting for the results of trials of vemurafenib and cobimetinib (Cotellic, Genentech) in combination with atezolizumab (Tecentriq, Genentech), and trials of dabrafenib and trametinib in combination with pembrolizumab (Keytruda, Merck).

Disclosures

Dr Chmielowski has served as an advisor or consultant for Bristol-Myers Squibb, Genentech, Janssen, Lilly, and Merck.

Suggested Readings

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364(26):2507-2516.

Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet.* 2012;380(9839):358-365.

Kloth JS, Pagani A, Verboom MC, et al. Incidence and relevance of QTc-interval prolongation caused by tyrosine kinase inhibitors. *Br J Cancer.* 2015;112(6):1011-1016.