Dabrafenib in advanced melanoma with BRAF V600E mutation

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In May 2013, dabrafenib was approved by the US Food and Drug Administration for treatment of unresectable or metastatic melanoma with BRAF V600E mutations as detected by an FDA-approved test. The THxID BRAF assay, for detection of BRAF V600E mutations was concurrently approved. Dabrafenib is not indicated for the treatment of patients with wild-type BRAF melanoma, because of the potential risk of tumor promotion. About 50% of melanomas have an activating mutation in the *BRAF* gene, with about 80%-90% of those having a V600E mutation, and 10%-20% having a V600K mutation. Dabrafenib is a reversible, ATP-competitive inhibitor that selectively inhibits BRAF V600E kinase; preclinical data indicate that dabrafenib inhibits the MAPK pathway in BRAF V600E-mutated melanoma cells, leading to decreased proliferation and regression in xenograft models. Dabrafenib also inhibits other mutated forms of BRAF kinases, including BRAF V600K and BRAF V600D enzymes and, at higher concentrations, wild-type BRAF and CRAF kinases and other kinases (eg, SIK1, NEK11, and LIMK1). However, in vitro experiments have shown paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells exposed to BRAF inhibitors.

The approval of dabrafenib was based on results of a phase 3 international open-label trial showing significantly improved progression-free survival (PFS) with dabrafenib compared with dacarbazine.[1] In this trial, 250 patients with previously untreated, histologically confirmed, unresectable stage 3 or 4 melanoma determined to be BRAF V600E mutation-positive based on centralized testing were randomized 3:1 to receive dabrafenib 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m^2 IV once every 3 weeks (n = 63).

The dabrafenib and dacarbazine groups were well balanced for age (median, 53 and 50 years, respectively), sex (60% and 59% male), ethnicity (100% white in both), Eastern Cooperative Oncology Group performance status (0 in 66% and 70%; 0 = fully active, 5 = dead), M status at screening (M1a in 12% and 16%, M1b in 18% and 19%, M1c in 66% and 63%), and previous therapy (97% and 98%, including immunotherapy in 28% and 24% and radiotherapy in 20% and 16%).

At data cut-off, 57% of patients in the dabrafenib group and 22% in the dacarbazine group remained on study treatment, with 44% of the dacarbazine group crossing over to dabrafenib after progression. Median time on study for all patients was 4.9 months. PFS on investigator assessment, the primary end point, was 5.1 months in the dabrafenib

What's new, what's important

It is amazing to see the evolution of treatment of melanoma over the past 4 years. Last spring, the US Food and Drug Administration approved dabrafenib for patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. The recommended dose and schedule for dabrafenib is 150 mg orally twice daily until disease progression. Confirmation of the presence of BRAF V600E is needed before initiation of dabrafenib because of the potential risk of tumor promotion in patients with BRAF wild-type melanoma.

More recently, the agency granted accelerated approval to trametinib and dabrafenib for use in combination in patients with metastatic melanoma with a BRAF V600E or V600K mutation. Trametinib had been approved as a single agent for therapy for BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma. The recommended dose and schedule for the trametinib–dabrafenib combination is trametinib 2 mg orally once daily with dabrafenib 150 mg orally twice daily, at least 1 hour before or 2 hours after a meal. Short duration of response and rapid development of resistance are still major problems in most patients. Ongoing clinical trials with newer combination therapies and immunotherapies will continue to change the landscape of melanoma treatment.

– Jame Abraham, MD

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group, compared with 2.7 months in the dacarbazine group (hazard ratio [HR], 0.30; $P < .0001$). On independent review, PFS was 6.7 months, compared with 2.9 months (HR, 0.35; 95% confidence interval [CI], 0.20-0.61). Benefit of dabrafenib was observed in all subgroups analyzed.

At the time of analysis, death had occurred in 11% of dabrafenib patients and 14% of dacarbazine patients (HR, 0.61; 95% CI, 0.25-1.48); follow-up of overall survival is ongoing. Confirmed objective response on independent review occurred in 50% of the dabrafenib group, including complete response in 3%, and in 6% of the dacarbazine group, including complete response in 2%. Median time to response was 6.3 weeks in the dabrafenib group. Most patients receiving dabrafenib exhibited reduction in target lesion size, with this effect being observed across all disease stages. Median duration of response was 5.5 months in the dabrafenib group and not reached in the dacarbazine group. Stable disease was observed in an additional 42% of dabrafenib patients and 48% of dacarbazine patients. Of 28 dacarbazine patients who crossed over to dabrafenib, 13 (46%) exhibited partial response to dabrafenib.

Treatment-related adverse events of grade 2 or higher occurred in 53% of dabrafenib patients and 44% of dacarbazine patients. Among treatment-related adverse events of grade 2 or higher occurring in ≥ 5% of patients, skin reactions were observed only in dabrafenib patients, including hyperkeratosis (grade 2 in 12%, grade 3 or 4 in 1%), palmar-plantar erythrodysesthesia/palmar-plantar hyperkeratosis (grade 2 in 6%, grade 3 in 2%), and squamous cell carcinoma/keratoacanthoma (grade 2 in 2%, grade 3 in 8%). Dacarbazine patients had a greater incidence of gastrointestinal adverse events, including nausea (grade 2 in 1% vs 14% in dabrafenib patients) and vomiting (grade 2 in 1% vs 5%), and hematologic adverse events, including neutropenia (grade 2 in 0% vs 3%, grade 3 in < 1% vs 5%, grade 4 in 0% vs 7%), thrombocytopenia (grade 3 in < 1% vs 2%, grade 4 in 0% vs 3%), and leukopenia (grade 2 in 0% vs 3%, grade 3 in 0% vs 2%). Other adverse events occurring in ≥ 5% of patients consisted of arthralgia (grade 2 in 5% vs 0%, grade 3 in < 1% vs 0%), asthenia (grade 2 in 3% vs 5%), fatigue (grade 2 in 5% vs 5%, grade 3 in 1% vs 0%), headache (grade 2 in 5% vs 0%), and pyrexia (grade 2 in 8% vs 0%, grade 3 in 3% vs 0%).

Of the 12 dabrafenib patents with squamous cell carcinoma/keratoacanthoma, none required dose modification or treatment interruption. In addition to these cases, 4 dabrafenib patients had basal cell carcinomas of the skin, 1 had grade 1 mycosis fungoides, and 2 had new primary malignant melanomas considered related to dabrafenib treatment. Phototoxic reactions (all grade 1) occurred in 7% of dacarbazine patients and 3% of dabrafenib patients (grade 2 in 2%, grade 3 in 1%). Adverse events resulted in dose reduction in 28% of dabrafenib patients and 17% of dacarbazine patients and treatment discontinuation in 3% and 3%.

Dabrafenib is marketed as Tafinlar by GlaxoSmithKline. It carries warnings/precautions for new primary cutaneous malignancies, tumor promotion in *BRAF* wild-type melanoma, serious febrile drug reactions, hyperglycemia, uveitis and iritis, glucose-6-phosphate dehydrogenase deficiency, and embryo-fetal toxicity. The THxID BRAF Kit is manufactured by bioMérieux.

How I treat mutated metastatic melanoma

The therapeutic landscape of metastatic melanoma before 2010 was occupied solely by high-dose interleukin-2 and single-agent or combination chemotherapy (dacarbazine, temozolomide, carboplatin plus paclitaxel), or occasionally a combination of both, termed biochemotherapy. The clinical approach to patients with metastatic melanoma has changed dramatically in the last 4 years, with the US Food and Drug Administration's approval of 4 novel agents – ipilimumab, vemurafenib, dabrafenib, trametinib – and most recently a combination of dabrafenib and trametinib.

Determining the mutational status of the tumor is the first step in ascertaining whether targeted therapy will enter the therapeutic algorithm. If the patient's tumor harbors the BRAF mutation, then starting a BRAF-targeted agent is not the automatic next step because the benefit is limited in time. If the patients are young, fit, and asymptomatic, then high-dose interleukin-2 may be an excellent option given its track record of durable benefit, albeit in a small subset of patients not exceeding 15%. If the patients are not good candidates for this rather toxic therapy, then immunotherapy with ipilimumab remains a first-line approach given its durable benefit and impact on overall survival rates, regardless of mutational status. The initiation of BRAF-directed therapy is most appropriate in the first line only in symptomatic patients for whom a rapid response is required for palliation.

The presence of brain metastases is challenging, but local control with surgery or stereotactic radiosurgery is our first approach. If the brain lesions are not amenable to local control, then I prefer single-agent dabrafenib over whole-brain radiation therapy given its superior activity.

The availability of clinical trials is a paramount factor in my therapeutic decisions as it is always prioritized in our practice upon the presence of novel promising agents such as PD-1 directed therapy and ever-expanding combinatorial approaches whether building on BRAF inhibition, immune checkpoint blockade, or tumor vaccine strategies.

– Hussein Tawbi, MD, PhD

Reference

1. 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;380:358-365.