ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Melanoma in Focus

Combination Therapies for Treating Metastatic Melanoma

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H&O What is the premise behind combination therapy for metastatic melanoma?

HT To give some background, the treatment of metastatic melanoma was revolutionized by the development of targeted therapy using specific BRAF inhibitors: vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) and dabrafenib (Tafinlar, GlaxoSmithKline).

Vemurafenib, which was approved first, showed very impressive responses in patients who had *BRAF* V600-mutated melanoma, even in the phase 1 trial by Flaherty and colleagues published in the *New England Journal of Medicine* in 2010. In addition, a phase 2 trial by Sosman and colleagues that was published in the *New England Journal of Medicine* found an overall response rate of 53% and a median duration of response of 6.7 months. In a phase 3 trial by Chapman and colleagues that was published in the *New England Journal of Medicine*, called BRIM-3, the response rate with vemurafenib was 48%. These findings were mirrored by the results of BREAK-3, published by Hauschild and colleagues, which had a similar response rate for dabrafenib.

An important side effect of BRAF inhibitors is skin toxicity. This includes photosensitivity and the development of keratotic lesions such as keratoacanthoma or cutaneous squamous cell carcinoma. This skin toxicity occurs because even though BRAF inhibitors completely shut off the mitogen-activated protein kinase (MAPK) pathway in *BRAF*-mutated cells, they paradoxically activate the MAPK pathway in cells with normal BRAF protein. This activation leads to cell proliferation, which is especially dangerous and can lead to cancer in cells with upstream *RAS* mutations. Another common side effect is febrile reactions; approximately 10% to 15% of patients taking a BRAF inhibitor develop a low-grade or occasionally high-grade fever.

Several mechanisms have been elucidated that explain why patients develop resistance to BRAF inhibitors, usually within 6 months. Up to 60% to 70% of the resistance is driven by reactivation of the MAPK pathway, which can occur either upstream or downstream of the BRAF protein. In other words, the tumor learns to bypass the blocked BRAF and go straight into activating MEK, which in turn activates ERK. That is why the development of MEK inhibitors is so important.

The US Food and Drug Administration (FDA) approved the MEK inhibitor trametinib (Mekinist, GlaxoSmithKline) in 2013 as a single agent for patients with BRAF V600-mutated metastatic melanoma, albeit with lower response rates and duration of response. As soon as we had evidence that single-agent treatment with either a BRAF inhibitor or a MEK inhibitor was effective, and that a large proportion of resistance to BRAF inhibitors is driven through MEK, it was expected that combining these agents might be effective. The combination of a BRAF inhibitor and a MEK inhibitor emerged as a natural progression.

H&O Could you discuss the research on BRAF inhibition plus MEK inhibition?

HT In a phase 1 and 2 trial by Flaherty and colleagues published in the *New England Journal of Medicine* in

2010, researchers compared dabrafenib alone (150 mg twice a day) vs dabrafenib plus 2 different doses of trametinib (1 or 2 mg per day). One would expect increased toxicity from combining these agents, and that was true for certain toxicities, such as fever. Nearly 40% to 50% of patients taking the combination experienced fever. However, because skin toxicities with dabrafenib are driven by MEK, there was far less skin toxicity with the combination than with dabrafenib alone—the rate of keratoacanthoma or cutaneous squamous cell carcinoma went from 15% to just 2%. This is one of the remarkable observations in melanoma treatment, because most of the time you see more toxicity when combining agents.

The response rates also were higher with the combination than with dabrafenib alone, given that almost 90% of patients had shrinkage of their tumor. The objective response rate went from 50% to approximately 75%. And instead of half the patients progressing at 6 months, now half the patients progressed at 10 months.

That is why the FDA approved a combination of dabrafenib and trametinib in January 2014, and why this is now the standard of care for BRAF-positive metastatic melanoma.

H&O What other studies have looked at BRAF inhibition plus MEK inhibition?

HT The FDA required that phase 3 trials be done, and in these the advantages of the combination were not as impressive as they had been in the earlier trial. In COMBI-d, which was published by Long and colleagues in the *New England Journal of Medicine*, the median progression-free survival (PFS) with dabrafenib and trametinib was not as long as it had been in the phase 1 trial—it was only 9.3 months. Another interesting result in this trial was that PFS was unexpectedly high with dabrafenib alone: 8.8 months. Still, the combination decreased the risk of progression by about 30% compared with dabrafenib, which is an important outcome.

COMBI-v, which compared vemurafenib alone vs dabrafenib plus trametinib, was published in the *New England Journal of Medicine* with Caroline Robert as the first author. This trial also found that combination treatment was superior to a single-agent BRAF inhibitor, boosting the objective response rate from 51% to 64%.
Another study of combination therapy is coBRIM, which is a phase 3 trial comparing vemurafenib alone vs vemurafenib plus the experimental MEK inhibitor cobimetinib that was published in the *New England Journal of Medicine* with Larkin as the first author. The study found that PFS was 9.9 months in the combination arm, vs 6.2 months with vemurafenib alone. The risk of progression was decreased by 40%.

H&O Could you talk about your own work with combination therapy for patients with brain metastases?

HT Brain metastases affect up to 40% of patients with advanced melanoma. Melanoma has the greatest propensity of any solid tumor to go to the brain, even though there are more brain metastases from cancer of the lung and breast because these cancers are more common. Autopsy data reveal that more than 70% of patients with melanoma have brain metastases when they die. BREAK-MB, which was published by Long and coinvestigators in the *Lancet Oncology*, was the first international collaboration to study a targeted agent, dabrafenib, in patients with untreated melanoma brain metastases and it confirmed the activity of dabrafenib in intracranial melanoma lesions. In a national study called coBRIM-B (NCT02230306), we are examining the use of vemurafenib plus cobimetinib in patients with melanoma who have brain metastases.

H&O What other drug combinations have been studied in patients with melanoma?

HT Right now the standard of care is a BRAF inhibitor plus a MEK inhibitor, but as I mentioned earlier, reactivation of the MAPK pathway does not account for all the resistance. Another pathway of resistance in BRAF-mutated melanoma is the PI3-kinase (PI3K) pathway, so combinations of a BRAF inhibitor and a PI3K inhibitor are being studied. BRAF inhibitors are also being studied in combination with AKT inhibitors and in patients with BRAF-mutated cancer.

Approximately 20% to 25% of melanoma patients have a mutation in NRAS. A phase 1 study that was presented at the 2014 annual meeting of the American Society of Clinical Oncology (ASCO) by Sosman and colleagues looked at combining 2 experimental agents: the MEK inhibitor binimetanib and the cyclin-dependent kinase 4 (CDK4) inhibitor ribociclib (LEE011). This study was based on work that found that NRAS-mutated melanoma has significant dysregulation of the CDK4 pathway. The study found impressive results from adding a MEK inhibitor to a CDK inhibitor.

H&O What is the role of immunotherapy in combination therapy?

HT So far, immunotherapy has been approved for use only as a single agent. We have interleukin-2, which has been available for more than 2 decades and produces a response in approximately 15% of patients. Those patients whose tumors respond tend to get a very durable response, and the response is complete in about one-third of cases.

Interleukin-2 is a highly toxic treatment, however. It is very difficult to handle—we only give it to relatively healthy people.

The second agent that was approved in the metastatic setting is the monoclonal antibody ipilimumab (Yervoy, Bristol-Myers Squibb), which targets cytotoxic T-lymphocyte–associated antigen 4 (CTLA4). Ipilimumab is only effective in approximately 15% to 20% of patients, but the most important finding is that it doubles overall survival. One-year overall survival with melanoma went from 25% to 48% thanks to ipilimumab, according to a study published by Hodi and colleagues in the *New England Journal of Medicine*.

We have now data showing that patients who continue to show a response at 2 or 3 years will continue to respond at 5 and even 10 years. Data by Schadendorf and colleagues from the expanded access program in both Europe and the United States showed that approximately 25% of patients were seeing this long-term benefit from single-agent ipilimumab.

Since then, we have seen at least 3 combinations of note with ipilimumab. One of them is ipilimumab plus the granulocyte-macrophage colony-stimulating factor (GM-CSF) sargramostim; this Eastern Cooperative Oncology Group (ECOG) study by Hodi and colleagues was recently published in the *Journal of the American Medical Association.* This study was very interesting. It showed that the addition of GM-CSF to ipilimumab improved survival in advanced melanoma, although not dramatically. What was dramatic was the improvement in severe toxicity, which decreased from 58% to 45%. The rate of severe gastrointestinal toxicity dropped even more, from 27% to 16%.

A second combination is ipilimumab plus bevacizumab (Avastin, Genentech), which is being examined in a phase 2 ECOG study (NCT01950390). A third combination, which we studied here at the University of Pittsburgh, was ipilimumab plus interferon alfa-2b. We found the interferon improved responses without affecting toxicity. This combination is being further explored in a phase-2 ECOG study (NCT01708941).

H&O How about combination therapy with a programmed death 1 (PD-1) inhibitor?

HT The approval of 2 PD-1 inhibitors in 2014 represented a major advance in treating metastatic melanoma. Pembrolizumab (Keytruda, Merck), which was approved in September, and nivolumab (Opdivo, Bristol-Myers Squibb), which was approved in December, are essentially 3 times more effective than other single-agent immunotherapies. The objective response to single-agent immunotherapy with ipilimumab or interleukin-2 is 10% to 15%, whereas the response to single-agent pembrolizumab or nivolumab is 40% to 50%. In addition, the rate of grade 3 or 4 toxicity is approximately 10% with pembrolizumab and nivolumab instead of the 30% one would expect with ipilimumab. The twin attributes of high efficacy and low toxicity make PD-1 inhibitors excellent agents to study in combination with other drugs.

The most impressive immunotherapy combination we have seen is ipilimumab and nivolumab; a study of this combination by Wolchok and colleagues was published in 2013 in the *New England Journal of Medicine*. The objective response rate in this study was tremendous: 53% or higher with higher-dose treatment. We know that tumor responses with immunotherapy tend to be durable. Unfortunately, toxicity affected more than half of patients. This is an example of the benefit of greater and more durable efficacy coming at the expense of more toxicity.

I am leading a study with the Cytokine Working Group of ipilimumab plus nivolumab in in patients with untreated melanoma brain metastases with the hope of extending the benefit to this population.

Pembrolizumab is also being studied with trametinib and dabrafenib in a phase 1 and 2 trial called KEYNOTE-022 that is currently recruiting patients (NCT02130466).

H&O Are there any other reasons to combine immunotherapy with other agents?

HT One interesting finding is that using a BRAF inhibitor against a BRAF-mutated tumor not only kills the cells, it changes the tumor microenvironment so it becomes much more receptive to immune cells. As a result, B cells flood into the tumor right after the BRAF inhibitor is started. Some of the most interesting work on this is by Boni and colleagues in *Cancer Research*, who showed that 2 weeks of therapy with a BRAF inhibitor not only increases expression of programmed death ligand 1 (PD-L1), it also changes the chemokine profile and allows B-cell infiltrates into the tumor. This finding really spurred on researchers to start testing combinations of targeted therapy and immunotherapy.

The first BRAF inhibitor/immunotherapy combination to be tested was vemurafenib plus ipilimumab; these were the 2 relevant drugs that were approved by the FDA at the time. The results of this 12-patient study were published as a letter by Ribas and colleagues in the *New England Journal of Medicine*. Unfortunately, the combination caused significant liver toxicity and the study was closed early.

Now that we have PD-1 inhibitors, there is a renewed interest in combining immunotherapy with BRAF inhibitors. Igor Puzanov and colleagues are testing a combination of ipilimumab, dabrafenib, and trametinib,

but the triple combination may be difficult to deliver (NCT01767454).

At the University of Pittsburgh, we are getting ready to launch a study examining the combination of nivolumab with dabrafenib and/or trametinib (NCT02357732). Antoni Ribas is leading a study of a PD-L1 inhibitor with dabrafenib and trametinib (NCT02027961). Also, Roche is studying the experimental PD-L1 antibody MPDL3280A in combination with vemurafenib and cobimetinib (NCT01656642).

We also have proposed a study through ECOG-American College of Radiology Imaging Network (ACRIN) in which we compare 2 different combinations of dabrafenib and trametinib vs the triple combination of nivolumab, dabrafenib, and trametinib.

H&O Is there anything that you would like to add?

HT This is an amazing time in the history of melanoma therapy and investigation. We have had 7 new drugs approved in the last 3 to 4 years, and we are finally making an impact on a disease that was so hard to treat in the past.

We still have a lot to learn, though. Not everybody responds to treatment, a lot of patients continue to progress, and we have not had a great impact in patients with brain metastases. We also need to learn better how to select the right patient for the right treatment.

One anecdote from my own practice relates to a patient I treated with a single-agent BRAF inhibitor. She had tumors throughout her body and was in severe pain, and 10 days after starting vemurafenib she returned to the clinic and I could not find a single tumor to biopsy. She continued taking vemurafenib without progression for more than 26 months. So that goes to show that as promising as combination therapy may be, we can still get excellent results with single-agent therapy.

Suggested Readings

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