FEATURE ARTICLE

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Malignant Melanoma

Advances in Treatment

Vanessa Smith, Shernaz Walton

ABSTRACT: We discuss the recent breakthroughs in the treatment of metastatic malignant melanoma. New therapies, which target the mitogen-activated protein kinase pathway, such as BRAF inhibitors and MEK inhibitors, may provide hope for those with metastatic disease where, historically, treatment has not been successful.

Key words: BRAF Inhibitors, (MAP) Kinase Pathway, MEK Inhibitors, Melanoma

INTRODUCTION

Melanoma accounts for 4% of incident cancers in the United States, and its mortality rate is increasing (Jemal, Siegel, Xu, & Ward, 2010). Although melanoma is often diagnosed later in life, 20% of cases occur in young adults aged between 15 and 39 years. If diagnosed early, melanoma is curable by excision, but until recently, adjuvant medical therapies in the management of advanced melanoma have been limited, and as such, metastatic melanoma carries a poor prognosis. The 5-year survival rate for advanced melanoma involving the lymphatic system is approximately 20%–30%, and once metastatic deposits are detected elsewhere, rates fall to approximately 7%–20% (Jemal et al., 2010).

The treatment of melanoma depends on the stage of the disease. As per the American Joint Committee on Cancer, there are four stages of the disease depending on tumor size, regional lymph node involvement, and whether distant metastases are present. This article will be discussing management of stage 4 melanoma. This is the most advanced stage where metastatic disease is always present regardless of other parameters.

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Adjuvant treatment of advanced disease has included interleukin-2 and dacarbazine, but response rates were low and neither showed an overall survival benefit (Atkins et al., 1999; Carbone & Costello, 1976). More recently, ipilimumab, a fully humanized antibody that binds to cytotoxic T-lymphocyte-associated antigen 4, sustains an immune attack on neoplastic cells and has been used for metastatic disease. A randomized study showed that ipilimumab improved survival from 6 to 10 months compared with an experimental vaccine (Hodi et al., 2010). This advance promised new effective treatment of metastatic melanoma, and more research is now underway to investigate other molecular pathways that may be targeted in an effort to produce improved therapies.

The mitogen-activated protein kinase (MAPK) pathway is an important driver in melanoma and is made up of several potential targets providing therapeutic options (Wellbrock & Hurlstone, 2010). In this pathway, the activation of rat sarcoma (RAS) proteins stimulates the rapidly accelerated fibrosarcoma (RAF) kinases: ARAF, BRAF, and RAF1.

RAF kinases are a family of three serine/threonine-specific protein kinases that are related to retroviral oncogenes. The mouse sarcoma virus 3611 contains a RAF kinase-related oncogene that enhances fibrosarcoma induction.

RAF kinases participate in the RAS–RAF–MEK–ERK signal transduction cascade, also referred to as the MAPK cascade (Roskoski, 2010). Activation of RAF kinases requires interaction with RAS-GTPases.

The three RAF kinase family members are the following:

- A-RAF
- B-RAF
- C-RAF (RAF-1)

RAS is an abbreviation of "rat sarcoma" reflecting the way the first members of the protein family were discovered. This process causes the phosphorylation of the MEK kinases, which phosphorylate the ERK kinases. Activated ERK regulates cyclin D1, which, in turn, regulates multiple cellular processes involved in cell division (Figure 1).

The MAPK/ERK pathway (Figure 1) is a chain of proteins in the cell that communicates a signal from a

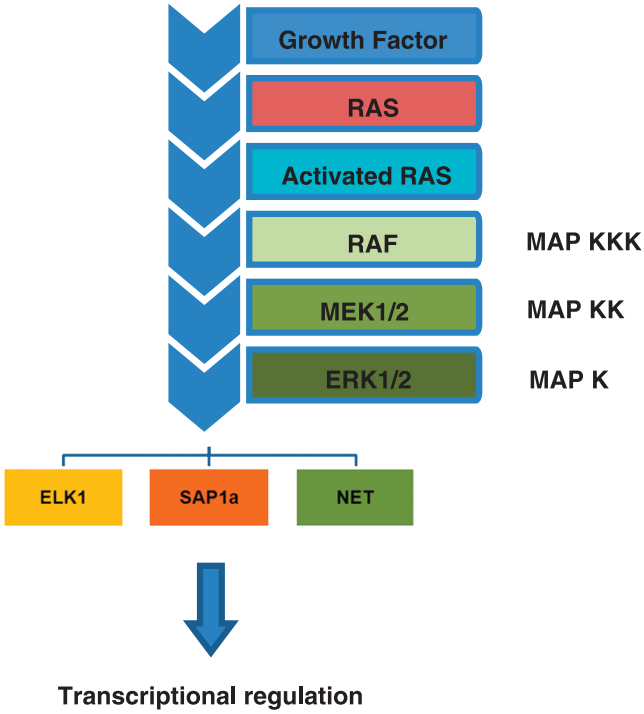

FIGURE 1. MAP kinase pathway.

receptor on the surface of the cell to the DNA in the nucleus of the cell. The signal starts when a signaling molecule binds to the receptor on the cell surface and ends when the DNA in the nucleus expresses a protein and produces some change in the cell, such as cell division. The pathway includes many proteins, including MAPK (originally called ERK), which communicate by adding phosphate groups to a neighboring protein that acts as an "on" or "off" switch—also known as the RAS–RAF–MEK–ER.

BRAF Inhibitors

Approximately 40%–60% of melanomas contain a mutation in the gene that encodes BRAF V600 that leads to constitutive activation of downstream signaling in the MAPK pathway. In a series of 197 patients, BRAF mutations were found to be associated with features of high-risk melanoma, including truncal primary, earlier age of onset, lack of chronic skin damage, and shortened survival (Long et al., 2011). Theoretically, therefore, in those with BRAF mutations, inhibition of the kinase domain of BRAF may provide a therapeutic option for preventing the advancement of metastatic melanoma.

Vemurafenib is an oral inhibitor of BRAF. It is a potent inhibitor of the kinase domain of mutant BRAF containing V600 mutations, such is the case in 80%–90% of melanoma caused by a BRAF mutation (Fennira et al., 2014; Huang, Zhuge, & Zhang, 2013). As such, vemurafenib leads to decreased cell proliferation through reductions of phosphorylated ERK and cyclin D1. Early trials of vemurafenib reported overall response rates of 52% (Ribas et al., 2011). Common side effects to treatment include the development of keratoacanthoma-type squamous cell carcinomas. Other side effects included arthralgias, rash, photosensitivity, nausea, palmar–plantar dysesthesia, and pruritus. Management of symptomatic adverse drug reactions may require dose reduction, treatment interruption, or treatment discontinuation. Dose reductions resulting in a dose below 480 mg twice daily are not recommended (Flaherty, Pusanov, et al., 2010).

Later, a phase 3 trial, comparing vemurafenib with dacarbazine, closed early because of clear improved overall and progression-free survival end points in those randomized to vemurafenib. Vemurafenib was associated with 63% of relative risk reduction for death and 74% of risk reduction for disease progression or death; the response rate with vemurafenib was 48% versus only 5% with dacarbazine. At 6 months, 84% of patients who had been given vemurafenib were still alive versus only 64% of those who received dacarbazine. Of note, the median time to response to vemurafenib was 1.45 months, and the median progression-free survival was 5.3 months (Chapman, Hauschild, Robert, Haanen, et al., 2011).

Another agent that blocks the action of BRAF is dabrafenib. Dabrafenib is a reversible, adenosine triphosphate-competitive inhibitor that selectively inhibits BRAF Val600Glu. Preliminary results of a phase 1 or 2 study of dabrafenib showed a 63% objective response rate in the 57 patients with BRAF V600 mutations (Kefford et al., 2010). The BREAK-3 study was conducted in 250 patients with untreated BRAF V600 mutation-positive metastatic melanoma. Results showed that dabrafenib significantly improved the median progression-free survival compared with chemotherapy with dacarbazine (5.1 vs. 2.7 months; $p < .0001$; Hauschild et al., 2012).

Vemurafenib and dabrafenib have both been approved by the Food and Drug Administration (FDA) for patients with unresectable or metastatic melanoma with BRAF V600 mutations. Currently, only vemurafenib has the approval of the National Institute of Clinical Excellence for this indication with debrafenib currently being under review.

Dabrafenib has a mild and manageable toxicity profile. Cutaneous squamous cell carcinomas and pyrexia are the most significant adverse effects. These are managed by resecting the cutaneous malignancies and by treating the pyrexia with antipyretics. Dabrafenib appears similar to vemurafenib with regard to efficacy but is associated with less toxicity.

MEK Inhibitors

Trametinib is an orally available, small-molecule, selective inhibitor of MEK1 and MEK2. It has been approved in 2013 by the FDA, but National Institute of Clinical Excellence guidelines for its use are still in development. Trametinib is indicated for unresectable or metastatic melanoma with BRAF V600E or V600K mutations. A phase 3 open-label trial comparing trametinib with either dacarbazine or

paclitaxel showed a median progression-free survival of 4.8 months in the trametinib group and 1.5 months in the chemotherapy group ($p < .001$). At 6 months, the rate of overall survival was 81% in the trametinib group and 67% in the chemotherapy group (Flaherty et al., 2012).

Other

Sorafenib is a tyrosine kinase inhibitor that blocks wild-type BRAF but not the V600E mutated oncogenic BRAF. A phase 3 trial of sorafenib combined with carboplatin and paclitaxel failed to show good response rates (Flaherty, Lee, et al., 2010). A small number of melanomas, particularly those of the acral lentiginous type, have changes in the C-KIT gene. Clinical trials are now testing drugs such as imatinib and nilotinib, which are known to target cells with changes in C-KIT.

SUMMARY

The manipulation of the various stages of the MAPK pathway looks to provide promising advances in the treatment of metastatic melanoma. However, it is as yet unknown how BRAF inhibitors might be used most effectively in the clinic. As trials suggest that vemurafenib has a rapid onset of response but a short duration of response, it might be best suited to those with rapidly progressing and/or symptomatic disease. One of the challenges of B-RAF inhibition is that the responses, although dramatic and rapid in onset, last, on average, approximately 6–7 months. Resistance quickly develops, and this is now an active area of investigation.

In August 2011, the U.S. FDA approved vemurafenib (Zelboraf, Plexxikon/Roche) for the first-line treatment of both metastatic and unresectable (inoperable) melanoma. Vemurafenib is the second new cancer drug approved that shows an improvement in overall survival in patients with melanoma. Vemurafenib is a threonine kinase inhibitor, one of a new class of medicines known as epidermal growth factor receptor inhibitors. Vemurafenib blocks a critical protein molecule called B-RAF, which is mutated (changed) in up to 50% of patients with melanoma. B-RAF is a protein that is part of the cell signaling pathway that controls cell growth in a number of different tissues in the body. Mutations that lock the B-RAF protein in an active state can cause excessive signaling in the pathway, leading to uncontrolled growth of melanocytes (pigment cells). When the activity of mutant B-RAF is blocked, cancer cells stop growing and die.

Vemurafenib is specifically indicated for patients with melanoma whose tumors express a gene mutation called BRAF V600. The BRAF protein produced because of this gene mutation has the amino acid (building blocks of protein) glutamate instead of the amino acid valine at position 600. Vemurafenib is not indicated for use in patients without the V600 mutation.

The FDA approval of vemurafenib was based on results from two clinical studies (BRIM3 and BRIM2) in patients with BRAF V600E mutation-positive, inoperable, or metastatic melanoma as determined by the Cobas BRAF mutation test.

BRIM3

BRIM3 (B-RAF inhibitor in melanoma phase 3) is a global, randomized, open-label, multicenter, advanced (phase 3) study that compared 960 mg of vemurafenib given orally twice daily with dacarbazine (standard of care) of 1000 mg/m^2 given intravenously on day 1, every 3 weeks in 675 patients with untreated BRAF V600E mutation-positive, unresectable (inoperable), or metastatic melanoma. Treatment was continued until disease progression, unacceptable toxicity, and/or consent withdrawal (Chapman, Hauschild, Robert, Larkin, et al., 2011). Key results are tabulated in Table 1.

TABLE 1. Results of BRIM3 Study

	Vemurafenib, No. of Patients = 337 (%)	Dacarbazine, No. of Patients = 338 (%)
Overall survival (OS)		
Number of deaths	78 (23)	121 (36)
Median OS, months	Not reached	7.9
Estimated OS at 6 months (% of patients)	84	64
Median follow-up, months	6.2	4.5
Progression-free survival (PFS)		
Median months	5.3	1.6
Complete tumor shrinkage (% of patients)	1	0
Partial tumor shrinkage (% of patients)	47.4	5.5

Note: BRIM3 = B-RAF inhibitor in melanoma phase 3.

BRIM2

BRIM2 is a global, single-arm, multicenter, open-label early-phase (phase 2) study that enrolled 132 patients with treated BRAF V600 mutation-positive metastatic melanoma. The primary end point of the study was best overall response rate (Ribas et al., 2011).

Data showed the following:

- 53% of patients treated with vemurafenib had tumor shrinkage.
- Three patients (2.3%) showed complete tumor shrinkage, and 66 (50.0%) showed partial tumor shrinkage.
- Patients who participated in BRIM2 lived a median of 6.7 months without their disease getting worse (median Progression Free Survival [PFS]).
- Median overall survival has not yet been reached after a median follow-up of 10 months.

In March 2011, the FDA approved ipilimumab (Yervoy), another new treatment of late-stage melanoma that also showed that patients lived longer after receiving the drug. Combinations of vemurafenib with other medications, such as the MAPK signaling pathway inhibitor trametenib, may prove useful in patients with melanoma. It is expected that new combinations of targeted drugs, such as the combination of dabrafenib and trametinib (GSK1120212, an MEK inhibitor), will provide higher response rates and more durable clinical benefit than dabrafenib monotherapy.

For patients with a more indolent disease, ipilimumab may be able to elicit an initial immune response with vemurafenib being reserved for when disease progression becomes apparent (Jang & Atkins, 2013). As yet, no data exist on the sequencing of these drugs.

Given that BRAF mutation is an important predictor for response to treatment, it is necessary that testing for this is done early for those with newly diagnosed, rapidly progressing metastatic melanoma. These new treatments offer huge steps forward in the management of advance metastatic melanoma; the like of such has not been seen before. However, the specifics regarding the optimum timings and combinations of classes of agents will take time to be fully established. In addition, with reports of tumor resistance, further work in this field is still very much needed.

Future research lies in observing the longer-term survival of patients with advanced melanoma with the use of these drugs and the influence of combining combinations of these drugs to detect long-term benefits. ■

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