Metastatic melanoma and vemurafenib: novel approaches

Ramon Andrade De Mello[1,2]

[1]Department of Medical Oncology, Portuguese Oncology Institute and [2]Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal

Abstract

Metastatic melanoma (MM) presents a treatment challenge to oncologists worldwide. Dacarbazine is the first line chemotherapy treatment for MM, though the overall response rates are very poor. Recently, the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) *V600* mutation was found to play a main role in MM. This mutation is present in 40-60% of melanoma patients. Vemurafenib is a *BRAF* kinase inhibitor that showed impressive results in phase I-III trials and was thus recently approved for the treatment of MM. This paper will briefly focus on vemurafenib in the treatment of MM and highlight concerns

Introduction

Recently, GLOBOCAM estimated that there will be approximately 12 million new cancer cases and 7.6 million cancer-related deaths per year worldwide. In more developed areas, melanoma has an incidence of 9.5/100,000 men and 8.6/100,000 women.[1] Although malignant melanoma is the most common cause of skin cancer-related death, metastatic disease accounts for a small fraction of all melanoma cases. In this situation dacarbazine and linterleikine-2 have been the only chemotherapeutic option approved by the Food and Drug Administration (FDA) for metastatic melanoma (MM) treatment, though the response rates are very poor (10-20%).[2] The v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E mutation has been found to play a role in MM, and it is present in 40-60% of melanoma cases.[3] Vemurafenib (previously known as PXL4032) has demonstrated impressive results in MM management in phase I - III trials.[2-4] Thus, this paper will briefly discuss vemurafenib in the treatment of MM and highlight concerns regarding its use.

V-raf murine sarcoma viral oncogene homolog B1 and melanoma

A search for mutations in components of the mitogen-activated protein (MAP) kinase pathway in a large panel of common cancers revealed that 40-60% of melanomas and 7 to 8% of all cancers carry an activating mutation in the gene encoding the serine-threonine protein kinase BRAF (BRAF).[3,5] Ninety percent of reported BRAF mutations results in a substitution of glutamic acid for valine at amino acid 600 (the V600E mutation).[2] This BRAF mutation constitutively activates BRAF and its downstream signal transduction in the MAP kinase pathway.[6] BRAF mutations are also found in a small percentage of several other tumor types.[2]

Vemurafenib and metastatic melanoma

Pre-clinical models initially showed that vemurafenib, a potent orally administered inhibitor of the BRAF V600 mutation, blocked cell proliferation *in vitro* in cells that carried the *BRAF* V600 mutation. However, vemurafenib did not show significant biological effects in cells lacking the BRAF V600 mutation.[2] In 2010, Flaherty *et al.* studied 32 metastatic melanoma patients who presented with *BRAF* V600 mutations. Flaherty's group included patients aged 18 or older with solid tumors that were refractory to standard therapy, for which curative therapy did not exist, with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 (without symptoms) or 1 (mild symptoms that do not interfere with daily activities), a life expectancy of 3 months or longer, an absence of known progressing or unstable brain metastases, and adequate hematologic, hepatic, and renal function.[2] Among the 16 patients who received 240 mg or more of PLX 4032 twice daily, 10 had a partial response and 1 had a complete response. The estimated progression-free survival among all of the patients was 7 months.

Vemurafenib outcomes in phase II and III trials

In 2011, Chapman *et al.*[3] published a phase III trial (BRIM3) that assessed 675 previously untreated metastatic melanomas for the *BRAF* V600 mutation. This study considered patients with unresectable tumors, aged 18 years or older, with a life expectancy of 3 months or longer, an ECOG PS score of 0 or 1, and adequate hematologic, hepatic, and renal function. The previously untreated stage IIIC or stage IV melanoma patients had positive *BRAF* V600 mutations as determined by a real-time polymerase-chain-reaction assay (Cobas® 4800 *BRAF* V600 Mutation Test, Roche Molecular Systems) that was performed among 5 central laboratories in the United States, Germany, and Australia.[3] Furthermore, patients were excluded if they had a history of cancer within the past 5 years (except for basal- or squamous-cell carcinoma of the skin or carcinoma of the cervix) or non-controlled brain metastases. Concomitant treatment with any other anticancer therapy was not allowed. In approximately one third of the participants, *BRAF* was sequenced retrospectively by Sanger and 454 sequencing at a central laboratory.3 However, the Cobas® test used in the BRIM3 study occasionally incorrectly detect a V600D or V600K mutation as a V600E mutation.[4,7] Thus, the BRIM3 study included 20 patients with V600D (1/675) and V600K mutations (19/675). In the BRIM3 study,[3] patients were randomly assigned to receive either vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg per square meter of body-surface area intravenously every 3 weeks). In the vemurafenib group, a survival benefit occurred in each pre-specific subgroup, according to age, gender, ECOG PS, tumor stage and geographic region. The results of this trial were impressive: at six months, overall survival (OS) was 84% (CI 95%, 78-89) in the vemurafenib group and 64% (CI 95%, 56-73) in the dacarbazine group. The authors also reported a 63% (P<0.001) reduction in the risk of death in their interim analysis, and either 73% risk

Correspondence: Ramon Andrade De Mello, Department of Medical Oncology, Portuguese Oncology Institute, Rua Dr. António Bernardino de Almeida, 4200-072, Porto, Portugal.
Tel. +351.91.2040770 - Fax.: + 351.225.084010.
E-mail: ramonmello@med.up.pt

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of death or disease progression (P<0.001), as compared with dacarbazine. Progression free survival (PFS) was assessed in 549 patients. The estimated PFS duration was 5.3 months for the vemurafenib group and 1.6 months for the dacarbazine group. Superior PFS times were observed in all subgroups analyzed: age, gender, ECOG PS, tumor stage, region, and lactate dehydrogenase level.[3] Also, among 439 patients who could be evaluated for tumor response, 106/219 the vemurafenib group had a confirmed objective response (48%; 95% CI 42 to 55), including 2 complete responses and 104 partial responses, with a median time to response of 1.45 months.[3] In the dacarbazine group, only 12/220 (5%; 95%, CI, 3 to 9) patients presented an objective response (partial response), with a median time to response of 2.7 months (P < 0.001 determined by the chi square test).[3] Among the 10 *BRAF* V600K patients, 4 had a partial response with vemurafenib treatment (40%).[3] In February 2012, Sosman *et al.* reported a phase II trial with 132 patients who had *BRAF* V600-mutant MM (122, with the V600E mutation and 10 with the V600K mutation) and had a median follow-up of 12.9 months (range 0.6 to 20.1). A complete response was achieved in 8/132 (8%) patients and a partial response in 62/132 (47%) patients. Only 18/132 (14%) patients had primary progressive disease. Among the 10 patients with *BRAF* V600K mutations, 4 (40%) had a partial response, 3(30%) had stable disease, 2 had progressive disease (20%), and 1 could not be assessed.[4] The median duration of response was 6.7 (95% CI, 5.6 to 8.6) months. The median PFS among 33/132 patients was 6.8 months (95%, 5.6 to 8.1). Further, 62/132 patients were alive at the cut-off date and the median OS was 15.9 months (95% CI, 8 to not reached).[4]

Vemurafenib toxic effects

Furthermore, 618 patients (92%) were evaluated in the BMIR3 study for toxic effects.[3] Common adverse events associated with vemurafenib were arthralgia grade 2 (18%) and grade 3 (3%), rash grade 2 (10%) and grade 3 (8%), fatigue grade 2 (11%) and grade 3 (2%), alopecia grade 2 (8%), keratoacanthoma grade 2 (2%) and grade 3 (6%) or squamous-cell carcinoma grade 3 (12%), photosensitivity, nausea grade 2 (7%) and grade 3 (1%), and diarrhea grade 2 (5%) and grade 3 (<1%); however, only 126/336 (38%) of patients required dose modification because of the toxic effects in the vemurafenib group and 44/282 (16%) in the dacarbazine group.[3]

Other class I RAF inhibitor: GSK2118436 (dabrafenib)

Another selective *BRAF* inhibitor for MM *BRAF* V600 mutated patients is in development.[6] Dabrafenib (GSK2118436) is a highly potent and selective ATP competitive *BRAF* inhibitor with more than 100-fold selectivity for mutant *BRAF* over wild-type *BRAF* in cell lines.[8] In 2010, dabrafenib was presented at American Society of Clinical Oncology annual meeting, in Chicago, USA. The results of phase I/II trials were presented that evaluated 61 (52 *BRAF* V600 mutated) patients who received dabrafenib 12-400 mg daily.[9] At the two highest doses evaluated, 150 mg and 250 mg twice daily, objective responses were observed in 10/16 patients with *BRAF* V600, mirroring the results of the vemurafenib dose-escalation study. One patient reported dose-limiting syncope (200 mg BID).[9] More frequent adverse effects were skin changes (23/62 patients, 1 patient grade 3), low grade cutaneous squamous cell carcinoma (2/62), headache (12/62 patients, 1 patient with grade 3), nausea (11/62 patients with grade 1), fatigue (9/62 patients with grade 1), and vomiting (8/62 patients, 4 patients with grade 2).[9] Clinical trials comparing GSK2118436 to dacarbazine in the treatment of naive metastatic melanoma patients are accruing patients (NCT01227889) and the results may be promising.[6]

Conclusions

Biological therapies and alternative options are under investigation for the treatment of MM, but none of them has shown satisfactory results.[5,10] Recently, molecular and translation research has become of interest in cancer.[11-15] In addition to breast,[11] lung[13,14] and colon rectal cancer, the malignant melanoma field now has molecular tools that can help medical oncologists make more informed decisions for the treatment of patients.[16] Recently, vemurafenib was approved by the FDA, and it is recommended to be approved by the European medicine agency for the treatment of metastatic melanoma with the *BRAF* V600 mutation. Thus, patients with advanced melanoma may benefit from this novel therapeutic treatment.

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