MAEDICA – a Journal of Clinical Medicine
2017; 12(4): 293-296

MÆDICA - a Journal of Clinical Medicine

STATE OF THE ART

Tyrosine-kinase Inhibitors Treatment in Advanced Malignant Melanoma

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ABSTRACT

Objective: *To put in perspective recent advances in the treatment of malignant melanoma with novel tyrosine-kinase inhibitors.*

Methods: *We reviewed the largest trials that support the treatment with tyrosine-kinase inhibitors (TKIs) in cutaneous malignant melanoma, the base of the current guideline recommendations.*

Conclusions: *Mitogen-activated protein-kinase (MAPK) pathway inhibition via modern TKIs is a major breakthrough in the treatment of melanoma, with a very high benefit for patients with disease harboring BRAF-gene mutations, in terms of rates of response and survival.*

Keywords: malignant melanoma, tyrosine-kinase inhibitors, BRAF mutation.

BACKGROUND

The general landscape of the treatment in malignant melanoma, a terrible disease with few treatment options until recently, has suffered major changes in the past few years. The progress consists mostly in the acquisition of new systemic treatment options in the setting if advanced/inoperable or metastatic disease, respectively by monoclonal antibodies capable of directly amplifying anti-tumoral immune response *via* inhibition of cellular immunity control mechanisms, the so-called "checkpoint inhibitors" (ipilimumab, nivolumab, pembrolizumab, etc.) and the tyrosine-kinase inhibitors (TKIs), capable of directly influencing the intracellular signaling pathways that control tumoral growth (vemurafenib, dabrafenib, trametinib, etc.).

The BRAF protein is a serine/threonine-kinase involved in the mitogen-activated protein-kinase (MAPK) signaling pathway (B-Raf/Mek/Erk proteins). The literature describes a proportion of around 40-50% of malignant melanomas as having mutations in the BRAF gene (more than 90% V600E type mutations, where valine is substituted for glutamic acid in position 600), these mutations being associated with amplification of

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Article received on the 23rd of October 2017 and accepted for publication on the 22nd of December 2017.

tumoral proliferation mechanisms, mainly by dysregulation of MEK/ERK receptors (1) (Figure 1). Currently, the treatment in advanced unresectable/metastatic malignant melanoma that harbors a BRAF V600 activating mutation is represented by tyrosine-kinase inhibitors, according to international guidelines (2, 3).

BRIM-3 is the first phase III randomized trial that demonstrated an improvement of overall survival by treatment with vemurafenib in patients with cutaneous malignant melanoma with BRAF V600E mutation. A total of 675 patients with advanced BRAF mutated malignant melanoma who had not been previously treated were randomized 1:1 between vemurafenib 960 mg *per os* twice a day and dacarbazine 1000 mg/sqm intravenously every three weeks (the previous standard treatment for advanced disease) as control. Overall survival (OS) at six months was increased from 64% in the dacarbazine arm (95% CI, 56-73%) to 84% in the vemurafenib arm (95% CI, 78-89%). The trial enabled cross-over of patients under dacarbazine to vemurafenib upon progression of disease. Response rates (RR) were also increased: 48% for vemurafenib and only 5% for dacarbazine, comparable to historical references. Adverse effects associated with vemurafenib treatment were arthralgia, cutaneous rash, fatigue, alopecia, keratoachantomas or cutaneous squamous cell carcinoma, photosensitivity, nausea and diarrhea (4). A subsequent extend analysis, at a median follow-up of 12.5 months for patients started on vemurafenib (IQR 7.7-16.0) and 9.5 months for subjects on dacarbazine (IQR 3.1-14.7), after the cross-over of 25% patients who had been treated with dacarbazine, showed a significant increase in overall survival in the vemurafenib arm [13.6 months (95% CI, 12-15.2)] compared to dacarbazine [9.7 months (95% CI, 7.9-12.8)], with a hazard ratio of 0.7 (95% CI, 0.57-0.87) and a P value of 0.0008; median progression free survival (PFS) was also increased to 6.9 months (95% CI, 6.1-7) for vemurafenib *vs.* 1.6 months (95% CI, 1.6-2.1), HR=0.38 (95% CI, 0.32-0.46), P<0.0001. Subgroup analyses demonstrated that survival benefits were maintained in both BRAF V600E mutations and V600K mutations (5).

Another tyrosine-kinase inhibitor, dabrafenib, showed an increase in PFS as compared to dacarbazine in malignant melanoma stage IV or unresectable stage III, with V600E BRAF mutation, in previously untreated patients. The randomized phase III trial included 733 patients and demonstrated an increase in median PFS from 2.7 months with dacarbazine (1000 mg/sqm iv every three weeks) to 5.1 with dabrafenib (150 mg po twice daily), with a HR of 0.3 (95% CI, 0.18-0.51; P<0,0001) (6).

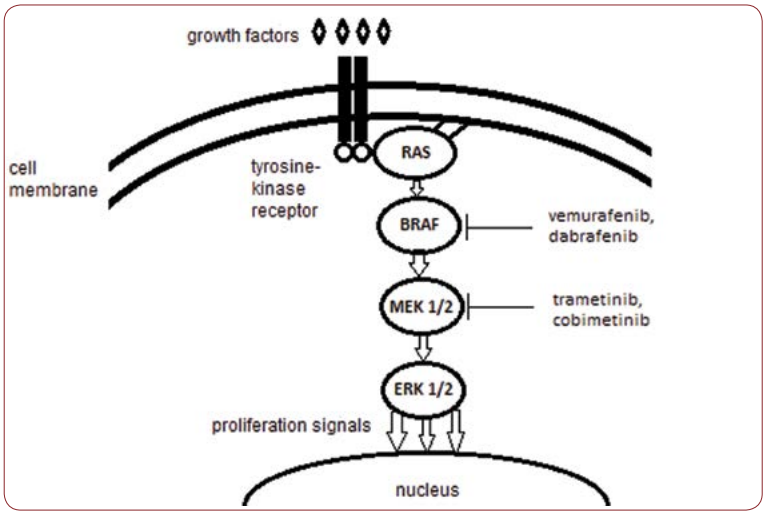

FIGURE 1. The MAPK pathway and TKIs sites of action

The relatively short-lived response to these treatments has led to the hypothesis that the clinical benefit of anti-BRAF treatment can be enhanced by concomitant inhibition of the MEK enzyme, another downstream effector of the MAPK pathway. As such, clinical research in BRAF mutated melanoma has been extended to combinations of BRAF and MEK inhibitors (cobinetinib, trametinib), BRAF-monotherapy, having demonstrated efficacy and being further used as control, with positive results.

One of the first combinations of this type that has been studied is vemurafenib and cobimetinib. A multicentric multinational phase III randomized study compared the therapeutic effect of combined vemurafenib (BRAF inhibitor) plus cobimetinib (MEK inhibitor) *versus* vemurafenib plus placebo (1:1 randomization) in a population of 495 patients with advanced (unresectable) or metastatic melanoma in whom BRAF mutation was present (V600E and V600K; in 38 patients, it was not known whether they had a BRAF mutation). Median PFS was 9.9 months in the group treated with vemurafenib/cobimetinib and 6.2 months in the group treated with vemurafenib alone, HR=0.51 (95% CI,

0.39-0.68; P<0,001). The response rate in the combination arm was 68% compared to 45% in the monotherapy group (P<0.001), including 10% and 4% complete response, respectively. An interim analysis also showed an increase in OS at nine months, from 73% (95% CI, 65-80%) in the monotherapy arm to 81% (95% CI, 75-87%) in the combination arm (7).

Another randomized trial conducted in medical centers in 14 countries (423 patients distributed 1:1) compared the combination of dabrafenib plus trametinib *versus* dabrafenib plus placebo in patients with malignant melanoma stage IV or unresectable stage IIIC in whom V600E/K BRAF mutation was present. Median OS was 25.1 months (95% CI, 19.2- not reached) in the combination treatment arm as compared to 18.7 months (95% CI, 15.2-23.7; P=0.0107) in the monotherapy arm (8).

All the above mentioned trials were performed in advanced/unresectable and metastatic disease, supporting the use of these treatments in palliative settings, with the hope of controlling symptoms and prolonging survival for as long as possible. But what about the currative inteng? What about those stages of the disease where complete cure is aimed, despite the considerable risk of relapse after surgery? For years, in these stages, interferon – either high-dose or pegylated – has been the standard adjuvant treatment, which was very hard to endure and provided only a modest benefit in terms of disease free survival (DFS), with no clear benefit in terms of overall survival (3).

The results of the COMBI AD trail were presented for the first time at the 2017 ESMO congress in Madrid, Spain. It was a phase III trial that enrolled patients with stage IIIA, IIIB or IIIC melanoma with BRAF V600E/K mutation who had undergone complete resection of their disease. A total of 870 patients from 26 countries at 169 sites were enrolled over a period of two years (from January 2013 to December 2014) and randomized 1:1 to receive either oral dabrafenib 150 mg twice daily plus trametinib 2 mg once daily, or two matched placebo tablets, for an intended duration of 12 months after surgery. Notably, in stage III completely resected melanoma, as of yet, follow-up (without active treatment) represented a standard option. The primary end point was relapse free survival; secondary end points included overall survival and distant metastasis-free survival. At a median follow-up of 2.8 years, an estimated three-year relapse free survival was 58% in the active treatment group and 39% in the placebo group, with a HR for relapse or death of 0.47 (95% CI, 0.39-0.58; P<0.001). The three-year overall survival was 86% in the combination arm *versus* 77% in the placebo arm, with a HR for death of 0.57 (95% CI, 0.42-0.79; P=0.0006); this level of improvement did not cross the specified interim analysis boundary that was determined at a P=0.000019. Further follow-up is needed. Rates of distant metastasis-free survival and freedom from relapse were also higher in the combination therapy group. The safety profile of active treatment was consistent with the results from trials in metastatic melanoma. The authors concluded that the adjuvant treatment with dabrafenib plus trametinib significantly reduced the risk of recurrence in patients with stage III resected melanoma that harbors BRAF V600E or K mutations (9). At ESMO, this strategy was claimed to be a potential new standard of care in melanoma.

The transition of this treatment strategy from metastatic/advanced to adjuvant setting greatly underscores the large clinical benefit and the step forward made in a disease where, until recently, systemic treatment options were very limited, if at all existent, especially considering the potential for a dramatic evolution of this disease.

In Romania, the treatment with TKIs has been registered for years but only recently has it been reimbursed. Starting with 2017, there is full reimbursement for either the combination of dabrafenib and trametinib or the dabrafenib monotherapy in metastatic/advanced melanoma that is BRAF V600E/K mutation positive, which represents a valuable treatment option and a great opportunity for high-quality medicine, important to both patients and clinicians. ❑

Conflicts of interest: none declared.
Financial support: none declared.

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