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ORIGINAL ARTICLE

Efficacy of Vemurafenib Treatment in 43 Metastatic Melanoma Patients with BRAF Mutation. Single-Institute Retrospective Analysis, Early Real-Life Survival Data

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Abstract BRAF inhibitor vemurafenib achieved improved overall survival over chemotherapy and have been approved by the FDA and EMA for the treatment of BRAF-mutated metastatic melanoma. The aim of our retrospective analysis was to determine the efficacy and safety of vemurafenib therapy for BRAF mutated metastatic melanoma and subsequently to prove the clinical benefit for the studied 43 patients, based on real-life data. From November 2012 to October 2015 we have selected 43 BRAF mutated, metastatic melanoma patients, treated with vemurafenib. The median follow-up time was 15.9 months. We evaluated progression free survival (PFS), overall survival (OS) and toxicities. According to the AJCC staging system 70% of the patients had stage M1c metastasis, including 6 with stable brain metastasis. Objective responses were noted in 51.1%, the disease control rate was achieved in 79% of the patients. Complete responses were attained by 5 patients (11.6%). Median PFS was 6.48 (95% CI:4.8–15.0) months, median OS was 11.47 (95% CI:8.08-NA) months. We found significant association between LDH level and OS in univariate (p = 0.000613) and multivariate analysis (p = 0.0168). The most common adverse events (AEs) included follicular hyperkeratosis, rash, arthralgia and photosensitivity. Grade 3 AEs, such as cutaneous squamous-cell carcinoma, QTcB interval prolongation, rash, arthralgia were reported in 7 patients (17%). We had no Grade 4 side effects. Similar to the previously published data our analysis confirms the improved survival with vemurafenib treatment (11.47 months) in patients with BRAF V600 mutation. Vemurafenib therapy was well tolerated, the AE profile was almost consistent with the previously reported data of randomised clinical trials.

Keywords Vemurafenib · Melanoma · LDH level · Targeted therapy · Treatment · Survival

Introduction

Cutaneous melanoma is the most aggressive form of all skin cancers. The incidence and mortality rate has been increasing over the past four decades. Despite being a rare form of all skin cancers, it accounts for nearly 75% of skin cancer deaths [1]. In 2014 more than 2000 new cases of melanoma were diagnosed in Hungary alone. Until 2011 metastatic melanoma had no accepted effective therapy, the treatment options as chemotherapies displayed a very low level of efficacy. The prognosis of metastatic melanoma patients was poor, with a median survival of 6–10 months, the five-year survival rates were estimated to be less than 5% [2]. In 2011 the treatment landscape has changed with the approval of two new treatment options involving immunotherapy [3] and targeted agents, which have demonstrated a significantly higher survival benefit for metastatic melanoma patients. Vemurafenib is the first selective small molecule inhibitor of mutated BRAF. Approximately 40 to 60% of cutaneous melanoma carry mutations in BRAF leading to constitutive activation of downstream signalling through the MAP kinase/ERK-signalling pathway, responsible for transferring signals for cell growth from the cell surface to the nucleus [4].

Vemurafenib achieved improved overall survival over chemotherapy and have been approved by the FDA in August of 2011 and EMA in February of 2012 for the treatment of BRAF-mutated metastatic melanoma, demonstrating the a

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median progression-free survival of 6 to 8 months [5]. The aim of our retrospective study was to determine the progression free survival, overall survival and safety of vemurafenib therapy for BRAF mutated metastatic melanoma and subsequently to prove the clinical benefit for the studied 43 patients, based on real-life data in a single institute analysis.

Material and Methods

Patients and Treatment

From November 2012 to October 2015 we have selected a number of 43 BRAF mutated, metastatic melanoma patients, treated with vemurafenib. Patients were at least 18 years of age and all of them had unresectable stage IIIC or stage IV (M1a, M1b or M1c disease) melanoma with measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [6]. In baseline characteristics the following parameters were registered: gender, age, Eastern Cooperative Oncology Group (ECOG) performance status, mean Breslow tumor thickness, exulceration, melanoma metastasis stage (M1a, M1b, M1c), lactate dehydrogenase (LDH) level at enrollment (normal or elevated), treatment lines (first, second, third, fourth), genotype of the BRAF mutation status (V600E, V600 K, undefined). Patients with brain metastasis were included in case of stable disease. The baseline characteristics of the patients are shown in Table 1.

Cobas 4800 V600 mutation test, which is for the assessment of the BRAF mutation status from DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue was used to identify BRAF ^{V600} mutation status. The Cobas test was designed to detect the predominant BRAF^{V600E} mutation with high sensitivity and was performed at the Department of Pathology at the National Institute of Oncology. Study patients were stratified based on the American Joint Committee on Cancer stage (IIIC, M1a, M1b or M1c), ECOG performance status. All patients received continuous vemurafenib therapy according to the approved prescribing information (at a dose of 960 mg twice daily orally) unless unacceptable side effects or disease progression occurred. Safety evaluations were conducted every 4 weeks, including physical examination, electrocardiography, dermatologic evaluation and laboratory tests, that included complete blood count, chemical testing and urine analyses. The patients were monitored for adverse events at each visit and the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 were used for all grading.

Dose reductions/interruption were determined for intolerable Grade 2 toxic effects or worse. When toxicity that resulted in a dose reduction improved to Grade 1 or less, the dose was restarted at 720 mg after a second presence of the toxic effects at 480 mg twice daily. Cutaneous squamous-cell carcinoma did not require dose modification. At baseline, patients underwent computed tomography and magnetic resonance imaging of the brain. We conducted tumor assessment according to RECIST, version 1.1, at baseline, at weeks 9, and every 12 weeks thereafter until tumor progression, death or intolerable toxicities.

Table 1 Patients characteristics

Patients characteristics	
Age, Years	57 (27–77)
Sex	
Women	22 (48.8%)
Men	21 (51.2%)
Breslow mean tumor thickness (mm)	4.9 (1–15)
Exulceration	19 (59.4%)
ECOG performance status	
0	21 (49%)
1	18 (42%)
2	4 (9%)
Metastatic status	
Unresectable stage IIIC	5 (11%)
M1a	3 (7%)
M1b	5 (12%)
M1c	30 (70%)
Normal lactate dehydrogenase level at enrolment	21 (49%)
Treatment lines	
First	12 (27.9%)
Second	19 (44.2%)
Third	8 (18.6%)
Fourth or more	4 (9.3%)
History of brain metastasis	6 (13.9%)
BRAF mutation subtype	
V600E	39 (90.6%)
V600 K	2 (4.7%)
Not specified	2 (4.7%)

Statistical Analysis

We evaluated median progression free-survival (PFS) and median overall survival (OS) as multiple endpoints by using the Kaplan-Meier method. Overall survival was defined as the time beginning from starting the therapy until melanoma specific death. The effect of factors such as age, gender, Clark invasion level, Breslow tumor thickness, exulceration, lactate dehydrogenase level at the beginning of the therapy, on overall survival was determined by univariate and multivariate Cox regression analyses. The significance of the models was evaluated by the log-rank test and results with two-sided P-values <0.05 were considered significant. All analysis was performed in R statistical software (R Foundation for statistical Computing, Vienna, Austria; version 3.0.3.) using the survival package in R.

Results

A total of 43 metastatic melanoma patients received vemurafenib. The median follow-up time was 15.9 months. The study included 22 women (51.2%), 21 men (48.8%), the

mean age was 57 years (range: 27–77). We found an ECOG 0–1 performance status in 91% of the patients. According to the AJCC staging system 70% of the patients had stage M1c status, including 6 patients with a history of stable brain metastasis. LDH blood level was 49% < ULN. 72.1% of the patients received vemurafenib therapy in second or third line. Out of these patients 39 had V600E, 2 of them had V600 K BRAF mutation genotype, while 2 patients' mutation was undefined.

22 (51.1%) patients had a confirmed objective response. Complete response was achieved in 5 patients (11.6%) and 17 (39.5%) patients achieved a partial response. Stable disease was seen in 27.9% of patients. We experineced primary resistance in 5 patients (11.6%). Median PFS was 6.48 (95% CI:4.8–15.0) months (Fig. 1.), median OS was 11.47 (95% CI: 8.08-NA) months (Fig. 2). We observed a non-significant difference in median PFS between the V600E and the V600 K mutation subtype groups (6.7 months versus 1.8 months) and in median OS between the V600E and the V600 K mutation groups (12.3 versus 8 months). 46.51% of the patients are still alive, the longest period of administering vemurafenib has been 26 months in this population. Analysing our subgroup with cerebral metastasis, 50% objective responses were observed; complete response was achieved in 1 patient (16.6%), partial response in 2 patients (33.3%) with vemurafenib treatment. 3 patients had progressive disease (50%). Median PFS was 4.5 months, median OS was 6.8 months in the group of patients with cerebral metastasis. We found significant association between LDH level at enrolment and OS, as the strongest predictive factor, both in univariate (HR:4.89, CI: 1.97–12.13, $p = 0.000613$) and multivariate analysis (HR:4.65, CI: 1.32–16.38, $p = 0.0168$).

The most common adverse events (AEs) included follicular hyperkeratosis, maculo-papular rash, arthralgia and photosensitivity. Grade 3 AEs, such as cutaneous squamous-cell carcinoma, QTcB interval prolongation, rash and arthralgia were reported in 7 patients (17%). We found no Grade 4 side effects and in our population there were no patients with assigned to vemurafenib developed second primary melanoma. Most of the toxic effects were related to the skin (52%) as vemurafenib associated skin manifestations: follicular hyperkeratosis, maulo-papular rash, photosensitivity, alopecia, verruca vulgaris, keratoachantoma, pruritus, palmo-plantar hyperkeratosis, squamosus cell carcinoma. 1 patient had serum bilirubin level elevation. Table 2.

Development of keratoachantoma or cutaneous squamous cell carcinoma was detected in 5 patients (12%). Median development of the first keratoachantoma or squamous cell carcinoma was 8 weeks (range: 7 to 32 weeks). Out of the 5 patients 1 patient had cutaneous squamous cell carcinoma KA mixed type. 2 patients (5%) experienced herpes zoster in this population and in case of both patients the infection developed after 6 month of treatment. After 1 month of vemurafenib treatment 1 patient developed 1 to 2 cm, subcutaneous, painful nodules, located dominantly in the under extremities. After the excision of one of these nodules the histopathology showed vemurafenib associated neutrophilic panniculitis. In this population we had no cases of permanent treatment discontinuation. Dose-reduction was required in 13 patients (30%). 13 patients' treatment was discontinued because of adverse events and after their resolution these patients were able to continue vemurafenib. In 8 patients a level 1 (75%) dose modification, in 5 patients a level 2 (50%) dose modification was required. The most common reasons for treatment discontinuation were maculopapular rash and arthralgia.

Discussion

Up to 2011 metastatic melanoma patients' treatment options were limited. Since the discovery of the metastatic melanoma molecular pathway mechanisms and the mutations concerning BRAF, poor prognosis patients have numerous promising

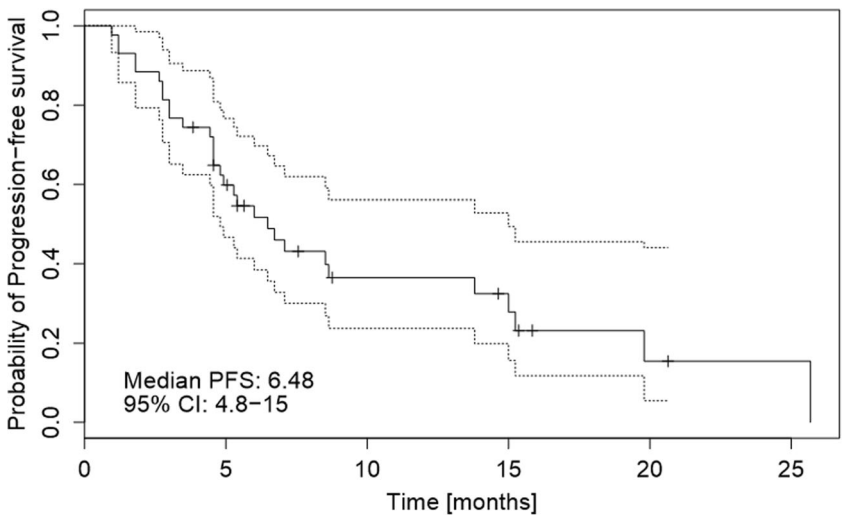

Fig. 1 Kaplan-Meier curve of progression-free survival in all patients. Median Progression-free survival, 6.48 months (95% CI:4.8–15.0)

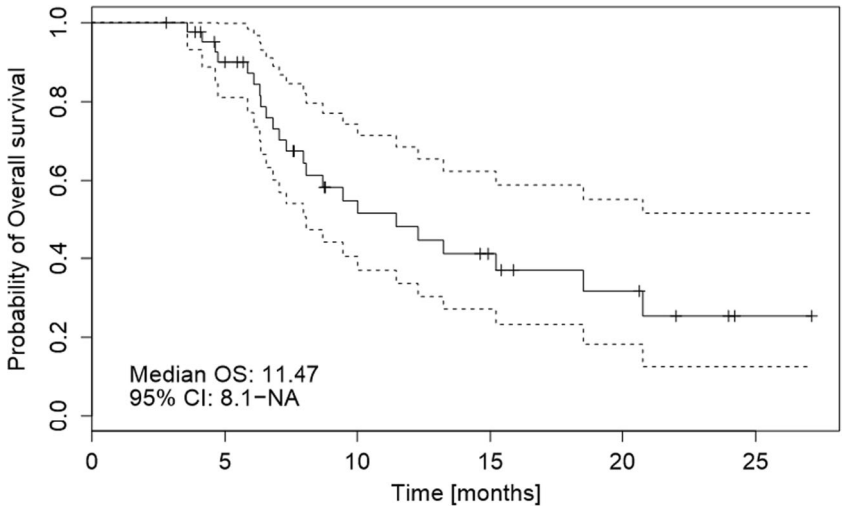

Fig. 2 Kaplan-Meier curve of overall survival in all patients. Median overall survival 11.47 months (95% CI: 8.08-NA)

approaches. Clinical studies evidenced effectiveness of targeted agents, such as BRAF-inhibitors vemurafenib approved by the Food and Drug Administration (FDA) in 2011 and dabrafenib approved in 2013. Dabrafenib is another BRAF-inhibitor that proved to have clinical benefit in BREAK-2 and BREAK-3 trials. The responses were observed in 50% (47% partial response (PR), 3% complete response (CR)) of the patients receiving dabrafenib. Median progression free survival in the dabrafenib group was 5.1 months vs. 2.7 months [7].

The phase 1 study for vemurafenib included patients with solid tumours, the dose escalation part included 55 patients followed by a dose-extension cohort of 32 additional patients with metastatic melanoma. The 32 patients with metastatic melanoma had BRAF V600 mutation, and provided evidence that inhibition of the oncogenic MAPK pathway resulted in antitumor activity with the suggested dose of 960 mg twice daily. The estimated median PFS showed >7 months. A total of 26 of the 32 patients 81% had a response, with a CR in 2 patients and a PR in 24 patients [8]. The phase 2 trial (BRIM-2) involved 132 previously treated, stage IV metastatic melanoma patients with BRAF mutation. The aim of this study was to investigate the efficacy of vemurafenib with respect to objective response rate (ORR), OS and duration of response (DoR). The median follow up was 15.9 months, the confirmed ORR 53%, and the median duration of response was 6.7 months. 6% of the patients reached CR. The median PFS was 6.8 months, the median OS was 15.9 months. The toxic effects were more or less related to the skin and the keratoachantomas or squamous cell carcinomas manifested in the first 8 to 12 weeks of the therapy [9].

Table 2 Summary of adverse events. Data are n (%)

Adverse events	Gr 1–2 no. of patients (%)	Gr3 no. of patients (%)
Follicular hyperkeratosis	17 (39%)	0
Photosensitivity	14 (33%)	0
Macular-papular rash	7 (16%)	2 (5%)
Arthralgia	10 (23%)	1 (2%)
Diarrhoea	5 (12%)	0
Fatigue	4 (9%)	0
Alopecia	5 (12%)	0
Verruca vulgaris	4 (9%)	0
Keratoachantoma	3 (7%)	0
Pruritus	2 (5%)	0
QTcB interval prolongation	0	2 (5%)
Increased total bilirubin level	1 (2%)	0
Palmo-Plantar hyperkeratosis	2 (5%)	0
Dysgeusia	1 (2%)	0
Cutaneous squamous-cell carcinoma	0	2 (5%)
Vemurafenib associated panniculitis	1 (2%)	0

The approval clinical trial for vemurafenib resulted in the BRIM 3, phase 3 study, comparing vemurafenib to DTIC involving 675, previously untreated metastatic melanoma patients with BRAF mutation. The patients receiving vemurafenib experienced longer median PFS (5.3 vs. 1.6 months) and median OS (13.2 [95% CI, 12.0–15.0] vs. 9.7 months). Objective response rate (ORR) proved to be 48% vs. 5.5%. The generally observed adverse events of vemurafenib occuring were arthralgia, rash, photosensitivity, fatigue, pruritus, hyperkeratosis, diarrhoea, alopecia. In the vemurafenib group 18% of the patients developed cutaneous squamous cell carcinoma, keratoachantoma, or both. 38% of the patients in the vemurafenib group required dose modification or interruption [4].

In our study population 27.9% of the patients received vemurafenib first line, and 71.9% second-, third-, or fourth-line. Similarly to the previously published data in phase II and III trials, the median overall survival was 11.47 months. Objective responses were noted in 51.1%. DCR was achieved in 79% of patients. Complete responses were attained by 5 patients (11.6%), which is a significantly higher rate than was achieved in the BRIM-2 trial (6%). We experineced primary resistance in 5 patients (11.6%), which results are almost similar comparing to the reported data of randomised clinical trials. Approximately 10 to 15% of vemurafenib treated patients do not experience tumor regression or disease stabilization, demonstrating intrinsic or primary resistance [10, 11].

From the analysed predictive factors LDH level was significantly associated as the strongest predictive factor. In our study vemurafenib therapy was well tolerated, the AE profile was almost consistent with the previously reported data. However, less squamous cell carcinoma was observed than the literature data (19%). In this population we had no cases of permanent treatment discontinuation. Dose-reduction was required in 13 patients (30%), compared to the 38% in the BRIM 3 study. The most common reasons for treatment discontinuation were maculopapular rash and arthralgia. Development of keratoachantoma or cutaneous squamous cell carcinoma was detected in 5 patients (12%) which is a better rate than what was published in the BRIM 3 study (18%). Median development of the first keratoachantoma or squamous cell carcinoma was 8 weeks, similar to the literature data. According to the literature data infectious disease developed rarely with vemurafenib treatment [12]. Vemurafenib associated neutrophilic panniculitis was detected in one patient. The mechanism by which vemurafenib causes panniculitis is not yet known. Clinically it could cause differential-diagnostic difficulties [13].

Although BRAF inhibitor monotherapy is effective in BRAF-mutant melanoma, the duration of response is often short lived with developing resistance after approximately 6 months. The mechanisms of resistance to vemurafenib is heterogeneous. Re-activation of MAPK signalling occurs in the majority of cases of acquired resistance to BRAF inhibitors [14]. In an attempt to delay the resistance and enable greater inhibition the combination of BRAF inhibitor and MEK inhibitor (cobimetinib, trametinib) target therapy was approved by the FDA in 2015. Combination therapy demostrated even more impressive clinical outcomes than vemurafenib monotherapy, therefore is now prefered over single agent therapy, unless there are contraindications existing.

BRIM 7, phase 3 trial compared combination of vemurafenib and cobimetinib with vemurafenib as monotherapy. Median PFS was 9.9 months vs. 6.2 months in the vemurafenib monotherapy arm. The ORR was 68% in the combination arm compared to the 45% in the control arm [15]. The study results were recently updated with a median follow up of 14.2 months, the median progression free survival reached 12.3 months for cobimetinib and vemurafenib vs. 7.2 months for placebo and vemurafenib. The median overall survival was 22.3 months vs. 17.4 months [16]. The safety profile was manageable. Toxicitieswere observed more frequently with the combination group compared to the vemurafenib monotherapy, including central serous retinopathy, diarrhea, nausea, photosensitivity, elevated aminotransferase levels and an increased creatine kinase level. The incidence of secondary cutaneous squamous cell cancers decreased with the combination therapy, compared to vemurafenib alone (2% vs 11%).

Two phase 3 trials were subsequently conducted with dabrafenib and trametinib. COMBI-d compared combination of first-line therapy with dabrafenib and trametinib patients to dabrafenib and placebo. Updated results were reported a median PFS of 11 months vs 8.8 and the median OS was observed at 25.1 months for the combination arm vs. 18.7 [17]. COMBI-v compared the dabrafenib-trametinib combination to vemurafenib monotherapy. Median PFS observed at 11.4 months vs. 7.3 with vemurafenib therapy, and the ORR 64% was vs 51%. Median OS was 17.2 month at the vemurafenib arm [18].

Combination of target agents currently recommended in the NCCN guidelines for the treatment of BRAF mutated, unresectable metastatic melanoma patients. In case of contraindication, such as serosus rethinopathy, retinal vein dysfunction or left ventricular dysfunction, according to our study 6.48 month progression free survival and 11.47 month overall survival are achievable.

Our real-life data proved almost similar results comparing to the literature data, moreover in our population we had no cases of permanent treatment discontinuation. This retrospective trial confirms that similar to the BRIM 3 trial (median PFS 5.3, median OS 13.2, objective response rate (ORR 48%)) there is an improved median survival of vemurafenib treatment (median OS 11.47 months) in patients with BRAF V600 mutation. Objective responses were noted in 51.1% of the patients. DCR was achieved in 79% of patients. Complete

responses were attained by 5 patients (11.6%). Vemurafenib therapy was well tolerated, the AE profile was almost consistent with the previously reported data.

The combination of BRAF and MEK inhibitor therapy already shows further improvement in the outcomes with response rates of approximately 70% and PFS of 11–14 months as clinically proved therapeutic agents, which are now part of the daily routine. Our experiences with vemurafenib monotherapy helps the enrolment and the management of patients with combination therapy.

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