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ORIGINAL ARTICLE

Dabrafenib Therapy in 30 Patients with Melanoma Metastatic to the Brain: a Single-centre Controlled Retrospective Study in Hungary

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Abstract Dabrafenib is a potent BRAF inhibitor, which showed intracranial tumor activity. The purpose of our retrospective analysis was to evaluate the efficacy of dabrafenib for patients with melanoma brain metastasis (BM). We studied 30 BRAF mutant melanoma patients with BM, who received dabrafenib after local control of the brain between 2014 and 2017. Eastern Cooperative Oncology Group Performance Status (ECOG) was 0–2. The control arm consisted of 204 melanoma patients from our institutional melanoma database with BM and ECOG 0–2 treated with local therapies and/or chemotherapy, between 2003 and 2015. We found the intracranial disease control rate (DCR) was 83% including four (13%) complete remissions (CR), nine (30%) partial remissions (PR) and twelve (40%) stable diseases (SD) in contrast to five (17%) progressive diseases (PD). With a median follow-up of 14 months, median progression-free survival (PFS) and overall survival (OS) were 5.5 months, and 8.8 months, respectively. If calculated from BM onset, the OS turned to be 11.8 months on the dabrafenib arm, while it was only 6.0 months in the control arm (HR = 0.45, p = 0.0014). Higher risk of progression was observed with increasing ECOG (HR =4.06, p = 0.00027) and if more than 2 extracranial organs were involved (HR = 3.4, p = 0.0077). Elevated lactate dehydrogenase (LDH) was non-significantly associated with worse clinical outcome. Remarkable intracranial activity of dabrafenib in real practice was confirmed by our analysis.

Keywords Dabrafenib · Melanoma · Brain metastases · Targeted therapy · BRAF

Introduction

Patients with advanced malignant melanoma have a high rate of intracranial spread and this serious, hard to treat complication determines life expectancy. For a long time therapeutic modalities for BM were limited to surgical resection, stereotactic radiosurgery and whole-brain radiotherapy as local control and systemic chemotherapy, all of them with modest therapeutic results. Although in the past 5 years numerous new therapies, like immunotherapies (anti-CTLA4 ipilimumab, PD1 blocking nivolumab, pembrolizumab), targeted monotherapies (vemurafenib, dabrafenib) and targeted BRAF inhibitor-MEK inhibitor combination therapies (vemurafenib-cobimetinib, dabrafenib-trametinib) were licensed by the American and European authorities for metastatic melanoma, we have inconclusive information about their intracranial effect, as the presence of BM was an exclusion criterion from the majority of clinical trials. This trend seems to change recently, and several clinical studies have demonstrated the intracranial activity of targeted therapies [1–3]. Interestingly, the incidence of BRAF mutation occurs more frequently in the brain than in any other metastatic sites [4], and BM might be more common in patients with BRAF mutation than in those with wild-type BRAF [5].

Dabrafenib is a new targeted therapy, a BRAF-kinase inhibitor, like vemurafenib, but theoretically with better effect on BM according to a recent preclinical study, which established that dabrafenib may show greater brain penetration in mouse brain compared with vemurafenib after a single oral dose of drug [6].

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Our aim was to confirm the promising clinical study results in real–life practice regarding the effect of dabrafenib monotherapy for BM.

Materials and Methods

We investigated 30 melanoma patients with asymptomatic BM, verified BRAF mutation, and ECOG 0–2 who received dabrafenib therapy between 2014 and 2017. 150 mg b.i.d. dabrafenib was administered orally for all patients, until disease progression, death or unacceptable adverse events (AEs), consistently with the labeled indication. Routine efficacy and toxicity data were collected throughout treatment scheduled in 28-day dosing cycles and studied retrospectively. Radiological assessments by magnetic resonance imaging (MRI) or contrast enchanced computed tomography (CT) were performed at baseline, at 2 months, and every 3 months thereafter. Intracranial and extracranial tumor response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. We extended RECIST to include up to 5 target lesions and allowed intracranial target lesions of at least 5 mm in diameter. AEs were assessed with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Dose modification and interruptions were carried out in case of grade 3 or worse treatment related AE.

We evaluated the benefit of dabrafenib versus other previously existing modes of treatment in melanoma patients with BM. We identified 281 patients from our melanoma database with BM who did not received dabrafenib but underwent local therapies and/or chemotherapy between 2003 and 2015. 204 patients with ECOG 0–2 was used as control group. There was no significant difference in terms of the age and ECOG between the patients in the two arms, however, the gender differed significantly, therefore we used it as a covariate while comparing the two patient groups. The BRAF status of the patients in the historical group were mostly not identified.

This study was approved by our institutional review board and it was done in accordance with both the Declaration of Helsinki and International Conference of Harmonisation Good Clinical Practice.

Statistical Methods

DCR was determined as the sum of CR, PR and SD rates, while ORR as the sum of CR and PR rates. All these measures were classified on the basis of the best response recorded. We determined responses for intracranial and extracranial sites separately. OS was defined as the time interval between the start of dabrafenib therapy and death or last date of follow-up. PFS was calculated from the beginning of the therapy to the first intracranial/extracranial progression or to death of any cause. PFS and OS were calculated using the Kaplan-Meier method.

The effect of the variables (ECOG, LDH level, number of BM, size of BM, number of extracranial organs involved, BRAF mutation type) on PFS and OS was determined by Cox regression analysis. 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.

Results

Patients

Clinical characteristics of the involved 30 patients are shown in Table 1. All patients had cerebral dissemination, 70% of patients had more than 2 BM. Four patients were previously untreated, and 26 treated with different combinations of „classic therapies" such as chemotherapy (6 patients) and local

Table 1 Patient population, dabrafenib arm

Age (years)	59.2 (21.8–75.1)
Gender	
Male	15 (50%)
Female	15 (50%)
Breslow tumor depth (median and range in mm)	3.9 (0.7–21)
Eastern cooperative oncology group performance status	
0	10 (33.3%)
1	12 (40%)
2	8 (26.7%)
Elevated lactate dehydrogenase level at baseline (higher than the upper limit of normal range)	17 (56.6%)
Number of brain metastases	
1	5 (16.7%)
2	4 (13.3%)
2<	21 (70%)
Number of extracranial organs involved with metastases	
2≥	21 (70%)
2<	9 (30%)
BRAF mutation	
V600E	25 (83%)
V600 K	5 (17%)
Previous treatment	
Surgical resection	9 (30%)
Stereotactic radiosurgery	10 (33%)
Whole brain radiotherapy	16 (53%)
Chemotherapy	6 (20%)
Vemurafenib therapy	2 (7%)

Table 2 Patient characteristics, control arm

Age (years)	56.7 (21–83.1)
Gender	
Male	131 (64%)
Female	73 (36%)
Eastern cooperative oncology group performance status	
0	41 (20%)
1	104 (51%)
2	59 (29%)
Number of brain metastases	
1	72 (35%)
2	40 (20%)
2<	92 (45%)
Number of extracranial organs involved with metastases	
2≥	169 (83%)
2<	35 (17%)
Treatment	
Surgical resection	90 (44%)
Stereotactic radiosurgery	88 (43%)
Whole brain radiotherapy	145 (71%)
Chemotherapy	149 (73%)

therapy (26 patients) including surgical resection (9 cases), stereotactic radiosurgery (10 cases) or whole brain radiation therapy (16 cases). Two patients received prior vemurafenib therapy until progression.

The control arm consisted of 204 patients (Table 2). Proportion of patients falling under ECOG categories of 0, 1, and 2 was 20%, 51%, and 29% respectively. More than 2 BM were detected in 45% of patients and more than 2 extracranial organs were involved in 17% of patients. The patients received complex oncotherapy, 44% of patients underwent surgical resection, 43% were eligible for stereotactic radiosurgery, 71% had whole brain radiotherapy and 73% received chemotherapy.

Tumor Response/ Clinical Outcome

During dabrafenib therapy four patients showed CR (13%), 9 PR (30%), 12 SD (40%) and 5 PD (17%), resulting intracranial DCR being 83% and the intracranial ORR 43%. Response rates were similar in extracranial sites (DCR: 77%, ORR: 37%), except that no CR was recorded extracranially. With a median follow-up of 14 months, median PFS was 5.5 months (Fig. 1a), OS was 8.8 months (Fig. 1b).

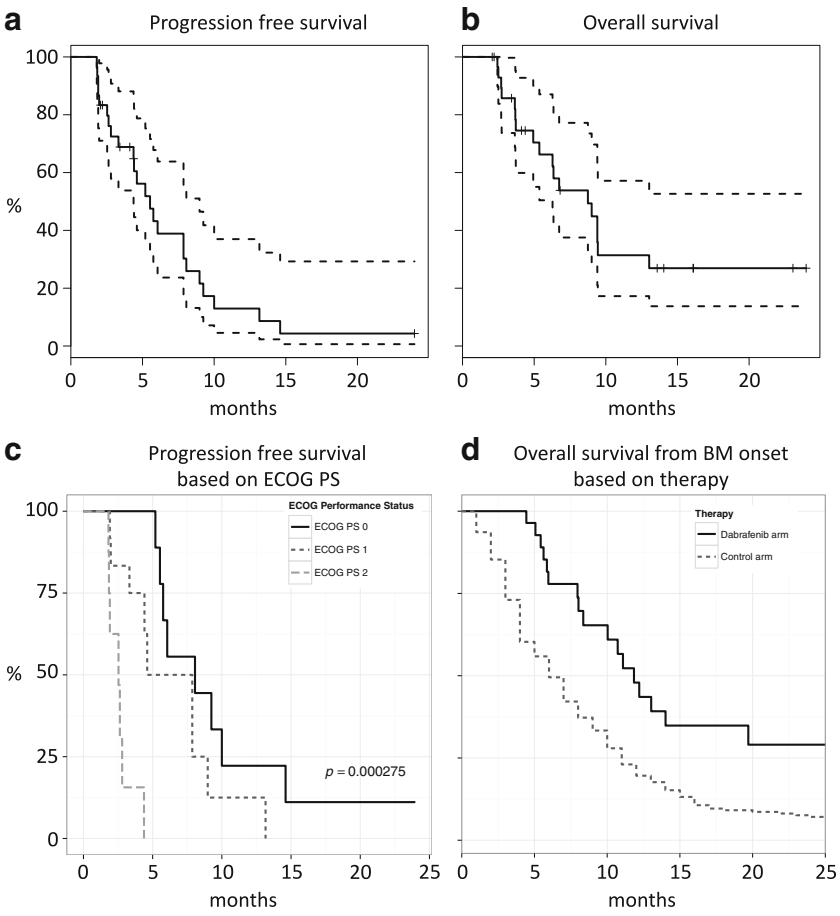

Fig. 1 Probability versus time Kaplan-Maier curves. **a** Progression free survival. **b** Overall survival. Solid line indicates survival, dashed line 95% CI. **c** Progression free survival by ECOG performance status. Solid line indicates ECOG 0, black dashed line ECOG 1 and grey dashed line ECOG 2. **d** Overall survival calculated from BM development on, comparing dabrafenib arm (solid line) to control arm where patients have not received dabrafenib (dashed line)

ECOG at study entry significantly predicted the PFS (HR = 4.06, 95% CI: 1.9–8.62; p = 0.00027) (Fig. 1c). The PFS was 8, 6.2 and 2.5 months for ECOG 0, 1 and 2 respectively. In cases of 0–2 extracranial organs were involved by melanoma, PFS turned to be 7.9 months, contrarily it was 2.6 months if more than 2 extracranial organs were affected (HR = 3.4, 95% CI: 1.39–8.65; p = 0.0077). Elevated LDH non-significantly associated with worse clinical outcome (HR = 2.25, 95% CI: 0.92–5.5; p = 0.07). Patients with normal LDH had a median PFS of 7.5 months, versus those with elevated LDH had it of 4.2 months. The number (p = 0.9) and size (p = 0.6) of BM and the presence of BRAF V600 K or V600E (p = 0.7) made no difference in PFS. There are 6 ongoing medications at the time of this analysis. We had to discontinue dabrafenib therapy due to intracranial progression in 5 cases, progression elsewhere despite stable BM in 8 cases and progression both in intracranial and extracranial sites in 11 cases.

The OS from BM development was 11.8 months in the dabrafenib group, and 6 months in the control arm (HR = 0.45, 95% CI: 0.27–0.74; p = 0.0014) (Fig. 1c). The OS of the entire dabrafenib free population irrespective of ECOG was 4 months.

Adverse Events

The most common treatment-related AEs were hyperkeratotic lesions, observed in 12 patients (40%), including verruca vulgaris (5 patients, 17%), keratoacanthoma (2 patients, 7%) and squamous cell carcinoma (1 patient, 3%) (Table 3). We detected liver enzymes elevation in 6 patients (20%). Five patients had rash (17%), four had decreased appetite (13%). Fatigue, balding and hacking cough was experienced by 3–3 patients (10%). In 3 of 30 patients (10%) treatment-related pyrexia occurred.

Three AEs was of grade 3: a maculopapular rash, 1 development of new melanoma and 1 development of squamous cell carcinoma as a result of the dabrafenib treatment. 27 patients (90%) had no treatment-related AE worse than grade 2, and 9 patients (30%) had no AE at all. No permanent discontinuation was necessary by reason of intolerable toxicity. Temporary dose interruption (1 or 2 weeks) was performed 5 times and 2 patients required dose reduction because of recurrent grade 2–3 adverse events (GGT elevation and squamous cell carcinoma after keratoacanthoma).

Table 3 Frequencies of toxicity (CTCAE criteria)

Any event	21 (70%)
Hyperkeratosis	12 (40%)
Verruca vulgaris	5 (17%)
Keratoacanthoma	2 (7%)
Squamous cell carcinoma	1 (3%)
Increased concentrations of liver enzymes	6 (20%)
Rash	5 (17%)
Grade 3>	4 (13%)
Grade 3	1 (3%)
Decreased appetite	4 (13%)
Fatigue	3 (10%)
Balding	3 (10%)
Hacking cough	3 (10%)
Pyrexia	3 (10%)
Rash	2 (7%)
Arthralgia	2 (7%)
Nausea	1 (3%)
Development of a second melanoma (Grade 3)	1 (5%)
All adverse events ≥ Gr3	3 (10%)
Dose interruption needed	5 (17%)
Permanent discontinuation	0 (0%)
Dose reduction needed	2 (7%)

Discussion

Malignant melanoma has a remarkably high propensity for BM and after having metastasized to the brain, it carries a poor outcome. Even with the use of all combinations of surgical resection, stereotactic radiosurgery, whole brain radiotherapy and systemic chemotherapy, the median OS time after BM onset is generally reported to be only approximately 4 months [7–9]. The recent discovery of targeted therapies has led to significant advances in treatment options, but initially their activity on BM was equivocal. A phase I study concluded dabrafenib as an efficacious treatment for untreated BRAF mutant melanoma with asymptomatic BM, showing the reduction of BM size in 90% of patients, including 40% CR [1]. The intracranial effect of the BRAF inhibitor dabrafenib was confirmed by the BREAK-MB phase II clinical trial which involved 171 patients with melanoma and asymptomatic BM and reported an OS of 33 weeks for whom had not received previous local treatment for BM and 31 weeks for those who had progressive BM after previous local treatments (7.2–7.7 months) [2].

Vemurafenib therapy could also achieve improvement in the outcomes of melanoma with BM according to retrospective analyses where PFS ranged from 3.3 to 5.4 months, OS from 4.9 to 10.7 months [3, 10, 11].

In contrast with randomized controlled trials, our observational study afforded the opportunity to characterize outcomes in the real-world setting. Results of our study suggest that beneficial outcomes are associated with dabrafenib. Our intracranial DCR of beyond 80% corresponded to the literature data [1, 2]. Although our intracranial CR rate of 13% differed from those of large clinical trial results, as Falchook et al. reported 40% and the BREAK-MB trial found only 0–3% CR rate, ours was roughly consistent with other studies of 8.7% [12] or 7% [13].

Our PFS of 5.5 months equalled to [12] or slightly exceeded the previously published PFS data of 4.2 months

[1], of 3.7–3.8 months [2] or of 4.6 months [14]. Our 8.8 months OS data was also similar to other reported OS results, like 7.2–7.7 months [2] or 8.5 months [12]. Based on the findings of BREAK-MB trial, which suggested the major benefit for patients with ECOG 0, V600E mutation and normal LDH level [2], we analyzed the clinical factors in connection with the PFS. Increasing ECOG (HR = 4.06, 95% CI: 1.9–8.62; p = 0.00027) and increased number of extracranial organs involved (HR = 3.4, 95% CI: 1.39–8.65; p = 0.0077) strongly affected the PFS despite the small sample size. Elevated LDH showed correlation to shorter PFS consistently with other studies [2, 13], however this effect was not significant. The number and size of BM and the presence of BRAF V600 K or V600E made no difference in PFS according to our analysis.

Our comparative analysis undoubtedly proved the benefit of dabrafenib versus other classical approaches in BRAF mutant melanoma patients with BM, since the OS calculated from BM onset was found to be 11.8 months versus 6 months in the control group with strong significance (HR = 0.45, 95% CI: 0.27–0.74; p = 0.0014).

Dabrafenib was safely administered. Our safety and tolerability results are mostly consistent with previous findings. The most relevant toxic effect, the transient fever occurred less frequently than reported [1, 15], palmoplantar dysesthesia was not experienced at all contrary to other studies [2], hyperkeratosis and liver enzymes elevations were detected more frequently compared with previously published studies [1, 2].

Our analysis confirms the findings of clinical studies on the intracranial effect of dabrafenib therapy. Our results exceed the reported data of randomized clinical trials, but mostly correspond to observational studies in terms of PFS, OS and ORR.

Combination therapy such as dabrafenib plus trametinib has been demonstrated to further prolong survival in melanoma patients compared to dabrafenib alone [16, 17], however data for BM population will be provided from ongoing clinical trials.

Conclusion

The current analysis succeeded to confirm that dabrafenib had therapeutic effect on BM from melanoma in patients with BRAF mutation. Both PFS and OS improved with the use of dabrafenib, the significant OS improvement was demonstrated even by our comparative analysis versus local therapies and/or chemotherapy. According to our study dabrafenib was safely administered. As no strict inclusion or exclusion criteria were applied to our brain metastatic patient population, our setting represents the typical oncological practice better than clinical trials do.

Compliance with Ethical Standards

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Conflict of Interest Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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