

## Melanoma Brain Metastases **Eszter Gorka\***

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Melanoma is an aggressive skin cancer with high metastasizing potential and high mortality rate. New diagnoses of melanoma are around 130,000-200,000 globally but it has the fastest growing global incidence rate of all malignancies, increasing in an exponential manner [1-3].

Brain Metastases (BM) are frequent in advanced melanoma: brain involvement is detected in 45-50% of patients and is revealed at autopsy in 75% [4,5]. Development of BM is a hard to treat complication which determines quality of life and life expectancy even with the use of new targeted and immunotherapies.

Early detection of BM can prolong survival because of better surgical and radiosurgical options for fewer and smaller lesions and because of better efficacy of therapies for patients with fewer tumors mass. Therefore early detection of BM has an increasing role in managing patients with melanoma.

We conducted a retrospective study aimed at finding the major BM predictors [6]. From our institutional melanoma database between 2003 and 2015 we identified 333 patients diagnosed with BM. Potential risk factors were registered: gender, age, Breslow tumor thickness, ulceration, location of the primary melanoma, histological subtype and sentinel lymph node status. These parameters were analyzed in association with the median elapsed Time to Brain Metastases (TTBM) which was calculated from the date of primary tumor diagnosis to the detection date of BM. TTBM was significantly correlated with older age, greater Breslow depth, ulceration and Head and Neck (HN) location of the primary melanoma.

With these factors further analysis was carried out to compare their predictive value. It was revealed that the HN region, and especially location in the scalp, was the strongest predictor for BM onset among all factors. The second prognostic factor was Breslow thickness >2 mm, followed by the presence of ulceration and older age respectively. Analyzing a detailed subdivision of primary tumor location and TTBM, we found that TTBM tended to gradually decrease with proximity to the scalp.

Based on these findings, we identified a high-risk group of patients for BM with HN (scalp) located primary melanoma greater than Breslow thickness of 2 mm. For this well-circumscribed relatively small subpopulation, closer evaluation using brain MRI is suggested which has not been part of routine follow-up protocols in clinical practice. In this way, BM would be discovered at an earlier stage and could be treated more effectively, particularly when in possession of new therapies.

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For a long time therapeutic modalities for melanoma 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. Even with the use of all combinations of these therapies, the median Overall Survival (OS) time after BM onset is generally reported to be only approximately 4 months [7-9].

Although in the past 6 years several 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 changed recently, and clinical studies have demonstrated more or less intracranial activity of these therapies [10-17]. Firstly dabrafenib was proved to be effective by the BREAK-MB phase II clinical trial of great importance with an OS of 7.2-7.7 months achieved [11].

For BRAF positive melanoma patients with BM dabrafenib seems to be the best choice so far: while BRAF+MEK inhibitor combination therapies prolonged the duration of response compared to BRAF monotherapies in melanoma patients without BM [18,19], the early report of COMBI-MB study assessed the median duration of response to be relatively short in the BM population receiving dabrafenib+trametinib [12].

For BRAF negative melanoma patients with BM anti-PD1 immunotherapy together with prior stereotactic radiosurgery showed the best OS data [16,17].

With the purpose to confirm the promising clinical trial results in real-life practice regarding the effect of dabrafenib monotherapy for BM, we performed a controlled retrospective study [20]. We investigated 30 melanoma patients with asymptomatic BM, verified BRAF mutation, and ECOG Performance Status (PS) 0-2 who received dabrafenib therapy between 2014 and 2017. 150 mg b.i.d. dabrafenib was administered orally for all patients, scheduled in 28<sup>th</sup> day dosing cycles until disease progression, death or unacceptable adverse events.

We evaluated the benefit of dabrafenib versus other previously existing modes of treatment for melanoma BM. We identified 204 patients from our melanoma database with BM and ECOG PS 0-2, who did not, received dabrafenib but underwent local therapies and/or chemotherapy between 2003 and 2015. These 204 patients were used as control group as there was no significant difference in terms of patient and disease characteristics between the two arms.

A disease control rate of 83% and intracranial overall response rate of 43% was found, with 13% of patients having complete remission intracranially. Response rates were similar in extracranial sites. Median Progression-Free Survival (PFS) and 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 on 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 was non-significantly associated with worse clinical outcome.

In conclusion, remarkable intracranial activity of dabrafenib in real practice was confirmed by our analysis. In the last years the targeted and immunotherapies prolonged survival to 9-10 months in this patient population with poor-prognosis. Despite the significant clinical benefit these results support the need for additional research to further improve outcomes in patients with BM.

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