Upfront targeted therapy for symptomatic melanoma brain metastases: paradigm changing?

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Practice points

- Multiple brain metastases from melanoma are usually treated by radiotherapy.
- In some particular clinical situations, such as BRAF V600E-mutated melanoma, with high kinetics and tumor load an alternative clinical treatment option to consider is targeted therapy.
- Direct comparison of BRAF/MEK double blockade versus BRAF inhibitors in brain metastasis from melanoma has not been explored yet.
- In the treatment of metastatic melanoma, compared with BRAF inhibitors alone, BRAF/MEK double blockade has shown a better therapeutic index with improved efficacy and less toxicity.
- This report illustrates the feasibility and efficacy of the BRAF/MEK inhibitors combination, warranting dedicated clinical investigation.
- The clinical efficacy of targeted therapies remains of limited duration.

The standard management of a single brain metastasis is usually maximal resection when feasible followed by radiotherapy. In case of multiple lesions, several options have to be considered depending on the natural behavior of the primary tumor, the localization of brain lesions, their functional impact and related symptoms. In case of life-threatening brain metastasis, debulking surgery is often proposed first, with the risk of major bleeding and postponing the initiation of other treatments. This approach is now challenged by the rapid tumor shrinkage that could be observed with novel targeted therapies. Here we report the case of a patient suffering from a melanoma with multiple brain metastasis, treated with BRAF and MEK double blockade, with impressive and rapid response.

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Melanoma brain metastasis can traditionally be treated with local therapies being either whole brain radiotherapy or stereotactic radiosurgery for small lesions and surgery when necessary [1]. Now sufficient literature has reported high tumor response rates with targeted therapies but the sequence and/or combinations of the various therapeutic tools, i.e., surgery, irradiation and small molecules reaching the tumor through blood–brain barrier, is not known.

Whether targeted therapies could be used upfront to treat patients with brain metastasis and the impact of such molecules on quality of life and patient autonomy are still open issues

KEYWORDS

- BRAF V600E mutation
- brain metastasis
- melanoma

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Case report

Here, we report the case of a 52-year-old patient diagnosed in 2008 with a melanoma of the left ankle, Clark III, Breslow 1.7 mm, with three positive sentinel left inguinal lymph nodes. Lymphadenectomy was performed, no additional metastasis was found. The outcome was favorable until April 2015 with the appearance of a left inguinal adenopathy. A biopsy was performed, revealing a massive involvement of the lymph node by BRAF V600E-mutated melanoma. There was no evidence of NRAS or PI3KCA

mutations. In addition, neurological symptoms rapidly appeared with ideomotor apraxia, dysgraphia and cognitive defects, as well as severe abdominal pain. Brain MRI confirmed the presence of multiple metastases, the biggest measuring 4.3 cm in the right parietal lobe and responsible for the clinical presentation. A complete imaging work-up showed multiple metastases in the lungs, adrenals and retroperitoneal space. Dexamethasone 8 mg was started immediately.

Given the presence of multiple retroperitoneal painful masses, the burden of the tumor

Figure 1. Complete remission of multiple intracranial brain metastases. (A & C) Two supratentorial lesions (two in the right parietal lobe seen in [A & C], one in the left temporal lobe in [A]). Other localizations not seen on these images. **(B & D)** Complete remission of all the described lesions.

outside the brain, and despite the neurological symptoms, the decision of the multidisciplinary tumor board was to favor the immediate initiation of a double blockade with BRAF and MEK inhibitors (i.e., dabrafenib and trametinib at standard schedules). Within a few days only, the patient reported an obvious alleviation of both neurological symptoms and abdominal pain, and the dose of dexamethasone was progressively tapered down. Follow-up imaging after 1 month showed a 46% decrease in tumor volume, and after 3 months a complete response of all brain lesions was observed (Figure 1), still ongoing at 6 months. Still even if response is impressive in all lesions, one should note that the largest brain metastasis being hemorrhagic, thus a considerable part of the shrinkage is from absorption of blood.

Discussion and conclusion

Several studies recently revealed the efficacy of BRAF inhibition (or double BRAF and MEK blockade) in melanoma metastatic to the brain, for patients previously treated or not [2–5]. The case reported here suggests that this treatment modality can also be considered upfront for patients with symptomatic and large brain metastases.

RT has not been considered upfront in this patient given the presence of multiple retroperitoneal painful masses – the burden and growth kinetics of the tumor outside the brain did not allow to a systemic therapy to be postponed.

The clinical benefit could be very important for patients with high kinetics of tumor growth and/or concomitant symptomatic metastasis outside the CNS. Even though there is no direct comparison between BRAF inhibitors alone versus double blockade for brain metastasis management – outside the CNS, BRAF/MEK combination increases the rate and duration of responses compared to BRAF therapy alone. As a result BRAF and MEK inhibitors should definitively be integrated in the complex algorithm of melanoma brain metastasis. However, the clinical efficacy of targeted therapies remains of limited duration (6 months follow-up in our case), and the next challenges are now to define when brain irradiation and/or immunotherapy should be delivered for responding patients [6].

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Informed consent disclosure

The authors state that they have obtained verbal informed consent from the patient for the inclusion of their medical and treatment history within this case report.

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