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Case report

Vemurafenib and concomitant stereotactic radiation for the treatment of melanoma with spinal metastases: A case report

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ABSTRACT

A 56-year-old man with BRAFV600E melanoma and spinal metastases treated with vemurafenib and stereotactic radiation showed a partial response without neurological, skin or mucosal toxicity, 8 months after completion of this combination. This case suggests that stereotactic radiation spares normal tissues and might be safer than conventional fractionated radiation with vemurafenib.

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1. Introduction and objective

Melanoma has the fastest-growing incidence of any cancer among men, and the second fastest-growing incidence among women.¹ It is also a major public health problem worldwide and its incidence doubles every 10 years.² In 2005, there were 7401 new cases in France and 1440 patients died of melanoma.³ Malignant melanoma represents 2.3% of all newly diagnosed cancers in France. The standard incidence rate is 7.6 among men, 8.8 among women and the sex ratio is 0.86.³ A

quarter of patients are diagnosed with locally advanced stage III or metastatic stage IV disease.⁴ The 5-year overall survival of patients treated with chemotherapy is only 10%.⁵

In a meta-analysis of 42 phase II trials of metastatic melanoma, the overall survival was 6.2 months (5.9–6.5 months). Some factors, such as performance status, visceral metastasis, gender and brain metastasis, seemed to impact the survival in a multivariate analysis.⁵ Between 1970 and 2010, more than 3000 clinical trials were conducted throughout the world without any significant impact on the overall survival of patients with advanced melanoma.

In 2011, the US FDA approved two agents for the treatment of advanced melanoma. Ipilimumab is an anti-CTLA-4

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Fig. 1 – MRI of the third lumbar vertebra before treatment and after irradiation.

monoclonal antibody that enhances cellular immunity and reduces tolerance to tumor-associated antigens. Vemurafenib, a small-molecule inhibitor of the serine threonine kinase BRAF, inhibits the abnormal activation of the MAPK pathway. It has a significant activity against tumor cells harboring the mutated BRAFV600E protein. BRAF mutations are expressed in about 50% of cutaneous melanomas (20% continuous sun-exposure, 50–80% intermittent sun-exposure). In areas of high sun exposure, like Australia, 80% of mutations are V600E, and this kind of mutation is present in about 90% of patients aged between 20 and 40 years-old.⁶

In Europe, and consequently in France, both ipilimumab and vemurafenib are approved for patients with metastatic melanoma. Also, some new BRAF inhibitors are currently being tested in clinical trials, such as dabrafenib and LGX818.

Studies have shown that selective BRAF kinase inhibition with vemurafenib induced effective radiosensitizing BRAF-positive cells associated with an enhancement of G1 arrest. Recently published data have shown that concomitant conventional fractionated radiation and systemic vemurafenib induced serious toxicity, especially in highly proliferative tissues, such as skin and mucosa. Consequently, vemurafenib is usually interrupted during radiation treatment.

Stereotactic radiation is an advanced radiotherapy method combining very sophisticated devices which allow tumor treatment with sub-millimeter precision. The treatment volume is thereby limited and tolerance is improved. Traditionally utilized for intracranial metastasis, stereotactic radiation is now available for full body targets using systems such as Cyberknife (Accuray, Sunnyvale, CA). Stereotactic radiation seems to be better tolerated and more effective than conventional fractionated radiotherapy in both brain and spinal cord metastasis and can be a useful alternative in these patients.

In a retrospective study, the treatment results of surgery plus whole-brain radiation therapy (WBRT) was compared with gamma knife radiosurgery alone as the primary treatment for solitary cerebral metastases suitable for radiosurgical treatment. The authors concluded that radiosurgery alone can result in local tumor control rates as good as those for surgery plus WBRT in selected patients. A large prospective study including 400 patients with 500 spinal metastases showed a long-term pain improvement in 85% of cases and tumor control in 90% of cases over a median follow-up of 21 months.⁷ An

ongoing phase II/III trial (RTOG 0631) is comparing single dose stereotactic radiation of 16 Gy to a single dose of conventional radiotherapy of 8 Gy in patients with 1–3 spinal metastasis; results are pending.

2. Description of the case

A 56-year-old man was hospitalized in the Department of Dermatology, CHU Caen, France, for an intestinal hemorrhage and left sciatic pain related to a metastatic melanoma. Extension studies found multiple intestinal metastases, mainly in the small bowel, a right adrenal metastasis, and a compressive bone tumor with epiduritis on the third lumbar vertebra. He had also mesenteric, inguinal and axillary lymph nodes. A complete clinical examination (skin and mucosal sites) was unable to identify the primary tumor site. An axillary lymph node biopsy confirmed the diagnosis of malignant melanoma harboring the BRAFV600E mutation. Therefore, a treatment with vemurafenib was started (960 mg twice daily). As the left sciatic pain was not associated with a neurological defect, surgery was not considered. The spinal column MRI performed prior to treatment showed a tumor mass of the third vertebra involving the spinal cord (Fig. 1). Concomitant stereotactic radiation that focused on the third lumbar vertebra, using the Cyberknife system that delivered 10 Gy in one fraction, was started 1 month after vemurafenib. We performed a careful dosimetric optimization to limit the volume of normal tissue receiving maximal doses, especially the skin, the small and large bowel and the spinal cord. The absolute maximal doses accepted were 11.62 Gy for the spinal canal, 10.26 Gy for the spinal cord, 13.3 Gy for the skin, 6.66 Gy for the large bowel and 8.16 Gy for the small bowel. The patient received steroids for several weeks. Sciatic pain decreased 1 week after radiation was completed and no neurological reactions were observed. MRI follow-up 2 months after radiation showed a significant regression of more than 75% of the vertebral tumor compared to the initial tumor (Fig. 2). Three months after vemurafenib was started, and 2 months after radiation, a relapse was observed at the axillary level and new lesions were observed at brain and subcutaneous sites. Vemurafenib was permanently discontinued and chemotherapy with fostemustine was started. Stereotactic radiation was also performed on the brain metastasis in the left temporal lobe. A second

Fig. 2 – Dose distribution and dose volume histograms of the treatment plan.

systemic progression was observed leading to death 8 months after completion of the concomitant treatment in the third lumbar vertebra. Neither local toxicity nor progression on the third lumbar vertebra had been observed previously.

Consent was obtained from the patient for publication of this case report and any accompanying images.

3. Discussion

We have observed an increase in brain and spine metastasis in our current clinical practice. Bone metastases are a growing problem in cancer patients due to increased life expectancy and the spinal cord is involved in most of the patients who have died due to the cancer (36% of patients).⁸ Spinal cord compression is the most common complication of spinal metastases and this entity must be considered as a medical emergency. The cumulative incidence of melanoma brain metastasis is <10% according to a large series.^{9,10} However, brain involvement increases substantially to 45–50% in those having advanced melanoma and 75% at autopsy.^{11,12}

Both brain and spinal cord metastases are managed with steroids, surgery and radiotherapy.

Vemurafenib, compared with dacarbazine, has shown an advantage in response rates, PFS and OS. Response rates of more than 50% for metastasis outside the brain were observed in patients with metastatic melanoma harboring the BRAFV600E mutation.¹³

Despite the efficiency of B-RAF inhibitors in treating metastases outside the brain, radiotherapy is sometimes required during systemic target therapy to treat compressive or symptomatic masses. Radiation is even more frequently needed in patients developing brain metastasis during systemic treatment. Due to the drug diffusion characteristics at this anatomical site, isolated brain progression cannot be considered as drug resistance and radiation is often necessary.

The safety and efficacy of the association between the newest therapeutic agents, such as anti-CTLA-4 monoclonal antibody (ipilimumab), BRAFV600 inhibitors (vemurafenib, dabrafenib) or MEK inhibitors, with radiotherapy is not completely understood. There are several ongoing trials combining ipilimumab with SRS for patients with brain melanoma metastasis.¹⁴

B-RAF is the most common oncogene found in malignant melanoma and many highly radioresistant cell lines are B-Raf+. The radiosensitivity of melanoma cell lines harboring mutations in B-Raf and N-Ras, at frequencies observed in patients, was analyzed to determine whether the pharmacological inhibition of B-RAF could induce radiosensitization in melanoma cells. The study showed that the inhibition of B-RAF with vemurafenib effectively radiosensitized B-Raf+ cells and also enhanced G1 arrest when analyzed by both colony formation and invasion assays.¹⁵

There is still a paucity of information on the association of stereotactic hypo fractionated radiotherapy and BRAFV600 inhibitors.

In a recently published article, high toxicity was reported when BRAFV600 inhibitors were associated with conventional fractionated radiotherapy. This toxicity seemed to especially affect highly proliferative tissues, such as the skin and mucosae.¹⁶ A 7-day-free interval between the vemurafenib treatment and the radiotherapy was recommended by the authors, i.e. a total of 3–4 weeks of systemic treatment interruption. These observations seem to confirm that vemurafenib has a radiosensitization effect.¹⁵

However, we consider that discontinuing vemurafenib treatment for 1 month in BRAF-positive metastatic patients can be very deleterious.

A recent phase II trial including 12 patients with oligometastatic melanoma to the brain has been reported. The patients received vemurafenib at a dosage of 960 mg twice a day. Six patients received SRS (15–20 Gy), five patients received focal hypofractionated radiotherapy (30 Gy/10 fractions) and one patient received SRS associated with focal hypofractionated radiotherapy. The overall survival rate was 13.7 months. The 6-month control rate was 75% and progression-free survival was 14.5 months. The treatment-related toxicity was acceptable: one patient presented brain radionecrosis and two patients had tumor hemorrhage after the treatment.

It seems likely that highly proliferative tissue is more sensitive to this association than tissues considered to be slowly proliferative, such as the central nervous system.

The approval of vemurafenib was positively received by clinicians treating patients with metastatic melanoma. However, this drug has well-known limitations when used in association with radiation therapy, even though some promising strategies are currently available to overcome at least some of these limitations.

New radiation therapy techniques, such as stereotactic radiation, could be included in these strategies and should be considered when treating a patient with vemurafenib who also needs local treatment for the disease. These new techniques seem to reduce the possibility of safety issues in the treatment of patients with melanoma harboring the BRAFV600E mutation and treated with vemurafenib.

4. Conclusions

Life-threatening metastasis located in the brain and spinal cord is a common and formidable challenge in patients with malignant melanoma. The combined treatment of the newest drugs, such as vemurafenib and radiotherapy, may improve

local control and may prolong time to neurological death. The clinical evidence regarding this association is limited. Several case reports have reported serious toxicity associated with the combined treatment, especially outside the central nervous system. In our case no neurological toxicity was recorded after 8 months of combined treatment with vemurafenib and stereotactic radiation for melanoma metastasis in the third lumbar vertebra. We expect that this, and similar cases, could lead to a controlled evaluation of the role of these new radiation techniques in concomitant use with vemurafenib or other new targeted therapies. New radiation therapy techniques deserve consideration, at least in selected patients, as part of the treatment strategy to eventually overcome the safety issues previously described with vemurafenib in association with radiation therapy.

Precaution is always advisable when radiation is associated with BRAFV600 inhibitors and clinical studies assessing these new techniques are needed.

Conflict of interest

None declared.

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