Dramatic response of an inoperable Merkel cell carcinoma with imatinib

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare type of skin tumor that is derived from epidermal neuroendocrine cells. It is an aggressive tumor for which the 5-year survival rate is estimated at 64% for localized tumors, 39% in cases of regional invasion, and 18% for metastatic tumors.1 The standard treatment of the primary tumor is based on surgical resection with wide margins in conjunction with adjuvant radiotherapy. At the metastatic stage, in the absence of consensus, the most commonly proposed treatment is platinum/etoposide or doxorubicin chemotherapy, resulting in only a suspensive effect.2 We report the dramatic and sustained response to imatinib achieved in a patient with inoperable locally advanced Merkel cell tumor.

CASE REPORT

We report the case of a 69-year-old woman with a MCC of the left eyebrow. This lesion developed within 3 weeks. It was a 6 cm firm reddish purple nodule with a central hemorrhagic ulcer (Fig 1, A). Active and passive palpebral openings were not possible given the size and infiltration of the tumor. The diagnosis of MCC was confirmed by histologic examination. The analysis of exons 11 and 13 of the C-KIT gene identified no mutation. CD117 and platelet-derived growth factor receptor (PDGFR) staining found a strong expression of PDGFR and no expression of CD117.

The patient’s medical history included insulin-dependent diabetes with retinopathy, nephropathy and neuropathy, hypertension, hypercholesterolemia, and a digestive tract hemorrhage from a bulbar ulcer.

A facial computed tomography (CT) scan highlighted a mass of $5.3 \times 5.4 \times 4.5$ cm with intraorbital extension at the internal upper quadrant without osteolysis (Fig 2, A). The thoraco-abdomino-pelvic CT scan showed no visceral metastasis.

Given the tumor size and location, surgical resection was refused by the patient because it would have significant morbidity. Because of anemia and multiple other comorbidities, chemotherapy was contraindicated. It was therefore decided during a multidisciplinary meeting to initiate a treatment with imatinib in conjunction with radiotherapy. Imatinib was prescribed at a dose of 400 mg/d. After 1 month of treatment, before initiation of radiotherapy, a dramatic clinical response was noted. The lesion mass was decreased by more than 50%, and the hemorrhage was stopped. Radiotherapy was cancelled given the excellent response to treatment and the significant risk of ocular complications. Four months later, the tumor regression was ongoing with a complete clinical remission of the entire tumor (Fig 1, B) and recovery of a palpebral aperture.

This dramatic clinical response was confirmed on CT scan examination at 6 months and 20 months (Fig 2, B). The palpebral mass regressed by 40% at 6 months and by 100% at 20 months.

The follow-up was made by fluorodeoxyglucose positron emission tomography CT. It showed a progressive decrease of the hypermetabolism of

Abbreviations used:

CT: Computed tomography
MCC: Merkel cell carcinoma
PDGFR: Platelet-derived growth factor receptor

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the left eyebrow (SUV MAX, 4.14 [maximal fixation intensity on fluorodeoxyglucose positron emission tomography CT]) after 10 months and 3.36 after 19 months.

The tolerance of the treatment was excellent with a total absence of clinical and biological adverse events and an improved general status. After 20 months of treatment, the patient was considered in complete clinical and radiologic remission and the treatment was stopped. This complete remission was maintained after 3 months of follow-up.

**DISCUSSION**

This case is interesting because of the dramatic and extremely rapid decrease in tumor mass. In this patient, imatinib allowed avoiding a damaging surgery and led to the complete disappearance of functional signs despite an initially unfavorable short-term prognosis.

The complete regression observed might be the result of spontaneous regression, which is an extremely rare event previously described in MCC. This hypothesis is unlikely because in the 22 cases reported in the literature of spontaneous regression of MCC, 15 cases occurred after incisional biopsy and 7 occurred after local recurence. In our case, the tumor did not decrease after biopsy but clearly started to decrease 7 days after imatinib initiation. Despite chemotherapy and radiotherapy, therapeutic failure is common in inoperable MCC, making it necessary to investigate new treatment options.

Imatinib is a targeted inhibitor of some tyrosine kinase receptors, including KIT receptor (CD117) and PDGFR, and it is used for the treatment of myelodysplastic syndrome, chronic myeloid leukemia and gastrointestinal stromal tumors. It is well tolerated, inducing mainly gastrointestinal adverse events (nausea and diarrhea) and hematologic toxicity, usually of grade 1 or 2.

Studies show that CD117 and PDGFR are expressed in MCC, suggesting a potential efficacy...
of imatinib on this tumor. However, no activating mutation has been found in the genes encoding these receptors. In our patient, the analysis of exons 11 and 13 of the C-KIT gene identified no mutation. The efficacy of the treatment for our patient might be explained by the strong expression of PDGFR in the tumor.

A phase II study was initiated in patients with metastatic or inoperable MCC treated with imatinib at a daily dose of 400 mg. However, the study was terminated early because of an excessive progression rate.

Moreover, 2 isolated cases of inoperable Merkel cell tumor treated with imatinib were reported in the literature. One of the cases was a 92-year-old woman who had an MCC of the cheek. She received imatinib 400 mg once daily as first-line treatment because the tumor stained CD117 and presented a 6-month total remission but died after 6 months of treatment of another condition. The second case was a 77-year-old man who had a multifocal MCC of the scalp, which was not amendable to surgical treatment or radiation. A first-line treatment with imatinib was therefore initiated at 400 mg twice a day for 6 months and then 400 mg once a day for 3 months. The partial response enabled a surgical excision of the main nodule after 3 months of treatment. Imatinib was continued, but the patient presented with a relapse 6 months after surgery, which was treated by radiotherapy. Our case is rare in that it has such a significant and rapid response to imatinib and a sustained efficacy.

Overall, the dramatic efficacy obtained in our patient, associated with an excellent tolerance, enables us to consider imatinib as a therapeutic option for inoperable or metastatic MCC for patients with contraindications for surgery, radiotherapy, and chemotherapy or with failure of those treatments. This observation underlines the need for a clinical trial comparing cytotoxic chemotherapy and imatinib in patients with locally advanced or metastatic Merkel cell tumors. It might be necessary to select patients with PDGFR or CD117 staining, because cases reported of imatinib efficacy seem to be of patients who have an overexpression of those receptors.

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