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Letter

C-Kit non-mutated metastatic melanoma showing positive response to Nilotinib

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Introduction

Melanoma is an aggressive tumor with advanced disease characterized by widespread metastatic lesions and the tumor has traditionally been resistant to most forms of treatment. Indeed, metastatic melanoma has a very poor prognosis with a median survival time of 8–9 months and an estimated 3-year survival rate of less than 15 % [1].

Recent advances in our understanding of the genetic profile of melanoma cells and the molecular factors that drive malignant transformation have resulted in the identification of numerous new therapeutic targets.

KIT is an established therapeutic target in cancers with activating mutations of KIT, such as gastrointestinal stromal tumors (GIST), and considerable efficacy has been achieved with various small molecule inhibitors of KIT including imatinib mesylate [2].

Nilotinib is an inhibitor of ligand-induced PDGFRα and PDFGRβ kinase activity and autophosphorylation of constitutively activated KIT harboring exon 13 or exon 11 mutations (IC_{50} values of 0.2 and 0.027 μmol/L, respectively), with efficacy comparable to that of imatinib [2].

We report a case of non-kit mutated metastatic vaginal melanoma showing impressive response to nilotinib.

Case synopsis

A 57 year old female, presented with vaginal melanoma on October 2008. An anterior pelvectomy was done. The extension assessment that was performed on July 2009 showed a right lymph node metastasis and a liver metastasis. The patient was treated with 6 cycles of fotemustine and dacarbazine between August 2009 and March 2010. The treatment was suspended due to an increase in the size of the iliac lymph node metastasis, and the appearance of a right inguinal lymph node metastasis and suspicious pulmonary micro nodules. We started the patient on nilotinib on April 2010 without knowing her KIT status (the technic was not available in our laboratory). The dose used was 800 mg per day.

The extension assessment that was performed every 6 months (the most recent being on January 2015) showed complete regression of lymph nodes and hepatic lesions, and stability of pulmonary lesion. The patient has an excellent general status,

and the patient reported no side effects. Considering the positive response to nilotinib, we sent a tumor sample to be tested for C-kit mutation: exons 9, 11, 13, 17, 18 were evaluated using electrophoresis and spectrophotometry . To our amazement, the sample was negative for any mutation or amplification.

Discussion

Some melanomas arising from acral, mucosal, and chronically sun-damaged sites harbor activating mutations and amplification of the type III transmembrane receptor tyrosine kinase KIT [3].

The mucosal origin melanomas which mostly arise from the mucosal membrane of the head and neck, the anorectal mucosa and the vulvovaginal mucosa have distinct biologic and clinical features compared with cutaneous melanomas [4].

A recent study was conducted on twenty-five patients treated with imatinib for metastatic mucosal, acral, or chronically sun-damaged (CSD) melanoma with KIT amplifications and/or mutations [5]. The study concluded that imatinib can be effective when tumors harbor KIT mutations, but not if KIT is amplified only [5].

Nilotinib is a small-molecule inhibitor of tyrosine kinase originally developed for the treatment of CML patients who had resistance or intolerance to imatinib [1].

It works by inhibiting the ligand-induced PDGFRα and PDFGRβ kinase activity and the autophosphorylation of constitutively activated KIT harboring exon 13 or exon 11 mutations (IC_{50} values of 0.2 and 0.027 μmol/L, respectively), with efficacy comparable to that of imatinib [2]. Nilotinib may achieve disease control in patients with melanoma harboring KIT alterations and whose disease progressed after imatinib therapy [6].

Our patient responded positively to nilotinib although the tumor sample didn’t show C-Kit mutation or amplification. We would have liked to do full genome sequencing but unfortunately it was not possible due to the insufficient amount of the remaining tumor DNA.

In conclusion, we report a case of mucosal metastatic melanoma responding positively to nilotinib in the absence of any C-KIT aberration. Do we need to look for new exons aberrations in mucosal melanomas? Does this finding put in question the sensitivity of the available technics?

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