Sustained Response of a Clivus Chordoma to Erlotinib after Imatinib Failure

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Key Words

Chordoma · Erlotinib · Imatinib

Abstract

Chordoma is a rare malignant axial tumour that develops from embryonic remnants of the notochord. Surgery and irradiation are the standard initial treatment. However, local recurrence is frequent and cytotoxic chemotherapy is inefficient. Transient activity of imatinib, a platelet-derived growth factor receptor inhibitor, was described in a phase II study. Activity of epidermal growth factor receptor (EGFR) inhibitors (erlotinib, gefitinib) has also been shown in a few recent case reports. We describe a 68-year-old female in whom clivus chordoma recurred after surgery and radiotherapy. The tumour progressed despite imatinib treatment. A partial and sustained response (28+ months) was obtained using erlotinib, an EGFR inhibitor. Erlotinib should be evaluated in a prospective trial investigating new potential therapies against recurrent chordoma.

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Introduction

Chordoma is a rare tumour that arises from embryonic remnants of the notochord. The incidence rate is approximately 0.1 per 100,000 persons per year. The median age is 60 years. Main tumour sites are the sacrum (50–60%), the skull base (25–35%) and the spine, mainly cervical (15%). The median survival is 6 years. Lung, bone, liver or soft tissue metastases sometimes arise, but local recurrence is the main cause of death [1, 2]. Initial treatment is based on complete surgical resection. However, safe margins are difficult to achieve due to the vicinity of vital or functional anatomic structures. Radiation therapy is often performed

after surgery to limit the risk of a local recurrence. Proton beam therapy is the most recommended technique in order to deliver a high dose to the tumour with limited damage to adjacent tissues [3]. Conventional cytotoxic drugs are not active against this tumour type. A modest but significant activity of imatinib, an inhibitor of platelet-derived growth factor receptor (PDGFR) and c-kit, has been described in several case reports and in a phase II study [4–6]. More recently, clinical activity of erlotinib, a tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR), was observed [7–10]. We report a new, well-documented case of a locally advanced chordoma that responded to erlotinib after the failure of imatinib.

Case Report

A 57-year-old woman presented with a diplopia in September 2003. An MRI showed a heterogeneous mass involving the sphenoid bone, with suprasellar and left cavernous sinus extension. A transphenoidal resection was performed in November 2003. Diplopia regressed. Histological analysis demonstrated the presence of large cells disposed in heaps with round nuclei leading to the diagnosis of clivus chordoma. Pituitary insufficiency was offset with thyroxin, cortisol and fludrocortisone. A second partial surgical resection was performed in January 2006 due to tumour progression into the upward sella and close contact to the chiasma. Proton therapy was then carried out (68 Gy). Diplopia recurred in October 2009 due to paralysis of the right abducens nerve (VI). In September 2011, ptosis of the right palpebra developed, and it was accompanied by a deficit of the right oculomotor nerve (III) and by mydriasis. The MRI showed an extension into the right cavernous sinus (fig. 1a). Imatinib (400 mg/day, then 800 mg/day) was given for 5 months, but the tumour nevertheless progressed toward the frontal lobe (fig. 1b). Erlotinib (150 mg/daily) was then started. A partial response was registered in September 2012 (fig. 1c). To date (July 2014), ptosis persists, but without any new neurological symptoms. An MRI (fig. 1d) displayed a persistent partial response (28+ months). The tolerance of erlotinib was relatively good, with a moderate rash on the face and diarrhea that was controlled by loperamide.

Discussion

Conventional chemotherapy is not effective for locally recurrent or metastatic chordoma. Activation of PDGFRA and PDGFRB was documented in chordoma [11, 12], leading to the clinical evaluation of imatinib, a PDGF inhibitor [4, 5]. A phase II study has been completed using 800 mg/day imatinib [6]. Among 50 patients, 70% had stable disease, and 64% obtained a clinical benefit. The median progression-free survival was 9 months.

EGFR expression and activation is also involved in chordoma progression. In the first study investigating EGFR expression in chordoma, it was reported that 12/12 chordomas expressed this membrane receptor [12]. Another study reported an EGFR expression in 83% of primary chordomas and 97% of recurrent chordomas among 52 patients [11], while a third study showed that the EGFR was expressed in 60% of chordomas and activated in 50% of cases among 173 chordomas [12]. EGFR is then the most significantly activated receptor tyrosine kinase in chordomas [14], and therefore a potential therapeutic target. In vitro studies have shown that pharmacological inhibition of EGFR had an anti-tumour effect on the U-CH1 human chordoma cell line. Tyrphostin (AG1478), an EGFR inhibitor, diminished cell proliferation and EGFR phosphorylation [12]. Erlotinib is an EGFR inhibitor registered for clini-

cal use in lung adenocarcinoma. Erlotinib limits EGFR phosphorylation by binding to the intracellular part of the EGFR tyrosine kinase domain. Downstream inhibition of the RAS/MEK pathway inhibits the proliferation and survival of sensitive cancer cells [15]. Activation of EGFR by EGF enhanced cell proliferation in vitro, but erlotinib decreased proliferation of the U-CH1 and C24 human chordoma cell lines in a dose-dependent fashion [16, 17]. In the same study, treatment of a patient-derived xenograft with erlotinib resulted in a significant reduction of tumour volume compared to control, and molecular analyses revealed reduced phosphorylation of the Tyr845 residue of EGFR. This molecular rationale led to a compassionate use of erlotinib in patients with relapsed chordoma, especially when the disease progressed despite imatinib treatment. To date, there are 4 case reports describing the activity of erlotinib when used in association with bevacizumab in chordoma [9, 10]. The role that can be ascribed to erlotinib is then difficult to define, but to our knowledge, bevacizumab alone has no effect on chordoma. Only 2 case reports have described a tumour response with erlotinib treatment alone. In the first case, a 30% tumour reduction was observed with erlotinib treatment in a sacral metastatic chordoma with gluteal mass and iliac lymph nodes that was resistant to imatinib. The duration of the response was 11 months [7]. In the second case, a 70% regression of a thoracic chordoma with lung metastases and cervical lymph nodes were registered after 7 months of erlotinib treatment, while the disease was refractory to imatinib. This response lasted for 12 months [8]. Our study is the 7th study to be published to date investigating the role of erlotinib in chordoma, and the third using erlotinib alone. Here, we report the longest response duration to erlotinib described in the literature to date (28+ months).

Conclusion

Our case report corroborates previous studies, showing that erlotinib is an effective drug in patients with advanced chordoma, even those refractory to imatinib. A prospective clinical trial comparing erlotinib and imatinib as a first-line treatment of recurrent chordoma is mandatory.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Fig. 1. Comparative axial sections of cerebral MRI (T1 after gadolinium injection). **a** Before imatinib (August 2011). **b** After 800 mg/day imatinib for 5 months (January 2012). **c** After ertlotinib, 150 mg/day for 7 months (September 2012). **d** After ertlotinib, 150 mg/day for 28 months (July 2014).