Response to erlotinib in a patient with treatment refractory chordoma

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Chordomas are rare tumors arising from the axial skeleton. The disease is characterized by slow local growth, frequent local recurrences, and rare systemic spread. Surgery and local radiation remains the mainstay of treatment with minimal role of systemic therapy. Imatinib has been shown to be active in a phase II trial with symptomatic and radiological responses. We report a case where treatment with erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, induced symptomatic and radiological response in a patient with disease refractory to imatinib and vascular disrupting agent. ***Anti-Cancer Drugs*** **20:953–955 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2009, **20**:953–955

Keywords: chordoma, epidermal growth factor receptor, epidermal growth factor receptor tyrosine kinase inhibitors, erlotinib, imatinib

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Received 25 March 2009 **Revised form accepted** 13 July 2009

Introduction

Chordomas are rare neoplasms arising from remnants of the embryonic notochord in the axial skeleton. Median age of presentation is 60 years. The clinical course is characterized by slow growth, long natural history, and frequent local recurrences. The systemic spread is uncommon. The cornerstone of treatment is surgical resection and local radiation. Systemic therapy has been found to be largely ineffective with no role of chemotherapy [1]. Imatinib has been shown to have antitumor activity with symptomatic and radiological responses noted initially in a series of 18 patients [2] and subsequently in a multicenter phase II study [3]. Recently, two cases have been reported suggesting benefit of anti-epidermal growth factor receptor (EGFR) therapy. Hof *et al.* [4] treated a patient with recurrent chordoma successfully with a combination of gefitinib and cetuximab and Linden *et al.* [5] reported regression of cervical chordoma using the same drug combination.

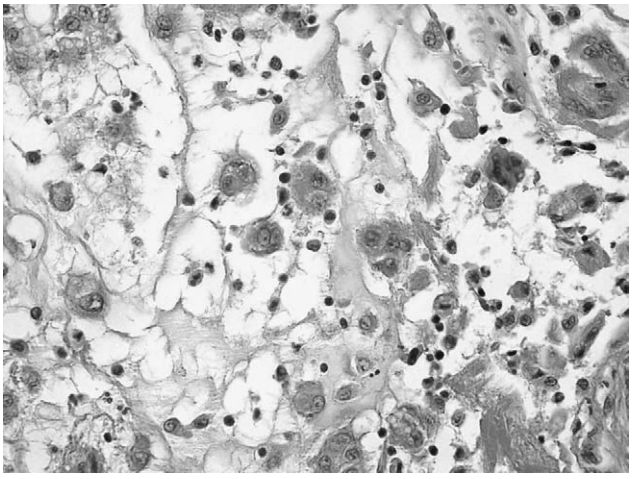
We present the case of a patient who initially did not respond to imatinib (Glivec; Novartis AG, Basel, Switzerland) and a vascular disrupting agent but subsequently had a gratifying response to third-line erlotinib (Tarceva; F. Hoffmann-La Roche Ltd., Basel, Switzerland), a small molecule EGFR tyrosine kinase inhibitor.

Case report

A 53-year-old male presented in 2004 with a 2-year history of coccygeal pain. He had suffered a fracture of the coccyx 5 years before his presentation and had had increasingly severe pain for about 14 months. His only medical history was that of thyroid carcinoma treated 17 years before the current presentation with total thyroidectomy and ^{131}I therapy with complete remission.

Imaging of the sacro-coccygeal region showed a 7×5 cm soft tissue mass adjacent to the right side of the sacrum and involving the fourth and fifth sacral segments, displacing but not invading the rectum. Biopsy confirmed the diagnosis of chordoma and he underwent a distal sacral and coccygeal resection together with the resection of the presacral tumor mass and preservation of the rectum. The resected tumor was a classical chordoma with strong immunoreactivity for epithelial membrane antigen and cytokeratins; mitotic activity was low but vascular invasion was observed (Fig. 1).

Fig. 1



Large polygonal-shaped cells with abundant clear cytoplasm, vesicular nuclei, and physaliphorous cells.

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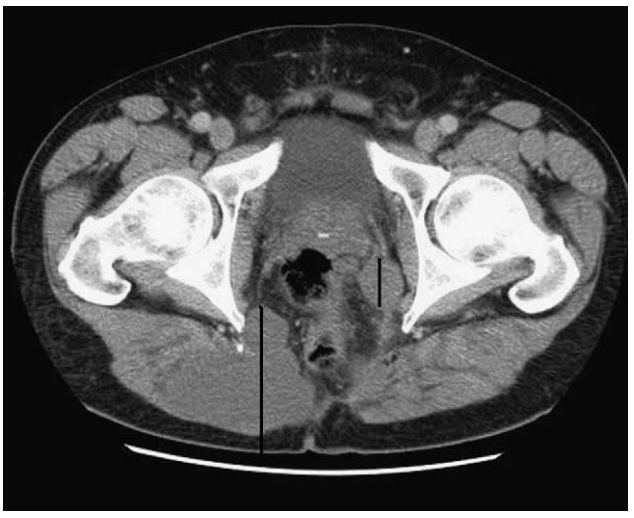
DOI: 10.1097/CAD.0b013e328330c7f0

Six months after the resection, a local recurrence was diagnosed and a course of radiation therapy was administered using 66 Gy in 33 fractions. In 2007, pelvic recurrence was found on routine follow-up which was managed by surgical excision but soon thereafter further pelvic and cutaneous recurrences were again seen. The lesion was once again excised with positive margins requiring additional surgical procedures. Owing to the progressive nature of disease, the patient was enrolled in a clinical trial using imatinib at a dose of 600 mg/day in January 2008. Reassessment MRI after 3 months showed significant disease progression at various pelvic sites with the largest lesion (5×6 cm) involving the right gluteus maximus muscle as well as enlarged internal iliac nodes. The patient was enrolled on a phase I clinical trial with a vascular disrupting agent CYT997 in June 2008. Three cycles of therapy were administered at 2 weekly intervals, but further disease progression was noted on reassessment imaging with enlargement at all disease sites, the largest gluteal mass now measuring 9.5×7.5 cm (Fig. 2). Significant increase in pelvic and perineal pain was noted by the patient.

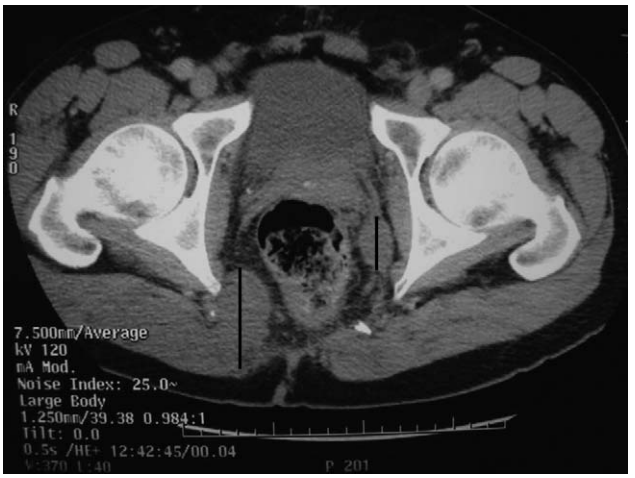
As a result of the report of EGFR expression and case reports reporting activity of cetuximab and gefitinib in chordomas, the patient was offered therapy with the EGFR tyrosine kinase inhibitor, erlotinib at the standard dose of 150 mg/day in August 2008. Within days of starting treatment, his pain improved substantially and a reassessment computed tomography scan 3 months after commencing erlotinib showed reduction of all known tumor deposits (Fig. 3). The large gluteal mass reduced from 5.5×9.5 cm to 3.2×7.5 cm. There was reduction in all previously enlarged and involved lymph nodes. Overall response assessment by RECIST criteria was partial response with greater than 30% reduction in tumor bulk.

Fig. 2



Computed tomography scan of pelvis performed on 24 July 2008 showing large tumor deposits.

Fig. 3



Reduction in previously noted pelvic mass. Scan dated 18 November 2008.

The tumor was tested for EGFR mutation and sequencing of exon 18–24 of EGFR gene did not show any activating mutation. Fluorescence in-situ hybridization for EGFR and PDGFR-β failed to show any amplification or other abnormality.

The only complication of treatment was a grade 2 skin rash which appeared within 2 weeks of the commencement of the drug and improved with symptomatic measures. At the time of writing this report, the patient had undergone 11 months of treatment with ongoing clinical response.

Discussion

The present case report highlights antitumor activity of EGFR-based therapy in chordomas. The interesting aspect of the case history is the earlier nonresponse to imatinib and a vascular disrupting agent. The present case report differs from the previous ones where EGFR-based therapy was used as first-line treatment and the response was noted with single EGFR tyrosine kinase treatment rather than combination.

There is a biological rationale for using EGFR-targeted therapy in chordomas. Weinberger *et al.* [6] have reported strong expression of EGFR and c-Met in a series of 12 chordomas. There have been reports of expression of activated PDGFR-α and PDGFR-β in tumor cell and stroma in chordoma samples [7,8], the basis for the suggested imatinib activity in these tumors. Recently, Ostroumov and Hunter [9] have shown the importance of c-MET oncoprotein in the metastatic process in chordoma cell lines.

Two case reports have previously shown activity of gefitinib and cetuximab and our case report is the third in the literature showing benefit with erlotinib. The present case report raises the question of whether we need to combine anti-EGFR antibody with a small molecule tyrosine kinase inhibitor as we have shown benefit with just one agent.

How does this case report impact the management of chordomas? The activity of EGFR-directed therapies as shown in these three case reports is exciting as it opens a new therapeutic option for our patients where there is no established systemic treatment. We also need to establish the role of the EGFR axis in the pathogenesis of chordomas. Is it important in tumor initiation or does the pathway become activated at the time of disease progression?

As stated before, this disease is uncommon and it would need a coordinated and collaborative effort to further evaluate the role of such newer therapies.

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