European Journal of Cancer 79 (2017) 119–128

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Advanced chordoma treated by first-line molecular targeted therapies: Outcomes and prognostic factors. A retrospective study of the French Sarcoma Group (GSF/GETO) and the Association des Neuro-Oncologues d'Expression Française (ANOCEF)☆

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Received 11 January 2017; received in revised form 27 March 2017; accepted 28 March 2017
Available online 4 May 2017

☆ Presented in part as an abstract at the 2016 Annual Meeting ASCO, Chicago, Illinois, June 3–7, 2016.

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http://dx.doi.org/10.1016/j.ejca.2017.03.037

KEYWORDS
Chordoma;
Molecular targeted therapy;
Imatinib;
Antiangiogenics;
Anti-EGFR;
Prognostic factors

Abstract ***Background:*** To assess the role of first-line Molecular Targeted Therapies (MTTs) in Advanced chordoma (AC) patients.
Methods: Retrospective study of 80 patients treated between January 2004 and December 2015 at 15 major French Sarcoma or Neurooncology Centres.
Results: The sex ratio M/F was 46/34. The median age was 59 (6–86) years. The primary sites were the sacrum (50, 62.5%), mobile spine (12, 15.0%), and skull base (18, 22.5%). Metastases were present in 28 patients (36.0%). The first line of MTTs consisted of imatinib (62, 77.5%), sorafenib (11, 13.7%), erlotinib (5, 6.3%), sunitinib (1, 1.2%) and temsirolimus (1, 1.2%). The reported responses were: partial response (5, 6.3%), stable disease (58, 72.5%), or progressive disease (10, 12.5%). Symptomatic improvement was seen in 28/66 assessable patients (42.4%) and was associated with an objective response occurrence ($p = 0.005$), imatinib ($p = 0.020$) or erlotinib use ($p = 0.028$). The median progression-free survival (PFS) was 9.4°months (95% CI, [6.8–16.1]). Two independent factors of poor prognosis for PFS were identified: a skull-based primary location (HR = 2.5, $p = 0.019$), and the interval between diagnosis and MTT of <52months (HR = 2.8, $p < 0.001$). The median overall survival (OS) was 4.4°years (95% CI, [3.8–5.6]). Four independent factors of poor prognosis for OS were identified: the presence of liver metastases (HR = 13.2, $p < 0.001$), pain requiring opioids (HR = 2.9, $p = 0.012$), skull-based primary location (HR = 19.7, $p < 0.001$), and prior radiotherapy (photon alone) (HR = 2.5, $p = 0.024$). The PFS and OS did not significantly differ between the MTT.
Conclusions: The prognostic factors identified require validation in an independent database but are potently useful to guide treatment decisions and design further clinical trials.

1. Introduction

Chordoma is a rare primary bone tumour with an incidence lower than 1 case per million of inhabitants and has a peak incidence in patients aged between 50 and 60 years. Derived from undifferentiated notochordal remnants, the disease develops at the spine level in the sacrum (50%), mobile spine (20%), and skull-base (30%). Surgery is the theoretical best option treatment for localised chordoma followed by high-dose radiation therapy. Nevertheless, because of the primary location, a large en-bloc resection is not achievable in most cases (>50%), and the sequelae of surgery are a major concern in decision-making [1].

In cases of local relapse not amenable to reasonable curative surgery or for those with metastatic disease, quality of life is the main goal of palliative treatment. Debulking surgery or radiotherapy can be discussed to avoid or delay the devastating impact of local persistent disease. Most advanced chordomas (AC) display an indolent course but require systemic treatment at the end to alleviate compressive symptoms. Chemotherapy is recognised as inactive in this setting [1]. The indications for using molecular targeted therapies (MTTs) are largely based on a few prospective phase-II studies, small retrospective series, and case reports with putative biological targets. The targets include (1) the stem cell factor receptor (KIT) and the platelet-derived growth factor receptors (PDGFRA and PDGFRB) targeted by imatinib and dasatinib [2,3]; (2) epidermal growth factor receptor (EGFR) and erbB-2/ human epidermal growth factor receptor 2 (HER2/neu) targeted by lapatinib [4], erlotinib, gefitinib, and cetuximab [5]; (3) angiogenesis elements, such as vascular endothelial growth factor receptor (VEGFR), targeted by sorafenib [6], pazopanib, and sunitinib [7]; and (4) the phosphoinositide 3-kinase (PI3K)/AKT signalling axis/ mammalian target of rapamycin (mTOR) pathway targeted by temsirolimus and sirolimus [5].

The present study aimed to describe the real-life outcomes of AC patients treated with a first line of molecular targeted therapy (MTT) and to identify some clinical prognostic factors that could help guide treatment.

2. Patients and methods

2.1. Patients

From August 2004 to August 2015, all consecutive patients with a diagnosis of chordoma that was histologically confirmed, metastatic or locally advanced, who were admitted to one of the 15 participating centres in France (French Sarcoma Group – GSF/GETO and Association des Neuro-Oncologues d'Expression Française – ANOCEF) for treatment with first-line MTTs were eligible for the study. The MTTs were started at clinical or radiological progression for the patients previously treated by surgery, radiotherapy or chemotherapy, and for the others when these treatments were not feasible. Clinical and pathological data for each patient were collected retrospectively by reviewing the