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Molecular targeted therapies in advanced or metastatic chordoma patients: Facts and hypotheses

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Abstract

Chordomas, derived from undifferentiated notochordal remnants, represent less than 4% of bone primary tumors. Despite surgery followed by radiotherapy, local and metastatic relapses are frequent. In case of locally advanced or metastatic chordomas, medical treatment is frequently discussed. While chemotherapy is ineffective, it would appear that some molecular targeted therapies, in particular imatinib, could slow down the tumor growth in case-reports, retrospective series, and phase I or II trials. Nineteen publications, between January 1990 and September 2014, have been found describing the activity of these targeted therapies. A systematic analysis of these publications shows that the best

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objective response with targeted therapies was stabilization in 52 to 69% of chordomas. Given the indolent course of advanced chordoma and because of the absence of randomized trial, the level of evidence to treat chordomas with molecular therapy is low (level III), whatever the drug. Furthermore, we could not draw firm conclusion on the activity of imatinib. Other putative targets have also been described. Therefore, further clinical trials are expected, especially with these targets. Nevertheless, it seems essential, in those future studies, to consider the naturally slow course of the disease.

Keywords: Chordomas; Review; Molecular targeted therapies; Imatinib

1. Introduction

Chordomas account for less than 4% of primary bone tumors. Their incidence is lower than 1 case per million inhabitants. Chordomas are more frequent in men, and the peak of incidence is between 50 and 60 years of age. Chordomas are very rare before age 40 and exceptional in children. The distribution of primary locations is approximately one-third of cases in the skull base, one-third in the mobile spine and one-third in the sacrum [1].

There are three different histological variants: conventional, chondroid and dedifferentiated. Chordomas are microscopically identified by their physaliferous features (this term describes the numerous vacuoles observed in the tumor cell cytoplasm) and by immunoreactivity for S-100, epithelial markers (e.g., cytokeratins and epithelial membrane antigen) and brachyury. The pathogenesis of chordoma remains unclear. One of the most convincing hypotheses is that chordomas are derived from undifferentiated notochordal remnants. There is some evidence justifying this hypothesis: notochordal cell nests topographically correspond and distribute to the sites of occurrence of chordoma. In some cases of familial chordoma, there are some duplications in the transcription factor T gene (*brachyury*), an important transcription factor in notochord development. Chordomas inconstantly express some actionable targets, mainly stem cell factor receptor (c-KIT), platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), receptor tyrosine-protein kinase erbB-2 (HER2/neu) and epidermal growth factor receptor (EGFR) [1–3].

Chordomas are slow growing tumors but are invasive, spreading between the neural structure and axial skeleton. At the time of diagnosis, the tumor burden is usually large, making the management of this tumor very challenging [1,4,5]. Large en bloc surgery remains the cornerstone of curative intent surgery of sacral and spinal chordomas; nevertheless, the neurological impairment caused by this surgery could be very deleterious. Adjuvant radiotherapy is largely used to manage chordomas. The treatment of clival chordoma is much more challenging due to the critical role of adjacent neural structures; this management is usually based on cytoreductive surgery followed by radiotherapy [4]. There is no consensus on the ideal radiotherapy technique: intensity-modulated radiation therapy and stereotaxic therapies, both of which use conventional protons, or hadron therapies [6].

Nevertheless, large en bloc resection is feasible for less than 50% of sacral chordomas and even fewer clival chordomas. Local relapse and metastatic relapse are frequent. Furthermore, some cases are not amenable to surgery at the time of diagnosis. As a consequence, medical treatment of locally advanced or metastatic chordomas is frequently discussed. Chemotherapy is regarded as ineffective in advanced chordomas [1]. Recent case reports from multi-tumor phase II trials or dedicated phase II trials have suggested that some molecular targeted therapies could slow down the tumor progression of advanced chordoma. We report herein a systematic review on the role of molecular targeted therapies in the management of advanced chordoma with the purpose of designing a future clinical trial.

2. Materials and methods

Using Medline, we have reviewed all of the publications fulfilling the following criteria: (i) case report, retrospective studies or clinical trials focusing at least partly on chordoma, (ii) reports published in English, (iii) between January 1990 and September 2014, and describing the activity of molecular targeted therapies (non-cytotoxic agents). We have then calculated frequencies and median of data extracted from these publications.

Furthermore, we have reviewed the studies describing the expression or mutation of putative targets in human chordoma series.

3. Results

The number of eligible publications is limited: ($n = 19$). These publications could be scored in three categories: (i) case reports and retrospective series, (ii) chordomas enrolled in multi-tumor phase I or II trials, and (iii) dedicated phase II trials focusing exclusively on chordomas.

3.1. Case reports and retrospective studies

Most of publications are case reports of a single case. Stacchiotti et al. reported the outcome of 10 patients treated with an imatinib/sirolimus combination [7], and Casali et al. reported a retrospective series of 6 advanced chordomas