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Review

Medical treatment of advanced chordomas

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Abstract Chordoma is a very rare bone sarcoma that can arise from any site along the spine and from the skull base. *En bloc* resection is the gold standard for treatment while radiation therapy has been shown to provide both curative and palliative benefit. Unfortunately, local recurrences are common, even after a complete surgical resection, and up to 40% of patients suffer from distant metastases, while salvage treatments are challenging. Patients carrying an advanced disease need a systemic treatment. Unluckily, conventional chordoma are insensitive to cytotoxic chemotherapy that is considered the standard treatment option in patients with metastatic sarcoma. In the last decade, innovative therapies have been introduced, positively impacting disease control and patients' quality of life. In addition, a better understanding of the molecular characteristics of chordoma allowed to detect new potential targets. This review is focused on the pharmacological management of patients affected by an advanced disease, starting with a summary of data available on conventional chemotherapy, then moving to a deeper analysis of available data on molecular agents and immunotherapy, and finally providing an update on ongoing clinical trials and future prospective.

1. Introduction

Chordoma is a very rare tumour of the bone, with an annual incidence of approximately 0.1/100,000/year [1,2]. It can occur at any level of the spine, but the commonest site of origin is the sacrococcygeal region (50–60%), followed by the skull base (30%). Exceptionally, extra-axial cases have been reported [2–4].

Although the pathogenesis of chordoma remains unclear, tumour cells are characterised by a notochordal differentiation [5], as confirmed by the overexpression of brachyury, a nuclear transcription factor involved in the

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regulation of the notochordal growth. Positive nuclear immunostaining for brachyury is recognised as the diagnostic hallmark for chordomas [6–8]. Interestingly, chordomas are mostly sporadic, but the potential role of genetic predisposition is supported by the report of a small number of familial cases affected by tuberous sclerosis complex and some duplications in the transcription factor T gene (brachyury) [9–14].

Chordoma is more frequent in males, with an average age at diagnosis of about 60 years, while skull base presentation generally affects a younger population and children [2].

Pathologically, chordomas are solid gelatinous pinkish-grey masses with cystic components and an expansive growth. The classical, the chondroid and the dedifferentiated subtype are the three variants demonstrated microscopically [2]. Dedifferentiated chordoma is a rare variant, occurring in about 5% of patients, most commonly in children. It is marked by high-grade features with loss of nuclear brachyury positivity. In addition, dedifferentiated chordoma can show the deletion on integrase interactor 1 (INI1) [15,16]. On immunohistochemistry, chordomas are positive for epithelial markers, such as low-molecular-weight cytokeratins and nuclear brachyury. The expression of other markers, such as PAS, S100 and epithelial membrane antigen, is variable [2].

Chordomas are in general low-grade, locally aggressive tumours, and in most cases, the clinical course of the disease is indolent, with the exception of dedifferentiated chordoma that shows an aggressive behaviour [2].

The mainstay of care is complete *en bloc* resection of the tumour, with the goal of negative microscopic margins and/or high-dose hadron radiation therapy, with a view to the long-term outcome [17–27]. However, most chordoma patients have locoregional relapses. In addition, metastases can occur in 30–40% of them, usually after a local relapse and commonly at a late stage of disease [19]. They can be seen at almost any site, typically to the lungs, liver, bone, soft tissues and even lymph nodes [2].

In the advanced setting, patients with chordoma are not amenable to cure and need a systemic treatment, to be combined with appropriate supportive care. We review herein the most recent available data on the role of medical anticancer treatment in advanced chordoma. Notably, at present, none of the potentially active drugs is registered, resulting in discrepancies across the world. Only a few trials are open in the disease [17].

2. Systemic management of advanced chordomas

As chordoma is a potentially indolent disease, active surveillance is a reasonable option in many cases before starting any medical treatment, to assess the progression pace, reserving medical treatment to the symptomatic or progressive disease [17,21]. In addition, available data on the activity of systemic treatment in this tumour come from a few phase 2 trials and retrospective case series or even case reports [17,21]. An updated list of trials ongoing in chordoma is available at https://www.chordomafoundation.org/ and summarised in Table 1 as well.

2.1. Cytotoxic chemotherapy

No evidence is available at the moment to recommend the use of cytotoxic agents in advanced conventional chordoma, as chemotherapy has not demonstrated any clinically significant activity. However, chemotherapy may be employed in patients with the high-grade/dedifferentiated variant of the tumour [17,21,28–31].

Namely, the only prospective phase 2 study on chemotherapy in chordoma was done on irinotecan, a topoisomerase I inhibitor, in 15 evaluable patients with advanced chordoma: one objective response lasting at least 8 months and 14 stabilisations were detected with a median 6-month progression-free rate of 33% and a median time to progression of 10 months for all treated patients [32].

Small retrospective series and a few anecdotal case reports (Table 2) are available describing responses to regimens including anthracyclines, alkylating agents, cisplatin and etoposide. They refer mostly to childhood cases and/or to high-grade dedifferentiated chordomas [33–38].

Among cytotoxics, trabectedin, a drug used in the treatment of sarcomas, did not show efficacy in a retrospective study of 10 adult patients affected by advanced chordoma [39].

2.2. Target therapy

Recently, systemic therapy has focused on molecularly targeted agents. In addition to brachyury, many molecular potential targets, including epidermal growth factor receptor (EGFR), PDGFRB, PI3K/mTOR, MAPK, STAT, FGFR, MET, CDK4, vascular endothelial growth factor (VEGF) and INI1, are increasingly being identified in chordoma [2]. Notably, none of them have shown recurrent mutations or rearrangements, but available data point to their activation and, sometimes, to their amplification. In addition, there is preclinical evidence that the inhibition of some of them can impair tumour growth. This applies in particular to brachyury, EGFR, PDGFR, PI3K/mTOR, MAPK and MET. An updated list of all published available molecular, preclinical and clinical data on therapeutic targets in chordoma is available at https://www.chordomafoundation.org/ and is summarised in Tables 3 and 4 as well.

Notably, chordoma models, including cell lines and xenografts, have been reported in an effort to identify new treatment options. To date, few chordoma cell lines have been developed (e.g. U-CH1, U-CH2b and