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Review

Systemic therapy for selected skull base sarcomas: Chondrosarcoma, chordoma, giant cell tumour and solitary fibrous tumour/hemangiopericytoma

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ABSTRACT

This review highlights the data currently available on the activity of systemic therapy in chondrosarcoma, chordoma, giant cell tumour of the bone (GCTB) and solitary fibrous tumour, i.e., four rare sarcomas amongst mesenchymal malignancy arising from the skull base.

1. Introduction

Skull base tumours include a large number of benign and malignant entities. This review focuses on chondrosarcoma, chordoma, giant cell tumour of the bone (GTCB) and solitary fibrous tumour/hemangiopericytoma (SFT), i.e., those sarcomas which are relatively "typical" of the skull base. Each represents a very rare disease, with an incidence of less than 1/1,000,000/year (considering all primary sites).[1,2] Of course, all sarcoma subtypes can occasionally arise from the skull base.

In principle, the essential criteria for medical treatment of sarcomas arising from the skull base are basically independent from the primary site. On the other hand, as a general rule, given their rarity and heterogeneity, sarcoma patients should always be approached by a multidisciplinary team at a referral institution.[3]

Chondrosarcoma, chordoma and GTCB are all bone sarcomas that can arise from the bone component of the skull base,

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while SFT is a soft tissue sarcoma that, at the skull base level, can arise from the meninges. All of these tumours are usually marked by a low aggressive behaviour, but, due to their critical position, they can be life threatening even in the localised setting. In addition, they all have a metastatic potential, and their aggressiveness can increase over time, in case of recurrence.[3] In locally advanced or metastatic cases, a medical therapy is needed. Unfortunately, these tumours are marked by a low, if any, sensitivity to conventional cytotoxic chemotherapy. Doxorubicin plus or minus ifosfamide are regimens generally viewed as standard front-line therapy, but the expected response rate is low (i.e. 10–30%). Few prospective studies focusing on the medical treatment are available today. However, the recent characterisation of their molecular features has paved the way to the use of new targeted agents, which, in some cases, are very effective; the most recent and striking example being denosumab, a RANKL inhibitor, in GCTB.

In this paper we review data currently available in literature on the activity of systemic medical treatment in each of these histotypes.

1.1. *Chondrosarcoma*

Chondrosarcomas are a heterogeneous group of bone sarcomas marked by the production of chondroid matrix. The incidence is about 0.2/100,000/year, with a peak between the third and the fifth decade.[3] They may arise anywhere in the body, as sporadic forms or secondary to familial/hereditary disorders such as Maffucci syndrome, Ollier's disease, Paget's disease and osteochondromatosis. Chondrosarcomas arising from the skull base represent 1% of all chondrosarcomas, and about 6% of all skull base tumours. Endocranic chondrosarcomas almost exclusively origin from the skull base rather than from the vault (Fig. 1). This may be explained by the different embryogenesis of their respective composing bones, since the former develops through endochondral ossification, the latter through intramembranous ossification, and chondrosarcomas of the skull base are thought to arise from remnants of endochondral mesenchymal cells.[4]

As for what happens to chondrosarcoma arising from other sites of the body, most skull base chondrosarcomas show a conventional, low-grade histotype. However, in the latter case, they represent a therapeutic challenge because of their locally aggressive behaviour, while the metastatic risk is low.[5] Histological subtype and grade influence the prognosis and the choice of treatment.

As said, evidence on treatment from literature mainly refers to anecdotal studies. Chemotherapy has historically shown poor activity in conventional chondrosarcomas and it is not a standard in the adjuvant/neoadjuvant setting, while it can be considered in the locally advanced or metastatic disease.[35] Although most of the available Phase 2 studies have the confounding factor of including different histotypes, responses were reported to regimens commonly used in other soft tissue and bone sarcomas, i.e. anthracycline- and gemcitabine-based combinations, ifosfamide, cisplatin.[6,7] With conventional cytotoxic chemotherapy, RECIST disease stabilisations are more commonly observed than objective responses. In the largest retrospective series, published by Italiano et al., cumulative objective response rate (ORR) was significantly dependant on the histotype, being 11% for conventional chondrosarcoma, with a median progression-free survival (PFS) of 5 months.[6] In the same report, responses to cytotoxic chemotherapy were observed in 31% of the cases of mesenchymal chondrosarcoma and 20% of the cases of dedifferentiated chondrosarcoma, while no response was observed in two patients with a clear-cell chondrosarcoma.

Several molecular targets have been identified in conventional chondrosarcomas,[8–10] but no targeted therapy has proven effective so far.[7] Probably, molecular heterogeneity and different pathogenetic mechanisms within different chondrosarcoma variants complicate this issue.[11] The initial enthusiasm driven by pre-clinical data with Hedgehog pathway inhibitors has been frustrated after results of a Phase 2

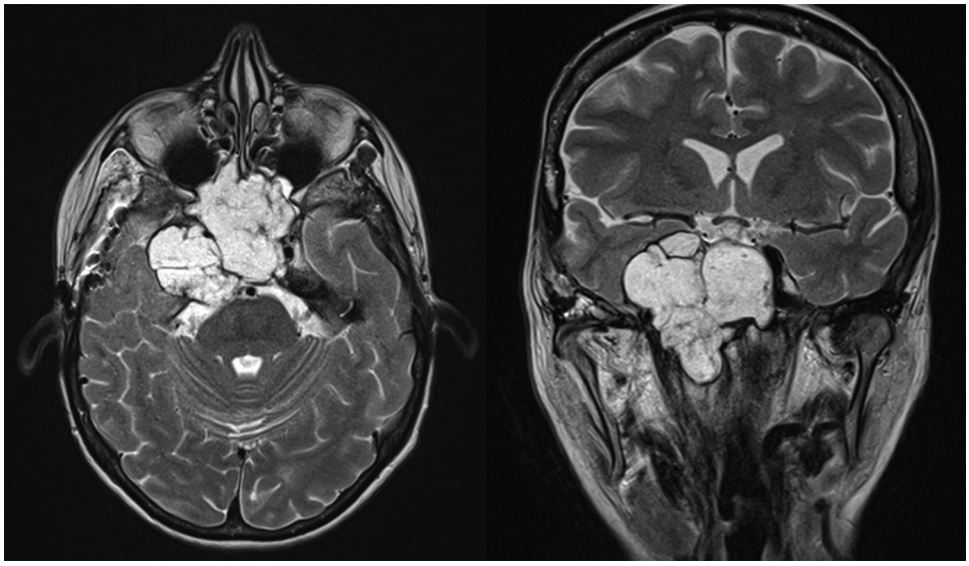

Fig. 1 – Conventional G2 chondrosarcoma of the skull base in a 52-year old woman, progressed after upfront radiotherapy (contrast enhanced MR, T2 sequence). The tumour appears as a hyperintense lesion extending from the sphenoid towards the nasal cavity, the optic chiasm, the right temporal bone.