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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

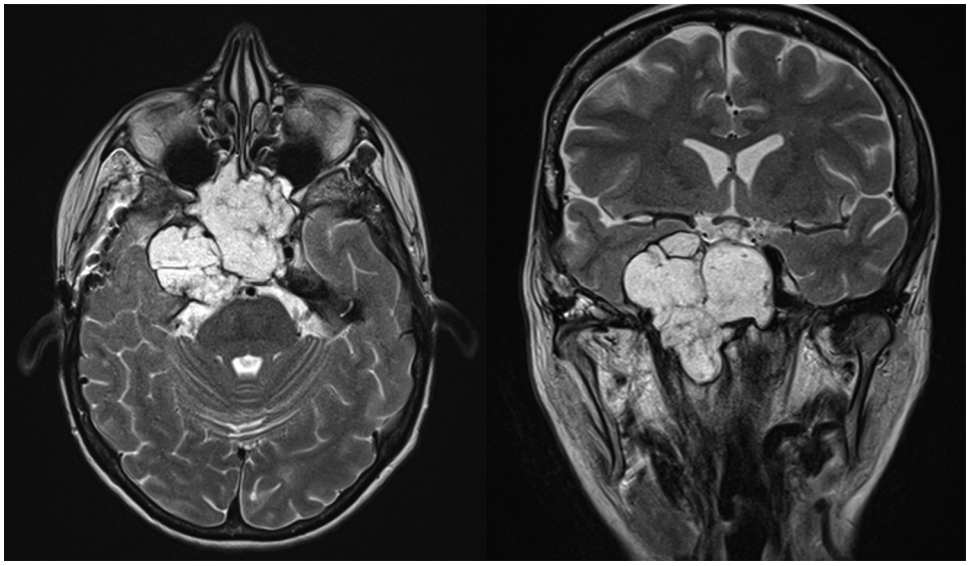

Fig. 1 – Conventional G2 chondrosarcoma of the skull base in a 52-year old woman, progressed after upfront radiotherapy (contrast enhanced MR, T2 sequence). The tumour appears as a hyperintense lesion extending from the sphenoid towards the nasal cavity, the optic chiasm, the right temporal bone.

study in which no objective responses were observed.[12] Interestingly, two long-lasting, RECIST partial responses (PR) have been reported in patients with an advanced chondrosarcoma in a Phase 1 study with recombinant human APO2L/TRAIL,[13] but, to our knowledge, no further exploratory trials on this class of agent in chondrosarcoma are available. Trials evaluating VEGFR, mTOR pathways and immunomodulating agents are ongoing.

By contrast to conventional chondrosarcoma, dedifferentiated chondrosarcomas are a high grade tumour, marked by an aggressive behaviour and a high tendency to metastasis. Although it is not proven that they have the same chemosensitivity as osteosarcoma, they are often treated using the same combined treatment.[3]

Mesenchymal chondrosarcomas are characterised by an aggressive behaviour and a peculiar chemosensitivity,[14] reported to be similar to Ewing sarcoma, and are often treated with a multimodal strategy including chemotherapy with Ewing-like regimens.[3] In fact, retrospective evidence suggests a mesenchymal subtype being a main prognostic factor even in skull base chondrosarcomas.[15]

1.2. *Chordoma*

Chordomas are rare primary bone tumours that arise from the embryonic remnants of the notochord. They typically occur in the axial skeleton, but the skull base is the second most frequent site, accounting for about 30% of all chordomas, and only 0.1–0.25% of all intracranial tumours.[16] These tumours typically arise in adults (median age at diagnosis is 60 years), but chordomas of the skull base occur more often in younger patients and children. A possible genetic predisposition is suggested in a minority of patients, with a small number of familial cases of chordoma being reported.[17]

Although chordoma does have a metastatic potential, its long term outcomes are mostly dependent on its local aggressiveness and pattern of local recurrence, affecting >50% of patients and requiring repeated surgical procedures and/or radiation therapy.[18] Due to their deep anatomic site, the proportion of local relapse is higher in skull base chordomas,[19] even after macroscopic complete surgery and/or definitive radiotherapy. Metastases have been reported in 30–40% of patients, with a late clinical presentation, commonly to the lungs, liver, bone, sub-cutis, lymph nodes and other sites. Finally, an aggressive dedifferentiated high-grade variety may occur in around 5% of patients.[1]

Surgery and high-dose radiation therapy are of choice. In case of locally advanced or metastatic disease, a systemic treatment is needed. Chordomas are known to be relatively resistant to conventional chemotherapy. In fact, studies reporting the use of cytotoxic agents have not demonstrated a clinically significant activity.[20,21] The only prospective Phase 2 study on the topoisomerase I inhibitor irinotecan showed one objective response in 15 chordomas (27% affected by clival chordoma), with a median 6-month progression-free rate of 33%.[22] In high-grade dedifferentiated and paediatric cases, few anecdotal responses to regimens including anthracyclines, cisplatin, alkylating agents and etoposide have been reported.[23]

Recently, systemic therapy has focused on molecularly targeted therapies: many molecular biomarkers, including PDGFRB, EGFR, mTOR and MET are increasingly being identified.[1] Among molecular target-drugs, anti-PDGFRB imatinib mesylate has shown a certain activity, as detected in a prospective Phase 2 study[24] and reported in several observational retrospective series.[25–28] In a Phase 2 study on imatinib as a single agent in advanced patients, including some whose primary tumours were located to the skull base (9 cases, 16%), the PFS and overall survival were 9 and 35 months, respectively, and there was one PR and 35 stable diseases (SD) according to RECIST (Fig. 2).[24] Since chordoma is an indolent and slow growing tumour, the interpretation of PFS can be critical. However, it has to be considered that all patients who entered this study were progressive and that the observed 9-month PFS is superior to the one reported in the other only 2 formal studies ever performed in chordoma, on irinotecan and lapatinib.[22,29] In imatinib-resistant cases, a retrospective study on 10 advanced chordoma patients (1/10 with a clival chordoma) showed that the mTOR inhibitor sirolimus in combination with imatinib may be effective, indicating a possible synergism between the two drugs.[25] The results of a Phase 2 study of imatinib plus everolimus in advanced chordoma are under analysis (EUDRACT number: 2010-021755-34). In another trial, George et al. assessed the activity of sunitinib in different mesenchymal tumours. Among them, in 9 chordoma patients there were no objective responses, but 4 SD with a PFS of approximately 12 months, with a treatment duration of 17 and 18 months in 2 cases of clival chordomas and 51 and 70+ months in 2 cases of spinal/sacral chordomas.[27] EGFR inhibitors have also shown some activity in chordoma. There are reports on erlotinib plus cetuximab combination in 2 cases (1 SD with a PFS of 27 months) and erlotinib plus bevacizumab in 3 cases (2/3 with a clival chordoma; respectively, 1 PR with a PFS of 54 months and 1 SD with a PFS of 24 months).[30] No formal study on these agents have been performed, while a Phase 2 study was conducted on the EGFR/HER2-Neu inhibitor lapatinib, unfortunately with a very low activity in EGFR-positive advanced chordoma.[29]

Finally, in 2005, brachyury, a transcription factor associated with the regulation of the notochordal growth, was found to be overexpressed in the disease,[31–33] providing an excellent diagnostic marker. In addition, brachyury represents a promising target, and new inhibitory agents thereof are under evaluation within clinical studies. In particular, a Phase 1 study on yeast-brachyury GI-6301 vaccine has shown it to be immunogenic and to have clinical activity in advanced chordomas. This trial is still ongoing (ClinicalTrials.gov Identifier NCT015198170).

1.3. *Giant cell tumour of the bone*

According to the last WHO classification of soft tissue and bone sarcoma, giant cell tumour of the bone (GCTB) is defined as a benign but locally aggressive primary bone tumour (Fig. 3).[1] GCTB is marked by a high tendency to recur locally. The metastatic risk is very low, reported to be about 5%, the lungs being the most frequent site of metastases. Histologically, the metastatic lesions can retain the same so-called "benign" features of the primary tumour. In about 1% of GCTB,

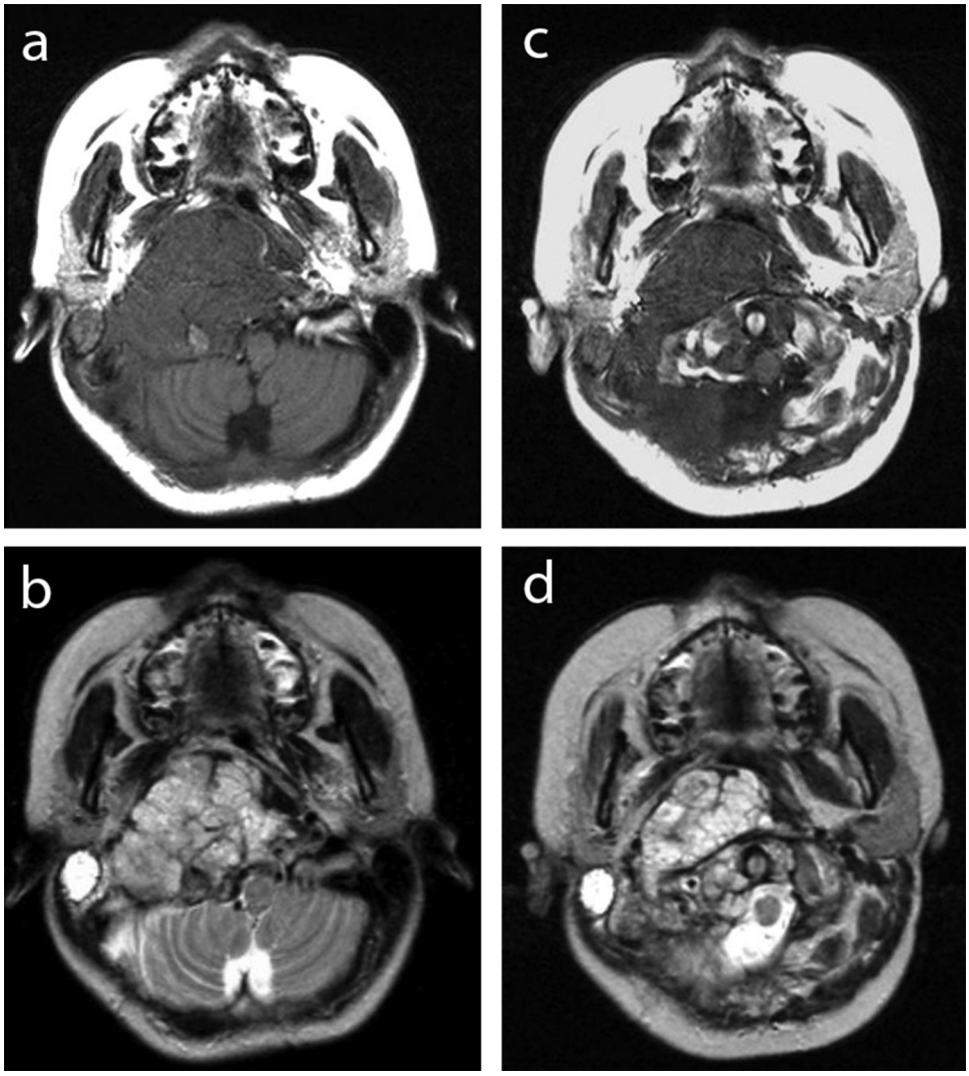

Fig. 2 – Chordoma of the skull base in a 19-year old girl (contrast enhanced MR, T1-T2 sequences) treated with imatinib 800 mg daily at baseline (a, b) and after 1 month of therapy (c, d), showing a response.

a malignant transformation into a high-grade spindle cell sarcoma can be observed.[1] The high-grade malignant aspects can be present at tumour onset (primary malignant GCTB) or can appear over time (secondary malignant GCTB). Malignant GCTBs have a poor prognosis, as expected with high-grade sarcomas.

Histologically, GCTB is marked by the presence of three cell components: spindle mononuclear stromal cells, which are the true neoplastic component, osteoclast-like multinuclear giant cells, and monocyte/macrophage family cells. The spindle tumour stromal cells secrete the Receptor Activator of Nuclear Factor Kappa-B-Ligand (RANKL), a membrane protein, into the extracellular matrix. RANKL affects the immune system and controls bone regeneration and remodelling by binding RANK, a receptor expressed on the surface of GCTB giant cells. The RANK/RANKL signalling pathway regulates osteoclasts differentiation and is associated with bone remodelling and immune cell function.

Surgery is a standard treatment in resectable GCTB. Due to the site, skull base cases can be difficult to be treated by complete surgery. In this event, and in the case of a metastatic disease, medical therapy is needed.

Conventional cytotoxic chemotherapy is not active in classic GCTB, even if anecdotal responses to osteosarcoma-like regimens containing platinum and anthracyclines were reported in the metastatic setting.[34–36]

Basing on RANK/RANKL expression in GCTB, the activity of denosumab has been explored in the disease, with impressive results. Denosumab is a fully human monoclonal antibody targeting RANKL, that prevents its interaction with RANK and thus inhibits the activation and recruitment of giant cells within the tumour. Denosumab was initially assessed in a Phase 1/2 trial on 37 patients with recurrent or unresectable GCTB: 86% of patients benefited from therapy, showing a pathologic response or a tumour growth arrest.[37] This trial was followed by an international, open-label, Phase 2 study,

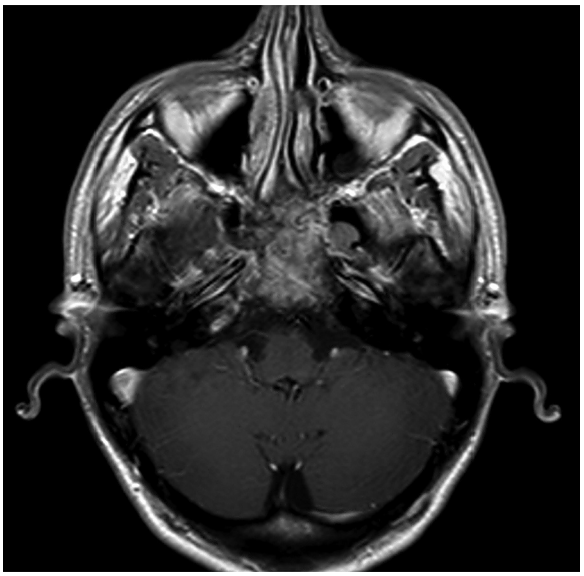

Fig. 3 – GCTB of the skull base in a 35-year old man (contrast enhanced MR, T1 sequence). The tumour appears as a hypointense lesion involving the clivus, the sphenoid, the nasal cavity.

that enrolled 500-plus patients. The results on the first 282 patients were published in 2013: denosumab provided long lasting responses in most cases (RECIST RR >40%, with 96% of progression-free patients at a median follow-up of 15 months). The drug was very well tolerated, except for 2 patients (1%) experiencing an osteonecrosis of their jaw. This study included also eight patients with skull base GCTB, with superimposable results. On this basis, the drug has been recently approved for GCTB by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA), and it is considered the standard front-line treatment in advanced GCTB.[3] Of interest, denosumab activity does not directly affect the tumour cell component of GCTB, i.e. the stromal cells, but it works by inhibiting the recruitment and the differentiation of the giant cell component of the tumour that is attracted to the tumour bed by RANKL. This was proven in patients biopsied after treatment with denosumab. In post treatment tumour samples,[38] a decrease in tumour giant cells of 90% or more and increased fibro-osseous tissue and/or new bone was observed together with a reduction in the tumour content of RANKL-positive tumour stromal cells that, however, appeared to be still detectable and viable at least in part. Since denosumab shows minimal efficacy against the stromal cells, a tumour re-growth is expected after denosumab discontinuation or in those cases in which a response to denosumab is followed by an incomplete surgical resection. This strongly suggests the need for a prolonged treatment, unless a surgical resection with a curative intent can be performed.[39] Many open issues on the role of denosumab in GCTB are still left to answer,[40] such as the optimal schedule, treatment duration, adjuvant setting, and the mechanism underlying resistance. Some of those questions will probably be answered by the final analysis of the phase 2 study that has been published only in part at the moment.[41] A recent update of this trial has for example shown that preoperative denosumab could downstage surgery in 38% of 222 of evaluable patients. On the other hand, prospective discontinuation studies are in principle needed to determine the treatment duration in patients who cannot be resected. Of notice, also pro-angiogenic factors seem to play a role in the pathogenesis of GCTB.[42,43] Interferon (IFN), an anti-angiogenic agent, was used in the advanced setting,[44] with anecdotal responses. Other anti-angiogenic drugs have shown some activity in GCTB, such as sunitinib[27] and pazopanib in combination with erlotinib (1 PR in a Phase 1 trial).[45]

1.4. *Solitary fibrous tumour/hemangiopericytoma*

SFT can arise at almost all anatomic sites, including the meninges. SFT shows complete morphologic and genetic overlap with hemangiopericytoma (HPC), a denomination that has been formally abolished in the most recent WHO classification of mesenchymal neoplasm.[1] However, the name HPC is still retained for tumours arising in the central nervous system (CNS).[46] A recurrent *NAB2-STAT6* gene fusion has been detected in SFT, regardless of anatomical location.[47] Interestingly, the same rearrangement has been observed in so-called meningeal HPCs, further proving that they represent the same entity.[48] SFT is marked by a broad spectrum of malignancy. Three clinical-pathologic variants can currently be recognised: the so-called “benign” (or “classical” or “usual”) (CSFT), the malignant (MSFT) and the dedifferentiated (DSFT) variants.[1] CSFT is characterised by a bland morphologic appearance and usually a favourable outcome after wide surgical resection, but recurrences with aggressive behaviour can be rarely observed.[49] MSFT is characterised by a mitotic index ≥4/10HPF, hypercellularity, necrosis and/or pleomorphism. DSFT hallmark is the presence of a sarcomatous overgrowth mimicking not otherwise specified or distinct high-grade sarcoma types.[50,51]

SFT natural history is characterised by a high cure-rate after complete surgery, with a 10–15% risk of metastasis. DSFT shows an aggressive behaviour with a higher metastatic potential.[1]

The expected RR to doxorubicin-based chemotherapy is indeed low, about 20%.[35] Also dacarbazine can be active in some cases (Fig. 4).[52]

Among molecular target agents, the activity of antiangiogenics as bevacizumab in combination with temozolomide,[53] sorafenib,[54,55] sunitinib[56,57] and pazopanib[58,59] was reported in the last years. Responses were non-dimensional in most patients and the molecular mechanisms by which the drugs inhibit tumour growth are still not well understood. Among anti-angiogenic agents, pazopanib is the only one currently approved for treatment of advanced STS, including SFT. Preliminary data on its activity in SFT are already available[60] and a European Multicentric Phase 2 study on pazopanib in this tumour is ongoing (EUDRACT Number: 2013-005456-15). A further study on axitinib, another antiangiogenic drug, is also ongoing in Italy in advanced SFT patients (EUDRACT Number: 2013-005596-40), based on preclinical data showing the potential anti-tumour effect of this agent in this sarcoma subtype.[60] Finally, anti-IGF1R inhibitors also sound potentially

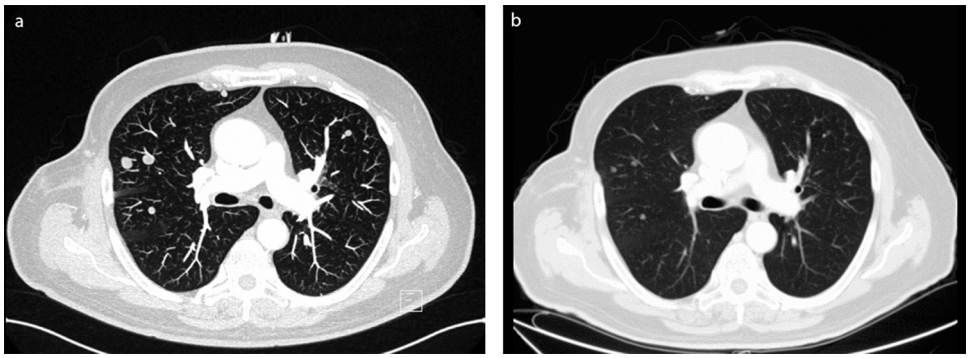

Fig. 4 – Bilateral, multiple, lung metastases from a malignant solitary fibrous tumour of the chest wall in a 67-year old man (contrast enhanced CT scan, arterial phase) before (a) and after 6 cycles of chemotherapy with doxorubicin and dacarbazine (b). A response in all lesions can be observed.

interesting in this tumour, given the molecular profile of the disease, but this class of agents is not available at the moment.[61–64]

2. Conclusions

This review refers to a subgroup of very rare entities, i.e., chondrosarcoma, chordoma, GCTB and SFT. Although exceedingly rare, they have been selected since they can occur at the skull base and often require a medical treatment. Interestingly, they are all rather insensitive to cytotoxics, with the only exception of mesenchymal chondrosarcoma. In part, this may be related to the fact that most of these entities are essentially low-grade sarcomas.

However, in spite of the low-grade biology, local relapse/progression is a common event in skull base sarcomas. Medical therapy is administered with a palliative intent to decrease tumour bulk, diminish symptoms, and improve the quality of life. When compared to sarcomas arising from other sites, in skull base sarcomas pain and neurologic impairment are major issues, often as from the onset of disease. Therefore, treatment with anti-cancer agents needs to be combined with palliative therapy.

Sarcomas are a heterogeneous family of tumours and this has made the study of chemotherapy regimens challenging. Currently, the notion of a 'histology-driven' approach to the medical therapy of sarcomas is widely pursued. An example with chemotherapy in these forms was the use of temozolomide or dacarbazine in SFT. Furthermore, recent discoveries about several molecular pathways involved in sarcoma tumourigenesis led to the use of molecularly targeted agents, sometimes with impressive results, as in the case of denosumab in GCTB. Imatinib in chordoma and antiangiogenic agents in SFT are other examples in which encouraging results have been obtained.

Despite the improvements made in the last years, the expected cure rate of soft tissue sarcomas is still around 50%. Patients with local tumour recurrence have a lower disease-specific survival, and those with metastatic relapse have definitely low 5-year survival rates.[65] Prognosis is worse when the primary site is critical, like the skull base.

It is evident that there is an urgent medical need for new systemic therapeutic options for the treatment of patients with advanced sarcomas, including very rare subtypes such as chondrosarcoma or chordoma. On the other hand, it seems that some rare sarcoma subtypes are currently the most likely to respond to the new targeted agents. Then, the issue may prove the efficacy of new agents in rare entities. In this regard, an effort to improve the methodology of research in rare cancers is in place within the European community.[66] In addition, given the heterogeneity of sarcomas, an endeavour to centralise the treatment of sarcoma cases into reference centres or collaborative networks is also strongly requested, since it is a prerequisite to increase our chances to intensify clinical and translational research.

Conflict of interest

Stacchiotti S. – Lectures: Amgen; Research funding for clinical studies in which I was involved: Amgen, Glaxo SK, Novartis, Pfizer.

Casali PG – Advisory: Amgen Dompé, ARIAD, Bayer, Blueprint Medicines, Glaxo SK, Lilly, Merck SD, Merck Serono, Novartis, Pfizer, PharmaMar; Honoraria: Novartis, Pfizer, PharmaMar. Travel coverage for medical meetings: Novartis, PharmaMar; Research funding for clinical studies in which I was involved: Amgen Dompé, Blueprint Medicines, Eisai, Glaxo SK, Molmed, Novartis, Pfizer, PharmaMar.

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