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CASO CLÍNICO

Targeting IDH1: Long-Term Efficacy and Tolerance of Ivosidenib in Advanced Chondrosarcoma

IDH1 como Alvo Terapêutico: Eficácia e Tolerância a Longo Prazo do Ivosidenib no Condrossarcoma Avançado

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ABSTRACT

Around 20% of primary bone malignancies are chondrosarcomas. Advanced or recurrent conventional chondrosarcomas are typically resistant to chemotherapy and radiotherapy and overall survival remains poor, highlighting the need for other therapeutic options. We present two cases of metastatic chondrosarcoma with isocitrate dehydrogenase 1 (*IDH1*) mutation treated with ivosidenib. In case 1, a 70-year-old woman with recurrent metastatic grade 2 chondrosarcoma achieved well-tolerated, durable stable disease for 12 months in second line (no response to conventional first line chemotherapy). In case 2, a 63-year-old man with recurrence of grade 2 chondrosarcoma maintained stable disease for 16 months on ivosidenib first line. In both cases, there were no relevant toxicities with no need for dose adjustments. These cases highlight the usefulness of ivosidenib as a targeted therapeutic option for patients with metastatic or recurrent unresectable chondrosarcomas with *IDH1* mutation. Long-term efficacy with very good tolerance was achieved.
Keywords: Chondrosarcoma/drug therapy; Chondrosarcoma/genetics; Isocitrate Dehydrogenase/genetics; Ivosidenib/therapeutic use; Molecular Targeted Therapy; Mutation

RESUMO

Cerca de 20% das neoplasias ósseas malignas primárias são condrossarcomas. Os condrossarcomas convencionais avançados/recorrentes são, tipicamente, resistentes à quimioterapia e radioterapia, tendo uma sobrevivência global desfavorável, evidenciando a necessidade de novas opções terapêuticas. Apresentamos dois casos de condrossarcoma metastático com mutação do isocitrato desidrogenase 1 (*IDH1*) tratados com ivosidenib. No caso 1, uma mulher de 70 anos com condrossarcoma grau 2 metastático recorrente, alcançou doença estável duradoura durante 12 meses em segunda linha, após ausência de resposta à quimioterapia convencional de primeira linha. No caso 2 um homem de 63 anos, com recidiva de condrossarcoma grau 2, manteve doença estável durante 16 meses com ivosidenib em primeira linha. Em ambos os casos, o tratamento foi bem tolerado, sem toxicidades relevantes nem necessidade de ajustes posológicos. Estes casos evidenciam a utilidade do ivosidenib como opção terapêutica-alvo em doentes com condrossarcoma metastático ou recorrente irressecável com mutação do *IDH1*, demonstrando eficácia prolongada e excelente tolerabilidade.
Palavras-chave: Condrossarcoma/genética; Condrossarcoma/tratamento farmacológico; Isocitrato Desidrogenase/genética; Ivosidenib/uso terapêutico; Mutação; Terapia de Alvo Molecular

INTRODUCTION

Chondrosarcomas (CSs) are rare bone cancers arising from cartilage-producing cells, accounting for about 20% of primary bone malignancies[1,2] and most cases (approximately 85%) are of the conventional form.[1]

The reported five-year average survival rates for patients with conventional CSs are around 68%, though highly dependent on tumor grade and location with high grade (grade 3 and dedifferentiated) and axial/pelvic location being associated with a worse prognosis. The typical approach with curative intent is surgery (often associated with significant morbidity),[3] with local recurrence occurring in approximately 25% of patients.[1]

In cases of recurring and/or unresectable disease, radiotherapy is usually ineffective and there are few effective systemic therapies (most subtypes are chemoresistant). Despite advances in understanding molecular pathogenesis, there are no approved molecular target therapies specific for conventional CS.[1]

Mutations in isocitrate dehydrogenase 1 (*IDH1*) – responsible for regulating cellular metabolism and redox balance, with its dysregulation promoting epigenetic changes – are present in approximately 50% - 70% of CSs, with gain-of-function mutations in *IDH1* (and *IDH2*) that lead to the production and accumulation of the oncometabolite 2-hydroxyglutarate (2-HG), causing aberrant methylation of DNA and histones implicated in the tumorigenesis.[2,3] Isocitrate dehydrogenase inhibitors have been investigated for the treatment of chondrosarcomas with promising results.[1]

However, there are very few real-world case reports regarding the use of ivosidenib, an oral *IDH1* inhibitor, in the treatment of chondrosarcoma, with limited data on response and tolerability.

We present two patients with *IDH1*-mutant chondrosarcoma who received ivosidenib and experienced sustained benefit with preservation of functional status and quality of life.

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CASE REPORT

Case 1

A 70-year-old woman with a known medical history of type 2 diabetes, hypertension and dyslipidemia. The patient presented progressive left hip pain in early 2022.

Pelvic imaging revealed a destructive lesion of the left iliac bone involving the bone and ischial regions (Fig. 1) and the patient underwent an internal hemipelvectomy. Histopathology showed conventional (central) chondrosarcoma, grade 2, with a myxoid-rich stroma. Surgical margins were positive (R1 resection due to involvement of the lower margin of the soft tissues). After a multidisciplinary tumor board discussion, the patient was placed on surveillance.

Seventeen months after surgery, surveillance imaging showed locoregional recurrence in the right femur as well as distant metastases in the lumbar spine and contralateral femur. She began systemic treatment with doxorubicin. However, a follow-up assessment four months after the beginning of chemotherapy revealed progressive local disease with enlarging soft-tissue masses in the left thigh.

Next-generation sequencing (NGS) using the TruSight Oncology 500 assay (Illumina) identified an IDH1 R132C mutation. The variant allele frequency was 28.4%, meaning that about one in four DNA sequencing reads from this region contained the mutation.

Based on this result, the patient was deemed a candidate for targeted therapy. Following a multidisciplinary tumor board discussion, off-label ivosidenib (500 mg daily) was initiated, with tolerance and only grade 1 anorexia (loss of appetite without alteration in oral intake), according to CTCAE v5.0,[4] and no other relevant adverse events. Treatment response was assessed every three months, aligned with Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 principles.[5] Stable disease was maintained for 12 months.

Case 2

A 63-year-old man with known smoking history. The patient was diagnosed with CS of the right fourth finger treated with complete amputation in 2003 and remained disease-free for years.

The patient began follow-up in Pulmonology due to respiratory complaints, with a chest CT showing a left lower-lobe mass, prompting referral for surgical management. He underwent *en bloc* resection of a posterior mediastinal mass involving the diaphragm, left lower-lobe lobectomy and mediastinal lymphadenectomy. The revised histopathology was consistent with metastatic grade 2 chondrosarcoma. During surveillance, the disease recurred as multiple lung and pericardial nodules. Next generation sequencing was performed using TruSight Oncology 500 (Illumina), revealing an IDH1 NM_005896.2:c.394C>G p.(*Arg132Gly*) mutation. After a multidisciplinary tumor board discussion off-label ivosidenib (500 mg daily) was initiated, with good tolerance and an improved quality of life, with only grade 1 asthenia (fatigue relieved by rest) and no other relevant adverse events. Treatment response was assessed every three months, aligned with RECIST 1.1 principles, with a sustained stable disease for 16 months.

DISCUSSION

Precision medicine searches for targetable alterations that are intrinsically related to disease progression. Actionable mutations like *IDH1/2* alterations may present as a solution for some patients[6,7] and are present in a significant percentage of patients.[8]

Approximately 40% - 50% of conventional chondrosarcomas harbor *IDH1* mutations, more commonly found at codon R132 and more prevalent in higher-grade tumors and older patients.[2]

The relevance of the mutation status of IDH in CS patients' survival remains controversial with reports showing worse prognosis in some cohorts while others showed opposite results[6,8] and the importance of *IDH* mutation as a reliable prognostic marker in CS requires further investigation.

Early-phase studies investigating the use of ivosidenib, showed promising efficacy results, and ivosidenib demonstrated a median progression-free survival (PFS) of 7.4 months, an objective response rate (ORR) of 23.1%, and a median duration of response of 53.5 months.[1] Notably, some patients experienced durable disease control continuing therapy for over six years. No serious adverse events, treatment discontinuations or treatment-related deaths were reported.[1] Importantly, this favorable safety profile appears consistent with that reported in other *IDH1*-mutated malignancies, such as cholangiocarcinoma, where treatment is generally associated with low-grade adverse events, most commonly fatigue/asthenia and gastrointestinal symptoms.[9]

These data prompted the ongoing randomized phase 3 CHONQUER study (trial registration number NCT06127407) evaluating ivosidenib *versus* placebo in locally advanced or metastatic *IDH1*-mutant conventional CS, with PFS as the

primary endpoint, currently recruiting.[10]

Nonetheless, these cases exemplify the clinical course of conventional chondrosarcoma: poor chemotherapy responsiveness, limited radiotherapy benefit and reliance on surgery whenever feasible. The identification of an IDH1 mutation provided a therapeutic avenue with ivosidenib in the recurrent setting.

These cases add to growing real-world evidence supporting the role of IDH1 inhibition as an option in selected patients with advanced CS. Ivosidenib demonstrated durable disease control and favorable safety, suggesting potential benefits where standard treatments are limited. Furthermore, ivosidenib's oral administration and favorable toxicity profile make it a convenient and well-tolerated option for patients.

These cases support growing evidence that targeting IDH1 is a rational, clinically relevant approach in selected patients with advanced chondrosarcoma.

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AUTHOR CONTRIBUTIONS

DLR: Literature review, writing and critical review of the manuscript.

MaA, AM, JM, MiA: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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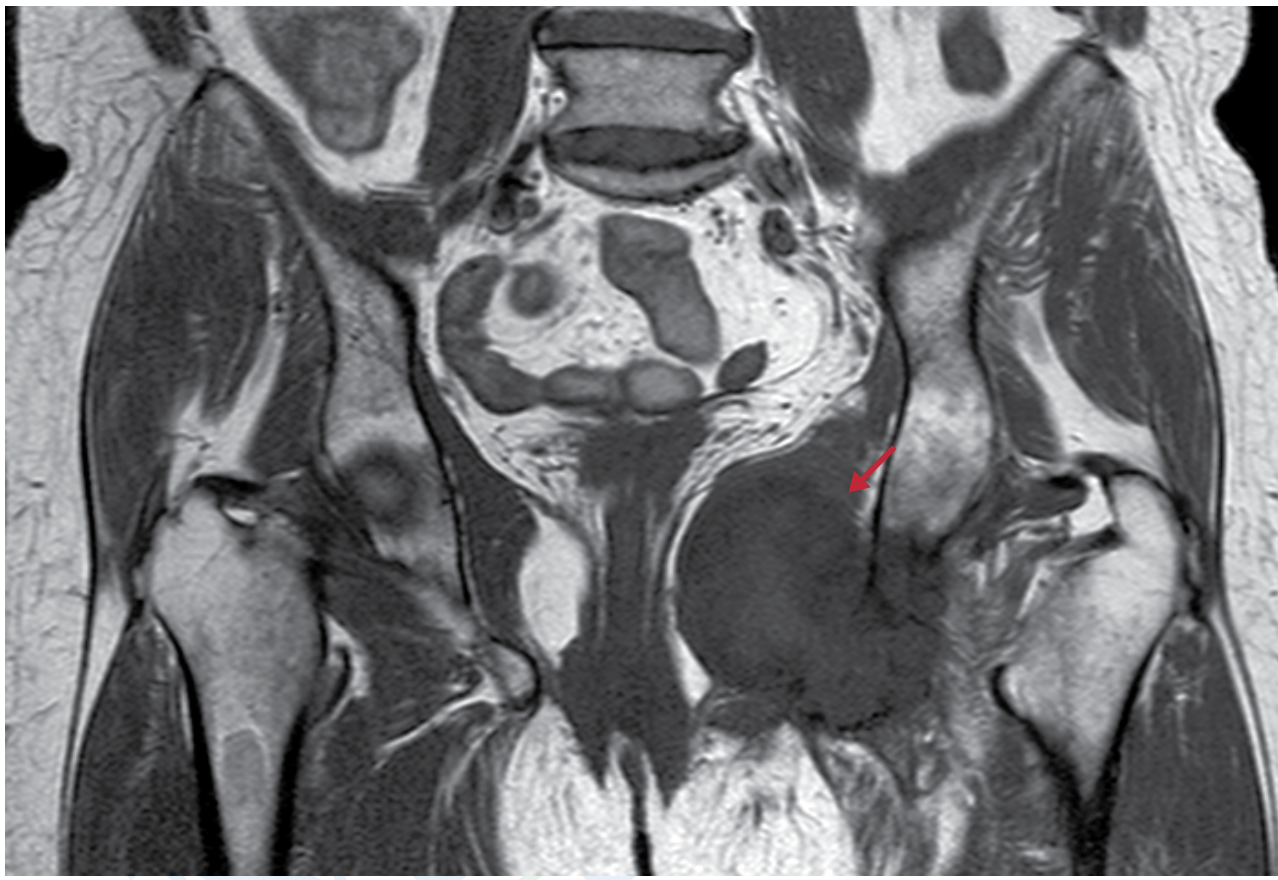

Figure 1 – Pelvic magnetic resonance imaging showing a destructive lesion of the left iliac bone involving the bone and ischial regions