Genomic characterization of chondrosarcoma: a rare sarcoma with clinical responses to immune checkpoint inhibition

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OBJECTIVES

Chondrosarcomas are rare cancers of cartilage. Conventional chondrosarcoma, the most common subtype, has no known effective systemic therapies. Mesenchymal and dedifferentiated chondrosarcoma are treated with Ewing sarcoma or osteosarcoma regimens, although the efficacy of this approach is not firmly established. More effective systemic therapies are urgently needed.

After the identification of *IDH* mutations in chondrosarcoma, IDH inhibitors are now being studied in this disease. Reports of patients responding to immune checkpoint inhibitors are published, but without a clear mechanism for why some chondrosarcoma patients respond to immunotherapy. Small prospective studies of immune checkpoint inhibitors were negative.

We sought to characterize the molecular and immune landscape of conventional, dedifferentiated, and mesenchymal chondrosarcomas using a large database of clinical-grade sequencing results.

METHODS

- A sample of de-identified records from patients with a histologic diagnosis of conventional chondrosarcoma, dedifferentiated chondrosarcoma, or mesenchymal chondrosarcoma in the Tempus database who had completed tissue DNA sequencing with the Tempus xT assay were included for this retrospective analysis (Tempus Labs, Chicago, IL).
- Tempus xT is a targeted, tumor/normal-matched panel that detects single-nucleotide variants, insertions and/or deletions, and copy number variants in 648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity.
- Microsatellite instability (MSI) and tumor mutational burden (TMB) were determined from sequencing data.
- Expression of PD-L1 and mismatch repair enzymes were evaluated in cases with available immunohistochemistry (IHC) data.

CONCLUSIONS

- These findings reinforce current therapeutic efforts to target IDH signaling in chondrosarcoma and, given PD-L1 expression in a minority of cases, provide insight into why some patients respond to immune checkpoint inhibitors.
- Biomarker-driven trials are needed to understand the significance and potential applications of these results in clinical practice.

RESULTS

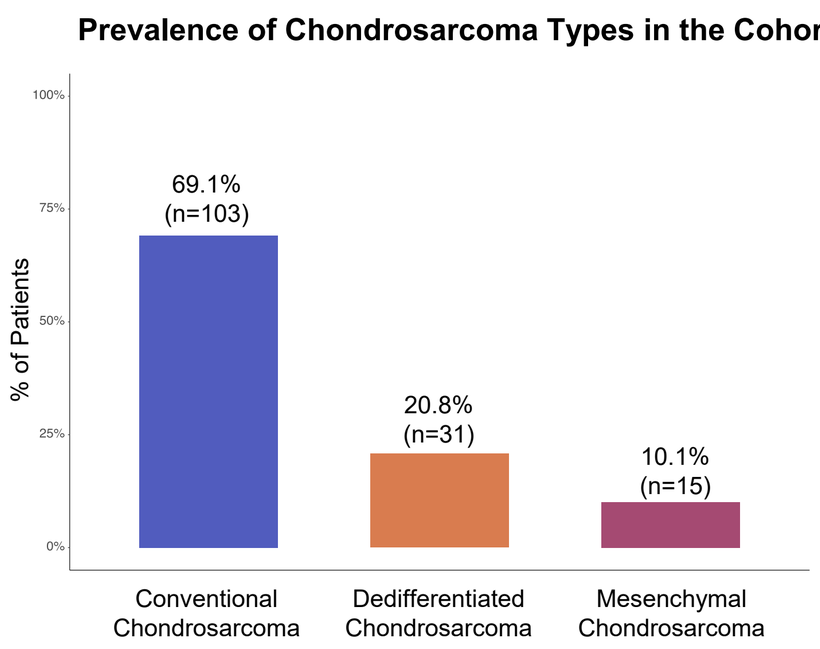

Figure 1. There were 149 patient records identified consisting of 103 conventional chondrosarcoma, 31 dedifferentiated chondrosarcoma, and 15 mesenchymal chondrosarcoma samples.

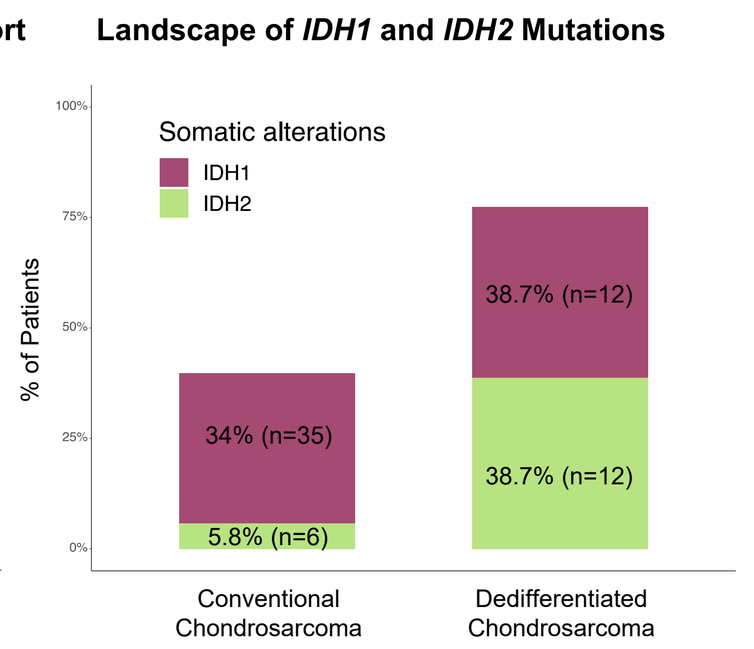

Figure 2. Of the total cohort (N=149), 44% had either an *IDH1* or *IDH2* mutation (n=65). *IDH1* mutations were present in 34% of conventional (n=35), 38.7% of dedifferentiated (n=12), and 0% of mesenchymal cases. *IDH2* mutations were identified in 5.8% of conventional (n=6), 38.7% of dedifferentiated (n=12), and 0% of mesenchymal cases.

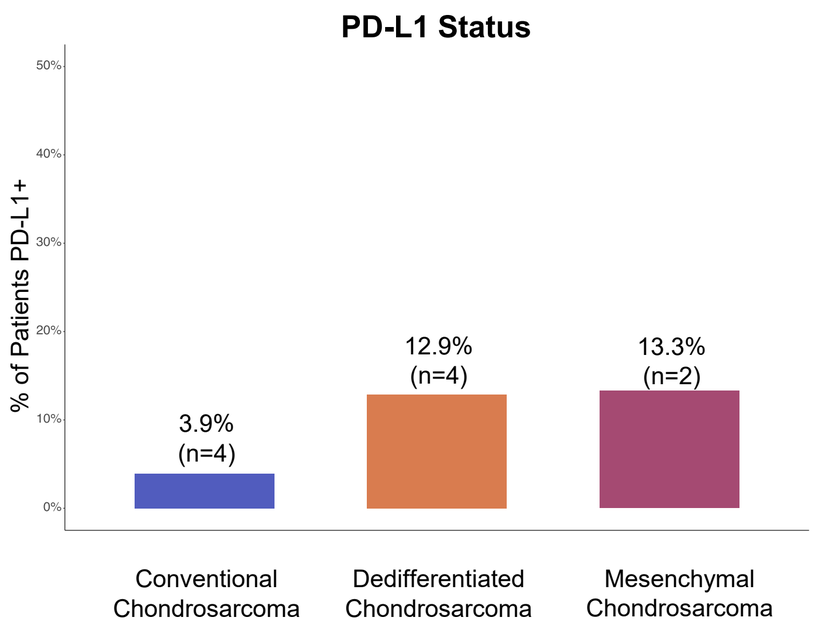

Figure 3. Among 86 patients with available PD-L1 IHC data, 3.9% of conventional (n=4), 12.9% of dedifferentiated (n=4), and 13.3% of mesenchymal cases (n=2) were PD-L1 positive.

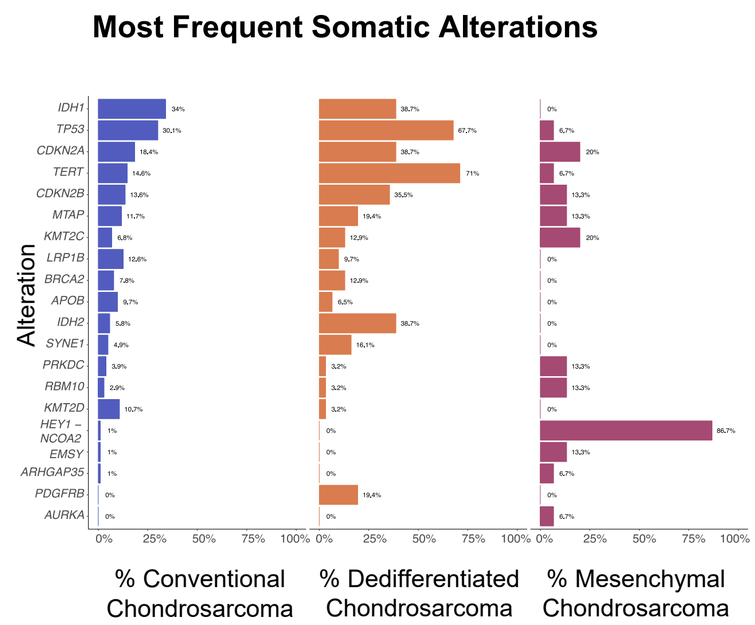

Figure 4. The most common somatic alterations were *IDH1* (34%), *TP53* (30%), *CDKN2A* (18%), *TERT* (15%), *CDKN2B* (14%), *LRP1B* (13%), *MTAP* (12%), and *KMT2D* (11%) in conventional chondrosarcoma, *TERT* (71%), *TP53* (68%), *IDH2* (39%), *CDKN2A* (39%), *IDH1* (39%), *CDKN2B* (35%), *MTAP* (19%), and *PDGFRB* (19%) in dedifferentiated chondrosarcoma, and *HEY1-NCOA2* fusions (87%), *KMT2C* (20%), *CDKN2A* (20%), *EMSY* (13%), *PRKDC* (13%), *RBM10* (13%), *CDKN2B* (13%), and *MTAP* (13%) in mesenchymal chondrosarcoma.

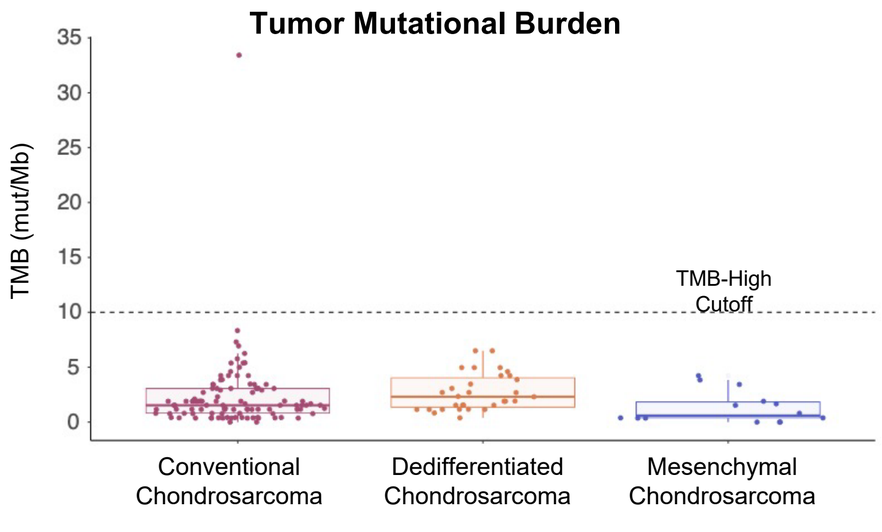

Figure 5. Across the cohort (N=149), one conventional chondrosarcoma case had a TMB >10 mut/Mb.

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