Chordoma

Chordomas are rare malignant tumors of the axial skeleton, characterized by their locally invasive and slow but aggressive growth.

Etiology

They show dual epithelial-mesenchymal differentiation.

These neoplasms are presumed to be derived from notochordal remnants with a molecular alteration preceding their malignant transformation.

Epidemiology

These tumors are most frequently observed on the skull base and sacrum.

Primarily affect adults, but also rarely affect pediatric patients.

Pediatric chordomas more often affect females and occur most frequently at the craniocervical junction with decrease in incidence distally in the spine, whereas adult chordomas most frequently involve the craniocervical and sacrococcygeal regions [1)].

They account for 1-4 % of primary malignant bone tumors and usually occur in the axial skeleton, most commonly the sacrum. Although typically locally recurrent, chordoma metastasis rates as high as 10-42 % have been reported. While spread to multiple organ systems has been documented, metastatic disease to skeletal muscle is extremely rare [2)].

Classification

Chordomas are divided into the following 3 histological types: classical (conventional), chondroid, and dedifferentiated chordoma.

see Chordoma of the posterior fossa in children.

see Skull base chordoma.

see Spinal chordoma.

Diagnosis

see Chordoma diagnosis

Molecular biology

Little is known about the molecular biology of chordomas.

All chordoma cell lines had a typical physaliphorous morphology and expressed brachyury, S100-protein and cytokeratin. By expression analyses we detected differentially expressed genes in the clivus derived cell lines as compared to the sacral cell lines. Among these were HOXA7, HOXA9, and HOXA10 known to be important for the development of the anterior-posterior body axis. These results were confirmed by qPCR. Immunohistologically, clivus chordomas had no or very low levels of HOXA10 protein while sacral chordomas showed a strong nuclear positivity in all samples analysed. This differential expression of HOX genes in chordomas of the clivus and sacrum suggests an oncofetal mechanism in gene regulation linked to the anatomic site [3)].

In a study, miR-31, anti-miR-140-3p, anti-miR148a, and miR-222 were transiently transfected to chordoma cell lines and an MTS assay, apoptosis assay, and cell-cycle analysis were conducted to evaluate the effects. The mRNA level of predicted and confirmed targets of each MicroRNA, as well as the EMT and MET markers of U-CH1 and MUG-Chor1, were assessed with real-time polymerase chain reaction. Transient transfection of MicroRNA mimics was achieved, as each mimic increased or decreased the level of its corresponding MicroRNA. miR-31 decreased cell viability in MUG-Chor1 and U-CH2 after 72h, which is consistent with previous findings for U-CH1. Both miR-31 and anti-miR-148a induced apoptosis in all three cell lines. Although each MicroRNA had a similar pattern, miR-31 had the most effective S-phase arrest in all three cell lines. RDX, MET, DNMT1, DNMT3B, TRPS1, BIRC5, and KIT were found to be targeted by the selected MicroRNAs. The level of miR-222 in chordoma cell lines U-CH1 and MUG-Chor1 correlated positively with EMT markers and negatively with MET markers. This study uncovered the potential of miR-31, miR-140-3p, miR-148a, and miR-222-3p to be key molecules in the cell viability, cell cycle, and apoptosis in chordomas, as well as initiation, differentiation, and progression. [4)].

Immunohistochemistry revealed LMX1A to be dominant in skull base chordoma, SALL3 to be unique to spine chordoma, and T to be common to both chordoma subtypes. In both chordoma subtypes, the genes with the highest expression were predominantly development-related genes, mostly transcription factors.

Findings indicate that these developmental genes play important oncogenic roles in chordoma, mainly causing high plasticity and resistance to therapy in both these cancer subtypes but also determining their differentiation status and proliferation activity, pointing to features expected of heterogeneous stem cell-like tissues with similarities to their notochord origins [5)].

Treatment

see Chordoma treatment.

Outcome

Chordomas are locally aggressive bone neoplasms showing dual epithelial-mesenchymal differentiation. The high plasticity probably is the main reason for the high variety in phenotypes of chordoma, from its high heterogeneity on a cellular level to its subtype variations depending on tissue location, with its potential to develop from an inactive quiescent form to an aggressive cancer with extreme adaptability and resistance to drugs and other treatments.

Patients suffering from a chordoma present with debilitating neurological disease, and have an overall 5- year survival rate of 65%.

1)
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