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Review article

Therapeutic Approach to Chordomas

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Abstract

Chordomas are neoplasms that come from the notochord's cellular remnants. Immunotherapy is a cancer treatment alternative to chemotherapy and radiation therapy. Its goal is to use a patient's own immune system to fight the tumor. The immune system can be stimulated by exposing synthetic immune molecules into a subject's system. In this paper, we discuss the potential causes of chordomas, the pathophysiology of the disease, and potential ways to cure the disease using different immunotherapy techniques.

Keywords: Bone Cancer; Immunotherapy; Chondrosarcoma; Osteosarcoma; Ewing Tumors; Chordomas

Introduction

Chordoma is a rare subtype of sarcoma among adult population. Available studies from the United States indicated that 400 microscopically confirmed cases of chordoma have been reported from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, between 1973-1995. The age-adjusted chordoma incidence rate (IR) of 0.08 per 100,000 was age-dependent and more common in males (IR 0.10) than females (IR 0.06). It was rare among patients aged <40 years and blacks. Anatomically 32% of cases were cranial, 32.8% spinal and 29.2% sacral within the axial skeleton.

Young age (<26 years; p = 0.0001) and female sex (p = 0.037) were more associated cranial presentation. There was no overall increased risk for second primary and secondary cancers after chordoma. Median survival was 6.29 years, whereas 5- and 10-year relative survival rates were 67.6% and 39.9%, respectively. Bone sarcomas revealed racial disparities in incidence for the two developmental tumors, chordoma and Ewing's sarcoma [1].

Pathophysiology and molecular basis of chordomas:
There are various genetic studies, which are conducted on chordomas, that examine DNA microsatellites, chromosome analysis, loss of heterozygosity (LOH), telomere reduction and activity, and different clonal studies. A wide variety of molecular and cytogenetic conclusions point out the loss of 1p36 is a reliable transformation in the sporadic and inherited chordomas [2]. Moreover, studies conducted on 12 cases of chordomas recognized MSI in 50% of the patients at one or more loci. LOH was also recognized in two cases of chordomas [3].

Various structural and numerical modifications have been detected in chromosomes 3 and 21. Most of the cases indicated a hypodiploid or diploid chromosome number [4]. The chromosome 3, 4, 10 and 13 are normally lost. In half of the cases the following segments are lost up to the telomere: 1p31, 3p21, 9p24, 3q21, and 17q11. Since the LOH is established at 1p36 band, which is a tumor suppressor gene (TSG), it persists on distal 1p [5]. The tumor suppressor gene, retinoblastoma (RB), and its proteins bind to the nuclear DNA and are involved in the regulation of cell cycles. The chordomas have demonstrated LOH at intron 17 of the RB gene [6].

Targeted therapy for Chordomas:

A. Kinase inhibitors:
A tyrosine kinase inhibitor (TKI) is a pharmaceutical drug

that inhibits tyrosine kinases. Tyrosine kinases are enzymes responsible for the activation of many proteins by signal transduction cascades. The proteins are activated by adding a phosphate group to the protein (phosphorylation), a step that TKIs inhibit. Various kinase inhibitors under trial for chordomas are listed in table 1.

1. Imatinib [7,8]: A tyrosine kinase inhibitor with antineoplastic activity. Imatinib binds to an intracellular pocket, located within tyrosine kinases (TK), thereby inhibiting ATP binding and preventing phosphorylation and the subsequent activation of growth receptors and their downstream signal transduction pathways. Based on the available phase II clinical trials dealing with cases of chordomas with Imatinib, among 50 patients evaluable by RECIST, the best response was one partial response (PR) obtained at 6 months (ORR, 2%). There were 35 patients with stable disease (SD, 70%) and a 64% clinical benefit rate (ie, RECIST complete response + PR + SD ≥ 6 months). A minor dimensional response (< 20%) was detected in nine patients. A maximum standard uptake value decrease ≥ 25% was observed in 10 (39%) of 26 patients evaluable for PET response at 3 months. Changes in the Brief Pain Inventory score were consistent with the response assessment. Median PFS (intention-to-treat population, 56 patients) was 9 months. From safety point of view, no unexpected toxicities were observed [9].

2. Nilotinib: An orally bioavailable, aminopyrimidine-derivative, Bcr-Abl tyrosine kinase inhibitor with antineoplastic activity [10].

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Imatinib	NCT00150072	Phase II	Open Label	PDGFR
Imatinib	NCT01175109	Phase I	Safety Study, Open Label	PDGFR
Nilotinib	NCT01407198	Phase I	Safety Study, Open Label	Bcr-Abl

Table 1. Kinase inhibitors [7-11].

B. Vaccines:

GI-6301: It is a cancer vaccine composed of a heat-killed, recombinant form of the yeast *Saccharomyces cerevisiae*. It is genetically modified to express the transcription factor, brachyury protein, which has potential antineoplastic activity. Upon subcutaneous administration, the brachyury-expressing yeast vaccine GI-6301 is recognized by dendritic cells, processed, and presented by class I and II MHC molecules on the dendritic cell surface. This elicits a targeted CD4+ and CD8+ T-lymphocyte-mediated immune response. This process kills brachyury-expressing tumor cells. The NCI is conducting a Phase 1 safety, immunology and early efficacy trial of GI-6301 monotherapy in patients with late-stage cancers known to express the brachyury protein, including chordomas as in table 2. This presentation updates data Globe Immune previously reported on seven chordomas patients in the trial. Results to date from the eleven chordoma patients in this trial stated that GI-6301 has been generally well tolerated, immunogenic, and has shown evidence of clinical activity in both advanced epithelial cancers and chordomas [12].

Drug	Clinical trial identifier no.	Phase	Study Design	Target
GI-6301	NCT02383498	Phase II	Randomized, Safety/Efficacy Studt, Double blind	CD4+ and CD8+ T-lymphocyte

Table 2. Vaccine [11-12].

Conclusion

Chordoma is not a rare cancer. Conventional treatment for chordoma consists of chemotherapy, surgical resection and radiation therapy, but clinical outcomes by these therapeutic modalities have not significantly improved in recent decades. Under this situation, immunotherapy is expected to be a new therapeutic option for the treatment of bone cancer. Multiple drugs of different categories are under clinical trials for the treatment of chordomas such as mAbs, mTOR inhibitors, kinase inhibitors, adoptive therapy and vaccines. These trials suggest that immunotherapy is moving to the forefront of therapy of these rare cancers.

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