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Review article

Targeted therapy for Chondrosarcoma

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Abstract

Primary malignant bone tumors occur 1/100,000, of which 17-24% consists of chondrosarcoma. Unfortunately, the cause is unknown, but there have been several risks factors accused of causing the disease. Targeted therapy is a cancer specific treatment alternative to chemotherapy and radiation therapy. Its goal is to control and inhibit cancer promoting pathways as well as activating patient's own immune system to fight the tumor. The patient's immune system is stimulated by exposing synthetic immune molecules into their system. In this paper, we discuss the potential causes of chondrosarcomas, the pathophysiology of the disease, and potential ways to cure the disease using different targeted therapy techniques.

Keywords: Bone cancer; Chondrosarcoma; Targeted Therapy; TKIs; mTOR Inhibitors

Introduction

Chondrosarcoma (CHS) is a cancer composed of cells derived from transformed cells that produce cartilage [1]. Chondrosarcoma is the third most common primary malignancy diagnosed in the bone after myeloma and osteosarcoma [1]. Most of these tumors grow slowly and metastasize occasionally. They have an excellent prognosis after adequate surgery. Due to the involvement of the extracellular matrix, a low percentage of dividing cells, and poor vascularity, these tumors are resistant to chemo and radiotherapy. Wide surgical excision remains the best available treatment option.

Few patients recur with metastatic disease, and up to 13% of recurrent chondrosarcomas are of a higher grade than the original neoplasm [2,3]. In adults, over 40% of primary bone cancers are chondrosarcoma, which is less than 0.2% of all types of cancer. In children and teenagers (those younger than 20 years), osteosarcoma (56%) and Ewing sarcoma (34%) are much more common than chondrosarcoma (6%) [4].

The exact cause of most chondrosarcomas is not known. Several risk factors have been found that increase the risk of developing the disease. These include genetic mutation, chromosome amplification, deletion, or loss, and deregulation of signaling pathways.

Pathophysiology/Molecular basis of Chondrosarcoma (CHS): With the advancement of the grade of CHSs, the level of genetic mutation is increased. The role of p53 in CHS progression is not clear, but the over expression of p53 protein in 17p1 and alterations and mutations in TP53 have led to the hypothesis that mutations in p53 are associated with CHS, but in later stages [5-7].MDM2, which negatively regulates p53, is encoded at 12q13 locus. CDKN21/p16/INK4A and INK4A-p14ARF regulate the cell cycle and are encoded at the 9p21 locus. In the case of CHS, the 12q13 region is amplified, while 9p21 is deleted. Both the INK4A and p16 expression is lost only in higher grades of CHS. This elucidates that they are associated with the progression of CHS [8,9].

In dedifferentiated CHS, variations in the number of chromosomes, their amplification, deletion and loss of heterozygosity (LOH) have been observed [10]. According to recent studies, this class of CHS was associated with the frequent deletions at 5q13.2, 5q14.2-9q21.3, 6q12-q13, 6q16-q25.3, 9p24.2-q12, and 9p21.3 loci [11]. Cyclin D1, p53, CD44 and plasminogen activator inhibitor (PAI-1) are proposed to be frequently expressed in this form of CHS. Along with this,

parathyroid hormone like hormone (PTHLH) signaling pathway is negatively regulated, while the fibroblast growth factor (FGF) pathway is positively regulated [12].

In two cases of mesenchymal CHS, the translocations at chromosome 13 and 21 have been reported [13]. Even after the over-expression of p53 in 60% of cases, no signs of mutation have been observed between regions 5-9 of the exons [14].

The Figure 1 below summarizes the different steps of carcinogenicity in both central and peripheral chondrosarcomas and the potential therapeutic targets for this type of cancer based on the sequential molecular pathogenesis:

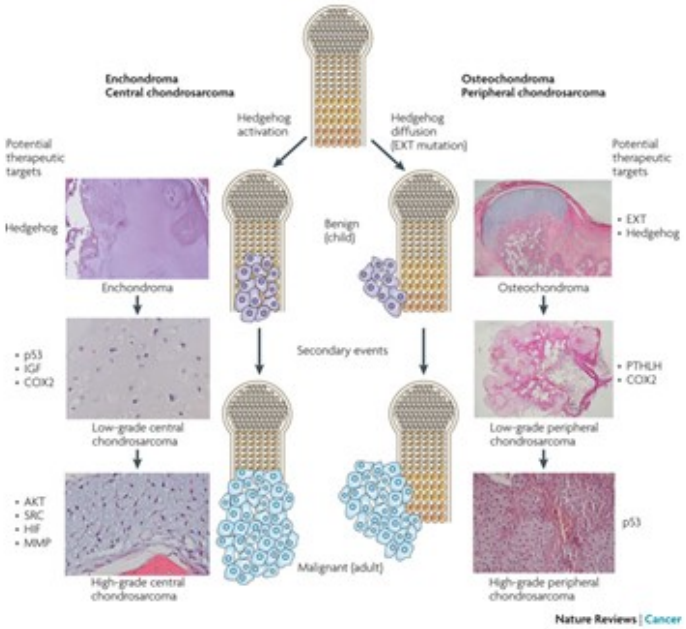

Figure 1. Steps of carcinogenicity and the potential therapeutic targets [15].

Targeted therapy for Chondrosarcoma

A. Kinase inhibitors: The following are under clinical trials phase I-III.

1. **Imatinib:** 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. It has been suggested for chondrosarcoma and has been found to be well tolerated; however, phase II clinical trials have failed to demonstrate meaningful clinical activity in terms of both objective response and freedom from disease progression. (http://www.ncbi.nlm.nih.gov/pubmed/20925044)

2. **Pazopanib:** Pazopanib selectively inhibits VEGFR -1, -2 and -3, c-kit and platelet derived growth factor receptor (PDGF-R), which may result in inhibition of angiogenesis in tumors in which these receptors are upregulated. This targeted therapy has gained FDA approval in 2012 for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy. Its efficacy in chondrosarcoma is under clinical investigation in a phase II clinical trial.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
ImatinibMesylate	NCT00928525	Phase II	Efficacy Study Open Label	TK
Pazopanib	NCT01330966	Phase II	Efficacy Study Open Label	VEGFR-1, -2 and -3, c-kit and platelet derived growth factor receptor (PDGF-R)

Table 1. Non-FDA approved kinase inhibitors [16, 17].

B. mTOR inhibitors:

1. Everolimus: This is a derivative of the natural macrocyclic lactone sirolimus with immunosuppressant and anti-angiogenic properties. In cells, everolimus binds to the immunophilin FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that binds to and inhibits the activation of mTOR. Inhibition of mTOR activation results in the inhibition of T lymphocyte activation and proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation and the inhibition of antibody production. The mTOR inhibitor, everolimus, blocks cell proliferation, Glut1 expression and HIF1a expression, and prevents in vivo chondrosarcoma tumor progression in both macroscopic and in adjuvant phase post R1 resection in animal model [18].

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Everolimus	NCT02008019	Phase II	Randomized, Efficacy Study Open Label	FKBP-12

Table 2. mTOR inhibitors [19].

Conclusion

Chondrosarcoma is not a common cancer. Conventional treatment for Chondrosarcoma is surgical resection and radiation therapy, but clinical outcomes by these therapeutic modalities have not significantly improved in recent decades for the advanced and recurrent tumors. Advanced developments in field of targeted therapies and their successful application in many types of both solid tumors and hematologic malignancies such as breast and colorectal cancer as well as B cell lymphoproliferative disorders has been suggested these targeted therapies as an attractive rather less toxic therapeutic approach compared with conventional chemotherapy and radiation. Moreover, the extensive investigation in molecular aspects of carcinogenesis

has led to recognition of many potential targets in any type of cancer. Interestingly, many types of tumors irrespective of the organ or tissue origin they arise, share similarities in the carcinogenesis pathways and superficial antigens and many of these pathways and antigens have been successfully exploited in targeted therapies. Under this situation, targeted and immunotherapy is expected to be a new therapeutic option for the treatment of bone and cartilage tumors. Multiple drugs of different categories are under clinical trials for the treatment such as monoclonal antibodies, mTOR inhibitors and kinase inhibitors. These trials suggest that targeted therapy is moving to the forefront of therapy for bone cancer. However, none of these attractive targeted therapies has gained FDA approval and suggested as a distinct line of treatment in cancer treatment guidelines. Further clinical studies and enrolling patients in clinical trials as well as combining conventional therapeutic approaches with targeted therapies might turn light into this concept of cancer treatment and improve the prognosis of these groups of patients in near future.

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