Chapter

Introductory Chapter: Integrating Basic Science with a Multidisciplinary Clinical Approach for Osteosarcoma

Scott Barnett and Matthew G. Cable

1. Introduction

Primary bone neoplasms are relatively uncommon. Among these tumors, osteosarcoma is the most common bone sarcoma, comprising approximately 35% of all malignant bone tumors [1]. Osteosarcoma affects approximately 500 children and adolescents annually in the United States with incidence peaking in the second decade of life during periods of rapid bone turnover and growth spurts [2]. Osteosarcoma arises from sites of rapid bone turnover, making the distal femur, proximal tibia and proximal humerus the most typical locations [3].

Although a genetic predisposition with mutations in various tumor-suppressor genes incurs a higher likelihood of developing osteosarcoma, most cases of osteosarcoma are sporadic. These chromosomal abnormalities yield defects in proteins involved in cell cycle regulation, resulting in uncontrolled cell proliferation [4]. These mutations are seen in a variety of disorders including Li-Fraumeni syndrome, which involves the p53 gene, or retinoblastoma, which involves the RB1 gene [5]. Some existing bone diseases such as Paget disease, fibrous dysplasia, enchondromatosis, and hereditary multiple exostosis in addition to environmental risk factors, including radiation, have been identified as contributors to developing osteosarcoma.

Osteosarcoma serves as a broad term used to envelop the several different types of osteosarcoma that exist. These subtypes distinguish themselves through both clinical appearance as well as behavior. Unfortunately, the histological pictures of bone tumors do not definitively differentiate between osteogenic sarcoma, benign tumors, or other malignancies of bone [6]. Therefore, incorporation of both radiological and clinical tools is required to make the final diagnosis of osteogenic sarcoma [7].

In the setting of osteosarcoma, advanced imaging is warranted to evaluate the extent of tumor invasion, neurovascular involvement, bone marrow replacement, and presence of discontinuous metastases. Combination of MRI and CT imaging are helpful in demonstrating both soft tissue parameters of the tumor as well as cortical integrity and the presence of pathologic fracture [8, 9]. New focus on advanced techniques in medical image processing for the detection and analysis of osteosarcoma aims to better evaluate tumor locations, size, infiltrations of surrounding tissues, and identify the presence of satellite metastasis. Current research work utilizes positron emission tomography (PET) combined with MRI volumetry to better assess histological responses in bone sarcoma afflicted individuals, yielding

improvements in classification accuracy compared single modality evaluation [10]. The coupling of FDG-PET and MRI volumes offers improved prognostic and predicting capabilities for assessing the aggressiveness of tumors and aiding earlier clinical decisions regarding the utility of treatment options for patients.

A multidisciplinary approach is used for the treatment of patients with osteosarcoma, offering survival rates of greater than 70% with metastatic disease [11, 12]. For high-grade osteosarcoma, treatment involves preoperative chemotherapy, wide surgical resection, and postoperative chemotherapy. Intratumor heterogeneity, a resultant of tumor evolution, is the fundamental challenge in cancer medicine. From heterogeneity stems disease relapse, metastatic behaviors, and drug resistance [13]. Recent studies of cancer stem cells report a metabolism pathway that is predominantly through oxidative phosphorylation rather than glycolysis [14]. Targeting this metabolic pathway presents a potential therapeutic option against tumor cells. Within the mitochondria, a "two metabolic hit" theory has been proposed to utilize the synergistic effects of combining oxidative phosphorylation inhibition with c-Myc inhibition, which target both the oxidative phosphorylation-dominant cancer stem cells and glycolysis-dominant non-cancer stem cells [15]. Novel compounds such as pterostilbene and honokiol have emerged as dual metabolic inhibition compounds that may lead to improvements in osteosarcoma prognosis, especially in the setting of metastatic disease [16].

Additional studies have shown that molecules belonging to the non-protein coding transcriptome may play essential roles in biological processes [17]. These non-protein coding RNAs are involved in gene expression regulation and have been found to play an important role in cancer development, progression, and chemoresistance of different tumors, including osteosarcoma [18]. Non-coding RNAs have emerged as potential prognostic biomarkers and therapeutic targets, being involved in cell signal transduction pathways, cell cycle and death regulation, chromatin remodeling, and gene expression regulation at both transcriptional and posttranscriptional levels [19]. Several tumors, such as urothelial carcinoma, colon carcinoma, and hepatocellular carcinoma have exhibited aberrant expression of non-coding RNAs, suggesting a new means of observation that may be exploited for diagnostic, prognostic preventative, or therapeutic processes [20]. A large number of long non-coding chain RNAs (lncRNAs) with oncogenic or tumor suppressive activity are differentially expressed in osteosarcoma. MALAT-1 (metastasis-associated lung adenocarcinoma transcript 1), a lncRNA involved in recruiting mRNA splicing factors to transcription sites, is overexpressed in osteosarcoma and has expression levels linked to tumor metastatic potential [21]. The identification of lncRNAs serves as a catalyst for further research validating lncRNAs as prognostic and predictive biomarkers, therapeutic targets, and structural models for future mimicking pharmaceutical agents.

New targetable compounds generate hope for novel osteosarcoma treatment regimens, specifically with the affected pediatric population where chemotherapy has become the mainstay of treatment. Surgical resection yielded a high frequency of relapse and metastasis for children with osteosarcoma, shifting the focus to intense chemotherapy [22]. Similar to the discovery of lncRNAs, new molecular biologic factors that determine sensitivity to chemotherapy, invasive and metastatic potential of the tumor, and the prognosis of the disease have been elucidated in recent pediatric osteosarcoma research. Expression of methylguanine methyltransferase (MGMT) as well as MGMT methylation is correlated with poor histological response in osteosarcoma patients undergoing cisplatin treatment [23]. Other molecular factors such as vascular endothelial growth factor (VEGF) and c-Myc are under intense focus for characterizing tumor behavior, response to treatment, and dictating further treatment protocols [24]. Although there is significant relapse and

refractory rates for children diagnosed with metastatic osteosarcoma, comprehensive assessments of these markers for histological response to chemotherapy may enhance current treatment protocols and guide future regimens.

Emphasis on basic science research remains a prime avenue for uncovering molecular mechanisms and biologic pathways that may lead to additional targeted therapies, less-toxic agents, and improved long-term survival in osteosarcoma [25]. Molecular biomarkers such as non-coding RNAs and cell-cycle regulator proteins are an area of current interest for the development of sensitive screening modalities as well as target-selective chemotherapeutic drugs. Progress in combined advanced imaging techniques offer better, non-invasive means for evaluating tumor, size, location and behavior, which facilitates clinical decision making. Treatment of osteosarcoma, an aggressive and malignant tumor, requires a multidisciplinary approach that incorporates progressive basic science research at all levels of care including diagnosis, treatment, and surveillance.

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Author details

Scott Barnett and Matthew G. Cable*
Department of Orthopaedic Surgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA

*Address all correspondence to: mcabl1@lsuhsc.edu

References

[1] Dorfman H, Vanel D, Czerniak B, Park Y, Kotz R, Unni K. Introduction, WHO Classification of Tumours of Soft Tissue and Bone. In: Fletcher C, editor. 4th ed. IARC; 2013

[2] Horner MJ, Ries LAG, Krapcho M, et al. SEER Cancer Statistics 1975-2016. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2016. Accessed [6 July 2019]

[3] Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: An analysis of 1.702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. Journal of Clinical Oncology. 2002;**20**:776-790

[4] Hayden JB, Hoang BH. Osteosarcoma: Basic science and clinical implications. The Orthopedic Clinics of North America. 2006;**37**:1-7

[5] Wang LL. Biology of osteogenic sarcoma. Cancer Journal. 2005;**11**:294-305

[6] Klein MJ, Siegal GP. Osteosarcoma: Anatomic and histologic variants. American Journal of Clinical Pathology. 2006;**125**:55-581

[7] Murphy MD. World Health Organization classification of bone and soft tissue tumors: Modifications and implications for radiologists. Seminars in Musculoskeletal Radiology. 2007;**11**(3):201-214

[8] Scully SP, Ghert MA, Zurakowski D, Thompson RC, Gebhardt MC. Pathologic fracture in osteosarcoma: Prognostic importance and treatment implications. The Journal of Bone and Joint Surgery. American Volume. 2002;**84**:49-57

[9] Bedi SS, Agarwal J, Agarwal P. Image fusion techniques and quality assessment parameters for clinical diagnosis: A review. International Journal of Advanced Research in Computer and Communication Engineering. 2013;**2**(2):1153-1157

[10] Eugene T, Corradini N, Carlier T, Dupas B, Leux C, Bodet-Milin C. 18F-FDG-PET/CT in initial staging and assessment of early response to chemotherapy of pediatric rhabdomyosarcomas. Nuclear Medicine Communications. 2012;**3**(10):1089-1095

[11] Meyers PA, Schwartz CI, Krailo M. Osteosarcoma: The addition of muramyl tripeptide to chemotherapy improves overall survival. Journal of Clinical Oncology. 2008;**26**:633-638

[12] Ferrari S, Smeland S, Mercuri M. Neoadjuvant chemotherapy with high-dose ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity. Journal of Clinical Oncology. 2005;**23**:8845-8852

[13] Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates form a primitive hematopoietic cell. Nature Medicine. 1997;**3**:730-737

[14] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science. 2009;**324**:1029-1033

[15] Lin CY, Loven J, Rahl PB, Paranal RM, Burge CB, Bradner JE. Transcriptional amplification in tumor cells with elevated c-Myc. Cell. 2012;**151**:56-67

[16] Hahm ER, Singh KB, Singh SV. C-Myc is a novel target of cell cycle arrest by honokiol in prostate cancer cells. Cell Cycle. 2016;**15**(17):2309-2320

[17] Sandberg K, Samson WK, Ji H. Decoding noncoding RNA: The long and short of it. Circulation Research. 2013;**113**(3):240-241

[18] Crea F, Clermont PI, Parolia A, Wang Y, Helgason CD. The non-coding transcriptome as a dynamic regulator of cancer metastasis. Cancer Metastasis Reviews. 2013;**33**(1):1-16

[19] Huarte M. The emerging role of lncRNAs in cancer. Nature Medicine. 2015;**21**(11):1253-1261

[20] Min L, Garbutt C, Tu C, Hornicek F, Duan Z. Potentials for long noncoding RNAs (kncRNAs) in sarcoma: From biomarkers to therapeutic targets. International Journal of Molecular Sciences. 2017;**18**(4):731

[21] Smolle MA, Pichler M. The role of long non-coding RNAs in osteosarcoma. Noncoding RNA. 2018;**4**(1):7

[22] Punanov YA, Andreeva TV, Gafton GI, et al. The results of combined therapy in children and adolescents with osteosarcoma. Oncopediatrics. 2014;**1**(2):49-53

[23] Cui Q, Li D, Liu C, et al. The significance of MGMT protein detection in evaluation of osteosarcoma necrosis rate after cisplatin chemotherapy. Bosnian Journal of Basic Medical Sciences. 2011;**11**(2):80-83

[24] Rossi B, Schinzari G, Maccauro G, et al. Neoadjuvant multidrug chemotherapy including high-dose methotrexate modifies VEGF expression in osteosarcoma: An immunohistochemical analysis. BMC Musculoskeletal Disorders. 2010;**11**(34):1471-2474

[25] Messerschmit PJ, Garcia RM, Abdul-Karim FW, Greenfield EM, Getty PJ. Osteosarcoma. The Journal of the American Academy of Orthopaedic Surgeons. 2009;**17**(8):515-527