News & Information

Juntendo University
Juntendo University Hospital

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Medical and health

Discovery of novel candidates for target therapies in osteosarcoma
- Development of a new treatment for osteosarcoma in the era of precision medicine -

Abstract

Yoshiyuki Suehara M.D., Ph.D (Department of Orthopedic Surgery, Juntendo University Graduate School of Medicine) recently led a study at Memorial Sloan Kettering Cancer Center (MSKCC), New York, USA, as a Visiting Investigator (supported by the Japan Society for the Promotion of Science). Takuo Hayashi M.D., Ph.D (Department of Human Pathology, Juntendo University Graduate School of Medicine) also participated in this study as a Visiting Investigator at MSKCC. The cancer clinical sequence test *1 (MSK-IMPACT) *2 revealed that genetic alterations at specific sites in chromosomes can be novel candidate target therapies in osteosarcomas *3.These results show the possibility to open the way to the treatment of osteosarcoma, which is a high malignant bone tumor in the era of precision medicine *4. This study was published in the online version of "*Clinical Cancer Research*" on June 7, 2019.

Point of this research results

- **We confirmed the usefulness of cancer clinical sequence test (MSK-IMPACT) in osteosarcoma for personalized medicine.**
- **We found that copy number abnormalities at specific sites on chromosomes (4q12, 6p12, 12q14) were mutually exclusive. And they are potentially clinically actionable alterations for approximately 40% of osteosarcoma.**
- **These findings might provide novel candidates for target therapies in osteosarcoma.**

Background

Osteosarcoma is the malignant bone tumor that occurs most in children and recently it often occurs in the elderly (bimodal age distribution). The treatment for osteosarcoma consists of a multidisciplinary treatment combining chemotherapy and surgery. As the 5-year survival rate of advance or treatment-resistant osteosarcomas are approximately 30%, the development of new treatments is needed. Genetic risk (Li-Fraumeni syndrome) exists in a part of osteosarcoma, however the involvement of other cancer-related genes was unknown in clinical setting. Furthermore, as chemotherapy regimen including the main anti-cancer drug for osteosarcoma has not changed for 30 years, development of new treatment has been desired. Therefore, our research group analyzed osteosarcomas using large-scale cancer clinical sequence examination to elucidate the genomic background of osteosarcomas and develop a novel therapeutic strategies.

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Contents

We analyzed genomic data from 71 OS samples from 66 pediatric and adult patients sequenced using MSK-IMPACT, a hybridization capture-based large panel NGS assay. Potentially actionable genetic events were categorized according to the OncoKB[*5] precision oncology knowledge base, of which Levels 1-3 were considered clinically actionable. We found at least one potentially actionable alteration in 14/66 patients (21%), including amplification of CDK4 (n=9, 14%: Level 2B) and/or MDM2 (n=9, 14%: Level 3B), and somatic truncating mutations/deletions in BRCA2 (n=3, 5%: Level 2B) and PTCH1 (n=1, Level 3B). Additionally, we observed mutually exclusive patterns of alterations suggesting distinct biological subsets defined by gains at 4q12 and 6p12-21. Specifically, potentially targetable gene amplifications at 4q12 involving KIT, KDR and PDGFRA were identified in 13 of 66 patients (20%), which showed strong PDGFRA expression by immunohistochemistry. In another largely non-overlapping subset of 14 patients (24%) with gains at 6p12-21, VEGFA amplification was identified **(Figure 1)**.

Next deployment

This study revealed the clinical efficacy of clinical sequencing (MSK-IMPACT) in high grade osteosarcoma. We found potentially clinically actionable alterations in approximately 21% of OS patients. Additionally, at least 40% of patients have tumors harboring PDGFRA or VEGFA amplification, representing candidate subsets for clinical evaluation of additional therapeutic options. These findings may provide a rationale for closer evaluation of multi-kinase inhibitors targeting these kinases (4q12 genetic amplification_Pazopanib[*6] , Regorafenib[*7], Olaratumab. 6p12-21genetic amplification_Sorafenib、Pazopanib, Bevacuzumab) . Furthermore, These inhibitors have been used for osteosarcoma cases as clinical trials. In this study, we propose a new genomically-based algorithm for directing OS patients to clinical trial options **(Figure 2)**.

The MSK-IMPACT test is available at Juntendo University School of Medicine through an arrangement with Riken Genesis.

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Figure 1 Genetic alteration in osteosarcoma

We analyzed genomic data from 71 OS samples from 66 pediatric and adult patients sequenced using MSK-IMPACT(468 genes). Potentially actionable genetic events were categorized according to the OncoKB precision oncology knowledge base, of which Levels 1-3 were considered clinically actionable. We found at least one potentially actionable alteration in 14/66 patients (21%). Additionally, we observed mutually exclusive patterns of alterations suggesting distinct biological subsets defined by gains at 4q12 and 6p12-21. Specifically, potentially targetable gene amplifications at 4q12 involving KIT, KDR and PDGFRA were identified in 13 of 66 patients (20%). And 14 patients (24%) with gains at 6p12-21, VEGFA amplification was identified.

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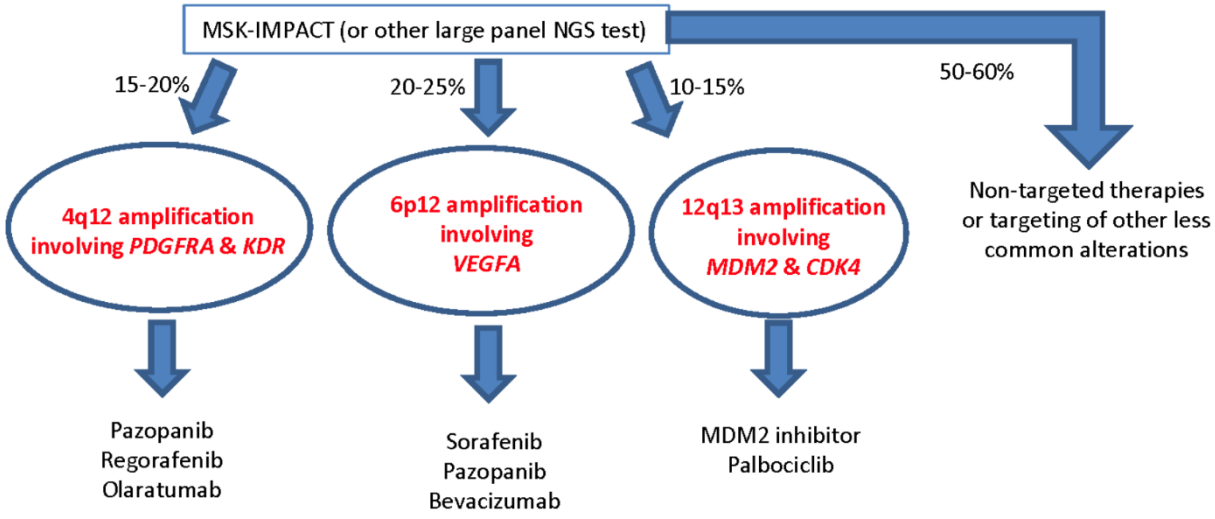

Figure 2

This figure shows that at least 40% of patients have tumors harboring PDGFRA or VEGFA amplification, representing candidate subsets for clinical evaluation of additional therapeutic options. These findings may provide a rationale for closer evaluation of multi-kinase inhibitors targeting these kinases (4q12 genetic amplification_Pazopanib, Regorafenib, Olaratumab. 6p12-21genetic amplification_Sorafenib、Pazopanib, Bevacuzumab). We propose a new genomically-based algorithm for directing OS patients to clinical trial options.

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Glossary

***1. Cancer clinical sequence test :** Cancer clinical sequence test include DNA and RNA analysis through next-generation sequencing (NGS) technologies, including cancer panels that profile multiple actionable driver genes and tumor characteristics that may guide the selection of targeted therapies.

***2. MSK-IMPACT :** The MSK-IMPACT assay is cancer clinical sequence test and was developed by MSKCC. MSK-IMPACT analyzes 468 genes and provides information on somatic mutations and microsatellite instability (MSI) for use by qualified healthcare professionals in accordance with professional guidelines. In November 2017, MSK-IMPACT was authorized by the US Food and Drug Administration.
https://www.mskcc.org/msk-impact

***3. Osteosarcoma :** Osteosarcoma is the malignant bone tumor that occurs most in children and recently it often occurs in the elderly (bimodal age distribution).

***4. precision medicine :** According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."
https://ghr.nlm.nih.gov/primer/precisionmedicine/definition

***5. OncoKB :** OncoKB is precision oncology knowledge base and developed by MSKCC (Chakravarty D et al JCO Precis Oncol. 2017). OncoKB, a comprehensive and curated precision oncology knowledge base, offers oncologists detailed, evidence-based information about individual somatic mutations and structural alterations present in patient tumors with the goal of supporting optimal treatment decisions.

***6.** Publication regarding pazopanib (Longhi A et al. *Acta Oncologica*, 58, 124-128, 2019. Longhi A et al. e23501 ASCO 2018.). Clinical trail (Study of Pazopanib in the Treatment of Osteosarcoma Metastatic to the Lung. NCT01759303).

***7.** Publication regarding regorafenib (Duffaud E et al. *Lancet Oncol* 20, 120–133 2019. Davis LE et al. *J Clin Oncol*. 2019 Epub ahead of print). Clinical trail (A Phase II Study Evaluating Efficacy and Safety of Regorafenib in Patients With Metastatic Bone Sarcomas. NCT02389244).

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Title: Clinical genomic sequencing of pediatric and adult osteosarcoma reveals distinct molecular subsets with potentially targetable alterations

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