Real-World Age-Based Treatment Patterns and Outcomes of Osteosarcoma from a Nationwide Database: What Is the Optimal Strategy for Patients Aged Over 40?

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INTRODUCTION:

The standard treatment paradigm for osteosarcoma, particularly in pediatric and young adult populations, generally comprises surgical resection in combination with perioperative multi-agent chemotherapy. The chemotherapeutic agents most frequently employed include high-dose methotrexate (MTX), doxorubicin, and cisplatin (CDDP), often administered in both neoadjuvant and adjuvant settings. These multimodal strategies have significantly improved survival outcomes in younger patients over the past few decades. However, the applicability and efficacy of these regimens in middle-aged and elderly populations remain poorly defined. Nevertheless, due to limited clinical trial data and an absence of consensus guidelines, the optimal management approach for these patients is still a matter of debate. Therefore, this study aimed to analyze real-world treatment patterns and oncological outcomes among adult patients aged over 40 years diagnosed with localized high-grade osteosarcoma, using a comprehensive national registry in Japan.

METHODS:

Data were obtained from the Japanese Nationwide Bone and Soft Tissue Tumor Registry (BSTTR), encompassing 89 Japanese Orthopaedic Association (JOA)-certified hospitals. Eligible patients were those diagnosed with localized, high-grade osteosarcoma between 2011 and 2020. Inclusion criteria mandated histopathologically confirmed diagnosis, documented disease stage, and complete treatment and follow-up data. Patients with metastatic disease at diagnosis, secondary osteosarcoma, or unknown staging were excluded. The cohort was stratified into three age groups for comparative analysis: ≤40 years, 41–64 years, and ≥65 years.

RESULTS:

A total of 886 patients met inclusion criteria, comprising 622 (70.2%) aged ≤40 years, 156 (17.6%) aged 41–64 years, and 108 (12.2%) aged ≥65 years. The distribution of tumor stage was overwhelmingly skewed toward stage IIA and IIB (98%), with only 2% of patients presenting with stage III disease. Tumors originating in the axial skeleton (trunk) were significantly more prevalent in older age groups: 5% in ≤40 years, 29% in 41–64 years, and 38% in ≥65 years ($p < 0.001$). Definitive surgical resection of the primary tumor was performed in 98%, 91%, and 85% of patients in the ≤40, 41–64, and ≥65 year groups, respectively ($p < 0.001$). Among these, perioperative chemotherapy was performed in 93%, 87%, and 41% in patients aged ≤40 years, 41–64 years and ≥65 years, respectively ($p < 0.001$). Among those receiving chemotherapy, neoadjuvant regimens were employed in 96%, 80%, and 68% of cases in the respective age groups ($p < 0.001$). Among chemotherapeutic drugs used as perioperative adjuvant therapy, the use of MTX and CDDP declined with age: MTX, 91%/41%/8%; CDDP, 94%/76%/42% (≤40 / 41–64 / ≥65 years). Five-year disease-free survival (DFS) was 78.6%, 61.9%, and 48.0% in the ≤40, 41–64, and ≥65 age groups, respectively ($p < 0.001$). Multivariate analysis identified lack of definitive surgery as an independent predictor of poorer disease-specific survival (DSS) in patients ≤65 years ($p < 0.001$). Notably, in patients who received chemotherapy, no significant difference in survival was observed between those treated with neoadjuvant plus adjuvant chemotherapy and those receiving adjuvant chemotherapy alone.

DISCUSSION AND CONCLUSION:

Despite advances in the multimodal treatment of osteosarcoma, significant uncertainty remains regarding optimal therapeutic strategies for middle-aged and elderly patients. The present study represents one of the largest real-world analyses to date focusing on adult and elderly osteosarcoma patients within a single national healthcare system. Our findings reveal that the majority of patients over 40 years of age—particularly those between 41 and 64 years—were treated with protocols traditionally developed for younger patients. However, the utilization of chemotherapy, especially MTX and CDDP, declined significantly with advancing age, reflecting both concerns about tolerability and the paucity of age-specific evidence.

These findings are consistent with the results of the Euro-B.O.S.S. study, which is the only prospective (observational) trial specifically focusing on middle-aged and elderly patients with osteosarcoma. In the Euro-B.O.S.S. study, among 151 patients older than 41 years with localized disease, 110 patients (73%) received neoadjuvant chemotherapy, which resulted in a good histological response (defined as ≥90% tumor necrosis) in only 22 patients (21%). Notably, the 5-year disease-free survival (DFS) was 48% in the primary chemotherapy group and 64% in the upfront surgery (adjuvant chemotherapy) group. Given the reported decline in histological response rates and the increased toxicity associated with chemotherapy in older patients, upfront surgery may represent a viable and potentially non-inferior approach. These findings prompted us to initiate preparations for prospective randomized trials, with the goal of defining optimal strategies for the timing of surgery and chemotherapy in patients over 40 years of age with osteosarcoma, through international collaboration.