



## Review Article

# Chemotherapy for Osteosarcoma: Literature Review and Experience of Taipei Veterans General Hospital

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## Abstract

**Objective:** This article reviews the current standard of care for osteosarcoma and the experience of Taipei Veterans General Hospital. **Data Sources and Study Selection:** We searched PubMed using the keyword “osteosarcoma” and article type “Clinical Trial.” Prospective, randomized, Phase II/III clinical trials which resulted in practice change were enrolled. In addition, retrospective studies from Taipei Veterans General Hospital were also included. **Results:** For localized conventional osteosarcoma, combined perioperative chemotherapy with surgical resection dramatically improved long-term outcomes. Combination chemotherapy with methotrexate, Adriamycin, and cisplatin (MAP) is currently widely accepted to be the optimal regimen. The efficacy of chemotherapy has increased the likelihood of a limb-salvage approach, which has become the mainstay of surgery. In Taipei Veterans General Hospital, MAP plus ifosfamide was used and could achieve a 5-year overall survival (OS) rate of 77% and progression-free survival (PFS) rate of 70% for all patients. For nonmetastatic osteosarcoma, the 5-year OS and PFS rates reached 90% and 83%, respectively. For recurrent/metastatic disease, there is currently no satisfactory systemic therapy. Removal of all tumors should be attempted if clinically feasible, because one-third of patients may survive for 5 years or more if the tumors are completely resected. **Conclusion:** Perioperative chemotherapy is associated with excellent OS, PFS, and limb salvage rates and is the current standard of care for osteosarcoma.

**Keywords:** Adjuvant chemotherapy, limb-salvage surgery, neoadjuvant chemotherapy, osteosarcoma

## GENERAL FEATURES OF OSTEOSARCOMA

Primary bone cancers are rare, comprising <1% of all cancer cases.<sup>[1]</sup> However, the incidence of primary bone cancer is age related, and it comprises 5% of cancer cases in children and adolescents and is still an important health issue in those

aged 0–19 years.<sup>[1]</sup> Osteosarcoma is the most common subtype comprising nearly half of all cases, and the incidence peaks between the ages of 10–19 years.<sup>[2]</sup> Bone pain, especially at

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Submitted: 30-Jul-2020 Revised: 16-Sep-2020  
Accepted: 17-Sep-2020 Published: 01-Mar-2021

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Website:  
[www.ejcrp.org](http://www.ejcrp.org)

DOI:  
10.4103/JCRP.JCRP\_24\_20

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**How to cite this article:** Chen TH, Hung GY, Yen CC. Chemotherapy for osteosarcoma: Literature review and experience of Taipei veterans general hospital. J Cancer Res Pract 2021;8:9-12.

night, is the most commonly seen symptom. Around 20% of cases have metastasis at diagnosis, and the most common metastatic site is the lung in around 80% of cases, followed by bone.<sup>[3]</sup> Osteosarcoma can be further classified into several histological subtypes: conventional, telangiectatic, epithelioid, parosteal, periosteal, and other rarer subtypes.<sup>[4]</sup> Conventional osteosarcoma most commonly occurs at the medullary cavity of long bone metaphysis, especially around the knee joint and proximal humerus. Histologically, conventional osteosarcoma is mostly high grade and can be further divided into osteoblastic, chondroblastic, and fibroblastic types. Different histology components can be found simultaneously in one sample. The distinction of histologic variant is often arbitrary, and their prognostic impact is still controversial.<sup>[4-6]</sup> Parosteal osteosarcoma originates from the outer fibrous layer of the periosteum and usually presents as a low-grade tumor, with some cases gradually evolving to high-grade osteosarcoma. It comprises 5% of osteosarcoma cases and exhibits a tendency to occur at the metaphysis of long bones, especially the distal femur.<sup>[7]</sup> Low-grade central osteosarcoma comprises 1%–2% of all cases of osteosarcoma and most commonly occurs at the distal femur and proximal tibia. Both parosteal and low-grade central osteosarcoma tumors exhibit similar histological features, with mature bone trabeculae and low cellularity in a fibrous stroma background, and have murine double-minute type 2 and cyclin-dependent kinase 4 amplification.<sup>[4,8]</sup> Periosteal osteosarcoma originates from the inner layer of the periosteum and comprises 1% of cases of osteosarcoma. It is usually an intermediate-grade tumor, with a tendency to occur at the diaphysis of long bones, especially at the tibia.<sup>[7]</sup> In this review, we focus on the scope of systemic treatment strategy and combinations of chemotherapy for high-grade conventional osteosarcoma.

## LOCALIZED DISEASE ADJUVANT AND NEOADJUVANT THERAPY

For localized osteosarcoma, the curative management includes a combination of chemotherapy and surgery. In the prechemotherapy era, the 5-year survival rate after curative surgery was only 20%. Around 50% of cases of metastasis developed 6 months after surgery, and around 70%–90% developed within 1 year. The outcome of surgery alone for localized osteosarcoma was dismal. However, with the development of multiple chemotherapy agents, high response rates of Adriamycin (ADR; 43%), ifosfamide (IFO; 33%), methotrexate (MTX; 32%), and cisplatin (CDDP; 26%) have been reported in multiple Phase II trials.<sup>[9]</sup> These chemotherapy agents have been incorporated into multiple clinical trials and shown to improve the prognosis. The Multi-Institutional Osteosarcoma Study (MIOS), conducted from 1982 to 1984, enrolled cases of high-grade, localized, extremity osteosarcoma. After surgical resection, the patients were randomly assigned to receive either adjuvant chemotherapy (comprising bleomycin, cyclophosphamide, and dactinomycin [BCD], high-dose MTX [HD-MTX], ADR,

and CDDP with a 45-week schedule) or observation. The 6-year event-free survival (EFS) rate increased from 11% to 61%, and overall survival (OS) rate increased from 51% to 71% ( $P = 0.04$ ). The MIOS clearly demonstrated the benefit of chemotherapy.<sup>[10,11]</sup>

The MSKCC-T10 trial aimed to evaluate the role of a neoadjuvant strategy. Intensive chemotherapy with BCD, HD-MTX, and ADR was given before surgery, and the 3-year progression-free survival (PFS) and OS rates were 77% and 82%, respectively.<sup>[12]</sup> The POG-8651 trial was conducted to compare pre- and postsurgery chemotherapy. The 5-year PFS rates were 61% in the neoadjuvant arm and 69% in the adjuvant arm ( $P = 0.8$ ), and the 5-year OS rates were 76% in the neoadjuvant arm and 79% in the adjuvant arm. The limb salvage rates were similar in both the arms (50% for neoadjuvant chemotherapy and 55% for immediate surgery).

However, with improvements in chemotherapy, neoadjuvant chemotherapy has greatly increased the limb salvage rate. According to experience from the Rizzoli Institute, the limb preservation rate has increased from around 10% (1972–1978) to 94% (1997–2000), with a remarkable 5-year PFS of 64%.<sup>[13]</sup> Currently, the limb salvage rate in most reported series is around 80%–90%.<sup>[14-19]</sup> Neoadjuvant chemotherapy has greatly improved limb preservation rates without compromising long-term outcomes.

Another issue is the optimal chemotherapeutic regimen. In a meta-analysis comparing two-, three-, and four-drug regimens, a better PFS (Hazard ratio (HR): 0.70, 95% confidence interval [CI]: 0.62–0.80) and OS (HR: 0.79, 95% CI: 0.68–0.93) were seen with a three-drug combination than a two-drug combination. However, there were no differences in OS or PSF between a three-drug combination and a four-drug combination.<sup>[9]</sup> The INT-0133 trial was conducted with a  $2 \times 2$  factorial design, and patients were assigned randomly to one of four regimens. There were two chemotherapy arms, regimens A (HD-MTX, ADR, and CDDP [MAP]) and B (MAP plus IFO). Within these regimens, the patients were assigned randomly to receive or not receive liposomal muramyl tripeptide (MTP), a drug that can stimulate macrophage cytotoxicity. The addition of IFO to MAP did not enhance the EFS or OS for the patients with osteosarcoma. However, the addition of MTP to chemotherapy resulted in a statistically significant improvement in OS and a trend toward a better EFS.<sup>[9]</sup> The role of MTP in the treatment of osteosarcoma deserves further investigation.

In 2001, four clinical study groups agreed to collaborate to conduct OS studies more rapidly. The European and American Osteosarcoma Studies (EURAMOS) was formed from the Children's Oncology Group, Cooperative Osteosarcoma Study Group (COSS) of the German Society for Pediatric Oncology and Hematology, European Osteosarcoma Intergroup, and Scandinavian Sarcoma Group. The first study, EURAMOS-1, addressed separate treatment questions based on histological response. All participants received MTX, ADR, and

CDDP (MAP) as neoadjuvant regimens followed by surgery.<sup>[19]</sup> The patients with a good response (GR, tumor necrosis > 90%) were randomized to receive 4 cycles of adjuvant MAP plus a placebo or pegylated interferon-alpha 2b.<sup>[20]</sup> The patients with a poor response (PR, tumor necrosis ≤ 90%) were randomized to receive adjuvant MAP or MAP plus IFO and etoposide (IE) (MAPIE). Disappointedly, both studies failed to demonstrate the benefit of adding either pegylated interferon-alpha 2b or IE.<sup>[10,11]</sup> These studies indicated that three-drug combination chemotherapy with MAP should be regarded as the standard of care for localized osteosarcoma.

## TAIPEI VETERANS GENERAL HOSPITAL EXPERIENCE

The Orthopedic Oncology Team of Taipei Veterans General Hospital has a long experience in treating osteosarcoma. In an analysis of 74 patients (58 with nonmetastatic and 16 with metastatic disease) with osteosarcoma aged under 18 years treated with three protocols consisting of various cycles of high-dose MTX, ADR, CDDP, and high-dose IFO (MAPI regimens) during an 8-year study period, the 5-year OS and PFS rates were 77% and 70%, respectively, for all patients and 90.4% and 83.3% for those with nonmetastatic disease.<sup>[16]</sup> In a subsequent study, treatment outcomes were compared before and after 2004.<sup>[17]</sup> The results showed a significantly increased rate of limb-salvage surgery (from 90% to 98%,  $P = 0.03$ ), decreased rate of involved margin (from 5% to 1%,  $P = 0.007$ ), and increased pathologic GR (from 44% to 74%,  $P = 0.002$ ) in the post-2004 protocol cohort. In addition, there was an increase in OS rate of around 13%–16% after 2004. The post-2004 protocol consisted of perioperative MAPI chemotherapy. The preoperative component was in the order of HD-MTX, HD-CDDP, HD-ADR, and HD-IFO for 2 cycles with completion in 8–11 weeks. The postoperative component was given in a reverse order of HD-IFO, HD-ADR, HD-MTX, and HD-CDDP for 2–3 cycles with completion in 17–27 weeks. A possible explanation for the improved clinical outcomes with the post-2004 protocol may be attributed to reduced cycles of HD-MTX, increased cycles and doses per cycle of CDDP, increased doses per cycle of IFO, change from epirubicin to ADR, and no etoposide use. Similar protocols including MAPI have also been studied by other groups and institutes, and excellent outcomes have been reported, including 5-year OS rates ranging from 77% to 98%, 5-year EFS rates ranging from 64% to 83%, and 5-year limb salvage rates ranging from 90% to 100%.<sup>[21–23]</sup> The increased limb salvage rate and long-term survival revealed in both our study and from other institutes indicate that MAPI is a favorable treatment and the backbone of therapy for osteosarcoma.

## METASTATIC OR RECURRENT DISEASE

The outcome of metastatic and recurrent osteosarcoma is dismal. Several studies from Taipei Veterans General Hospital have reported a 5-year rate for metastatic disease of around 20%–25%.<sup>[16,17]</sup> In a study of 576 patients enrolled in the neoadjuvant COSS with subsequent recurrence, the most

common metastatic site was the lung (81.4%), followed by distant bone metastasis (15.6%). Recurrence within 18 months, multiple metastases, extrapulmonary metastasis, bilateral lung involvement, and pleural involvement were associated with poorer clinical outcomes. Of these patients, three quarters underwent surgery and two-thirds received second-line chemotherapy. The prognosis was strongly associated with surgery, and 38% of the patients were still alive at 5 years if macroscopically complete resection was achieved, compared to 0% at 5 years without macroscopically complete resection. The use of second-line chemotherapy affected outcomes less significantly ( $P = 0.089$ ). The 2-year and 5-year OS rates were 41% and 25% in the chemotherapy group, respectively, compared to 33% and 22% in the nonchemotherapy group. It was also suggested that multidrug combinations may have improved clinical outcomes compared with single-drug therapy. Both NCCN and ESMO guidelines suggest that surgical removal of metastatic lesions must be attempted, which may be why a third of the patients remained alive at 5 years of follow-up.<sup>[24]</sup>

## CONCLUSION

The introduction of neoadjuvant, adjuvant, or perioperative chemotherapy for osteosarcoma treatment has dramatically improved the long-term survival. The efficacy of adjuvant and neoadjuvant chemotherapy was comparable in this study, and neoadjuvant therapy could allow time to plan surgery, improve the elimination of micrometastasis, and evaluate the pathological response. In addition, with improvements in neoadjuvant chemotherapy, the likelihood of a limb-salvage approach is greatly increased. MAP was widely used as the backbone of osteosarcoma treatment. However, a perioperative MAPI regimen is the standard of care at Taipei Veterans General Hospital. Removal of all tumors should be attempted if clinically feasible, because one-third of patients may survive for 5 years or more if the tumors are completely resected.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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