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Chemotherapy in Osteosarcoma

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1. Introduction

Osteosarcoma is the most frequent primary solid malignancy of bone. It is defined by the presence of malignant mesenchymal cells which produce osteoid or immature bone^{1,2}. The incidence of osteosarcoma in the general population is only 2-3 per million per year. It is much higher in adolescents, where the annual incidence peaks at 8-11 per million at age 15-19 years and the tumor accounts for more than 10% of all solid malignancies. Males are affected approximately 1.4 times more often than females^{3,4}. High-grade osteosarcomas have a great propensity to metastasize. Primary as well as metachronous metastases usually involve the lungs or, less frequently, distant bones, while other sites are only rarely affected^{1,2,5,6}. At diagnosis, even the most accurate staging procedures detect metastases in only 10-20% of patients, but without adequate treatment, most patients with seemingly localized disease will develop secondary metastases and die within one to two years^{1,2,5,6}. With present day multimodality treatment, approximately 50- 70% of patients can hope to achieve long-term survival with an interdisciplinary treatment including surgery and multidrug chemotherapy⁷.

Amputation had been the standard method of treatment for most bone sarcomas, but the 1980s witnessed the development of limb-sparing surgery for most malignant bone tumors. Kenneth C. Francis at New York University and Ralph C. Marcove performed the original limb-sparing procedures in the United States^{8,9}. Today, limb-sparing surgery is considered safe and routine, but demanding, for approximately 90% to 95% of patients with extremity osteosarcomas. Before routine use of systemic chemotherapy for the therapy of osteosarcoma, fewer than 20% of patients survived more than 5 years. Further, recurrent disease developed in 50% of patients, almost exclusively in the lungs, within 6 months of surgical resection. The findings of two randomized clinical studies completed in the 1980s comparing surgery alone to surgery followed by chemotherapy demonstrated conclusively that the addition of systemic chemotherapy improved survival in patients presenting with localized high-grade osteosarcoma.

Prior to the use of neoadjuvant or adjuvant chemotherapy, 80 to 90 percent of patients with bone sarcomas developed metastases despite achieving local tumor control and died of their disease. It was demonstrated¹⁰ that subclinical metastatic disease was present at the time of diagnosis in the majority of patients and the use of chemotherapy can successfully eradicate these deposits if initiated at a time when disease burden is low. The benefit of adjuvant chemotherapy was demonstrated in two prospective randomized trials conducted in the

1980s in which the addition of postoperative chemotherapy improved survival in patients presenting with localized high-grade osteosarcoma when compared to surgery alone^{11,12,13}. Chemotherapy is now considered a standard component of osteosarcoma treatment, both in children and in adults. In addition, up to 35 to 40 percent of those with limited pulmonary metastases may be cured with multimodality therapy. In contrast, long-term survival can be expected in less than 20 percent of all other patients who present with or develop overt metastatic disease.

2. Historical aspect of chemotherapy in osteogenic sarcoma

Neoadjuvant chemotherapy evolved in concert with the use of limb-salvage surgical approaches. At Memorial Sloan-Kettering Cancer Center, customized endoprosthetic devices in limb-salvage procedures often required several months to manufacture. Rather than delaying treatment, investigators began to administer chemotherapy while waiting for the endoprosthesis to be made. This approach led to suggestions that preoperative chemotherapy improved survival of the patients. In addition, orthopedic oncologists developed their own opinions regarding the advantages and disadvantages of presurgical chemotherapy

3. Neoadjuvant versus adjuvant chemotherapy

Chemotherapy is now considered a standard component of osteosarcoma treatment, both in children and in adults. The choice of regimen and optimal timing (i.e., preoperative versus postoperative) are controversial; however, many centers preferentially utilize preoperative chemotherapy, particularly if a limb-sparing procedure is being contemplated for an extremity osteosarcoma.

These observations ultimately led to a randomized clinical study conducted between 1986 and 1993 by the Pediatric Oncology Group (POG trial 8651) that compared immediate surgery and postoperative chemotherapy versus 10 weeks of the same chemotherapy regimen followed by surgery in 100 patients under the age of 30 with nonmetastatic high-grade osteosarcoma¹⁴. Chemotherapy consisted of alternating courses of HDMTX with leucovorin rescue, cisplatin plus doxorubicin, and bleomycin, cyclophosphamide, and dactinomycin (BCD). The five-year relapse-free survival rates were similar between the two groups (65 versus 61 percent for adjuvant and neoadjuvant therapy, respectively) as was the limb salvage rate (55 and 50 percent for immediate and delayed surgery, respectively).

The study was criticized for the relatively low rate of limb-sparing surgery in both groups (by modern standards) and the inclusion of BCD as a component of the regimen. The contribution of BCD to the therapeutic efficacy of this regimen is unclear, while it can clearly contribute to long-term bleomycin-related pulmonary toxicity

Limb-sparing surgery – Due to its success in killing cancer cells (although actual tumor shrinkage during treatment is not common, particularly with chondroblastic osteosarcomas), neoadjuvant chemotherapy has evolved to a method of increasing the proportion of patients who are suitable candidates for limb-salvage surgery. The majority of limb-sparing surgical procedures for extremity osteosarcomas are now performed at institutions using presurgical chemotherapy. Neoadjuvant chemotherapy is never a substitute for sound surgical principles.

4. Response to neoadjuvant chemotherapy and its implications

Initial chemotherapy response and individualizing postoperative therapy – One of the most compelling rationales for neoadjuvant chemotherapy is its ability to function as an in vivo drug trial to determine the drug sensitivity of an individual tumor and to customize postoperative therapy. Many grading system for assessing the effect of preoperative chemotherapy on the tumor has been developed. (Table 1)¹⁵

Picci et al	Huvos et al
Total response-No viable tumour	IV-No histological viable tumour
Good response- 90%-99% necrosis	III- Scattered foci of viable tumour
Fair response- 60%-89% necrosis	II-Areas of necrosis with viable tumour
Poor response-<60% necrosis	I-Little or no chemotherapy effect

Table 1.

A consensus has emerged that uses greater than 90% necrosis and less than 90% necrosis as separating good and poor responses, respectively. Furthermore, most current studies use 10 to 12 weeks of preoperative chemotherapy (Fig 1).

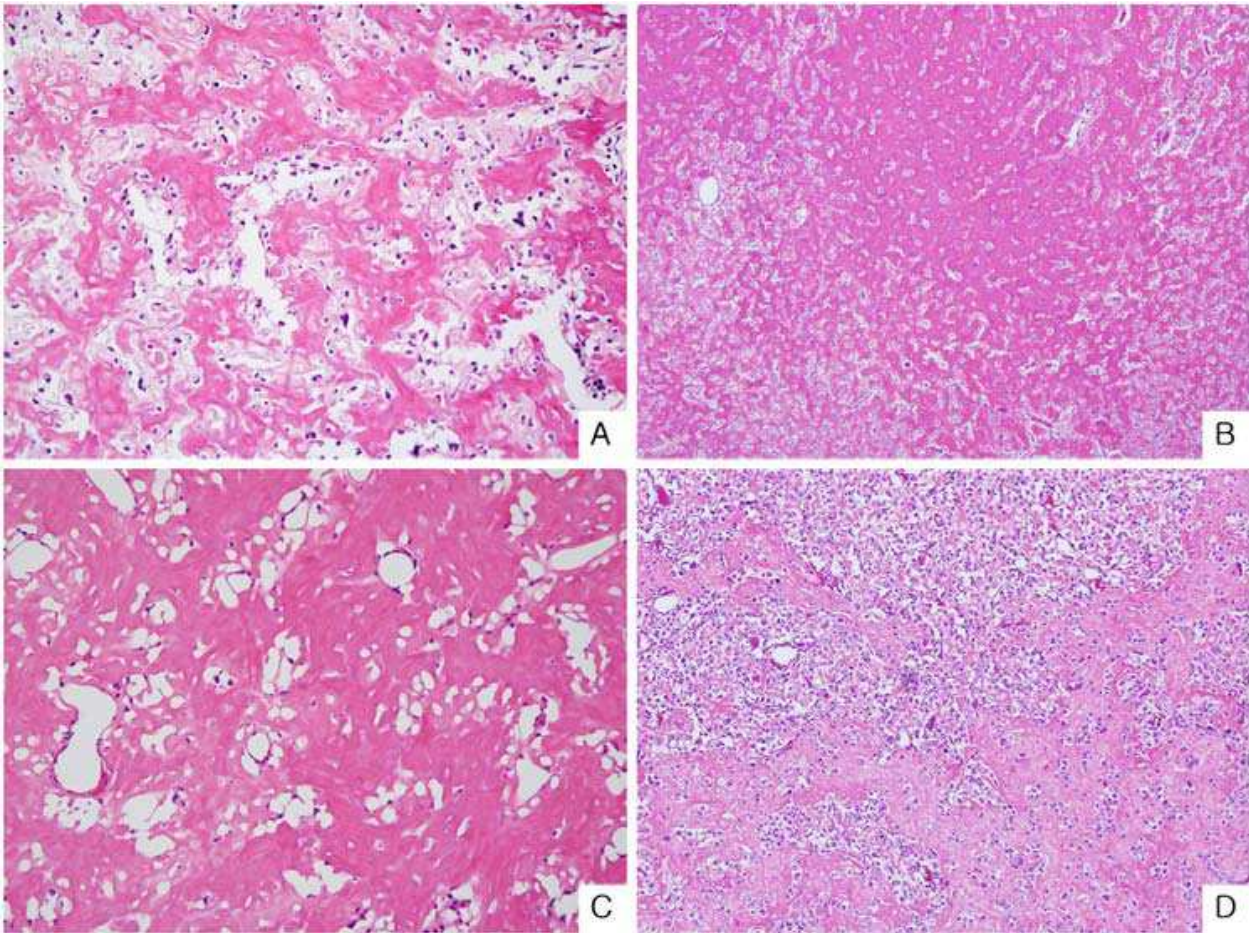


Fig. 1. The preoperative biopsy demonstrates osteoblastic osteosarcoma that contains malignant spindle cells with abundant well-formed osteoid matrix (A). The sclerotic sheet-like osteoid matrix with vascular channels is observed after chemotherapy (B, C), and viable tumor cells are remained among abundant eosinophilic matrix (D).

The IOR reviewed data on localized-extremity osteosarcoma in patients less than 40 years of age over the 19-year period from 1983 to 2002¹⁶. More than 1,000 patient records were analyzed. Fifty-nine percent of all patients had a good response to chemotherapy, and 41% had a poor response. Patients with a good histologic response to chemotherapy had a 5-year survival of 76%, whereas those with a poor response had a 5-year survival rate of 56%.

The COSS database was similarly reviewed and included 1,700 patients entered on study between 1980 and 1998. This analysis included all sites, ages, and presence or absence of metastases¹⁷. The data look remarkably similar to those of the Italian study, with 55.6% of patients classified as having a good response to therapy and 44.4% having a poor response. The 5-year survival rate was 77.8% for good responders and 55.5% for poor responders. Of further note, all the patients in both of these analyses received HD-MTX, and the majority also received ADM, CDDP, with or without IFOS.

The European Osteosarcoma Intergroup (EOI) analyzed data for two consecutive studies between 1983 and 1986 and 1986 and 1991¹⁸. A total of 570 patients were analyzed in the report. This analysis is notable for several differences compared to the COSS and IOR analyses. Only 28% of patients had a good histologic response, whereas 72% of patients had a poor histologic response. Patients with a good histologic response had a 5-year survival of 75%, whereas those with a poor response had a 5-year survival of 45%. Of note, many of the patients included in the analysis did not receive HD-MTX because many were treated on a randomized study comparing two drugs, ADM and CDDP, to more intensive therapy including HD-MTX, similar to the COSS and IOR studies [Table 2]. The large randomized study failed to show an advantage of multiagent therapy compared to ADM and CDDP alone¹⁹.

Trials	No of PTS	Good responders	Poor responders	HD-MTX used
COSS	1700	56.6%	44.4%	YES
IOR	1000	59%	41%	YES
EOI	570	28%	72%	NO

Table 2.

A factor that could possibly influence histologic response to therapy and its predictive value on survival is the histologic subtype of the tumor. In both studies, fibroblastic tumors had a higher rate of good histologic response (approximately 80% in the IOR study), whereas chondroblastic tumors had a lower rate of good responders (43% in the IOR study). Perhaps even more important, unlike other histologies, 5-year survival rates were identical for good and for poor responders in chondroblastic histology, at 68%.

5. Modification of chemotherapy based on necrosis

By knowing the histologic response to neoadjuvant therapy an exciting avenue of modifying post operative chemotherapy and hence attempting to improve survival in poor responders has opened. This has been earlier proven in hematolymphoid malignancy. In the early 1980s at Memorial Sloan-Kettering Cancer Center, poor responders had CDDP substituted for HD-MTX in addition to continuing BCD (bleomycin, cyclophosphamide, and dactinomycin) and ADM²⁰. Patients who had adjustments in their postoperative chemotherapy based on poor

initial response did not have improvement in survival compared to those who had no modifications²¹. Several other reports have also failed to demonstrate an ability to rescue poor responders^{22,23}. Although tumor necrosis correlates with outcomes, detection of this feature at such a late stage may not offer the chance to target therapy, and therefore, better methods to identify chemoresistant tumors at diagnosis are needed. Thus, to date, it has not been possible to improve the outcome of poor responders by altering postoperative chemotherapy.

6. Development of chemotherapy regimens

The choice of chemotherapeutic agents has largely been empirical with most groups using ADM, CPL or High dose methotrexate(HD-MTX).

Role of methotrexate – The role of HDMTX has been questioned (particularly in adults). There are no randomized studies that have shown an advantage for higher as compared to intermediate doses of methotrexate²⁴ or for HDMTX plus doxorubicin and cisplatin versus doxorubicin/cisplatin alone²⁵. Furthermore, investigators at St. Jude's Hospital have demonstrated good outcomes (five-year event free and overall survival rates 66 and 75 percent) with a non-methotrexate-containing chemotherapy regimen consisting of carboplatin plus ifosfamide and doxorubicin²⁶.

On the other hand, a benefit for HDMTX is supported by at least one series that demonstrates a superior outcome with high-dose as compared to intermediate-dose methotrexate in the context of a multiagent chemotherapy regimen. Furthermore, many studies have shown a correlation between peak serum levels of methotrexate, tumor response, and outcome²⁷⁻³⁰. Thus, it is possible that determining a benefit for HDMTX has been compromised by the use of insufficient doses³¹ or administration schedules. The role of HDMTX in chemotherapy for osteosarcoma requires further study³².

Benefit of ifosfamide-based therapy and mifamurtide – The upfront addition of ifosfamide with or without etoposide to HDMTX, doxorubicin, and cisplatin improves initial tumor response rates, but the influence on overall and event-free survival is unclear³³⁻³⁷. The benefit of ifosfamide and the liposomal formulation of immune stimulant muramyl tripeptide phosphatidylethanolamine (MTP-PE, mifamurtide, Junovan) were evaluated in a large phase III study involving 677 patients with nonmetastatic osteosarcoma³³. All patients received doxorubicin, cisplatin, and methotrexate, and were randomized in a 2 x 2 scheme to receive or not receive ifosfamide, and then to receive or not receive liposome encapsulated mifamurtide.

The addition of ifosfamide-based therapy improved the relapse-free survival rate, but only when used in conjunction with the mifamurtide. Thus, the routine addition of ifosfamide to adjuvant chemotherapy for osteosarcoma is not recommended outside of a clinical trial. However, the use of mifamurtide improved survival, which led to European regulatory approval of this agent for patients with osteosarcoma³⁸.

Chemotherapy for adults - In many (but not all series, adults, especially older adults, have a worse prognosis than children with osteosarcoma. This was shown in a population-based series from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute³⁹. Adults are most often offered doxorubicin plus cisplatin,

although the role of HDMTX remains a major unanswered question. For patients under the age of 35, we often employ all three agents, while for older patients, in whom the biology of the tumor may be somewhat different, we generally employ doxorubicin and cisplatin only, given the lack of difference between cisplatin/doxorubicin and the more complex T10-type regimen in the adjuvant setting in one study.

7. Chemotherapy in metastatic disease

Optimal management for patients who present with metastatic osteosarcoma has not been defined by randomized clinical trials, and thus, there is no single standard approach. The most active drugs in patients with measurable disease (HDMTX, doxorubicin, cisplatin, ifosfamide) have single-agent response rates between 20 and 40 percent⁴⁰⁻⁴⁵. Response rates are higher with multiagent regimens but a lower proportion of patients treated for metastatic disease show a good histological response to neoadjuvant chemotherapy as compared to those with apparently localized disease. This suggests an underlying difference in the biological behavior.

In an effort to improve outcomes, the Pediatric Oncology Group and others have utilized a strategy of applying novel agents to patients with newly diagnosed metastatic disease prior to standard therapy (termed the "therapeutic window" approach)^{40,42,46,47}. Using this approach, POG identified the combination of ifosfamide/etoposide as effective induction therapy, particularly for those with metastatic bone disease. Thus, although there is no accepted standard approach for the treatment of newly diagnosed metastatic patients, available data would suggest that such patients should be treated with currently available aggressive multiagent chemotherapy with complete surgical resection of all sites of disease if at all possible.

Nevertheless, few patients with metastatic osteosarcoma are cured, and new therapeutic approaches are needed. For patients who present with overt metastatic disease, participation in experimental trials should be encouraged.

A study evaluating the feasibility of adding trastuzumab to standard chemotherapy for patients whose tumors are HER2 positive was just completed by the Children's Oncology Group (COG)⁴⁸. The results of this study are not yet available. Numerous in vitro and xenograft studies support the concept that bisphosphonates have activity against osteosarcoma alone or in combination with chemotherapy⁴⁹.

8. Treatment of recurrent disease

Patients with a disease recurrence after resection alone can often be salvaged with additional surgery and chemotherapy, although their long-term survival is inferior to that of patients who received conventional multiagent chemotherapy in conjunction with surgery upfront^{50,51}.

Treatment of relapse in patients who have already received adjuvant and/or neoadjuvant chemotherapy is a more difficult situation. Such patients usually have received most of the effective drugs, and presumably their tumors are more chemotherapy-resistant than those that have never been exposed to antineoplastic agents⁵².

Salvage is still possible and is more likely in patients with a longer relapse-free interval. In a large database of 565 osteosarcoma patients who relapsed after being treated on one of three different neoadjuvant chemotherapy protocols within the European Osteosarcoma Intergroup, five year survival postrelapse in those whose disease recurred after two years versus within two years of randomization was 35 versus 14 percent, respectively⁵³. Other favorable prognostic factors in recurrent osteosarcoma include no more than one or two pulmonary nodules, the presence of unilateral pulmonary involvement, lack of pleural disruption, and achieving a second surgical remission,^{50,54-56}. In general, patients should be treated with any of the four most active agents noted earlier if initial therapy did not include one or more of these agents. Patients who have recurrences more than 1 year after completing prior systemic therapy may benefit from reintroduction of at least some of the same drugs in a salvage regimen. The use of high-dose chemotherapy with autologous hematopoietic stem cell rescue has been applied to salvage therapy. However, at least two small pilot studies failed to demonstrate an advantage to standard salvage therapy approaches^{57,58}.

9. Newer and investigational approaches

A study of the mTOR inhibitor ridaforolimus in patients with metastatic sarcoma suggests potential activity for this class of compounds in patients with osteosarcoma⁵⁹, raising the possibility of using these and other kinase-targeted agents in patients with metastatic disease. If activity is confirmed, it is expected that these agents will be studied in the adjuvant setting as well.

Among other interesting agents that may have clinical utility are inhibitors of insulin-like growth factor I receptor (IGF IR), since IGF signaling is critical for bone formation during development. Early studies with a variety of monoclonal antibodies and small molecule inhibitors of the IGF IR are underway.

Immunotherapy – Immune responses may influence the survival of patients with osteosarcoma. Cytotoxic lymphocytes are present in such patients^{60,61}, and in at least one study, the degree of lymphocytic infiltration correlated with survival⁶¹. These findings have prompted investigators to explore a variety of immunotherapeutic approaches for patients with advanced osteosarcoma.

The addition of Bacille Calmette-Guerin (BCG) and interferon did not improve survival when added to multiagent chemotherapy^{62,63}. However, encouraging preliminary results were obtained using liposomal muramyl tripeptide-phosphatidyl-ethanolamine (mifamurtide), an agent derived from BCG that activates macrophages and increases circulating cytokine levels^{64,65}. These data led to a randomized study, described above, in which patients were assigned, using a 2 x 2 factorial design, to standard chemotherapy with or without ifosfamide and then to receive or not receive mifamurtide. The addition of mifamurtide to standard chemotherapy resulted in a statistically significant improvement in overall survival (78 versus 70 percent at six years) and a trend toward improved event-free survival (67 versus 61 percent)

However, when the analysis was restricted to the 91 patients with metastatic disease at diagnosis, there was only a nonstatistically significant trend toward improved five-year

event free survival (42 versus 26 percent) and overall survival (53 versus 40 percent) that favored mifamurtide⁶⁶. The drug is not available in the United States. Thus, the role of mifamurtide in patients with metastatic osteosarcoma remains uncertain and a further randomized trial seems warranted.

Another immunotherapeutic approach that is being pursued for pulmonary metastatic disease is inhalation of aerosolized granulocyte macrophage colony-stimulating factor (GM-CSF). GM-CSF stimulates the proliferation and differentiation of hematopoietic progenitor cells and augments the functional activity of neutrophils, monocytes, macrophages, and dendritic cells. Recombinant GM-CSF has been used primarily to enhance neutrophil recovery after chemotherapy.

Preclinical as well as early clinical studies suggest that locally applied GM-CSF may provide antitumor effects^{67,68}. These data form the basis for novel therapeutic vaccine approaches using irradiated tumor cells or dendritic cells that are genetically engineered to produce GM-CSF locally and provide the rationale to explore local application of GM-CSF in other diseases.

Local application to the lungs (the most common site of metastatic disease) through inhalation of GM-CSF has been studied. Early data using aerosolized GM-CSF (250 micrograms per dose, twice daily) in a variety of cancers with pulmonary metastases suggest that this approach is safe and possibly effective; in one study, a patient with metastatic Ewing sarcoma had a complete response to therapy^{69,70}. In at least one case, upregulation of tumor-specific cytotoxic T lymphocytes has been shown.

Inhaled GM-CSF was evaluated in 43 patients with pulmonary relapse from osteosarcoma in the American Osteosarcoma Study Group [AOST] protocol 0221⁷¹. Inhaled G-CSF was administered at doses from 250 to 1750 microg twice daily every other week; after four weeks, resection was performed, and G-CSF was resumed for an additional 24 weeks or until progression. Although doses as high as 1750 microg twice daily were feasible with no dose-limiting toxicity, there was no detectable immunostimulatory effect on the pulmonary metastases or suggestion of improved outcomes post relapse (three-year event-free and overall survival rates were 8 and 35 percent, respectively).

10. Intra-arterial chemotherapy

The introduction of neoadjuvant chemotherapy into the multi-modality of treatment of osteosarcoma is the most important advancement in treatment of the disease. However, for the last 10 years, there has been less significant improvement in survival with the use of multiagent neoadjuvant chemotherapy. In these patients, the extent of chemotherapy-induced tumor necrosis is strictly correlated with prognosis. To increase the rate of chemotherapy-induced tumor necrosis, delivery of larger doses of drugs to the primary tumor has been attempted using intraarterial chemotherapy. Of the drugs which are effective in osteosarcoma, cisplatin is considered the most suitable for intraarterial infusion because intraarterial cisplatin is not associated with a significant local reaction and systemic drug levels are not compromised by intraarterial infusion^{72,73}.

The COSS-86 study was the only prospective controlled study designed to verify whether intraarterial infusion of cisplatin was more effective than intravenous infusion in a multiagent pre-operative chemotherapy setting. In this study, intraarterial or intravenous cisplatin were given with HD-MTX, adriamycin and ifosfamide and the response rate and 10-year event free survival were also identical. The authors themselves suggested that a selection bias may have influenced outcome.

In Bacci et al's study, the doses and the time infusion of cisplatin were the same for patients treated intraarterially and intravenously. When used within a three-drug regimen (HD-MTX, cisplatin, adriamycin), intraarterial cisplatin was significantly more effective on the primary tumor than the intravenous infusion. When cisplatin was delivered within a four-drug regimen (HD-MTX, cisplatin, adriamycin and ifosfamide), which significantly increased the good responses, the advantage of intraarterial cisplatin disappeared⁷⁴. Therefore, it seems that the addition of another active drug to cisplatin and adriamycin concealed the difference. The Instituto Ortopedico Rizzoli (IOR-OS) 2 and 3 studies demonstrated that the rate of histological response was significantly higher in the intraarterial cisplatin regimen than the IV regimen⁷⁵. Apart from histologic necrosis, response evaluation can also be done with pre and post chemotherapy angiograms [Fig. 2].

However there is lack of randomized trials of intraarterial chemotherapy in osteogenic sarcomas to draw any definitive conclusions on this promising modality of treatment. Future endeavors should involve a multi-institutional randomized study comparing this approach with another multiagent intravenous neoadjuvant protocol.

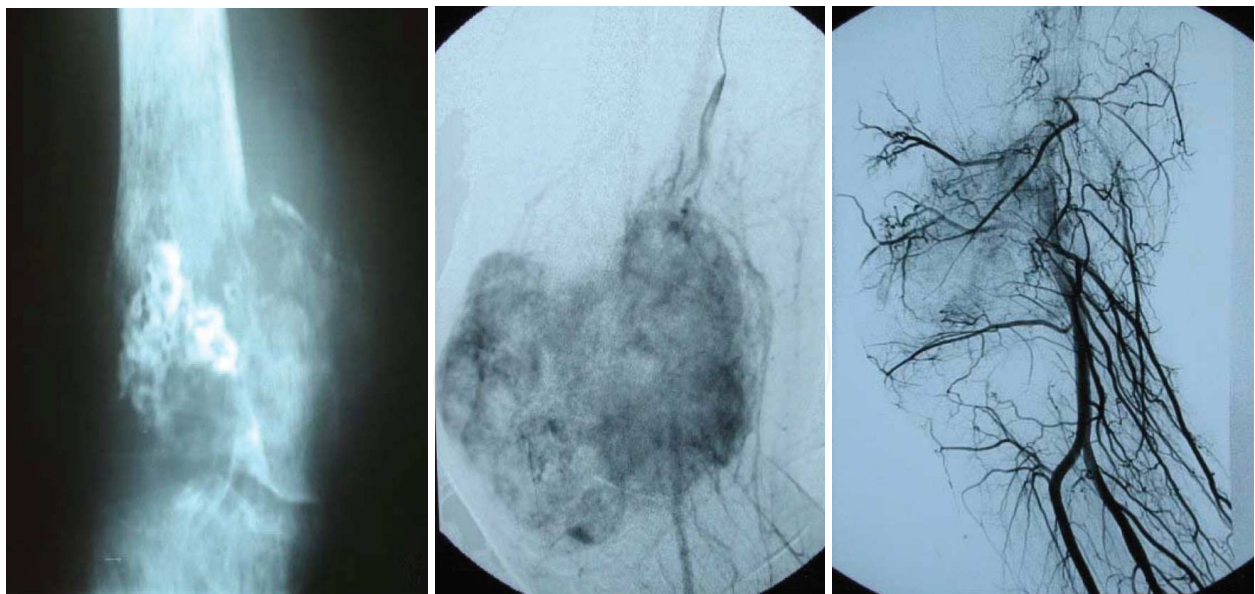


Fig. 2. (A) A radiogram of a man with osteosarcoma of the distal femur. (B) An arteriogram after the first course of chemotherapy shows viable tumor area with tortuous vessels and intense contrast uptake. (C) An arteriogram after the fourth course shows a decrease in contrast uptake with little evidence of residual tumor staining. It was estimated that there was > 90% decrease in neovascularity.

11. Conclusion

Chemotherapy in osteogenic sarcoma has remarkable impact evident by the fact that survival has increased from dismal 20% in pre-chemotherapy era to respectable 60% in present era. The impact of chemotherapy in Limb salvage approach is tremendous with limb salvage rates around 90-95% at most referral centres. The optimal regimen and timing (Neoadjuvant vs Adjuvant) of chemotherapy needs to be defined. The strategy of chemotherapy modification based on percentage necrosis after pre-op chemotherapy needs further clarification.

Despite impressive 60% survival in most western centers, the survival data of osteogenic sarcoma is not so encouraging in developing countries. The overall 5- and 10-year survival rates in the Brazilian osteosarcoma study group were lower than the rates reported in North American and European trials. A pattern of advanced disease at diagnosis was often present, with a high proportion of patients having metastases (20.8%) and large tumor size (42.9%)⁷⁶. The developing countries have low limb salvage rates secondary to non availability of costly hardware along with few referral centers with expertise to administer high dose Methotrexate. Development of indigenous, low cost and durable implants⁷⁷ and less costly effective chemotherapy⁷⁸ is needed to optimally treat this disease in developing countries. More patients need to be enrolled in randomized clinical trials testing optimal regimen, timing and low cost implants. Newer molecules in research pipeline provide ray of hope for metastatic and relapsed osteogenic sarcoma.

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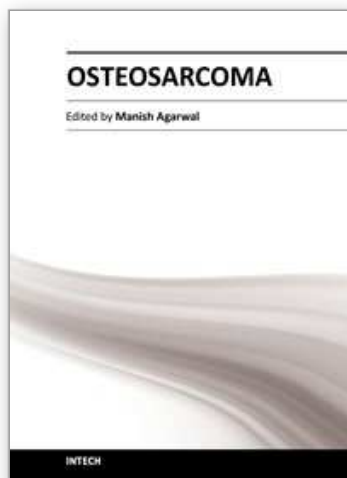
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This book is aimed at quickly updating the reader on osteosarcoma, a dreaded primary bone cancer. Progress in management of osteosarcoma has been slow after the evolution of chemotherapy and limb salvage surgery. Research is now directed towards identifying molecular targets for systemic therapy. Availability of chemotherapy drugs and low cost implants in developing world have allowed limb salvage surgery to develop. This book looks at current basic knowledge on osteosarcoma and some of the developments in research which have the potential to change the prognosis.

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