Role of Chemotherapy in Malignant Bone Tumors

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Abstract

The purpose of this study was to evaluate the functional and radiological outcome various chemotherapy treatment modalities regarding Malignant Bone tumors. A systematic review was completed. Medline, EMBASE, Pub Med and the Cochrane Central Registry of Controlled Trials (CENTRAL) were searched from January 2009 to January2019. Methods: 23 inclusion studies that described the role of different chemotherapeutic regimens in treatment of different types of malignant bone tumors, from which there were 14 prospective phase2 trial studies, 2 prospective phase 1 studies, 2 prospective phase 3 studies, while there were 5 retrospective studies. The onset of patients ranges from 15 to 40 ys in 10 studies, more than 40 ys in 2 studies, while no available date in 11 studies. The number of patients included in those studies ranges from 14 to 100 patients in 12 studies, from 100 to 200 patients in 1 study, while there were 10 studies that included more than 200 patients. The median follow up period used to obtain results ranges from 1.5 to 25 ys in 12 studies, less than a year in 2 studies, while no available date in 9 studies. Disease free survival rate ranges from <50% in 7 studies,>50% in 12 studies, while no available date on 4 studies. Overall survival rate ranges from <50% in 10 studies, ,>50% in 8 studies, while no available data on 5 studies. Most of studies that had >50% in the overall survival rate and disease free survival rate used neoadjuvant and adjuvant chemotherapy regimen as a part of treatment of non-metastatic Ewing and osteosarcoma. While most of studies that had <50% overall survival rate was due to the metastatic or advanced stage of the sarcomas on which those studies were done. For newly diagnosed osteosarcoma in <40 ys pts, neoadjuvant H.D.IFO+ADM+CDDP +surgery + adjuvant chemo (H.D.M.T) , is associated with very good results (the 5 year event free survival rate is 83%,the 5 year overall survival rate is 98%). In

high grade osteosarcoma, adding IFO to MTX, CDP, and ADM from the preoperative phase does not improve the good responder rate and increases hematologic toxicity. IFO should only be considered in patients who have a poor histologic response to MTX, CDP, and ADM. Patients with high-grade, localized osteosarcoma who received adjuvant chemotherapy after undergoing definitive surgical resection had a statistically significant benefit in disease-free and overall survival that was maintained through 25 years. Tumor necrosis after just 1 cycle of neoadjuvant chemotherapy and radiation was predictive of overall survival and disease-free survival in patients who received adjuvant chemotherapy.

The keywords: 'malignant bone tumor', Bone sarcoma and 'chemotherapy'

Introduction:

In the United States, it is estimated that approximately 3300 primary malignant bone tumors (excluding malignancies arising in the bone marrow) are diagnosed annually, and approximately half as many deaths result [1]

Adolescents with a bone tumor had consistently lower scores on quality of life as compared to healthy peers. Significantly on domains: physical well-being, autonomy, social support and school environment [2]

For many of the tumors, most not ably osteosarcoma and the Ewing sarcoma, remarkable progress in surgical techniques and multidisciplinary management over the last 40 years has resulted in significant improvements in the likelihood of cure and limb salvage [3].

Malignant bone tumors represent a small percentage of cancers nationwide and also are much less common than malignant soft-tissue tumors. The rarity of the condition makes it imperative that orthopedic surgeons in non-oncologic practices are able to recognizethesymptomsthatsuggestapossiblebonymalignancytoavoidinappropriate or delayed treatment [4]

Primary malignant bone tumors are uncommon but are a significant cause of cancer morbidity and mortality, especially among young people. Although relatively rare in childhood, primary malignant bone tumors represent the sixth most common neoplasm in children, while in adolescents and young adults, they are the third most frequent, exceeded only by leukemias and lymphomas [4].

The most common primary malignant bone tumors, osteosarcoma and Ewing's sarcoma, occur in childhood. Chondrosarcoma occurs more frequently in older adults. Rare tumors such as chordoma and adamantinoma have anatomic predilections for the sacrum and tibia ,respectively .The primary symptom of a patient with a malignant bone tumor is pain, which often occurs at rest or at night [4]

The biopsy can be an image-guided needle biopsy or an open incisional biopsy. Knowledge of specific tumor characteristics and treatment options for osteosarcoma, Ewing's sarcoma, chondrosarcoma, malignant fibrous histiocytoma, chordoma, and adamantinoma is important. Patients with osteosarcoma and resectable Ewing's sarcoma are treated with chemotherapy followed by surgical resection. Secondary sarcomas can occur in previously benign bone lesions and require aggressive treatment.

Specific techniques are available for the resection of malignant bone tumors from the Upper extremities, lower extremities, pelvis, and spine. Reconstruction options include the use of allografts, mega prostheses, and vascularized autografts [4]

Chemotherapy has had a major impact in malignant bone tumors. In osteosarcoma, metastasis-free survival has been achieved in approximately 50 to 75 per cent of patients [4]

Additional improvement based on the altered pattern of pulmonary metastases has also been reported. Preoperative chemotherapy has facilitated surgical resection of the primary tumor. The effects on the primary tumor may be utilized as a predictive factor and to design postoperative adjuvant therapy. Similar results have been achieved

In Ewing's sarcoma the survival rates is in the vicinity of 50 to 80 percent. The interaction of chemotherapy with radiation has augmented the ability to achieve local control of the primary tumor. The tumoricidal properties of chemotherapy in destroying micrometastases may possibly also contribute to local control. Finally, initial treatment with chemotherapy may yield a complete response and facilitate definitive surgical treatment of the primary tumor. This may eliminate the need for radiation therapy and its delayed consequences [4]

High-dose chemotherapy and hematopoietic support can produce long-term, disease- free remissions in selected patients with metastatic breast cancer. Occult bone marrow involvement may contribute to late relapse.[4]

Current chemotherapy regimens include doxorubicin, high dose methotrexate, cisplatin and sometimes ifosfamide. This multi-drug approach yields survival rates of approximately 70% in those patients with no evidence of metastasis at diagnosis. [4]

Induction chemotherapy significantly decreased bone marrow contamination as detected by flow cytometry and cytology in patients with breast cancer. The detection of immunostained cells in the bone marrow did not predict for relapse or overall survival. [4]

The use of multi-agent chemotherapy combined with aggressive surgery has improved the long-term survival in osteosarcoma patients to approximately 60 %. [7] Neo-adjuvant chemotherapy resulted in higher survival rates. [4]

Bone is a common site for malignant involvement. It is a major source of morbidity, and half of patients with bone involvement develop skeletal-related events such as pathological fractures or cord compression requiring surgery and/or radiation. Skeletal involvement also increases mortality, as pathologic fractures increase the risk of dying by 20-40%. [4]

Materials and Methods

Search Strategy and Eligibility:

A systematic literature review was performed to identify all papers relevant to the study objectives. Searches will be performed in the MEDLINE ,EMBASE ,Life Science Citations, PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/), Google Scholar (http://scholar.google.it/), CINAHL (http://www.ebscohost.com/cinahl/), Cochrane Central Register of Controlled Trials databases through 2017 0(ht0tp://www.thecochranelibrary.com/view/0/index.html) and Embase Biomedical (http://www.embase.com/) Databases were accessed to search studies with no limits set during research
A literature search was performed using combinations of keywords ‘malignant bone tumor’, Bone sarcoma and ‘chemotherapy’ with no limit regarding the year of publication.

Inclusion Criteria:

- Clinical human studies.
- Clinical studies with at least 6 months of follow up.
- Skeletally mature population with malignant bone tumors.
- Clinical studies within last 13years only.

Exclusion Criteria:

- Non-human studies.
- Cadaveric studies.
- Skeletal prematurity.
- Reviews, commentaries and general discussion papers not presenting data on impacts.

Study selection and data extraction:

Two independent reviewers first screened the study titles and abstracts for eligibility. The full text of the trials potentially meeting the eligibility criteria were reviewed to decide the final inclusion. Then, investigators independently extracted information,

including the lead author, publication year, randomization methods, participant number, patient characteristics (number, age and cancer type), follow-up time, all outcome measures (event free survival rate and overall survival rate). Discrepancies were resolved by consensus after discussion between the two reviewers.

Results

The literatures each identified 1210 abstracts**).**Of these, 936 were excluded during abstract review and 274 proceeded to full text review. During full-text review, an additional 8studies were excluded. A total of 23 studies met the inclusion criteria when assessed during full-text review and were included in the present systematic review. Hand-search in the references ofthe23 included studies identified on additional articles [7-21].

Stat method:

The collected data presented as suitable tables. Quantitative data summarized as mean ± SD and qualitative data as frequency and percentage. Analysis of data was performed by the aid of software package of SPSS using Suitable statistical tests.

No	Study	Intervention	No of Pts	Age(y)	Cancer	Fu(y)
1	Berntha. ,et al.(7)	Adju.Chemo or observation After Surg.resection	59		H.G.O.S	25
2	Bianchi, et al.(18)	Electrochemotherapy (IV belomycin followed by electroporation)	29	60	Bonemetastases	Half a year
3	Boye,et al. (8)	Neo adju.chemo (MTX,IFO,CDDP,ADM) and adjuv.chemo (HDChemo OF E,ADM,C+Stem cell rescue)	71		Metastatic OS	>5
4	Choy ,.et al. (15)	Post operative Olaparib tablets+PARP inhibitors After prior standard chemo.	22	20	ES (refractory metastatic)	<1
5	Ebb,et al.(9)	Targeted therapy Trastuzumab+Standard chemo(CDDP+ADM+MTX+IFO+E)	96		metastatic OS,HER2-positive	> 2.5
6	Ferrari11,et al. (18)	Neoadjuv.(VACAc-IE regimen	300	15	ES	5
7	Ferrari12,et al. (12)	Neo adjuv chemo (HDMT+CDDP+A+IFO) for 44 ws(Arm A) or 34 ws(Arm B)	246	<40	OS	5.5
8	Ferrari18,et al.(10)	Neoadjuv (HDMT+CDDP+IFO+ADM)	218	>40	HGOS	4
9	Gaspar,et al. (14)	For IR or SR tumors (IE) after 3courses of ADM+CDDP ForHR: busulfan,melphalan added	214		ES(Residual)	
10	Granow.,et al. (19	VDC/IE over 48 weeks or VDC/IE over 30 weeks.	478		nonmetastatic ESFT of bone or soft tissue	
11	Han,K.,et al.(15)	(VDC/IE) 1st line (HCPT)+(CTX) as second-line	27		Advanced.E.S	
12	Iwamot,et al. (11)	Neoadjuva.chemo (HD.MTX,CDDP,ADR),+IO	113		OS	
13	Kudawa.,et al. (15)	Neoadjuv(H.D.IFO ,ADM,CDDP) And adjuv Two cycles CDDP+H.D.M.T +Surgery	40	<40	non- metastatic OS	9.5
14	Laux,et al.(12")	Neoadjuvant chemotherapy	14	19	OS	
15	Machak.,et al. (22)	neoadjuvant chemotherapy of ICE or ICA		20	Relapsed OS	1.5
16	Marina., et al. (28)	Adjuv.MAP/IE versus MAP regimen	618		HGOS(poor response to preop.Chem	5
17	Meazza ., et al. (18)	Immunotherapy (IL2+LAK infusion) added to standard chemo (HDMT, ADM, CDDP, IFO)	35	<18	1RY Metasttic OS	10.5
18	Mora .,et al. (20)	Neoadjuv.Chemo(GD regimen>> gemcitabine and docetaxel)	43	<40	ES	3.5

NO	Study	Disease- free rate	Overall survival rate at 25 years	Additional comment
1	Bernthal, et al. (7)	28% for adjuvant chemotherapy	38%	Tumor necrosis >90% Statistically significant after single round of adjuvant chemo
2	Bianchi., et al.(19)			
3	Boye.,et al. (8)	27%	31%.	
4	Choy ., et al (15)			
5	Ebb, et al(9)	32% (in HER2 + and -)	In HER2 overexpression treated with **chemo.+ trastuzumab was 59%.** For HER2 overexpression, treated with **chemotherapy alone,52%**	
6	Ferrari.,et al. 2018(10)	66% in localized dis 22% in metastasis	29% in localized dis 70% for extremity 73% for craniofacial locations	Tumor necrosis >90 in 21% of cases
7	Ferrari ., et al. (2012).(12)	64%in arm A(44 ws) 55% in arm B. (34ws)	74% in arm A, B.	Tumor necrosis >90% good in
8	Ferrari ., et al. (2011). (18)	69%.	75%	

9	Gaspar, et al (14)	69%	60% .	
10	Granowetter, et al. (35)	71.1%	78.6%(for standard and intensified regimen)	
11	Hank, et al. (16)	8%	30%	Overall response rate was 30% disease control rate was 82%, complete response (8%), partial remission (22%), (52%) stable disease
12	Iwamoto ., et al. (11)	65.5%,	77.9%.	There were no significant differences between the OAS and EFS rates of the patients in terms of response to preoperative chemotherapy.
13	Kudawara ., et al. (15)	83%.	98%.	31 of the evaluable 40 disease-free, 7 were currently alive with no disease, and 2 died of disease.
14	Laux.,et al (12)			In good responders overall tumor volume decreased by47 %(p=0.345),while poor resonders(n=8)showed a 19% decrease(p=0.128). the bonycompartments of good responders showed a volume increase
15	Womer,	65% in the standard arm 73% in the intensified arm		
16	Machak,et al (22)		34.4	**In ICE regimen**, partial effect was in (17.6%),Stabilization in (58.8%), tumor progression-- (23.5%) **ICA regimen** :partial Effect(25%),stabilization(50%),tumor progression (25%) . Metastases were removed after a course chemotherapy in 16 cases.
17	Marina,et al (28)	51%		
18	Meazza, et al. (18)	34.3%	45.0%.	
19	Mora ., et al. (21)	51.0% For (SR) patients was 71.0%	55.0% For (SR) patients was 76% for HR 36.0%	
20	Piperno- Neumann., et al. (93)	63.4% for the chemotherapy gp , 57.1% for the zolendronate gp	70% for the chemotherapy gp 30% for the zolendronate gp	
21	Qi.,et al(25)	13%	34%	Overall response rate was 13% and disease control rate was 34.5%, with 3 partial responses and 5 stable diseases
22	Rasper, et al. (23)	45% in patients treated	30%	
23	Senerchia., et al	61%	40%	

Discussion

Patients with high-grade, localized osteosarcoma who received adjuvant chemotherapy after undergoing definitive surgical resection had a statistically significant benefit in disease-free and overall survival that was maintained through 25 years. Tumor necrosis after just 1 cycle of neoadjuvant chemotherapy and radiation was predictive of overall survival and disease-free survival in patients who received adjuvant chemotherapy (3).

According to Boye et al., the administration of high-dose chemotherapy with stem cell rescue was feasible, but associated with significant toxicity. Patient outcome seemed comparable to previous studies using conventional chemotherapy. They concluded that HDCT with carboplatin and etoposide should not be further explored as a treatment strategy in high-risk osteosarcoma [16].

Despite intensive chemotherapy plus trastuzumab for patients with HER2-positive disease In a study done by Ebb et al., the outcome for all patients was poor, with no significant difference between the HER2-positive and HER2-negative groups. Although their findings suggested that trastuzumab can be safely delivered in combination with anthracycline-based chemotherapy and dexrazoxane, its therapeutic benefit remains uncertain. [9].

In patients over 40 years of age with primary high-grade osteosarcoma, Ferrari et al., reported that an aggressive approach with chemotherapy and surgery can offer the probability of survival similar to that achieved in younger patients. Chemotherapy-related toxicity is significant and generally higher than that reported in younger cohorts of osteosarcoma patients treated with more intensive regimens [15].

Iwamoto and colleagues analyzed the results of the intensive neoadjuvant chemotherapy andtheeffectsofaddingIFOonpatientswithosteosarcomainJapan.Theresultssuggested efficacy of the high-dose IFO addition to the standard three-drug chemotherapy regimen. [11].

An Italian sarcoma group trial reported that neoadjuvant chemotherapy with methotrexate, cisplatin, and doxorubicin with or without ifosfamide is effective in non-metastatic osteosarcoma of the extremity.

IFO added to MTX, CDP, and ADM from the preoperative phase does not improve the good responder rate and increases hematologic toxicity. They mentioned that IFO should only be considered in patients who have a poor histological response to MTX, CDP, and ADM [12].

According to Snerchia study,et al., EFS with MAP plus MC is not statistically superior to EFS with MAP alone in patients with high-grade, resectable OSTs of the extremities [11]

Gaspar et al., results on Ewing sarcomas showed a potential benefit of a consolidation strategy including busulfan/melphalan as compared to conventional chemotherapy and they needed confirmation by a randomized trial. [14]

This was done by Choy et al., which was the first reporter of a prospective phase II trial to evaluate the safety and efficacy of a PARP inhibitor in patients with advanced ES after failure of standard chemotherapy .Olaparib administration was safe and well tolerated when administered to this small heavily pre-treated cohort at the 400 mg BID dose, although the median duration of dosing was for only 5.7 weeks. No significant responses or durable disease control was seen, and the short average interval to disease progression underscores the aggressiveness of this disease. Other studies to combine cytotoxic chemotherapy with PARP inhibition in EWS are actively ongoing [15].

According to Hank,et al.,a CTX-HCPT regimen can control disease progression effectively and the side effects can be tolerable for Chinese advanced Ewing's sarcoma patients. But they recommended further assessment to confirm the safety and efficacy of this treatment [15)

For localized Ewing sarcoma, Womer and colleages reported that chemotherapy administered every 2 weeks is more effective than chemotherapy administered every 3 weeks, with no increase in toxicity [14].

In another study, high-dose therapy added to the VACA-IE regimen in PR patients is feasible and effective. Selected groups of patients with ES can benefit from HDT [19].

ECT (Electrochemotherapy) should be considered a new feasible tool in the treatment of bone metastases in place or in combination with standard treatments; further developments are required to extend the use of this technique to spine metastases[16].

Summary and conclusion.

For newly diagnosed OS in <40 ys pts, neoadjuvant H.D.IFO+ADM+CDDP +surgery + adjuvant chemo (H.D.M.T) , is associated with very good results (the 5 year event free survival rate is 83%,the 5 year overall survival rate is 98%)

In high grade osteosarcoma adding IFO to MTX, CDP, and ADM from the preoperative phase does not improve the good responder rate and increases hematologic toxicity. IFO should only be considered in patients who have a poor histologic response to MTX, CDP, and ADM

Patients with high-grade, localized osteosarcoma who received adjuvant chemotherapy after undergoing definitive surgical resection had a statistically significant benefit in disease-free and overall survival that was maintained through 25 years. Tumor necrosis after just 1 cycle of neoadjuvant chemotherapy and radiation was predictive of overall survival and disease-free survival in patients who received adjuvant chemotherapy.

In patients over 40 years of age with primary high-grade osteosarcoma, an aggressive approach with chemotherapy and surgery can offer the probability of survival similar to that achieved in younger patients. Chemotherapy-related toxicity is significant and generally higher than that reported in younger cohorts of osteosarcoma patients treated with more intensive regimens.

For Ewing sarcoma the use of neoadjuvant VACAc/IE regimen was associated with good results (70% event free survival rate,75% overall survival rate)

Also Ewings sarcomas showed a potential benefit of a consolidation strategy including busulfan/melphalan as compared to conventional chemotherapy and associated with good outcome

For bone metastasis ECT may represent an active and safe treatment to achieve local control in advanced STS patients with symptomatic disease. Future research challenges include the improvement of electrode placement and voltage delivery together with the containment of soft tissue toxicity.

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