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Bone tumors

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Introduction

Malignant bone tumors have a low incidence and account for less than 0.5% of all tumors. They predominate in children and young people and affect equally in both sexes. Osteosarcoma and Ewing's Sarcoma are included within these lesions

Osteosarcoma

Osteosarcoma is a type of bone cancer that originates in osteoblastic cells, being one of the most frequent bone tumors in its presentation. In the United States, about 900 new cases of osteosarcorms are reported each year. It affects almost twice as many men as women and accounts for 5% of childhood cancers. It is twice as common as chondrosarcoma and three times as Ewing's sarcoma. It preferentially affects children, adolescents and young adults. It can appear at any age, but predominates between 10 and 30 years, with an average of higher incidence at 18 years. Osteosarcoma manifests itself preferentially in the metaphysis of the long bones surrounding the knee. It also usually appears less frequently, in the bones of the upper leg, in those of the thigh, in the lower leg, in the upper arm. Cases have been reported in other bones of the body outside of those mentioned, such as those of the pelvis, shoulder, and skull. It can originate inside the affected bone (classical osteosarcoma) or on the bone surface related to the periosteum or neighboring paraosseous connective tissue (parostal or juxtacortical osteosarcoma)

Etiology

The origin of osteosarcoma is not known, but it is believed that it could originate from DNA mutations, whether inherited or acquired at birth. Other theories and associations have been suggested as risk factors. With regard to a viral origin of the disease, the finding of antiviral antibodies in the serum of patients with osteosarcoma can be mentioned. To date, it has not been possible to isolate a possible viral vector in man, despite viral particles being found in hamsters and mice, after the virus had been passed through the serum from one animal to another in studies conducted by Finkel et al.

Regarding the genetic predisposition of the disease, there is no demonstrated familial tendency, except for the high incidence of osteosarcoma in patients with familial retinoblastoma. There are few published studies showing the presence of osteosarcoma in siblings of the same family

Histology

They are malignant tumors whose particularity is that the neoplastic cell directly generates osteoid substance. It is usually observed involvement of the entire metaphysis, extension to the diaphysis through the medullary canal, permeation of bone tissue, periosteum and invasion of soft parts, usually giving rise to a large tumor mass that can compromise even the skin. Invasion of metaphyseal cartilage is very rare.

Microscopically they show a proliferation of very anaplastic and spindle cells, which generate a variable amount of osteoid substance with different degrees of calcification. There are often atypical cartilaginous and fibroblastic cells. Neoplastic cells can be very pleomorphic. There are different varieties of osteosarcomas in addition to the classic one (See Table 1).

Table 1. Types of osteosarcomas

1. Osteoblastic or classical
2. Telangiectasis
3. Small cell
4. Well differentiated
5. Chondroblast
6. Fibroblastic
7. Periosteal

The telangiectasis has very prominent vessels and blood spaces, little calcified and very aggressive behavior. It usually affects children and young people, making a rapid metastatic spread.

The small cell is of rare presentation and very aggressive evolution. Microscopically it has few areas of osteoid and chondroid formation. It can be confused with an inflammatory picture due to its rapid evolution and involvement of neighboring soft tissues. It simulates an Ewing sarcoma and is sometimes classified as "Atypical Ewing Sarcoma". The well differentiated is formed by cells of scarce atypias and little aggressive evolution.

Chondroblast is characterized because in addition to the formation of osteoid substance, it presents cartilaginous tissue in its structure.

Fibroblastic has a large component of fibrous tissue added and requires a differential diagnosis with fibrosarcoma.

Periosteal is a rare variety (4% of all osteosarcomas), originating in the cortical of the bone and usually located in the distal third of the femur and tibia. It envelops the bone and after some time invades the cortex and marrow. It is very well differentiated, so it has sometimes been mistaken for an old myositis ossifican or a matured osteochondroma. It predominates slightly in women. Histologically it is a variety composed of malignant cartilaginous cells, elongated and with osteoid production. It has a much more benign evolution than the other variants. At 5 years, 75 to 85% of patients survive. Radiologically it looks like a radiolucent lesion with some evidence of bony spicules. The crust is unscathed and codman's triangle is not visible. It is of relatively good prognosis, if there is no involvement of the medullary canal. The small cell variety.

Risk factors

Possible risk factors for osteosarcoma include the following parameters:

a) Increased bone growth. In adolescence there is a period of increased bone growth at the level of the bones and that can favor the stimulation of osteoblasts.
b) Previous radiant treatments of another cancer, especially with high doses of radiation in young patients. A bone tumor can originate in the irradiated areas, with the risk period being between 5 and 20 years after such treatment. Amendola reviewed the evolution of 22,306 patients treated with radiation between 1934 and 1983 and found 23 patients with sarcomas (5 were osteosarcomas), with a latency period of 13 years.
c) Genetic factors. -The existence of certain rare inherited cancers, such as Li-Fraumeni syndrome, which is a rare familial predisposition to cause several types of cancers (soft tissue sarcoma, breast cancer, brain tumors, osteosarcoma, leukemia, melanoma, cancer of the adrenal cortex and others) caused by mutation in one gene, the tumor suppressor gene p53, which usually reduces the chance of getting cancer, especially retinoblastoma.

-The over-expression of the receptor for Cell Growth Factor and proto-oncogenes are amplified in the development of osteosarcoma.

-Her-2 (receptor 2 for epidermal human growth factor), which is a glycoprotein product of the proto-oncogene Erb-2, and structurally homologous to EGFR (epidermal growth factor receptor). Recent studies have reported that 42% to 45% of osteosarcoma over-express Her2 and this over-expression is correlated with worse survival and poor response to neoadjuvant chemotherapy. This aroused interest in investigating

the use of anti-Her2 monoclonal antibodies in the initial neoadjuvant treatment of patients with a poor prognosis. However, Wittig conducted a study with 32 patients with high-grade osteosarcomas in which Her2 and EGFR were measured, but over-expression did not have the expected prognostic correlation. Tsai studied the same parameters in 20 patients and her conclusion was that her2 overexpression may be associated with a higher percentage of relapse, while patients who do not over-express Her-2 or p53 have longer survivals (better prognosis). Uzel evaluated the value of Her-2/ErbB-2, P53 and P-glycoprotein in 47 patients with high-grade osteosarcoma. Fifteen (34.9%) of 43 showed high levels of p53. There was no correlation between p53 value and disease-free survival or response to chemotherapy. Of 45 patients, 23 (51.1%) had over-expression of P-glycoprotein. There was also no correlation between P-glycoprotein levels and survival or response to treatment. Disease-free survival in patients with a good prognosis (no over-expression to ErbB-2 and with a necrosis percentage greater than 90%), was significantly better than in those with a poor prognosis (p= 0.003). In patients with high-grade osteosarcoma, over-expression of ErbB-2 in tumor cells is associated with disease and can therefore be used as a prognostic factor regardless of response to chemotherapy. Biological response-modifying drugs such as Anti-Her-2 antibodies, Anti-Her-2 peptidomimetics, tyrosine kinase inhibitors, thyrofostines, cyclin-dependent kinase inhibitors, kinase activating mitogen gene inhibitors, and PI-3 kinase inhibitors may be used in conjunction with chemotherapy.

Clinic

Pain is the most frequent initial symptom in osteosarcoma and with the evolution of the lesion tumefaction of the adjacent soft parts is added. Usually the patient begins with pain or swelling in the knee area because it is the usual place of presentation. Then increased pain is added when performing physical activity and efforts, difficulty in walking and reduced movement of the affected limb. Sometimes it can occur through a pathological fracture of the diseased bone (in the lytic or telangiectatic varieties) that may or may not be associated with trauma.

Less commonly the disease can manifest with symptoms caused by the presence of metastases. If pulmonary spread occurs, it causes dry, irritating cough, and then dyspnea is added. If the metastases are bony, bone pain appears in different parts of the body. During the evolution of the disease, 90% of patients metastasizes, therefore the appearance of respiratory symptoms is common in these cases.

Diagnosis

In addition to performing the physical exam and complete medical history, procedures to diagnose osteosarcoma may include the following studies:

Laboratory: In patients with osteosarcomas, an elevation of alkaline phosphatase levels is usually found. It should be remembered that the normal values of phosphatase in children, during the period of growth are between 2.5 to 3 times higher than the value of the adult. The rest of the parameters show no differences with normal patients. In patients with advanced disease, anemia or alteration of liver enzymes is usually found.

Radiology: It is the first diagnostic method used to discover the lesion. Typical radiological manifestations include an increase in bone intramedullary radiodensity, alternating with radiolucent areas, destruction of bone and poorly defined edges, destruction of the cortical, elevation of the periosteum, and injury to soft tissues neighboring bone. The lesions described give rise to a radiological image known as the "Codman's Triangle". (Photo 1)

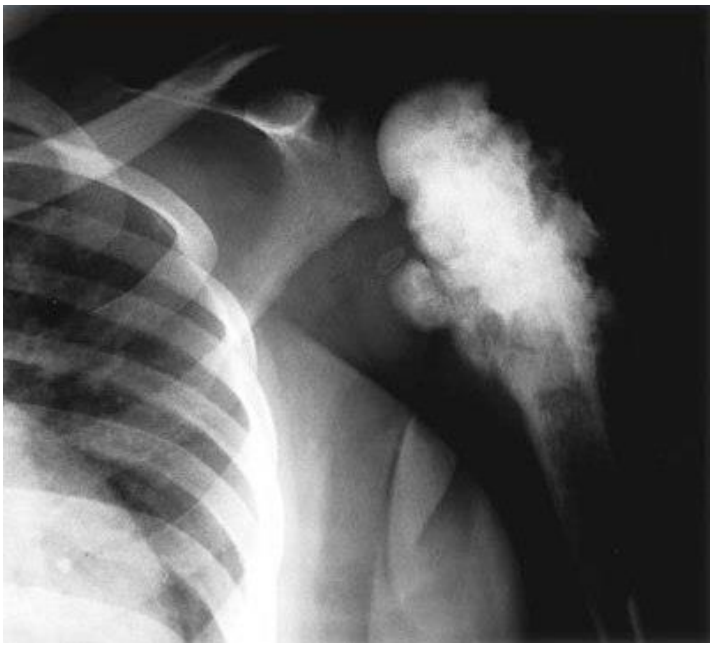

Photo 1"Codman's Triangle" in left humerus epiphysis (courtesy of Dr. Hunis)

According to the predominance of the bone lesion can be classified into:

a) Sclerotic osteosarcoma: 32% of lesions. There is a predominance of bone sclerosis.
b) Osteolytic osteosarcoma: 32%. Predominance of osteolysis
c) Mixed osteosarcoma: 46%, with a mixed pattern of sclerosis and osteolysis

These differences in the presentation of the lesions have no impact on the prognosis or evolution of each of the variants. Sclerotic and mixed forms are characteristic of osteosarcoma, with lytic forms sometimes being confused with other lesions. Differential diagnosis should be made with giant cell tumor, fibrosarcoma's, and malignant fibro histiocytomas.

Computed tomography: Allows to obtain images of cross-sections of the body, both horizontal and vertical. A CT scan shows detailed images of bones, muscles, fat, and organs. You can see in detail the bone lesion and the involvement of neighboring soft tissues.

Magnetic resonance imaging: It is the diagnostic procedure that complements the images obtained by the tomography and that allows to give greater precision to the affectation of the structures neighboring the lesion, as well as a greater detail of the bone damage. It is very useful for planning surgery as it allows to evaluate vascular and nervous commitments. (Photo 2)

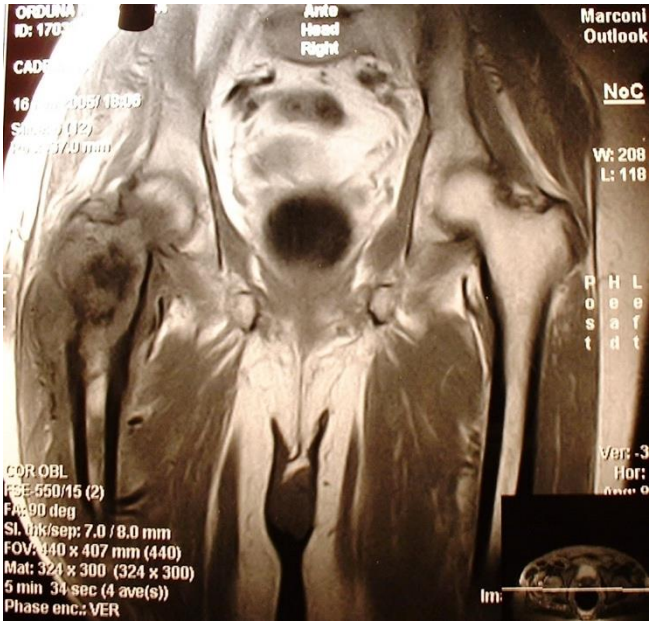

Photo 2 MRI injury to the right femur (courtesy of Dr. Hunis)

Bone scintigraphy: It is requested to evaluate the focus of the primary lesion and rule out associated bone lesions (metastases).

Biopsy of the tumor: It is performed by puncture or with an incisional shot of the affected bone. It is the necessary procedure to reach the diagnosis of certainty of the injury. It should be performed on suspicion of bone tumor.

Prognosis

Classically, 80% of patients with osteosarcoma died at 5 years. A bielack publication on 576 patients relapsed to the first line of treatment showed that 149 patients remained alive, and of those, 82 achieved a second complete remission of the disease with the therapy applied. The overall actuarial survival at 2, 5, 10 and 15 years was 38%, 23%, 18% and 15% respectively. Overall survival at 5 and 10 years was 34% and 25% for patients whose recurrences occurred after 18 months of initial diagnosis, while it was 11% and 9% for those who relapsed before 18 months ($p<.0001$). For patients with single metastases, survival at 5 and 10 years was 38% and 32% and for patients with multiple lesions 15% and 9% respectively ($p<.0001$).

The appearance of lung metastases is the usual cause of death in patients with osteosarcoma and usually occur within the first 2 years of its evolution.

Marcove reported in a study of 145 patients, that there were no prognostic differences between the patient's age, degree of differentiation, tumor size, or duration of symptoms. Pallotta et al. in a study of 40 patients found differences according to the volume of the lesion at the time of diagnosis. The mean survival was 48 months in tumors larger than 1500 cm3. (95% CI: 27-70) and 104 months in children under 1500 cm3. ($p=0.001$).

The location may have some prognostic implication since pelvic or spine tumors have lower survival than those of the extremities, probably due to the greater radical surgical possibility in limb lesions. According to Larsson, bone can have prognostic importance. Thus, tibial lesions have better evolution than those of the distal femur. Bostrom evaluated in 52 patients treated with surgery, the prognostic value according to size and location. Patients with distal lesions and less than 10 cm presented better evolution ($p < 0.01$) than patients with proximal lesions and greater than 10 cm. (43% vs. 12%). For Hudson20 in a study of

98 patients, the most important prognostic factor was the percentage of necrosis caused by chemotherapy ($p < 0.01$).

Serum alkaline phosphatase values may have prognostic significance. Francis showed in 155 patients that with normal alkaline phosphatase values, they had a survival of 85% at two years, while it fell to 12% in patients with elevated preoperative values. Stranton published similar results in 38 patients. (54% of survival at two years in patients with normal values and 18.7% in those with elevated values).

Look assessed the prognostic importance of DNA studies with flow cytometry in relation to the disease-free period and survival. Patterns of higher aneuploidy were associated with worse prognosis ($p < 0.003$). The tumor has genetically determined response to chemotherapy. Kreuter studied the relevance of angiogenesis in osteosarcoma. The increase in angiogenesis is a factor of good prognosis of response to chemotherapy and survival. It may be another useful prognostic factor before starting treatment.

It could be said that the prognosis of osteosarcoma depends on several factors, which are summarized in Table 2.

Feature	**Favorable prognosis**	**Unfavorable prognosis**
Age	Under 17 years old	Over 17 years old
Histological type	Differentiated parostal	Anaplastic, telangiectatic, small cell
Aneuploidía	Casualty	Loud
Angiogenesis	Scanty	Loud
Size	Less than 1500 cm^3.	Greater than 1500 cm^3.
Localization	Distal	Proximal
Affected bone	Jaw	Pelvis, vertebrae
Interval between initial symptom and treatment	Short	Long
Preoperative Alka periostealphosphatase	Normal	High
Presence of metastases in the diagnosis	No	Yes
Response to chemotherapy	Greater than 90%	Less than 90%

Table 2. Prognostic factors in osteosarcoma

Treatment

Before performing any therapeutic procedure in a patient with osteosarcoma, a correct staging must be carried out and metastasis must be ruled out, which disables any radical surgical treatment.

If the patient has localized disease, initial treatment may be surgical. Sometimes preoperative chemotherapy is used to reduce the volume of the lesion and have a prognostic idea.

1). Surgery: it must be radical in limb injuries, requiring in most cases, amputation. In these cases, the placement of prostheses, reconstruction or arthrodesis of the affected area must be planned in advance and carried out. (Photo 3)

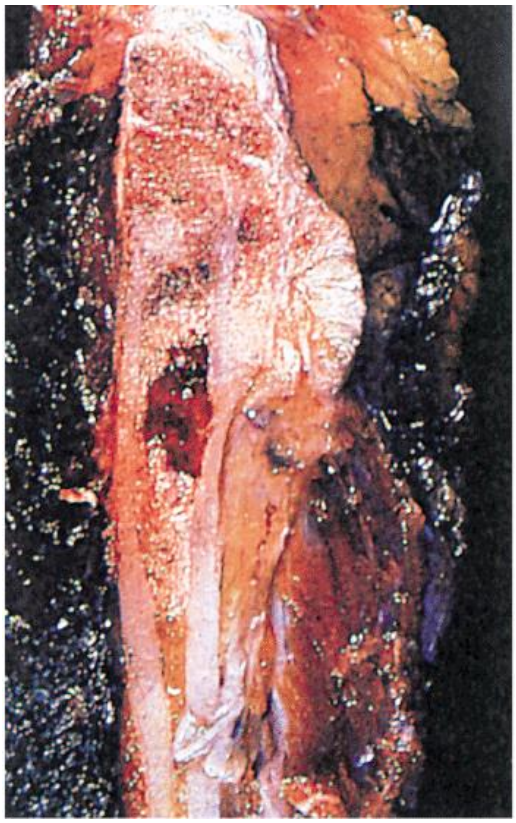

Photo 3 surgical specimen of an osteosarcoma

When the lesions are of the pelvis or the proximal third of the femur, a hemipelvectomy is required. In selected patients, minor resections can be made trying to reduce morbidity and sequelae, without substantially modifying the risk of recurrence. The effects of preoperative chemotherapy may facilitate smaller surgeries. The surgical team must have experience in the multidisciplinary treatment of osteosarcoma, to adapt the surgical procedure to the rest of the treatments.

In periosteal osteosarcomas of less aggressive and localized evolution, the treatment of choice is the wide excision of the lesion. Post-surgical chemotherapy is not used.

Local recurrences are of poor prognosis and very difficult surgical treatment. They can appear in pelvic or vertebral tumors in which the initial treatment did not have an adequate margin. A radical resection of the relapsed area should be done, but lung and bone metastases should have been ruled out beforehand.

Treatment of metastases is feasible in patients with peripheral lung lesions and are surgically accessible. They must have undergone previous chemotherapy treatment and remain stable. Surgery plays a "rescue" role, as it is rarely curative. It should be supplemented with subsequent systemic treatment. Molinas-Mandel presented a study with the performance of pulmonary metastasectomy in 18 patients with a mean control time of 39.1 months (95% CI 31.2-50.2). After surgery, the mean survival was 13.4 months (95% CI 7.2-19.7). The survival of patients with single lesions or lesions confined to one lung was better than patients with multiple metastases.

2) Radiotherapy: A dose of 7000 to 8000 cGys is used in 7 to 9 weeks and can be done preoperatively. If subsequent surgery is not performed, the 5-year survival is 22%.

Beck et al. observed an advantage in the survival of patients with preoperative radiation therapy over those who did not.

Osteosarcomas of the maxilla or jaw have a different biology from the rest since their evolution is much less aggressive and has a low risk of metastasis. Surgical treatment (hemi mandibulectomy with resection of neighboring soft tissues) combined with irradiation of the area is performed.

Radiation therapy may play a palliative role in the treatment of osteosarcoma. Inoperable lesions or painful bone metastases can be treated.

The EORTC conducted studies that included prophylactic radiant treatment of both lung fields with a dose of 1750 cGys in 10 fractions. At 4 years, 24% of patients were disease-free and with an overall survival

of 43%. These results were no different from patients who did not receive prophylactic pulmonary irradiation, therefore this therapeutic modality is not considered useful.

3) Chemotherapy: it can be performed adjuvant to surgery, in a preoperatory or palliative way.

Treatment with chemotherapy drugs in osteosarcoma began in the late 60s, in patients with advanced disease. The most commonly used drugs were alkylating agents with a 20% short-term response. Cyclophosphamide, Melphalan, Actinomycin D, Vincristine, and Mitomycin C were used. At the beginning of the 70s, studies with Adriamycin began, achieving 35% of responses in metastatic disease, while the first works with Methotrexate in high doses (5 to 10g / m^2) emerged, managing to match, and in some cases improve, the results of Adriamycin. Subsequently, work was included with Cisplatin proving to be another useful drug in advanced disease.

In relation to adjuvant chemotherapy, the first studies were conducted in the 1980s by two groups the Multi-Institutional Osteosarcoma Study (MIOP) and UCLA (University of Los Angeles) in randomized studies, demonstrating some advantages in patients who received chemotherapy. The theoretical foundations of its use are based on the high possibility of subclinical metastases at the time of diagnosis, which explains the appearance of metastases within the first 24 months of its evolution. Osteosarcoma has been shown to be a tumor quite resistant to chemotherapy drugs. The drugs that reported the best percentage of responses were Adriamycin, High-dose Methotrexate, Cisplatin and Ifosfamide (see Tables 3 and 4).

Drug	Patients	Answers	% RP+RC
Cyclophosphamide	28	4	15%
Melfalán	32	5	15%
Mitomicina C	23	3	13%
Vincristine/Vinblastine	21	0	0%
Hydroxyurea	10	0	0%
Procarbazina	10	0	0%
DTIC	14	2	14%
Adriamycin	109	28	26%
Fluorouracilo	11	0	0%
Actinomicina D	26	4	15%
Methotrexate	14	0	0%
Methotrexate in high doses every 21 days	26	11	42%
Methotrexate in high weekly doses	11	9	82%
Ifosfamida	18	6	33%
Cisplatin	24	8	33%

Table 3. Osteosarcoma Responses to Chemotherapy (Adapted from Bode)

Scheme	Author	Patients	% Free of Enf.	Ref.
MtxAD+Vcr	DFCI	12	42%	31-32
MtxAD+Vcr+BCG	NCI	39	38%	33
Adriatic Sea	CALGB	88	39%	34-35
Adria+MtxAD	CALGB	62	50%	36
Adria+Vcr+MtxAD	DFCI	22	59%	31
Adria+Vcr+MtxAD sem	DFCI	46	60%	31-37
Adria+Vcr+MtxAD	CCSG	166	38%	38-39
Cfm+Adria+Vcr+Pam	SWOG	43	49%	39-40
Cfm+Adria+Vcr+Pam+MtxAD	SWOG	53	35%	39-40
Cfm+Adria+Vcr+Pam+MtxAD	SWOG	84	38%	39
Adria+MtxAD+Cfm	St Jude	26	50%	41
Adria+MtxAD+Cfm	St Jude	50	56%	41
Adria+DDP	Roswell Park	22	61%	42-43
MtxAd+Vcr vs. Control	Mayo Clinic	38	40% 44%	44
Ble+MtxAd+Adria+DDP vs. Control	MINE	36 random. 165 no rand.	63% 12%	45-46
Ble+MtxAd+Vcr+Adria vs. Control	UCLA	59	55% 20%	47
Pulmonary Irradiation vs. Control	EORTC	86	43% 28%	48-49
Irradiación Pulmonary+Act vs. Control	Mayo Clinic	53	40%	50
MtxAd+Adria+Vcr+Cfm	MSKCC	52	48%	51-52-53
MtxAD+Adria+Ifo+DDP	Rizzoli. Italy	68	73% (3 years)	54

Table 4. Results of adjuvant schemes of polychemotherapy

References: MtxAD: Methotrexate in high doses, Adria: Adriamycin, Vcr: Vincristine, Cfm: Cyclophosphamide, Pam: Nitrogen mustard, DDP: Cisplatin, Ble: Bleomycin, Act: Actinomycin D, Ifo: Ifosfamide

DFCI: Dana Farber Cancer Institute, NCI: National Cancer Institute, CALGB: Cancer and Acute Leukemia Group B, CCSG: Children´s Cancer Study Group, SWOG: Southwest Oncology Group, MIOS: Multiinstitutional Osteosarcoma Study, UCLA: Universidad de Los Angeles, California, EORTC: European Organization for Research on Treatment Cancer, MSKCC: Memorial Sloan-Kettering Cancer Center.

Approximately 60 to 70% of patients with osteosarcoma treated with intensive adjuvant chemotherapy regimens remain alive and free of recurrence. Most current schemes include Adriamycin, Cisplatin and Methotrexate in high doses. While the effectiveness of methotrexate in high doses has been discussed for a long time, the responses range by 80%. A randomized study conducted by the Children's Cancer Group (CCG), compared Methotrexate in high doses, with intermediate doses, combined with Adriamycin, without showing differences in both groups. But another study conducted at the Rizzoli Orthopedic Institute published greater responses to the high-dose schedule than to the intermediate-dose regimen. A study carried out by the European Osteosarcoma Intergroup compared the combination of Adriamycin and Cisplatin or alternating this combination with Methotrexate in high doses in the pre and postoperative period. Disease-free survival for those who received the two-drug scheme was higher than those who added methotrexate. It should be clarified that in this study, the methotrexate scheme was not with high doses.

The effectiveness of Methotrexate depends on the dose of drug used, since increasing it can obtain responses in patients previously resistant to this scheme in lower doses.

Carboplatin has been used in replacement of Cisplatin trying to decrease renal and otological toxicity. However, this analogue demonstrated a lower percentage of responses than Cisplatin and is only used in the case of not being able to use the latter.

The use of a high-dose schedule with shorter, but intensive schedules was evaluated. The European Osteosarcoma Intergroup compared six cycles of Adriamycin and Cisplatin with the T-10 regimen at Memorial Sloan-Kettering Cancer Center (Fig. 1).

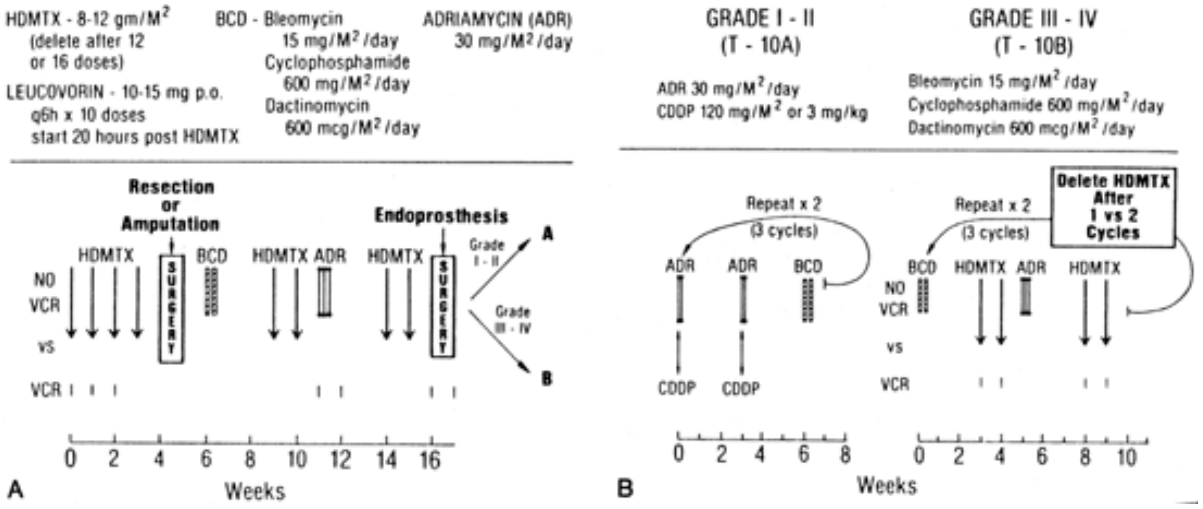

Fig.1 T-10 regimen

There was no difference in disease-free survival (47% at 3 years and 44% at 5 years) or overall survival (65% at 3 years and 55% at 5 years).

Ifosfamide has been incorporated as a useful new drug in osteosarcoma in studies conducted by the American Pediatric Cooperative Oncology Group.

The treatment was becoming more and more intense to try to increase the percentage of patients free of disease, being the most effective schemes, those that include Adriamycin and Methotrexate in high doses. The optimal regimen of adjuvant chemotherapy still remains under discussion.

Preoperative chemotherapy: The basis of the use of preoperative chemotherapy is to be able to histologically evaluate the response with the surgical piece. Itis a modality that has increased its use gradually, trying to optimize the treatment. It began in 1973 at the MSKCC with a group of patients who had to wait three weeks for the manufacture of stents, who while waiting for the prostheses to be made, were given chemotherapy. Those treated with this modality presented better evolution than those who did not receive preoperative chemotherapy.

With surgery, the degree of response to chemotherapy can be evaluated when performing the histological study. Responders have a better prognosis. Those who demonstrated good response to the initial chemotherapy treatment after surgery continued with the same scheme in an adjuvant form. Those who did not show significant responses had to change the adjuvant scheme.

The favorable prognosis of responders was confirmed by a study conducted by the German Society for a Pediatric Oncology, the Rizzoli Institute, the Children's Study Group and the MSKCC

The response to preoperative chemotherapy can be histologically evaluated according to the following parameters (See Table 5)

Effect Grade	
I	Small or no histological changes
II	Areas with osteoid, acellular, necrotic tumor or with fibrous material attributable to the effect of chemotherapy, but with areas of viable tumor.
III	Areas of acellular osteoid tumor, necrosis, or fibrous tissue a ttributable to the effect of chemotherapy predominate. There are only small foci with viable tumor.
IV	There is no histological evidence of viable tumor in all the tissue removed

Table 5 Effectiveness of chemotherapy according to the histological study of the operative piece. (Gradient of Huvos)

There are different criteria for assessing response to chemotherapy. The one used by the German Society of Pediatric Oncology (GPO) identifies six categories of responses. A study conducted by the Germany-Austria-Swiss Cooperative Osteosarcoma Study (COSS 80), defines the favorable response as the destruction of more than 50% of the tumor, but in subsequent studies, the same GPO evaluates it with more than 90% osteolysis.

The M. D. Anderson Cancer Center divides the response into three categories:

(1) No effect or less than 40% tumor destruction.

(2) Partial effect with tumor destruction between 40% to 60%.

(3) Good effectiveness with a destruction of tumor tissue greater than 60%, with the presence of fibrovascular regeneration.

What was done by the M. D. Anderson Cancer Center modifies the system proposed by Huvos with the "favorable" (Grade IV) or "unfavorable" (grade I, II and III) implication of response. Therefore, only grade IV patients who showed a good response to chemotherapy should be considered with a favorable prognosis.

Another issue not well clarified is the time that preoperative treatment should be performed. Longer schemes are associated with more favorable responses. But the intensity of the therapeutic scheme also influences.

In those patients whose response was favorable, after surgery the same scheme should be continued adjuvantly, while in non-responders it should be changed. The Memorial Sloan-Kettering Cancer Center proposed this therapeutic strategy using schemes such as T-10 that continued with the same scheme in the responders and changed it to Adriamycin and Cisplatin in the unresponsive patients. They reported that 39% had a favorable histological preoperative response (51% if those under 21 years of age were considered) and almost all of them remained disease-free. Non-responders were included in Cisplatin schemes, achieving that 85% remained disease-free at 3 years.

Regimen	Researchers	Pts	% Free illness	References
HDMTX+VCR+DOX+BCD (T-7 regimen)	MSKCC	54	74	51-53-66
HDMTX+VCR+DOX+ BCD+/ CDDP s/response (T-10 Schematic)	MSKCC	79	76	66-68-69
DOX+HDMTX+(BCD o CDDP) +/- Interferon (COSS 80)	GPO	116	68	70-71
HDMTX+DOX+CDDP	Mount Sinai	25	77	72
HDMTX+VCR+DOX+BCD+/ CDDP (based on response) (GCC-782)	CCG	231	56	73
HDMTX+DOX+CDDP+IFOS (COSS 82)	GPO	125	58	74
DOX+CDDP+/-HDMTX	EOIS	231	63	57-58
IA CDDP+(HDMTXvs. IDMTX) +DOX+/-BCD	Inst Ort Rizzoli	127	51 (general) 58 (HDMTX) 42 (IDMTX)	75
IA CDDP vs. HDMTX) +DOX	MD.Anderson	43	60	76
CDDP+HDMTX+HDIFOS+DOX	Inst Ort Rizzoli	68	75	77

CDDP+DOX+IFOS IA	G.Roussi	32	79	78
HDIFOS+DOX+CDDP	Japanese Group	26	79	79
HDIFOS+CDDP	FSG	63	54	80

Table 6 Summarizes the different preoperative schemes.

References:

BCD, bleomcin+Cyclophosphamide and Actinomycin D; CCG, Children's Cancer Group; CDDP, cisplatin; COSS, Germany-Austria-Swiss Cooperative Osteosarcoma Study; CTX, cyclophosphamide; DOX, Adriamycin; EOI, European Osteosarcoma Intergroup; EOIS, First European Osteosarcoma Intergroup Study; GPO, German Society for Pediatric Oncology; FSG: Frech sarcoma Group, HDMTX, methotrexate in high doses (12 g/m2 or more+ rescue with leucovorin; AI, intraarterial; IDMTX, intermediate-dose methotrexate (750 mg/m2)+ rescue with leucovorin; IFOS, ifosfamide; MSKCC, Memorial Sloan-Kettering Cancer Center; POG, Pediatric Oncology Group; TIOS, Treatment and Investigation Osteosarcoma Study; VCR, vincristine.

Responses to preoperative chemotherapy have shown percentages ranging from 30 to 85%. The importance of this treatment has been the identification of the prognostic groups and the adequacy of the treatment after surgery according to the effectiveness of the scheme used.

The T-10 scheme did not show favorable results in the first studies (only 28% showed good response), but the responder patients remained alive at 5 years by 87%. Non-responders had not benefited from rescue schemes, as only 49% were alive at age 5.

The studies of the Rizzoli Institute showed that with the therapeutic strategy that allows the study of the operative piece, it has been possible to improve the results. In a study conducted between 1986 and 1990, patients were initially treated with a regimen of high-dose methotrexate, Adriamycin, and intraarterial cisplatin. 71% of the patients achieved a favorable response (more than 90% of necrosis), and were then treated with the same scheme for 21 weeks, while the non-responders, who were 29%, went to a scheme that added to the previous one, Ifosfamide and Etoposide. 71% of responders were disease-free at 5 years and the percentage was similar in those who did not respond. Another subsequent study comparing high doses of Methotrexate, Ifosfamide, Cisplatin and Adriamycin in 68 patients achieved 73% of patients free of disease and with 89% alive at 3 years.

The results published by Memorial Sloan-Kettering Cancer Center showed great promise with preoperative chemotherapy but changed with the increase in the follow-up period.

The histological evaluation of the response to chemotherapy served to mark the prognosis regarding disease-free survival and overall survival. In patients who did not respond with a poor prognosis, the therapeutic scheme was changed, but they had little disease-free survival and general survival. The overall results showed no significant differences with those who used chemotherapy postoperatively. The Pediatric Oncology Group reported the preliminary results of a randomized study with preoperative versus postoperative chemotherapy. Disease-free survival was similar with pre- or postoperative use of chemotherapy. Therefore, the real value of the preoperative use of chemotherapy in the treatment of osteosarcoma remains under discussion, since it could only be useful to determine the prognosis in responders. Non-responders require a change in the therapeutic regimen without one having been found to date that has a favorable impact on survival.

The use of new or more intensive regimens could improve outcomes. We have sought to find a marker of poor prognosis by analyzing the DNA content of the tumor, the level of Glycoprotein P (MDR gene) and other proteins related to resistance (mutant P53 level), loss of heterogocity of the retinoblastoma gene but without conclusive results. Determination of high levels of ErbB-2 has been associated with poor histological response to chemotherapy and poor prognosis with shorter disease-free period. If these results are confirmed with the use of anti-Her-2 monoclonal antibodies, the results in this group of patients could be modified.

In patients resistant to first-line schemes, different drugs have been used, but with modest results. Picci et al. used high doses of Ifosfamide (15g/m2) in continuous infusion of 5 days and surgery of resectable lung nodules. Of 61 patients treated, 25 (41%) remained alive and without evidence of disease, with an average of 46 months since the last surgery (range between 8-86 months). 38% of the 37 patients treated with Ifosfamide were alive.

Cardoso et al. treated 27 patients with osteosarcoma previously treated with Adriamycin and Cisplatin, with an Ifosfamide regimen (12g/m2, in 4 days). Of those, 81% had localized disease. The overall response was 52% with a mean survival of 10.3 months and a survival per year of 32.5%84

Continuous follow-up is essential for a person who is diagnosed with osteogenic sarcoma, especially in the first 24 months of its evolution. Side effects of radiation therapy and chemotherapy, as well as the development of new cancers, may occur in survivors of osteogenic sarcomas.

Ewing's sarcoma

Ewing's sarcoma was first reported in 1921 by James Ewing. It comprises 6% of all malignant bone tumors in Dahlin's statistics in 1978 and up to 9.1% in Schajowicz's in 1982. It is a tumor of neuroectodermal origin, which originates in bone tissue and more rarely in soft parts. It is the second most common malignant tumor in childhood and predominates in males. It usually appears most often in children between 5 and 20 years of age. In the pre-adolescence stage, it affects boys and girls in equal proportion. However, after adolescence, the number of males affected is somewhat higher than that of females. It preferentially affects the diaphyseal and metaphyseal regions of the long bones (femur -in 20-25% of all lesions-, tibia, humerus), and some short bones (iliac, scapula) and being less frequent locations in vertebrae, ribs, clavicle, foot bones, jaw, and skull.

Etiology

Most Ewing sarcomas appear because of a chromosomal rearrangement between chromosomes 11 and 22. This rearrangement changes the positions and functions of genes and results in a gene fusion called "fusion transcription." More than 90 percent of people have abnormal fusion transcription that affects genes known as EWS and FLI1. This important discovery has improved the diagnostic process of Ewing's sarcoma.

As with osteogenic sarcoma, at the time of diagnosis it is usually detected by some trauma or injury linked to the site of the sarcoma. However, it is believed that this trauma has no causal relationship with the disease and only highlights the condition.

Pathology

Ewing's sarcoma is made up of small, round cells. Its appearance is similar to those of a neuroblastoma, some rhabdomyosarcomas and some non-Hodgkin lymphomas. Macroscopically it is a white, soft, shiny, somewhat friable tumor, with frequent hemorrhages and necrotic foci. The characteristic that allows to differentiate them, is the presence of bands of fibrous tissue that form cellular compartments, there is monotonous proliferation of small cells arranged in solid shoots. Necrotic and hemorrhagic foci are frequent. Sometimes viable cells are arranged only around a vessel, giving a characteristic pseudo-thick appearance. The nuclei are oval, small, basophilic, irregular. The cytoplasm is scarce, poorly delimited

and may contain small cytoplasmic glycogen granules, being an important element in the differential diagnosis with other small round cell tumors. The nucleus has a finely dispersed chromatin. Unlike the other neuroectodermal tumors, In Ewing sarcoma homer-Wright pseudorosestes cannot be found and by immunohistochemistry they show negativity to synaptophysin, specific neuronal enolase and other neural markers.

Ewing's sarcoma, at the membrane level, expresses positivity to CD99 (MIC2 gene). In 95% of patients, a genetic translocation t(11;22) or t(21;22) is found. These modifications combine the N-terminal regions of the chromosome 22 gene in C-terminated regions, with similar alterations in the related genes of chromosome 11 (FLI1) or chromosome 21 (ERG). Both FL11 and ERG belong to the Ets family of oncogenic activator genes. Most of these translocations contribute to deregulating cell growth and transformation. While the mechanisms of FL11-mediated tumorogenesis remain unknown, one study implicated the cell transformation factor beta receptor (TGF-beta) type II as a tumor suppressor gene. TGF-BR2 levels are decreased when FLI1 is introduced into embryonic cells. Fl11's antisense oligonucleotides restore sensitivity to TGF-beta and block tumor genesis in cell lines containing the fused gene. Studies of FL11 have shown a variety of genetic alteration points within different genes. This contributes to the clinical and prognostic heterogeneity of Ewing's sarcoma. The most common manifestation of these chromosomal alterations is Type I, which consists of the union of the first seven exons with exons 6 to 9 of FL11. This occurs in 75% of cases. The Type II alteration (appears in 25% of patients) consists of the union of the first seven exons with exon 5 of FL11. Type II alterations are associated with poor prognosis.

The identification of genetic alterations is done by fluorescence in in situ hybridization of tissue samples. Its individualization can facilitate the differential diagnosis with other tumors of similar morphology to Ewing.

Chow presented a work dosing the receptor tyrosine kinase (RTKs), CD117 and the receptor-α derived from platelet growth factor (PDGF-Rα), in 7 patients with Ewing sarcoma.

Clinic

The classic manifestation is the appearance of localized pain on a bone, in a child or adolescent. The pain progresses intermittently but steadily. Sometimes it prevents you from sleeping. Depending on the location

of the tumor, it may be associated with tumor, redness or both around the tumor area, loss of muscle strength or root pain. The tumor is usually seen earlier when it is in limbs.

In its beginning it simulates the clinical presentation of osteomyelitis and in 28% of patients it can be associated with fever.

Symptoms caused by metastases occur in 25% of patients, due to the rapid growth of the tumor. The sites that are most frequently affected are the lungs and other bones. It is manifested by dyspnea, dry and irritative cough, respiratory failure, multiple bone pains or neurological injuries due to paraplegia due to injuries to vertebral bodies. In 3% of patients, the first manifestation of the disease is paraplegia.

Weight and appetite loss is one of the manifestations of affectation of the general condition as the tumor grows.

Diagnosis

The evaluation of the patient with suspected Ewing sarcoma includes radiographic study of the affected bone and laboratory studies in the search for alterations in the levels of alkaline phosphatase and LDH. Bone lesions that originate in the long bones affect the diaphysis with subsequent invasion of the metaphysis. A lytic or mixed lytic-sclerotic lesion occurs in the bone. The formation of periosteal bone neoformation occurs in sheets (onion skin), or less frequently in the presence of radiated bony spicules (sun rays). Pelvic lesions usually show a mixed lithic and blastic pattern.

With tomography and resonance, you can see the involvement of soft tissues, and in much more detail, the characteristics of bone injury and vascular or nerve lesions. Differential diagnosis should be made with other pelvic masses.

Once the diagnosis is confirmed by a bone biopsy, staging should be performed trying to look for metastases. CT scans of the chest and abdomen should be performed with contrast and a total bone scintigraph.

Ewing sarcoma can metastasize to the lungs, other bones, and bone marrow. The most frequent metastases are pulmonary and up to 10% appear in other bones. Bone marrow should be sought in patients with pretreatment medullary hypoplasia.

Prognostic factors

Historical prognostic factors include tumor size, location, and extent of the disease. Other added poor prognostic factors are: the presence of metastatic disease, tumors larger than 8cm., or a tumor volume greater than 100ml. Pelvic localization is also associated with poor prognosis, due to the low possibility of including surgery as a therapeutic modality, as well as rapid spread to neighboring pelvic tissues. From the serum point of view, elevations in LDH are related to poor prognosis. With the use of preoperative chemotherapy, the histological outcome to treatment is also a prognostic factor. Responders have a disease-free survival at 5 years between 84% and 95%.

Studies conducted in the United States and Austria, trying to identify other prognostic factors, found that chromosomal disorder at the EWS-FLI1 level in patients without metastasis, showed a disease-free survival at 5 years of 70% for the Type I alteration, while it was 20% of patients with Type II alterations. As most patients have Type I alterations, a large number of patients must be included in the studies to draw valid conclusions. Several North American groups coordinated by the Children's Oncology Group (POG/CCG), are currently conducting studies trying to establish the genetic determination of EWS-FLI1, to know if it can be included as a prognostic factor.

A poor prognostic factor is the extraosseous extension of the tumor.

Extraosseous presentation is rare. Less than a third of cases originate in soft tissues, while in primitive neuroectodermal tumors (NETs), the ratio of bones to soft tissues is similar. The most frequent sites of primary location are: extremities, paraspinal region, trunk, chest wall and skull. In an El Weshi study of 35 patients with a mean follow-up of 25 months, disease-free survival and overall 5-year survival were 43% and 48% respectively. The therapeutic results and prognosis were similar to those obtained in patients with bone localization. Complete resection of the initial injury was an important prognostic factor.

Treatment

Surgery:

Due to the rapid spread of the tumor and the marked radiosensitivity, radiant local treatment is preferable to surgery, although there are some studies in which the operated patients presented better survival. A study from the German Cooperative Ewing's Sarcoma Study showed advantages in the surgically treated group and the most important prognostic factor was tumor volumn. Patients who had a tumor volume less

than 100 ml. were 78% alive and disease-free at 3 years, compared with 17% survival of patients with larger tumors.

The long-term sequela of radiation is a factor to consider, especially in those patients who can have adequate local control of the disease with surgery. Both the possibility of resectability as well as the functionability of the area to be treated should be considered. For limb injuries surgery may be considered, while for pelvic injuries the use of radiation is preferred. In limb tumors, chemotherapy treatment can be started for 12 to 15 weeks and then surgery can be performed on the residual lesion. Preoperative chemotherapy not only reduces tumor volume, but also decreases vascularization and tumor friability, facilitating its resection.

A study conducted by the First Intergroup Ewing's Sarcoma Study (POG/CCG) in 35 patients with chest wall tumors showed decreased incidence of residual tumor in patients treated with preoperative surgery, compared to those initially treated with surgery. After surgery, in patients who have left microscopic or macroscopic residual lesion, radiation therapy should be added. With the use of preoperative chemotherapy, the need for radiant treatment is reduced in patients with thoracic tumors in which radiation can cause pulmonary or cardiac sequelae.

Local treatment of pelvic tumors can be done with both surgery and radiation therapy. A retrospective study by El Foudeh compared surgery versus radiotherapy in 60 patients treated between 1985 and 1997 in two centres and with a mean follow-up of 35 months. It showed that in 40 patients treated with radiotherapy and in 16 with surgery, all with the addition of chemotherapy, there was a 40% survival at 5 years without differences between those who received surgery and those treated with radiotherapy.

Radiotherapy

Adequate local control of the disease can be obtained with the use of radiotherapy, especially in lesions smaller than 8 cm. or 3 cm3 of tumor. Good response to radiant treatment is one of the characteristics mentioned by Ewing in 1921. But as a single treatment, without the association with chemotherapy it only achieves 9% survival. Most patients develop metastases and die from disease progression55. Therefore, systemic treatment should always be associated with chemotherapy.

Adequate local control with radiation therapy depends on the dose/volume ratio of the tumor irradiated. With the previous use of chemotherapy it is possible to reduce the tumor volume and thus have less volume

of lesion and greater possibility of response, with fewer radiant sequelae. Doses between 45 and 65 Gy are used. Chemotherapy may also be used adjuvant to radiation therapy. Chan et al. reported that only 2.8% of patients had recurrence with the use of 60 Gy followed by chemotherapy, while in those treated with surgery alone, they relapsed in 33.3%.

The Intergroup Ewing's Sarcoma Study (IESS) studied the relationship between the primary tumor site, radiation dose, tumor volume, and adjuvant chemotherapy, in relation to local disease control. Recurrences occurred in 22.6% of patients with primary tumors of the humerus, 15.3% in those originating in the pelvis, 10.3% of those of the tibia and 6.7% of those of the femur. There was no difference in local control as long as the radiation dose was adequate to the tumor volume.

The technical failures that cause insufficient treatment of the tumor volume in the irradiation, cause the highest percentage of local recurrence. Local recurrence also occurs in 21.4% of patients with margins of less than 5 cm of normal tissue, included in the volume to be irradiated, compared to 7.9% of patients with margins of 5 cm or more cm.

Autopsy studies by the National Cancer Institute confirmed the importance of identifying local recurrences. Telles et al. found in autopsy studies, persistence or recurrence of tumor in 13 of 20 patients. Tepper et al. reported clinical recurrence in 5 of 20 patients and autopsy showed histological persistence in another 6 out of 20 patients.

Because metastatic spread occurs primarily by the cells of the primary tumor, tumor persistence gives increased risk of spread.

Another topic of discussion is whether irradiation should include the entire medullary cavity of the affected bone. Suit summarized the experience of the 1950s and 1960s that recommended irradiation of the entire volume of the affected bone, without evidence of intramedullary recurrences. In the planning of the field to be irradiated, the involvement of the soft tissues neighboring the diseased bone must be taken into account. The margin must pass, at least, from 3 to 5 cm. through healthy tissue, with the inclusion of the entire medullary cavity of the affected bone.

An IESS-I study demonstrated an increase in local recurrences in patients who had not included the opposite epiphysis in the irradiation field. While local recurrence increased from 7% to 20% in patients with inadequate radiant fields, the differences were not statistically significant. Subsequent studies demonstrated similar percentages in patients who had not received irradiation of the opposite epiphysis.

A study by the German Cooperative Ewing Sarcoma Study showed that the higher percentage of local recurrence is due to failures in irradiation techniques. Marcus et al. reported excellent local control, using fields formed in tumors smaller than 8cm with 4cm margins of healthy tissue, around the affected bone.

Doses greater than 40 Gy have not been shown to have significant importance in the local control of the disease, but with doses of 60 Gy radiant sequelae are more frequently associated. The dose of 40 Gy appears to be adequate, if used in conjunction with chemotherapy. The standard dose for POG and CCG trial is 55.8 Gy for bulky tumors and 45 Gy for microscopic residual disease. The use of smaller fields not only decreases the risk of local sequelae to radiation, but also reduces the appearance of secondary sarcomas in the irradiated area, which is 5 to 10% in the 20 years following primary treatment. The use of doses greater than 60 Gy not only did not demonstrate greater effectiveness, but also markedly increased the risk of complications.

Chemotherapy

Ewing's sarcoma demonstrates a good response to the use of different chemotherapy drugs and has been the determining factor in the increase in the cure rate of the disease.

The first publications on chemotherapy treatment in Ewing sarcoma in 1973 by the IESS-I, evaluated the benefit of associating Adriamycin and pulmonary prophylactic radiotherapy, in patients with Ewing sarcoma, followed by a scheme with Adriamycin, Vincristine, Cyclophosphamide and Actinomycin D. Patients treated with the four-drug regimen had higher disease-free survival. Subsequently, the IESS-II study evaluated the use of cyclophosphamide in high doses (1400 mg/m2) and Adriamycin (75 mg/m2) every 6 weeks, compared to the classic scheme. The 5-year results were that 73% of patients treated with the high-dose regimen were disease-free, against 56% of those treated with the classic regimen (P = .03).

Another study by the POG and THE CCG compared the classic combination of Vincristine, Doxorubicin, Cyclophosphamide and Actinomycin D, with another that included Ifosfamide and Etoposide. Disease-free survival at 5 years was 52% for the classic regimen and 68% for the six-drug regimen (P = .0005). The addition of Ifosfamide has been shown to increase survival in other studies conducted at the National Cancer Institute and in several studies of European cooperative groups.

The usual scheme for chemotherapy treatment consists of a regimen of five drugs: Vincristine, Adriamycin and Cyclophosphamide, alternating with Ifosfamide and Etoposide, every 21 days for 48 weeks. The study

intergroup for Ewing sarcoma POG/CCG compared the aforementioned scheme with another of dose intensity, lasting 30 weeks, using the same drugs and with the same cumulative dose. The results were similar in both groups. New combinations are being studied trying to improve the results obtained with the classic scheme.

In metastatic patients, the addition of ifosfamide and etoposide did not show the same benefits as in adjuvant. The best results were obtained with the addition of radiation in the affected areas.

In patients with pulmonary/pleural metastases only, the cure rate is approximately 30%. Patients with bone or bone marrow metastases only have approximately a cure rate of 20% to 25%. Patients with a metastatic combination of lung and bone/bone marrow have a cure rate of less than 15%.

Some studies performed high-dose chemotherapy schedules, associated with irradiation of all affected bones. Disease-free survival was achieved for 39% of patients.

The use of high doses, total body irradiation and anthological bone marrow transplantation (TAMO) has improved outcomes in high-risk patients. The analysis of these works is difficult due to the inclusion of patients with and without metastatic disease. One of the studies reports 43% disease-free at three years using the aforementioned scheme, while in another it is 36% disease-free at 6 years. , but the published results were not clearly superior to those using the classical scheme, with conventional doses and without radiotherapy.

Luksch treated 17 patients of high risk and poor prognosis with an intensive regimen with Melphalan 50 mg/m2, every 21 days, for 2 courses followed by 8 courses of polychemotherapy and consolidation with total body radiotherapy and bone marrow transplant. Responses were achieved in 13 of 17 patients (76%) with predictable and controllable toxicity.

Results from subsequent studies using dose intensification showed interesting results, but even the number of patients and follow-up is scarce to draw conclusions.

New useful drugs in resistant patients and the inclusion of new therapies with biological response modifiers on molecular targets are being sought. Memon et al. presented a study treating 20 resistant patients with Cisplatin, Ifosfamide and Etoposide, achieving 40% of responses. A Spanish study, also in resistant patients, using Cisplatin 120 mg/m2, Etoposide 600 mg/m2, alternating with Ifosfamide 8 g/m2 plus Paclitaxel 200-350 mg/m2, of 10 patients treated, 7 responded, including 4 complete responses (3

clinical and 1 pathological). The mean survival was 11.5 months (95% CI: 5.7-17.3) and the disease-free survival was 8 months (95% CI: 7.5-8.5), with a mean follow-up of 33 months.

Chow presented a study with 29 patients with Ewing sarcoma, who showed positivity to the c-Kit and the tyrosine kinase receptor (PDGFR-α) (TKRs). They were treated with the therapeutic regimen that included Vincristine, Doxorubicin and Cyclophosphamide alternating with Ifosfamide and Etoposide. They received radiation therapy during the 6th and 7th cycle. There was one patient who progressed and partial remission of the disease was achieved with the addition of Imatinib.

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