Secondary pathologic fractures in osteosarcoma: prognosis and evolution

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Abstract. – Secondary or pathologic fractures, associated with osteosarcoma, have been considered for a long time to be a negative prognosis regarding its evolution in the patients. The aim of this study was to evaluate the prognostic importance of such pathologic fractures in osteosarcoma patients receiving new therapies as well as the best conditions for surgery aiming at “limbs salvage”.

On a total of 22 patients affected by osteosarcoma, we performed a retrospective study with 12 patients showing pathologic fractures caused by osteosarcoma and 10 patients without any pathologic fracture. The patients enrolled into Timisoara University Hospital have been followed up along 5 years or until a reappearance of either the disease or metastases, distant or local.

Key Words: Osteosarcoma, Chemotherapy, Pathologic fracture, Adjuvant therapy, Limbs salvage.

Introduction

Fracture on pathologic basis associated with osteosarcoma was considered, for a long time, a negative prognostic index for the evolution of the disease in the patients\textsuperscript{1}. In the last period, the treatment of the osteosarcoma associated with the “limb salvage” procedure has become a more viable alternative than the “limb amputation” surgery\textsuperscript{2,3}. Non randomised studies have shown that the salvage procedures do not negatively influence the survival. So, whenever could be possible, the radical resection of the tumour, together with chemotherapy or not, could improve the functional results without compromising the “limb salvage” and the local control on the disease (Figure 1).

One risk factor, which could be considered as a contraindication for “limb salvage” procedure, is the pathological fracture, frequently associated with a poor outcome\textsuperscript{4}. Fractures are usually associated with haematomas which can theoretically disseminate the tumour cells to the neighbouring tissues and probably to the close vessels and/or joints. It could also facilitate an hypothesized closed areas microcirculation which could contribute for a metastasis development\textsuperscript{5,6}. The incidence of the pathological fractures, at the time of the diagnosis or of preoperative chemotherapy, is ranging between 5\% and 10\%\textsuperscript{7,8}. The aim of this study was to evaluate the prognostic importance of such pathologic fractures in patients affected by osteosarcoma who received new pharmacological therapies as well as the new procedures for the “limbs salvage” surgery\textsuperscript{9,10}.

Material and Methods

We performed a 5 years retrospective study on 22 patients treated for osteosarcoma which were divided in two groups: one group of 12 patients presenting osteosarcoma with pathological fractures at the time of the diagnosis or which developed preoperative fractures at the time of chemotherapy, and another group of 10 patients without pathological fracture treated for osteosar-
Figure 1. Patient with a osteosarcoma of the femoral condyle treated with a radical resection of the tumour and an artrodesis of knee: the performance of the leg is preferred to its amputation.

In the group with pathologic fractures and 97% in patients without fractures. In the group with pathologic fractures, the “limb salvage” resulted successful in 23% whereas in 4 patients the amputation resulted necessary. In five patients, the open reduction and internal fixation were performed before the surgical intervention trying a “limb salvage” procedure. All the patients, presenting the osteosarcoma at the “Enneking” stage IIb or III, developed distant metastases in 48% of the cases. In all the considered cases, the most common place of the primary tumour localization was the distal femur (58%) (Figure 2), followed by the proximal portion of the humerus (24%) and the proximal part of the femur (24%).

“Limb salvage” refers to successful resection of a tumour and reconstruction of a viable, functional extremity. In the setting of induction chemotherapy, limb-sparing resection and reconstruction, rather than amputation, can be safely performed in 90 to 95 percent of patients. Studies indicate that, compared with amputation, limb-sparing surgery using a wide margin does not appear to compromise the survival. It should be emphasized, however, that the primary objective of overall treatments is to achieve a long-term disease-free survival (cure). Consequently, preserving limb function undertakes a secondary objective. If an adequate limb-sparing resection cannot be performed, amputation should be considered. However, with modern chemotherapy regimens, limb removal is seldom necessary. After tumour resection, the large hard and soft tissues deficits must be reconstructed. For this purpose, many orthopedic surgeons prefer metallic endoprostheses which provide immediate stable

Results

The median age of the patients included in the study was 66.5 yrs. The patients were followed for a medium time of 2.5 yrs, ranging from 1.5 to 6 yrs.

The survival rate after 5 yrs was estimated to be 50% in the group with pathologic fractures and 79% in patients without fractures. The survival rate, without local recurrence, resulted 55% in the group with pathologic fractures and 97% in patients without fractures. In the group with pathologic fractures, the “limb salvage” resulted successful in 23% whereas in 4 patients the amputation resulted necessary. In five patients, the open reduction and internal fixation were performed before the surgical intervention trying a “limb salvage” procedure. All the patients, presenting the osteosarcoma at the “Enneking” stage IIb or III, developed distant metastases in 48% of the cases. In all the considered cases, the most common place of the primary tumour localization was the distal femur (58%) (Figure 2), followed by the proximal portion of the humerus (24%) and the proximal part of the femur (24%).

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Figure 2. Artroprotesis of the knee following revision of the distal third of the femur for osteosarcoma.

fixation and allow early deambulation together with weight bearing. They also provide joint stability with good to excellent function in most patients. The use of metallic endoprostheses result associated with only minimal early postoperative complications. After a diagnosed tumour, the chemotherapeutic protocol routinely applied in the Oncologic Clinic of Timisoara (Romania) was the standard protocol. Chemotherapy resulted vital in the treatment of osteosarcoma. Over the past 30 years a substantial progress in chemotherapeutic treatment has occurred, surely responsible for improved cases of “limb salvage” and increased survival rates.

Chemotherapy has also been shown to reduce the number of pulmonary metastases or to delay their appearance together with an easier surgical removal. Standard regimens now include preoperative (induction) and postoperative (adjuvant) chemotherapy. Preoperative chemotherapy induces tumour necrosis in the primary tumour and provides early treatment of eventual micrometastases. It also facilitates surgical resection with wide safety margins and, therefore, appears one of the main factors contributing to a significant improvement of limb salvage rates (Figure 3).

Drugs resulted effective against osteosarcoma include: doxorubicin, cisplatin, ifosfamide with mesna and high-dose methotrexate with leucovorin calcium rescue. For both induction and adjuvant chemotherapy, most standard protocols use doxorubicin and cisplatin with or without high-dose methotrexate. Recent trials incorporated ifosfamide into the treatment protocols. However, the benefit of ifosfamide with respect to the conventional regimens in improving patient survival has not yet been confirmed.

Rather a variant of Cooperative Osteosarcoma Study-86 (COSS-86), the initial protocol used for osteosarcoma treatment includes 3 months Methotrexate, Doxorubicin and Cysplatin (MAP) and MAP plus ifosfamide for poor responders (four cycles of doxorubicin, methotrexate and

Figure 3. Osteosarcoma of the third diaphysary medium of the femur treated with chemotherapy, with a wide resec-tion of the neoplasy and sintetized with a blocked endomedullar nail.
cisplatin).

For doxorubicin protocol, CCG-7921 uses continuous 25 mg/m²/day i.v. infusion over 72 h, not exceeding 450 mg/m².

For methotrexate protocol, CCG-7921 uses an high-dose on days 21 and 28 of each chemotherapeutic cycle, 12 g/m² i.v. infused over 4 h not exceeding 20 g/m²/dose.

For cisplatin protocol, CCG-7921 uses 120 mg/m² i.v. infused over 4 h on day 1 of each chemotherapeutic cycle.

Post surgical chemotherapy (up to 9 months) was made with the addition of ifosfamide at the following dosage: 1.8-3.6 mg/m²/d i.v. along 5 days for each cycle (i.e., total cumulative dose of 9-18 mg/m² per cycle).

The high dose polichemotherapy regimens with recent drugs enhanced the disease-free long-term survival rates up to approximately 60-80 percent in patients with localized (not metastatic) disease at presentation¹⁹.

The best long-term survival statistics have been reported in patients who achieved greater than 90 percent histologic tumour necrosis in the resected specimen²⁰.

Consequently, the amount of tumour necrosis achieved with induction chemotherapy is routinely estimated for all specimens following resection. Two out of the 22 enrolled patients required the amputation. For one patient the procedure was performed at the time of presentation while for the other it was performed after the chemotherapy induction. Taking in consideration the clinical evolution of the patients of the group presenting pathological fractures, there was no significant difference between the group leading to the amputation (among patients with pathological fractures) and the group undergone to surgical intervention performed for “limb salvage”. Local recurrences were recorded in 10 of the 12 patients undergone to the surgical intervention for “limb salvage” and in both patients where amputation was performed. No significant difference was observed about the overall survival rate among the patients undergone to amputation (at the time of presentation) and those who underwent to amputation at the time of chemotherapy or after it. Five patients underwent to open reduction and internal fixation followed by “limb salvage” procedure (Figure 4). One of them showed local recurrences and died 5 months after surgery.

The remaining patients resulted alive at the final period of the follow up. In eight patients, our data permit a significant association between fracture healing and the extension of the tumour necrosis. Into four of them, in which the fracture was consolidated, two patients showed tumour necrosis. The fracture displacement was not significantly related to the local recurrences or to overall survival despite the fracture consolidation. Up to now, for each clinical case taken in account, it isn’t available any significant multivariate relationship between the decreased rate of the local recurrence and the increased rate of survival able to induce clinicians to hypothesize a validated prognostic factor. The “non finding” of a fracture consolidation condition, seems to represent a significant independent prognostic factor which could be due to some other strong overlapping effects (i.e., response to chemotherapy and/or local resistance).

**Discussion**

Few scientific reports in the literature highlight the prognosis of the osteosarcomal pathological fractures⁶⁻²¹. This is because these lesions resulted very rare in the affected people (2/1.000.000) and even related to the indications of the proposed treatment: tumour resection and osteosynthesis, amputation and reconstruction, depending on the cases²². There are some studies, published in recent years, which report, in the osteosarcoma treatment, a reflecting correla-
tion between the fracture healing and the limb preservation using, in the children, an adequate chemotherapy (ifosfamide, doxorubicin, methotrexate)\textsuperscript{12}. In our study we have only considered cases showing stabilization and limb functionality. Our study demonstrates that the association of the pathologic fracture is a factor of poor prognosis, as reported in other scientific reports about it, as well as our results are according to the literature data recommending to preserve the limb and not to amputate it\textsuperscript{20,24,25}. There were not significant differences between the groups in which we have performed amputation and to those undergoing to stabilization and reconstruction. The fracture displacement (through fracture haematoma) is also a prognostic factor. About the possibility of tumour cells dissemination at the time of surgery, some Authors also recommend to immobilize into a plaster cast as the first line of treatment until the chemotherapy protocol is started. Dorey et al published a review reporting that the risk of local recurrences or death, the procedure for a “limb salvage” in selected patients with pathologic fracture doesn’t cause an increase in the rate of local recurrences or death. Predictive factors could give positive results but the response to chemotherapy or fracture consolidation should be factors to be also taken in account at the time of “limb salvage”.

**Conclusion**

The two considered groups have the similar disease stages, age, tumour localization. Predictive factor has a positive result still the response to chemotherapy or fracture consolidation should also be taken into consideration at the time of “limb salvage” intervention. In comparison with patients without pathologic fractures, patients with osteosarcoma associated with pathological fractures or who developed the fracture at the time of the postoperative chemotherapy, have an increased risk of local recurrence together with a decrease of the survival rate. The procedure for a “limb salvage” in selected patients with pathologic fracture doesn’t cause an increase in the rate of local recurrences or death. Predictive factors could give positive results but the response to chemotherapy or fracture consolidation should be factors to be also taken in account at the time of “limb salvage”.

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