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Original Research Article

Denosumab in Unresectable and Recurrent Giant Cell Tumors of Bone: About 70 Cases

E. Kerboua[1*], S. Lemmouchi[2], R. Nemmar[2], K. Meskouri[3], C. Mazouzi[4], R. Benyahia[5]

[1]Department of Medical Oncologie, Pierre and Marie Curie Center University, Algiers
[2]Department of Orthopedics and Traumatology, Mustapha Bacha Hospital, Algiers
[3]Department of Thoracic and Cardiovascular Surgery, Mustapha Bacha Hospital, Algiers
[4]Department of Medical Oncology, Khelil Amrane Hospital Bedjai
[5]Department of Imaging, Pierre and Marie Curie Center, Algiers

***Corresponding Author:** E. Kerboua
Department of Medical Oncologie, Pierre and Marie Curie Center University, Algiers

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Abstract: ***Introduction***: Giant cell tumour of bone (GCTB) is a locally aggressive and osteolytic tumour. The peak incidence is during the third and fourth decades of life. The majority of tumours occur in the meta-epiphyseal (end) region of the long bones. Surgical resection is the preferred treatment option, if possible but it is a tumor which always poses progressive problems. Denosumab is indicated in recurrent or unresectable GCTB. ***Materials & Methods***: We report a series of 70 patients treated for GCT at the medical oncology department of the CPMC of Algiers in collaboration with the orthopedics department of Mustapha University Hospital between between December 2018 to December 2023. ***Results*:** 70 patients (50 women and 20 men). The sex ratio is 0.54. The average age is 22 years (11-54 years).

Reason for Consultation*:*

- Pathological fracture: n=10 -Pain: n=30 - Functional impotence: n=20 - Tumor mass: n=5 - Concept of trauma: n=5
- Stage of the disease: -Localized: n=29 -Recurrence: n=30, -Recurrence + pulmonary metastases: n=10,
- Sarcomatous transformation: n=1
- Type of treatment: -Radiotherapy, n=1 -Exercised biopsy: n=10, -Curettage + cementoplasty: n=50
- Exeresis with osteosynthesis material: n=8, -Amputation: n=1
- Medical treatment: Denosumab: n=45 • The number of courses with denosumab was between 6 and 55 cycles . Denosumab was administered neoadjuvantly in 10 patients, in 20 patients with reccurence disease, 15 patients in the metastatic phase
- In terms of toxicity we noted hypocalcemia moderate in 3 patients.

Objective Responses: 95% clinical response, 5 complete radiological responses and 10 partial responses, 20 stable patients and 9 out of 10 patients who received neoadjuvant denosumab were able to operate. Progression Free Survival is 28 months. ***Conclusion***: GCTs are aggressive tumors with intermediate malignancy that should not be underestimated. The treatment is essentially surgical. Denosumab is indicated for both neoadjuvant and adjuvant use, it allows obtaining a clear clinical and radiological improvement.

Keywords: Giant Cell Tumour of the Bone (GCTB), Surgery, Reccurence, Denosumab.

INTRODUCTION

Giant cell tumor of bone (GCTB) is a generally benign bone tumor affecting the metaphysoepiphyseal region of long bones as well as, less often, flat bones. It represents 5% of bone tumors and 20% of all benign bone tumors [1]. This disease particularly affects young adults between 20 and 40 years old, with rare cases

occurring before the age of 18. Typically, in 90% of cases, the giant cell tumor is located in the metaphysoepiphyseal area of the long bones and it can extend to the subchondral bone and can even directly affect the articular cartilage but generally does not invade not the joint or the capsule [2]. Clinically, it has a local expression (pain and swelling of the affected region or even a pathological fracture). The ideal treatment is surgery but in certain cases and given the impossibility of carrying it out, other specific therapies have been tested and proven to be effective. a tumor which always poses progressive problems due to its propensity for recurrence, hence the importance of strict monitoring.

MATERIELS & METHODES

We report a series of 70 patients (pts) treated for GCT at the medical oncology department of the CPMC of Algiers in collaboration with the orthopedics department of Mustapha University Hospital between December 2018 to December 2022.

RESULTS

70 patients (50 women and 20 men). The sex ratio is 0.54 (figure 1) are the average age is 22 years (11-54 years).

- **Reason For Consultation*:***
  - Pathological fracture: n=10
  - Pain: n=30
  - Functional impotence: n=20
  - Tumor mass: n=5
  - Concept of trauma: n=5

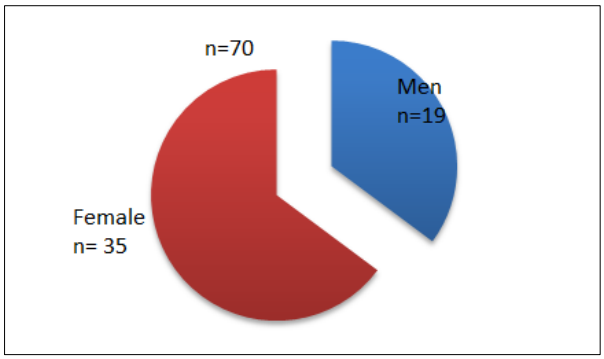

Figure 1: Sex repartition

- **Stage of the disease (figure 2)**
  - Localized: n=29
  - Recurrence: n=30,
  - Recurrence + pulmonary metastases: n=10,
  - Sarcomatous transformation: n=1
  - Type of treatment:- Radiotherapy, n=1 -Exercised biopsy: n=10, -Curettage + cementoplasty: n=50 -Exeresis with osteosynthesis material: n=8, -Amputation: n=1
  - Medical treatment: Denosumab: n=45 • The number of courses with denosumab was between 6 and 55 cycles. Denosumab was administered neoadjuvantly in 10 patients, in 20 patients with reccurence disease, 15 patients in the metastatic phase.
  - In terms of toxicity we noted hypocalcemia moderate in 3 patients.
  - Objective responses: we obtain 95% clinical response, 5 complete radiological responses and 10 partial responses, 20 stable patients and 9 out of 10 patients who received neoadjuvant denosumab were able to operate. Progression Free Survival is 28 months.

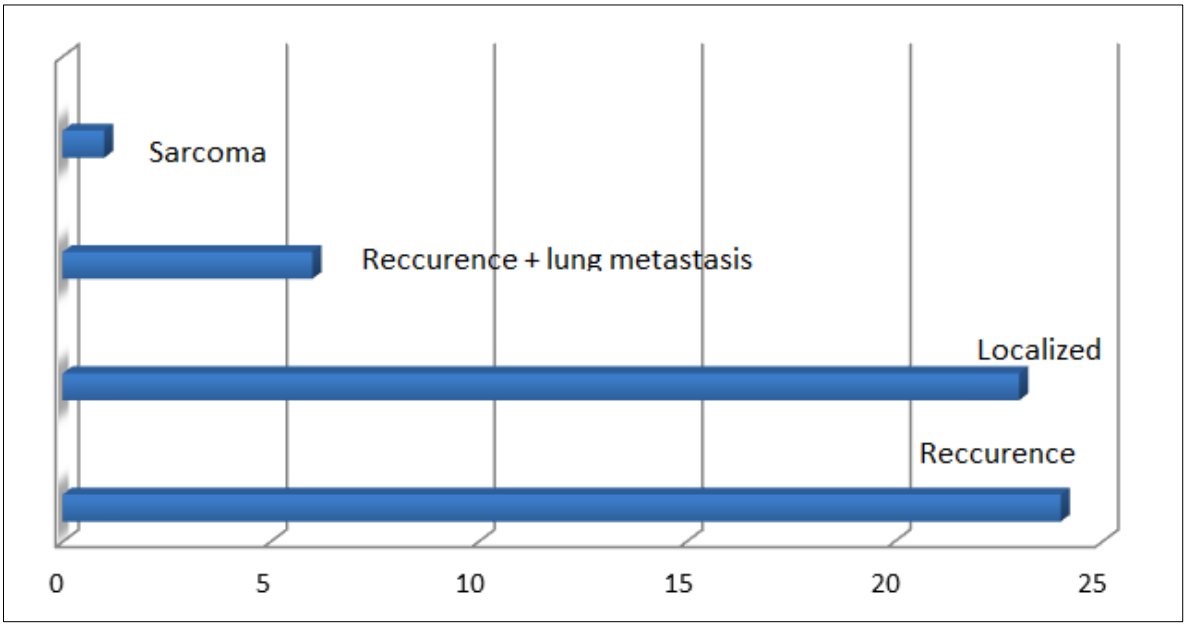

Figure 2: Stage of disease

DISCUSSION

In our study, it is very difficult to give an exact frequency of these tumors, we can reveal 70 patients in four years because our service is recognized as a reference service in bone oncology, Mejdoubi [3], reported 19 cases spread over a decade (1.9 cases/year) Ettaib [4], noted 8 cases in 9 years or 0.89 cases/year, Derrem [5], in his thesis reported 21 cases over 10 years representing 15% of all benign bone tumors, Miguel [6], reported 22 cases in 4 years, or 5.5 cases/year. We note that GCT remains a rare tumor both here and in the rest of the world. The average age is 22 years. In our series we found that the majority of cases are seen in young adults between 20 and 40 years (71%) with an average age of 31 years, Campanacci [7], and Tomeno [8], revealed an average age of 35 years with a majority of cases between 20 and 40 years.

Sex: We note in almost all series a slight female predominance with a percentage of 55 to 60% of cases [9-11], as in our serie.

Typically, in 90% of cases, the giant cell tumor is located in the metaphysoepiphyseal area of the long bones. In our study the epiphyso-metaphyseal location was found in 75%. The most affected bone sites are, in order: the distal femur, the proximal tibia, the distal radius and the sacrum, which is consistent with the data in the literature.

The time elapsed between the start of the symptoms and the consultation varied between 1 month and 36 months with an average delay of 6 months. There is no fixed and precise interval, as shown in litterature, it can range from a few weeks to several years [12, 13].

On the clinical level: In our series, pain is the revealing symptom in all our patients. It was mainly of mechanical type: 30 cases which is consistent with the literature since pain represents the main symptom. ETTAIB [4], reported that pain was indicative of the disease in 88%. - MELLOUKI [13], found that pain was indicative of the disease in all his patients.

Rarely it is the swelling which alerts the patient [5]. In our series, swelling was present in 5 cases which reflects the long evolution of the disease.

We have only 23 patients with Localized disease, 24 locally recurrence, 6 patient with locally recurrence and pulmonary metastases: one sarcomatous transformation.

Degeneration seems more frequent when localized to the trunk. This malignant transformation of a GCT must be differentiated from authentic sarcomas containing giant cells.

Type of treatment: Radiotherapy, n=1 Exeresis biopsy: n=10, Curettage + cementoplasty: n=40, Exeresis with osteosynthesis material: n=3, Amputation: n=1

In our series, curettage and cementing was performed in 40 pts, of which 10 cases were secondary recurrence surgery; and 30 cases underwent primary curettage-filling surgery. Fraquet [14], treated 30 cases of giant cell tumors of long bones by curettage and cementing.

Based on the possible role of RANKL expression by TCG stromal cells on the formation, activation and occurrence of osteoclast-like cells responsible for osteolysis in these tumors, some authors have proposed the use of 'a human monoclonal antibody that specifically inhibits RANKL, DENOSUMAB. Thomas DN *et al*., [15], on a phase II therapeutic study involving 37 patients with recurrent or unresectable GCT who received monthly doses of 120 mg of DENOSUMAB subcutaneously, with loading doses on D8 and D15 of the 1st month, obtained very encouraging results with 86% tumor response. These same authors also reported a case of recurrence after stopping the treatment, which raised many questions about the temporary nature of the inhibitory effect and the duration of the treatment for it to be effective.

Denosumab is currently indicated when surgery, first-line treatment, is impossible to perform or feasible at the cost of significant morbidity.

In operable patients, denosumab aims to facilitate the surgical procedure to allow resection of the tumor in a second step. For non-operable patients, denosumab aims to stabilize the disease and in this case the total duration of treatment is unknown.

We used Denosumab for 45 pts, it was administered neoadjuvantly in 10 patients [16], in 20 patients with reccurence disease, 15 patients in the metastatic phase [17].

Objective responses: 95% clinical response, 5 complete radiological responses (Figure 3) and 10 partial responses, 20 stable patients and 9 out of 10 patients who received neoadjuvant denosumab were able to operate.

Progression Free Survival is 28 months.

- In terms of toxicity we noted hypocalcemia moderate in 3 patients.

Metaphyseal Osteolysis

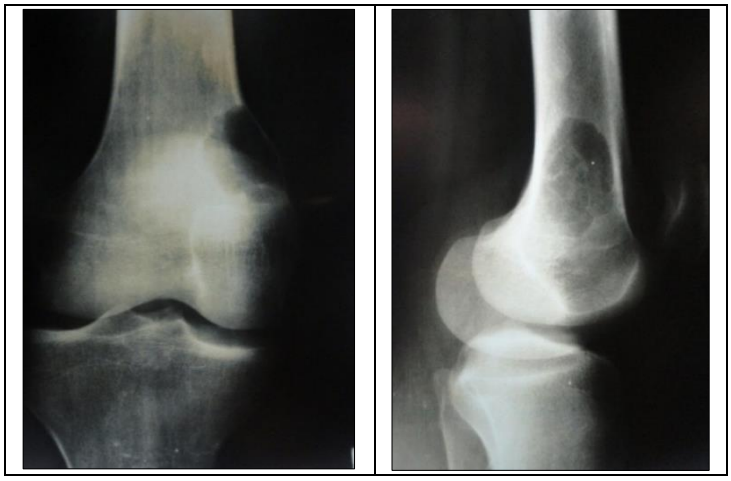

Figure 3A: TCG of the distal end of the femur before treatment with denosumab (Personal collection traumatology-orthopedics department Pr Salim Lemmouchi CHU Mustapha Bacha Algiers center)

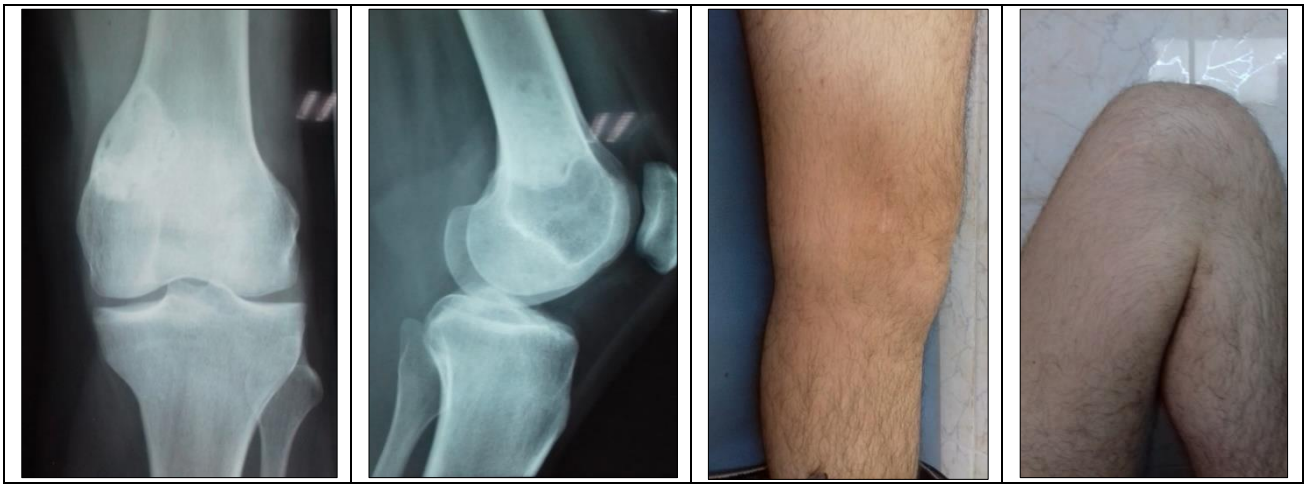

Figure 3B: complete ossification of the tumor at 3 years of follow-up after treatment with Denosumab with a good clinical evolution: normal extension and flexion with total indolence (Personal collection traumatology-orthopedics Pr Salim Lemmouchi department Mustapha Bacha Algiers center)

Figure 3: Treatment with Denosumab of a TCG of the lower end of the femur; 3 years follow-up (personal collection orthopedics traumatology department CHU Mustapha Bacha Algiers center)

CONCLUSION

GCTs are usually benign and relatively rare bone tumors affecting a relatively young population whose main characteristics are completely unpredictable evolution, propensity for recurrence and pulmonary metastasis. • The largest possible surgery remains the ideal treatment for this pathology if it is possible • The better knowledge of the histopathogenesis of this pathology has made it possible to improve the management in certain cases of inoperable tumors or with risk of severe morbidity, however the optimal use and in particular as an adjuvant, the long-term effects and the patient selection, in the young population mainly affected by TCG remains to be defined.

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