European Journal of Cancer (2014) xxx, xxx–xxx

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Adjuvant treatment with zoledronic acid after extensive curettage for giant cell tumours of bone

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Received 2 August 2013; received in revised form 9 May 2014; accepted 9 June 2014

KEYWORDS
Giant cell tumours of bone
Bisphosphonate
Bone curettage
Local recurrence

Abstract ***Background:*** Giant cell tumours (GCT) of bone are benign neoplasms associated with a high rate of local recurrence after extensive intra-lesional curettage. Recently, understanding of the biological molecular availability of strong anti-osteoclastic drugs has suggested their potential value in reducing local recurrences after curettage. Through a phase II clinical trial, we investigated the effect of a short treatment with zoledronic acid (ZOL) after intra-lesional curettage of GCT, as well as local recurrence and tolerance of the treatment.

Methods and patients: Twenty-four patients were enrolled in a multicentre, phase 2 study. The patients were treated with extensive intra-lesional curettage followed by five courses of ZOL (4 mg IV every 3 weeks).

The clinical and biological tolerance of each patient was assessed. Patients were reviewed clinically and by X-ray every 6 months until the end of the study (36 months).

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http://dx.doi.org/10.1016/j.ejca.2014.06.003

Results: Eighteen out of 20 patients reported side-effects with ZOL, mainly grade 1 and 2 effects. The local recurrence rate was 15%; three patients had a recurrence, one at 4 months (huge GCT of the sacrum), one at 24 months (patient who discontinued the treatment after the first course of ZOL), and one after the observational period, at 58 months. Finally, local relapse-free survival was 82 ± 9% at 60 months.

Conclusion: Short adjuvant treatments with ZOL after extensive intra-lesional curettage of GCT were associated with a low rate of recurrence but did not prevent local recurrence in this study. No serious general adverse effects were observed. More studies are needed to evaluate the potential benefit of medical bisphosphonate injections combined with intra-lesional curettage in the treatment of GCTB.

1. Introduction

Giant cell tumours of bone (GCTB) are benign bone neoplasms occurring in the metaphyseal–epiphyseal areas of long bones and in the axial skeleton of young adults, with aggressive osteolytic behaviour threatening major musculoskeletal functions. The treatment of choice in most cases of GCTB is curettage and bone filling [1]. However, curettage alone has been associated with a high rate of local recurrence (8.6–45%) [2–8]. Different types of local adjuvant have therefore been introduced to remove what are presumably remaining tumour cells. These local adjuvants include cryotherapy [9,10], heating the cavity with methylmetacrylate or argon gas [8,11–13], or with phenol [4,14–16], ethanol [17], aqueous zinc chloride solution [18] or anhydrous ethylalcohol [19]. Despite a local recurrence rate reported by most authors as ranging from 10% to 20%, none of these adjuvant local therapies have proved their efficacy when added to extensive curettage with high speed mechanical burring [20].

In addition, the pathogenesis of GCTB includes three types of cells: mononuclear spindle-shaped stromal cells considered to be responsible for the neoplastic nature of GCTB, mononuclear round cells which are non-neoplastic and express monocyte-macrophage markers [21] and giant multinucleated cells that resemble osteoclasts in their phenotype and function. The latter are the key players in bone resorption [22,23].

Major molecular factors that regulate osteoclast differentiation and bone resorption, namely osteoprotegerin/Receptor Activator NF-kB and its ligand RANK-L, have been identified in the cell types present in GCTB, with a much higher level of RANK-L on spindle-shaped stromal cells than in normal bone [24]. Compounds inhibiting osteoclast activity and promoting osteoclast apoptosis have thus been proposed to treat GCT of bone. Despite the lack of effect of calcitonin as a local and general adjuvant treatment to curettage [25], promising preliminary clinical results have been reported with Denosumab [26,27] and bisphosphonates (BPs) [28–36]. Nevertheless, for the latter, different types of BPs were used, different treatment regimens in terms of length and time, including both pre-operative and post-operative injections, were reported and primary as well as recurrent tumours were included. The role of BPs in the therapeutic strategy of GCTB thus remains unclear.

In the present study, we report the results of a phase II clinical trial, exploring the effect of a 3-month adjuvant treatment with zoledronic acid combined with extensive curettage of primary GCTB.

2. Patients and methods

Twenty-four patients were enrolled in a multicentre, phase II, clinical trial approved by the Regional Hospital Programme for Clinical Studies (Clinical Trials. gov US National institutes of Health Registry reference; NCT01564121) and the regional ethics committee (CCPPRB n°1091/2005) of our institution. All patients were asked to provide written consent for their involvement. The eligible patients (18 years old and over) had primary giant cell tumours of bones. Staging included X-ray and magnetic resonance imaging (MRI) scans. Extensive intra-lesional curettage was indicated in all cases. All patients had a surgical biopsy, and diagnosis was confirmed on the curettage tissue by an expert pathologist from the French Group of Bone Pathologists. Key exclusion criteria included a previous history of bone tumour, pregnancy or any contra-indication to zoledronic acid treatment (including atrial fibrillation, recent invasive dental procedures or poor dental condition).

3. Procedures and follow-up

In all cases, the surgical procedure was extensive intra-lesional curettage, involving subchondral bone when necessary. Bone surfaces were curetted manually with a curette, completed with high-speed burring. After curettage, the cavity was rinsed with saline water. The bone cavity was then filled according to the surgeon's habits: polymethyl methacrylate cement containing antibiotics or bone allograft. A titanium plate was inserted for lower limb localisations when it was considered that there was a high risk of post-operative fracture. With the

Please cite this article in press as: Gouin F. et al., Adjuvant treatment with zoledronic acid after extensive curettage for giant cell tumours of bone, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.06.003