شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
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تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

HANAA ALY

Comparative Study between the use of Denosumab and Zoledronic acid in Treatment of Giant Cell Tumor of Bone

(A Systematic Review and Meta-Analysis)

Thesis

For Partial Fulfilment of Master Degree
in Orthopedic Surgery

By

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List of Abbreviations

Abb.	Full term
BMPs	*Bone morphogenetic proteins*
EMA	*European Medicines Agency*
FGFs	*Fibroblast growth factors*
GCT	*Giant cell tumor of bone*
IGFs	*Insulin-like growth actors*
IKKs	*I-KappaB kinases*
IL	*Interleukin*
JNK	*c-Jun N-terminal kinase*
MAPK	*Mitogen-activated protein kinase*
MRI	*Magnetic resonance imaging*
NFATc1	*Nuclear factor of activated T cells, cytoplasmic 1*
OPG	*Osteoprotegerin*
PGE2	*Prostaglandin E*
PMMA	*Polymethyl methacrylate*
PTHrP	*Parathyroid hormone-releasing protein*
RANKL	*Receptor activator nuclear factor K-B ligand*
RT	*Radiotherapy*
SREs	*Skeletal related events*
TNF	*Tumor Necrosis Factor*
TNFR	*TNF family receptor*
TRAF	*Tumor Necrosis Factor Receptor Associated Factors*
US FDA	*United States Food and Drug Administration*

Introduction

Giant cell tumor of bone (GCT) is a benign primary but locally aggressive bone tumor, most commonly occurring in long bones of patients with range of age 30–50 years and might have a tendency to metastasize [1]. GCT is composed of reactive multinuclear osteoclast-like giant cells expressing receptor activator of nuclear factor k-B (RANK) and neoplastic mononuclear stromal cells expressing RANK-ligand (RANKL); the latter promotes osteoclast formation, migration, and survival, resulting in bone resorption [2].

Preferential treatment is curettage and high speed Burre with local adjuvants including phenol, alcohol or liquid nitrogen, and cavity filling with bone graft and/or poly-methyl-methacrylate (PMMA), with a rate of recurrence ranged between 27-31% [3,4]. In more advanced cases, when joint salvage is regarded impossible, en-bloc resection and endo-prosthetic joint replacement is often considered, resulting in decrease of recurrence risks, but high rates of complication and lesser functional outcome. Also, GCT in the axial skeleton and pelvis or other non-long bone localizations are less amenable to non-mutilating surgery and often intra-lesional surgery is the only achievable option surgically [5].

The high recurrence risk after intra-lesional surgery in advanced GCT, and subsequent need for (multiple) re-operations and sometimes extensive surgery can result in functional loss in this intermediate but locally aggressive

disease. This major clinical problem resulted in the quest for systemic targeted therapy aiming at the facilitation of less invasive surgery or even replaces surgery in metastatic patients or cases that are not amenable to surgery. Currently, two different drugs are used, first is the recently approved RANKL inhibitor denosumab inhibits recruitment of osteoclast-like giant cells by neoplastic stromal cells and thereby prevents osteolysis; a calcified rim is formed around tumorous soft tissue, facilitating intralesional surgery in previously 'uncurettable' GCT [6].

Second is the bisphosphonate zoledronic acid (ZA) that may stabilize local and metastatic disease by its apoptotic effect on neoplastic mononuclear cell population in GCT [7].

There are still some unanswered questions in the multidisciplinary treatment of GCT [8], especially now concerns have arisen on increased recurrence rate, side-effects after prolonged systemic therapy and case reports on secondary malignancy after denosumab. In this regard, optimal treatment dose and duration have not yet been affirmed. Linguistically, these concerns are reflected in titles of scientific articles, shifting from 'Denosumab: A breakthrough in treatment of GCT?' [9] towards 'Challenges' [10], 'Lessons learned from early experience' [11] and 'Present day controversies' [12]. In addition, due to denosumab's high efficacy, alternative targeted therapies including directly working zoledronic acid, are studied to a lesser extent.

Aim of the Work

The aim of this study was to review the literature about the use of denosumab vs zoledronic acid in treatment of GCT regarding their efficacy and oncological effects.

Chapter 1

Giant Cell Tumor of Bone

Overview of Giant Cell Tumor of bone

Giant cell tumor of bone (GCT) is a benign lesion with tendency toward local aggressive invasion but metastases may occur in 1% to 9% of patients and some earlier studies have correlated the incidence of metastases with aggressive growth and local recurrence [13].

It accounts for approximately 5% to 6% of primary bone tumors, usually occurs in the meta-epiphyseal region of long bones but may also occur in the axial skeleton or small bones in hands and feet [14].

Pathophysiology of GCT

Giant cell tumor of bone has a dark brown-to-reddish appearance that is friable in texture, while the histological appearance of GCT classically reveals numerous large multinucleated giant cells dispersed in the background stroma of mononuclear spindle cells and monocytes.The mononuclear spindle cell can also present plump and epithelioid in shape. The monocyte nuclei have features identical to those of the larger osteoclast-like giant cells, which can contain large numbers of these nuclei [>50] [Figure 1]. [15]