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Original Research

Effect of denosumab versus zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics

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Abstract ***Background:*** Analyses of phase III trials showed that denosumab was superior to zoledronic acid (ZA) in preventing skeletal-related events (SREs) irrespective of age, history of SREs, or baseline pain status. This analysis assessed the risk of SREs across additional baseline characteristics.

Patients and Methods: Patients (N = 5543) from three phase III trials who had breast cancer, prostate cancer, or other solid tumours and one or more bone metastasis were included. Superiority of denosumab versus ZA in reducing risk of first SRE and first and subsequent SREs was assessed in subgroups defined by the Eastern Cooperative Oncology Group performance

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status (ECOG PS), bone metastasis location, bone metastasis number, visceral metastasis presence/absence, and urinary N-telopeptide (uNTx) level using Cox proportional hazards and Anderson–Gill models. Subgroups except bone metastasis location were also assessed for each solid tumour type.

Results: Compared with ZA, denosumab significantly reduced the risk of first SRE across all subgroups (hazard ratio [HR] ranges: ECOG PS, 0.79–0.84; bone metastasis location, 0.78–0.83; bone metastasis number, 0.78–0.84; visceral metastasis presence/absence, 0.80–0.82; uNTx level, 0.73–0.86) and reduced the risk of first and subsequent SREs in all subgroups (HR ranges: ECOG PS, 0.76–0.83; bone metastasis location, 0.78–0.84; bone metastasis number, 0.79–0.81; visceral metastasis presence/absence, 0.79–0.81; uNTx level, 0.74–0.83). Similar results were observed in subgroups across tumour types.

Conclusion: Denosumab was superior to ZA in preventing SREs in patients with bone metastases from advanced cancer, regardless of ECOG PS, bone metastasis number, baseline visceral metastasis presence/absence, and uNTx level.

1. Introduction

Patients with bone metastases are at increased risk for skeletal complications, including pathologic fracture, spinal cord compression, and radiation or surgery to the bone, collectively termed skeletal-related events (SREs) [1]. SREs are associated with not only substantial morbidity but also greater mortality, increased pain, decreased quality of life, and increased treatment costs [2–6].

Bone-targeting agents have been shown to reduce SREs associated with bone metastases/lesions in patients with advanced solid tumours or multiple myeloma [6–11]. Denosumab is a fully human monoclonal antibody against RANK ligand (RANKL), an important regulator of osteoclast-mediated bone resorption [12]. In a prespecified combined analysis of three identically designed phase III randomised clinical trials, denosumab was superior to zoledronic acid (ZA) in reducing the risk of first on-study SRE (17% risk reduction; $P < 0.001$) and the risk of first and subsequent on-study SREs (18% risk reduction; $P < 0.001$) in patients with bone metastases/lesions from breast cancer, prostate cancer, or other solid tumours and multiple myeloma [13].

Previous publications have reported a variety of potential risk factors for the occurrence of SREs in patients with bone metastases from lung, breast, or prostate cancer, including history of SREs, Eastern Cooperative Oncology Group performance status (ECOG PS), extent of bone disease, pain status, and urinary N-telopeptide (uNTx) level, a frequently used bone turnover marker [14–19]. However, it is unknown whether such risk factors could be used to identify patients most likely to benefit from treatment with bone-targeted agents. Previous analyses of the phase III trials of denosumab described above have shown that denosumab was superior to ZA in preventing SREs regardless of patient age, SRE history, or baseline pain status [13]. In the current combined analysis of these three trials, we assessed the ability of denosumab every 4 weeks (Q4W) versus ZA Q4W to reduce the risk of SREs across a larger group of baseline characteristics, including ECOG PS, location of bone metastases, number of bone metastases, presence or absence of visceral metastases, and uNTx level, both in the overall population and by tumour type. These characteristics are typically considered by clinicians when evaluating patients for bone-targeted therapy.

2. Materials and methods

2.1. Patients

This was a post hoc analysis of three identically designed, double-blind, double-dummy phase III trials in patients with breast cancer (NCT00321464) [8], prostate cancer (NCT00321620) [9], or other solid tumours (NCT00330759) [10]. Patients with multiple myeloma were excluded (ZA, n = 93; denosumab, n = 87; Fig. 1). Eligible patients had radiographic evidence of at least one bone metastasis, adequate organ function, and ECOG PS ≤2. Exclusion criteria included creatinine clearance <30 ml/min (per ZA prescribing information) [20], life expectancy <6 months, and oral or intravenous bisphosphonate for treatment of bone metastases. Patients provided written informed consent; the trial protocols were approved by each site's ethics committee.

2.2. Trial design and treatment

Patients were randomised to receive subcutaneous denosumab 120 mg or intravenous ZA 4 mg Q4W (or equivalent creatinine clearance–adjusted dose of ZA per the prescribing information). Randomisation was