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Efficacy and safety of denosumab versus zoledronic acid in delaying skeletal-related events in patients with gastrointestinal cancer, pancreas-biliary system cancer, and other rare cancers

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ABSTRACT

Background: Bone is a metastatic site for various types of cancer. Cancer patients in whom bone metastases progress often have skeletal-related events (SREs). Denosumab and zoledronic acid are both bone-modifying agents that prevent the occurrence of SREs. Denosumab has been shown to be superior to zoledronic acid in delaying SREs in various types of cancer, such as breast cancer, lung cancer, and multiple myeloma. However, it is still uncertain whether denosumab is superior to zoledronic acid in delaying the time to SREs in other types of cancers, including gastrointestinal cancer, pancreas-biliary system cancer, and other rare cancers.

Patients and methods: This retrospective study was conducted based on medical records from 2009 to 2015. Eligible patients who had been diagnosed with bone metastases from gastrointestinal cancer, pancreas-biliary system cancer, and rare cancers were included. Patients were assigned to a denosumab group, zoledronic acid group, or group without bone-modifying agent treatment (no-treatment group).

Results: The study included 168 patients. The times to SREs in the denosumab, zoledronic acid, and no-treatment groups were 186 days [95% confidence interval (CI), 96–323 days], 79 days (95% CI, 45–118 days), and 31 days (95% CI, 13–76 days), respectively. Although, a few patients had grade 3 or 4 adverse events in the denosumab and zoledronic acid groups, the bone-modifying agent treatment was not terminated.

Conclusion: From the perspective of the efficacy and safety of denosumab for delaying the time to SREs, denosumab should be used to prevent SREs in patients with bone metastases from gastrointestinal cancer, pancreas-biliary system cancer, and other rare cancers.

1. Introduction

Bone is one of the metastatic sites for various types of cancer. It has been reported that 5–25% of patients with gastrointestinal cancer and pancreas-biliary system cancer suffer from bone metastases [1–4].

Patients with bone metastases frequently develop skeletal-related events (SREs), which include pathologic fractures, spinal cord compression, bone pain necessitating bone surgery or palliative radiation, and hypercalcemia [5]. Once SREs occur in patients with bone metastases, activities of daily life are restricted and quality of life is deteriorates. Zoledronic acid and denosumab are two bone-modifying agents that prevent SREs in patients with bone metastases.

Zoledronic acid is a third generation bisphosphonate that inhibits farnesyl diphosphate synthase and reduces the post-translational prenylation of proteins, such as small GTPases. This results in the lowering of bone turnover followed the inhibition of the bone reparative ability and also results in disruption of metabolic pathways that are essential for cancer cell survival in various types of cancer [6,7]. Previous retrospective study reported that zoledronic acid can delay the time to SREs in patients with bone metastases from colorectal cancer when compared to the time to SREs in these without treatment of zoledronic acid [8]. Denosumab is a fully human monoclonal antibody, which binds to the receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits osteoclast function and bone resorption [9]. It had been reported that by three international, randomized, phase 3 studies that subcutaneous administration of denosumab significantly delay the time to SREs than intravenous administration of zoledronic acid in the patients with bone metastases

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from breast cancer, prostate cancer and non-small cell lung cancer, multiple myeloma and other tumors [10–12]. Both these bone-modifying agents are used parenterally to prevent SREs in patients with bone metastases from various types of cancer. A few randomized studies have shown that denosumab is superior to zoledronic acid for delaying the time to SREs in patients with bone metastases from some types of cancers. However, it is uncertain whether denosumab is superior to zoledronic acid for delaying the time to SREs in patients with bone metastasis from gastrointestinal cancer, including esophageal cancer, gastric and colorectal cancer, and pancreas-biliary system cancer and other rare cancers.

Because there are no previous studies comparing the potency of denosumab and zoledronic acid on delaying the time to SREs in gastrointestinal cancer, pancreas-biliary cancer, and other rare cancers, investigation into which bone-modifying agent (denosumab or zoledronic acid) is more potent in delaying the time to SREs in patients with these cancers is valuable. Therefore, we conducted a retrospective study in our hospital to evaluate the efficacy and safety of denosumab and zoledronic acid in delaying the time to SREs in patients with bone metastases from gastrointestinal cancer, pancreas-biliary system cancer, and other rare cancers.

2. Patients and methods

The medical records of patients who were diagnosed with bone metastases from gastrointestinal cancer, pancreas-biliary system cancer, and other rare cancers, as confirmed using plain radiography, isotopic scintigraphy, computed tomography (CT) or magnetic resonance imaging (MRI), from 2008 to 2015 were retrospectively reviewed. Patients with histopathologically diagnosed cancers were eligible. In eligible patients, zoledronic acid (4 mg/body weight) was intravenously administered or denosumab (120 mg/body weight) was subcutaneously administered once a month depend on physician's choice. SREs were defined as pathologic fractures, spinal cord compression, bone pain necessitating bone surgery or palliative radiation, and hypercalcemia. The time to SREs in patients with bone metastasis was defined as the time from diagnosis of bone metastases, as confirmed on imaging, to the first occurrence of SREs. All statistical analyses were performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA). All toxicities were reviewed in the medical records and evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 [13].

3. Results

3.1. Patient characteristics

We identified 168 patients who were diagnosed with bone metastases on imaging. The patient characteristics are shown in Table 1. Zoledronic acid was intravenously administered in 99 patients (zoledronic acid group) and denosumab was subcutaneously administered in 50 patients (denosumab group). No bone-modifying agent was administered in the remaining 19 patients (no-treatment group). The reason why these patients were not treated any bone-modifying agent was unclear from medical records. The ratio of patients with gastrointestinal cancer, including esophageal cancer, gastric cancer, and colorectal cancer, was higher in each group. A few cases of rare cancers, including sarcoma, neuroendocrine carcinoma, cancer of unknown primary, melanoma, anal cancer, and adrenal cancer, were included in the study subjects (Table 1). Denosumab has been used in our laboratory from 2012 when it was approved in Japan. Therefore, there were no patients who were treated with denosumab from 2009 to 2012.

3.2. Efficacy

As a whole, denosumab was more effective than zoledronic acid in delaying the time to SREs in patients with bone metastases (Fig. 1). The median SRE-free survival times in the denosumab, zoledronic acid, and no-treatment groups were 186 days [95% confidence interval (CI), 96–323 days], 79 days (95% CI, 45–118 days), and 31 days (95% CI, 13–76 days), respectively. The rates of patients without SREs in the denosumab and zoledronic acid groups were significantly higher than those in the no-treatment group (Fig. 1). The number of patients without SREs was significantly higher in the denosumab group than those in the zoledronic acid group (Fig. 1. p=0.0053).

In total, 117 out of 168 patients had SREs during the study period. The ratios of patients who suffered from SREs in the zoledronic acid, denosumab, and no-treatment groups were 67.7%, 60.0%, and 94.7%,

Table 1
Patient's characteristics.

	Zoledronic acid	Denosmab	No-treatment	p-value
No	99	50	19	
Sex				
Female	21(21.2)	15(30.0)	3(15.8)	0.3496
Male	78(78.8)	35(70.0)	16(84.2)	
Performance status				
0	40(40.0)	18(36.0)	9(47.4)	0.6818
1	55(55.6)	30(60.0)	10(52.6)	0.8184
≧2	4(4.0)	2(4.0)	0(0.0)	0.6725
Cancer primary site				
Esophagus	37(37.4)	16(32.0)	6(31.6)	0.7638
Stomach	22(22.2)	9(18.0)	3(15.8)	0.73
Colorectum	15(15.2)	14(28.0)	6(31.6)	0.0896
Pancreas-biliary system	8(8.1)	3(6.0)	1(5.3)	0.8475
Sarcoma	3(3.0)	3(6.0)	2(10.5)	0.3303
Neuroendocrine carcinoma	7(7.1)	3(6.0)	0(0.0)	0.4907
CUP	6(6.1)	1(2.0)	0(0.0)	0.3161
Melanoma	1(1.0)	0(0.0)	0(0.0)	0.7043
Anal	0(0.0)	1(2.0)	0(0.0)	0.3051
Adrenal	0(0.0)	0(0.0)	1(5.3)	0.1561
Month from initial diagnosis of bone metastases to start administration of bone-modifying reagent	0.3	0.29	-	
Bone metastatic type				
Osteolytic	64(64.6)	29(58.0)	12(63.1)	0.7297
Osteoblastic	30(30.0)	17(34.0)	4(21.1)	0.8074
Mixed	5(5.1)	4(8.0)	3(15.8)	0.24
Site of bone metastases				
Pelvis	31(31.3)	18(36.0)	5(26.3)	0.716
Spine	53(53.5)	25(50.0)	12(63.2)	0.6193
Femur	3(3.0)	2(4.0)	1(5.3)	0.8743
Sternum	1(1.0)	2(4.0)	1(5.3)	0.36
Skull	4(4.0)	1(2.0)	1(5.3)	0.7484
Rib	19(19.2)	13(26.0)	4(21.1)	0.6324
Number of metastases				
1	76(76.8)	36(72.0)	14(73.7)	0.8096
2	13(13.1)	10(20.0)	4(21.1)	0.2587
≧3	10(10.1)	4(8.0)	1(5.3)	0.7656
Year of starting bone modifying agent				
2009	13(13.1)	0(0.0)	–	
2010	18(18.2)	0(0.0)	–	
2011	11(11.1)	0(0.0)	–	
2012	12(12.1)	13(26.0)	–	
2013	27(27.3)	5(10.0)	–	
2014	10(10.1)	24(48.0)	–	
2015	8(8.1)	8(16.0)	–	

CUP: Cancer of unknown primary.