Radiation therapy combined with bone-modifying agents ameliorates local control of osteolytic bone metastases in breast cancer

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ABSTRACT

Bone-modifying agents (BMAs) are frequently used for the treatment of bone metastases. Both BMA and radiation therapy (RT) are effective; however, there are few studies that have evaluated the efficacy of the combination treatment. We evaluated the effectiveness of RT + BMA in breast cancer-induced osteolytic bone metastasis as compared to BMA alone. A total of 43 lesions in 25 patients were evaluated. The median follow-up period was 18 (range, 2–90) months. None of the lesions was treated with chemotherapy or molecular targeted drugs during the follow-up period for evaluating the local response. Patients with complete or partial response were considered as responders, while those with stable or progressive disease were considered as non-responders. The rate of response with RT + BMA was significantly higher than that with BMA alone (P = 0.001). The cumulative incidence rate of response at 6 months was 54.4% in the RT + BMA group and 27.5% in the BMA alone group. The median time to response was 4 (range, 2–11) months in the RT + BMA group and 6 (range, 4–16) months in the BMA alone group. The overall survival rate in the responder group (83.1% at 1 year) was significantly higher than that in the non-responder group (37.5% at 1 year) (P = 0.029). In conclusion, RT combined with BMA was found to be more effective than BMA alone for the treatment of osteolytic bone metastasis, which thereby improves the prognosis.

Keywords: radiotherapy; bone-modifying agents; osteolytic bone metastasis; breast cancer

INTRODUCTION

Breast cancer had the highest estimated age-adjusted incidence rate in 2018 in the world [1]. It was associated with a high incidence of bone metastases, and about 70% of the autopsy cases involved bone metastases [2]. Bone metastases may be asymptomatic, but may present with symptoms such as pain, pathological fractures and spinal cord compression. It is well known that radiation therapy (RT) is effective against pain caused by bone metastases [3–6].

Bone-modifying agents (BMAs) are frequently used for the treatment of bone metastases. Two types of BMA are currently available for the treatment of bone metastases in Japan, zoledronic acid (ZA) and denosumab (Dmab). Pamidronic acid is indicated only for osteolytic metastases of breast cancer. The practical guidelines for bone metastasis published by the Japanese Society of Medical Oncology strongly recommend the use of BMA for the treatment of breast cancer-induced bone metastases [7]. In the guidelines, RT is strongly recommended for painful bone metastases. The guidelines published by the Japanese breast cancer society also recommend RT for painful bone metastases. Both BMA and RT are effective, but there are only a few studies that have evaluated the efficacy of the combination treatment.

ZA is one of the bisphosphonates that has been proven to prevent skeletal-related events (SREs) or delay the first SRE [8, 9]. Although the efficacy of ZA has been reported in bone metastases from breast cancer, it is also effective in bone metastasis originating from other types of cancer [10, 11]. Dmab has also been reported to delay the occurrence of SRE [12, 13]. SREs include pathological fracture, spinal cord compression, surgery to bone, RT to bone and hypercalcemia of malignancy [14]. It should be mentioned that RT is a kind of SRE.
At the same time, RT is primarily indicated for the prevention of spinal cord compression or pathological fractures (SRE). Therefore, there is a contradiction that RT, as a treatment to prevent SRE, is also a kind of SRE. In recent years, the concept of a symptomatic skeletal event (SSE) has also been used [15]. Herein, we evaluated the effectiveness of RT for the treatment of bone metastasis as compared with BMAs alone.

MATERIALS AND METHODS

Patients

This study was conducted after obtaining the approval of our institutional review board. All patients provided informed written consent. Patients with osteolytic bone metastases from breast cancer were enrolled in this study. Osteoblastic bone metastases were excluded because of the lack of appropriate methods of response evaluation. Patients with mixed metastases, including osteolytic changes that could be evaluated, were enrolled. Patients who did not undertake response evaluation using imaging modality were excluded. To evaluate the effectiveness of prophylactic radiotherapy, bone metastases of the body weight-bearing spine or pelvic bone in patients having a risk of pathological fractures were evaluated. The medical charts from January 2010 to December 2017 were assessed retrospectively.

Treatment

3D conformal radiation therapy was administered using Clinac 21 EX (Varian Medical Systems, Palo Alto, CA, USA) or Novalis Tx (Varian Medical Systems and BrainLAB, Munich, Germany). The indication of radiotherapy was adjudicated following discussion among breast surgeons, radiation oncologists and orthopedic surgeons about the risk of pathological fractures based on the imaging findings. When a patient had multiple bone metastases, the indication of radiotherapy for each lesion was judged. Gross tumor volume (GTV) was defined as an osteolytic lesion apparent on the images. In patients with mixed metastases, osteoblastic lesions around lytic lesions were also included as GTV. In the case of vertebral metastases, the clinical target volume (CTV) was defined by adding an upper and lower vertebral body. In the case of pelvic bone metastases, CTV was defined as GTV plus a sufficient margin. The planning target volume (PTV) margin was 5–10 mm. The energy of the X-ray used was 6 or 10 MV. The dose fractionation schedule was decided by the radiation oncologist, taking into account the performance status and life expectancy of the patients.

In Japan, two types of BMA are available, ZA and Dmab. ZA has been approved since January 2005 and Dmab has been on sale since April 2012. Both drugs have been available since April 2012, and the breast surgeon selected the one to use. BMA was administered as follows: ZA (4 mg) once every 3–4 weeks and Dmab (120 mg) once every 4 weeks.

Evaluation

The response evaluation was performed by using the same imaging modality as used before treatment, including computed tomography (CT), magnetic resonance imaging (MRI) or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). The timing of imaging was determined by the clinical judgment of the breast surgeon or radiation oncologist.

None of the lesions was treated with chemotherapy or molecular targeted drugs during the follow-up period for evaluating the local response. For calculation of the overall survival (OS) rate, the periods when chemotherapy or molecular targeted drugs were used following treatment of the bony lesions were included. The response to therapy was evaluated based on the revised Response Evaluation Criteria in Solid Tumors guidelines version 1.1 [16]. Patients with complete or partial response (CR or PR, respectively) were considered as responders, and those with stable or progressive disease (SD or PD, respectively) were considered as non-responders.

Statistical analyses

The response rates between RT + BMA and BMA alone groups were compared by Fisher’s exact test. The estimated cumulative response rate and survival rate were calculated by the Kaplan–Meier method. A log-rank test was performed for comparison between the two groups. The follow-up period was calculated from the date of initiation of treatment of the bony lesions (start date of irradiation or BMA administration). The OS rates were calculated on a case-by-case basis and not lesion-wise. In cases with multiple lesions, if one lesion was determined to be CR or PR, it was treated as a responder. The comparison of the time to response was performed using an unpaired t-test. Adverse events were evaluated using Common Terminology Criteria for Adverse Events [17]. A P-value of < 0.05 was considered statistically significant.

RESULTS

Imaging was performed for the 28 lesions before and after RT + BMA and the 15 lesions before and after BMA treatment. In total, 43 lesions in 25 patients were evaluated. The median age of the patients was 62 (range, 42–82) years. The number of patients presenting with a performance status of 0, 1 or 2 was 15, 7 and 3, respectively. The median follow-up period was 18 (range, 2–90) months. The duration of BMA use until evaluation of local control in BMA alone and BMA + RT groups were 5 (range, 2–43) and 4 (range, 2–11) months, respectively. The characteristics of the patients are shown in Table 1. In total, 26 of 43 lesions showed improvement in the imaging findings.

Most of the lytic lesions treated with RT + BMA showed bone reformation (75.0%) (Fig. 1). A reduced FDG uptake and an improvement of the signal abnormalities in MRI were also noted. Although some lytic lesions improved following the administration of BMA alone (33.3%), most remained unchanged or gradually worsened. Only one patient in the BMA-alone group developed an SRE after bone treatment. The SRE was a pathological fracture. The rate of improvement with RT + BMA was significantly higher than that with BMA alone (P = 0.001) (Table 2). The estimated cumulative incidence rate of response at 6 months was 54.4% in the RT + BMA group and 27.5% in the BMA alone group (Fig. 2).

The median time to response was 4 (range, 2–11) months in the RT + BMA group and 6 (range, 4–16) months in the BMA alone group. The time to response tended to be shorter in the RT + BMA group than that in the BMA alone group (P = 0.0581).

The estimated OS rate in the responder group (83.1% at 1 year) was significantly higher than that in the non-responder group (37.5% at 1 year) (P = 0.029) (Fig. 3).
Table 1. Characteristics of bone metastases

| Lesion                  | BMA alone group | RT + BMA group |
|-------------------------|-----------------|----------------|
| Median age, years (range) | 62 (44–82)      | 61 (42–82)     |
| Lesion                  | n = 15 (%)      | n = 28 (%)     |
| Cervical spine          | 0 (0)           | 3 (11)         |
| Thoracic spine          | 10 (67)         | 8 (29)         |
| Lumbar spine            | 5 (33)          | 11 (39)        |
| Sacrum                  | 0 (0)           | 3 (11)         |
| Ilium                   | 0 (0)           | 3 (11)         |
| Bone metastases         | n = 13 (%)      | n = 23 (%)     |
| Solitary                | 0 (0)           | 6 (26)         |
| Multiple                | 13 (100)        | 17 (74)        |
| BMA                     | n = 15 (%)      | n = 28 (%)     |
| Zoledronic acid         | 12 (80)         | 19 (68)        |
| Denosumab               | 3 (20)          | 9 (32)         |
| Extra-osseous lesions   | n = 13 (%)      | n = 23 (%)     |
| Yes                     | 2 (15)          | 4 (17)         |
| No                      | 11 (85)         | 19 (83)        |

Fig. 1. A case showing amelioration of osteolytic bone metastases following administration of zoledronic acid and irradiation of 28 Gy in 7 fractions.

Table 2. Response rate after treatment

| Treatment       | CR or PR | SD or PD |
|-----------------|----------|----------|
| BMA alone       | 5        | 10       |
| RT + BMA        | 21       | 7        |

There were no adverse events (≥ grade 3) related to the combined use of RT + BMA. Adverse events related to BMA included hypocalcemic Grade 2 in one case, Grade 1 in two cases, hypophosphatemic Grade 2 in one case, Grade 1 in three cases, and creatinine increased Grade 1 in two cases.

DISCUSSION

RT is effective in alleviating pain caused by bone metastasis, and hence, it is often used. Since RT can control tumor growth in irradiated bone metastases, it is used not only to relieve pain but also to prevent pathological fractures or spinal cord compression [18, 19]. There is a contradiction that although RT is a kind of SRE, it is used as a treatment to prevent SRE. Contrarily, BMA is an effective treatment that can prevent
RT + BMA suppresses bone metastasis

Because RT and BMA prevent SRE by different mechanisms, their combined use improves the response rate.

The synergistic effects of ZA and RT have been reported in in vitro studies [20, 21]. Kijima et al. compared RT alone and RT + BMA in 23 cases of bone metastasis of renal cell carcinoma (RCC) [22]. The RT + BMA group had a significantly better response rate than the RT alone group. They also reported that SRE-free survival was significantly better with RT + BMA than with RT alone. Similarly, Takeda et al. compared RT alone and RT + BMA for 34 lesions in 27 patients with bone metastases of RCC, and reported that the RT + BMA group had significantly better SRE-free survival than the RT alone group [23]. Both reports suggest the effectiveness of RT + BMA, however, the comparator was RT alone. It is necessary to compare the response to BMA alone, which is the standard treatment for bone metastasis without pain as per the guidelines. However, to the best of our knowledge, this is the first clinical report comparing BMA alone and RT + BMA.

In our study, RT + BMA showed a significantly better response rate than BMA alone. The time to response also tended to be shorter in the RT + BMA group than in the BMA alone group. If the improvement on the image correlates with a reduced risk of pathological fracture, there was a tendency that the prophylactic effect against pathological fracture was noted early in the RT + BMA group. In our study, the OS rate in responders was significantly higher than in non-responders. There are several possibilities for this. Patients with controlled bone metastases may have avoided SRE and maintained quality of life. Patients who responded to the treatment in this study were more likely to also be sensitive to treatment for other metastases than those who did not respond, so systemic treatment may have been successful.

In an in vivo experiment, Arrington et al. transplanted breast cancer cells into the femur of mice and compared the efficacy of RT alone with that of RT + ZA [24]. They reported that mice in the RT + ZA group had significantly higher bone density and bone volume after treatment than those in the RT alone group. Pichon et al. reported that only one patient had a pathological fracture following combined stereotactic body radiation therapy (SBRT) of 27 Gy in 3 fractions along with ZA for body metastases of the vertebrae from various cancers, which was less frequent than following SBRT alone [25]. Thus, it is suggested that the combined use of RT and BMA not only enhances the treatment efficacy but also reduces the adverse effects of fracture caused by irradiation. Dmab has a long serum half-life of about 4 weeks [26]. By repeated administration every 4 weeks, a sufficient concentration can be maintained for a long period of time. ZA has a short serum half-life, but has high affinity for bone, so as bone half-life is ~1 year ZA can be effective for a long time [27]. Therefore, it is expected that the entire irradiation period would be a combination use of BMA and RT.

Our study has several limitations. It was a retrospective one, the number of cases was small, the fractionation dose was not uniform, the use of endocrine-related drugs was not restricted and osteoblastic metastases were excluded. Although imaging was used to evaluate changes in bone metastases caused by improvement of bone quality after treatment, the correlation between the radiological response and reduction of clinical risk for pathological fractures has not yet been proven [28].

In conclusion, RT combined with BMA is more effective than BMA alone for osteolytic bone metastasis treatment. Thus, patients with ameliorated osteolytic bone metastases might expect good prognosis.

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CONFLICT OF INTEREST
None declared.

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