



Diagnosis and treatment of bone metastasis: comprehensive guideline of the Japanese Society of Medical Oncology, Japanese Orthopedic Association, Japanese Urological Association, and Japanese Society for Radiation Oncology

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ABSTRACT

Diagnosis and treatment of bone metastasis requires various types of measures, specialists and caregivers. To provide better diagnosis and treatment, a multidisciplinary team approach is required. The members of this multidisciplinary team include doctors of primary cancers, radiologists, pathologists, orthopaedists, radiotherapists, clinical oncologists, palliative caregivers, rehabilitation doctors, dentists, nurses, pharmacists, physical therapists, occupational therapists, medical social workers, etc. Medical evidence was extracted from published articles describing meta-analyses or randomised controlled trials concerning patients with bone metastases mainly from 2003 to 2013, and a guideline was developed according to the Medical Information Network Distribution Service Handbook for Clinical Practice Guideline Development 2014. Multidisciplinary team meetings are helpful in diagnosis and treatment. Clinical benefits such as physical or psychological palliation obtained using the multidisciplinary team approaches are apparent. We established a guideline describing each specialty field, to improve understanding of the different fields among the specialists, who can further provide appropriate treatment, and to improve patients' outcomes.

INTRODUCTION

Bone metastasis is a devastating condition that can have a negative impact on the lives of patients with advanced cancer in many ways. Patients may experience limitations in the activities of daily living (ADL), decreases in quality of life (QOL), threat of survival

and increases in medical expenses. Large-scale aetiological studies on the prevalence or incidence of bone metastasis have not been conducted in Japan or in other countries. A smaller study on autopsy cases over the period from 1959 to 1997 recorded by the Shikoku Cancer Center in Japan indicated that the frequencies of bone metastasis varied among cancers; they were as high as 75% in cancers such as of the breast and prostate, and as low as 22% in stomach and colon cancers.

Recently, the number of cancer survivors pertaining to breast and colorectal cancers has globally increased, and the 5-year survival rates are $\geq 60\%$ and $\geq 85\%$, respectively. In many countries, the 5-year survival rate for prostate cancer is $\geq 95\%$.¹ An increase in the survival time may increase the incidence of bone metastasis.

Recently, cancer chemotherapy has also made considerable progress in increasing survival of patients with far-advanced cancer. For example, gefitinib improved disease-free survival of epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC).² Pertuzumab and trastuzumab increased the median overall survival (OS) of patients with EGFR 2-positive metastatic breast cancer.³

In addition to these therapeutic measures, agents that target bone metastatic lesions have provided clinical benefits to patients. Medicines targeting bone metastasis include

bone-modifying agents (BMAs) and radiopharmaceuticals. To date, zoledronic acid (ZA) is the most promising of the bisphosphonates (BPs). Denosumab (D-mab), another potent BMA, which targets the receptor activator of nuclear factor κ -B ligand, has also been approved for skeletal-related events (SREs). β Emitters such as strontium-89 (^{89}Sr) and samarium-153 (^{153}Sm) have been shown to be effective for palliation of cancer pain induced by bone metastases.

Furthermore, surgical and interventional measures such as vertebroplasty and ablation have been developed. Caregivers should consider comprehensive strategies to treat patients with bone metastasis, using multimodal measures.

METHODS

The guideline was developed according to the Medical Information Network Distribution Service (MINDS) Handbook for Clinical Practice Guideline Development 2014. The clinical algorithm is depicted in figure 1, and clinical questions (box 1) were derived on the basis of this algorithm.

Medical evidence was extracted from published articles describing meta-analyses or randomised controlled trials (RCTs) in PubMed, the Cochrane Library, CINAHL and the Japan Medical Abstracts Society. A systematic literature search was performed by Japan

Library Association, mainly from 2003 to 2013. Medical evidence was evaluated critically and divided into four levels, A–D, covering estimated effects with higher reliability (A) to those that were mere speculations (D). On the basis of these levels, preliminary recommendations were elicited. Forward questions were fundamentally written in Patient, Intervention, Comparison, Outcome style. For forward questions, the synopsis of recommendations was assessed as strong or weak. To achieve consensus, majority voting (>70%) of the conference was adopted according to the Delphi technique.

RESULTS

Diagnostic procedures

Symptoms (CQ 1)

'Spinal cord compression (SpCC) and hypercalcaemia need to be treated emergently'. Among SREs, SpCC and malignant hypercalcaemia (MHC) should be emergently treated. The frequencies of SpCC and MHC are reported to be 3% and 13% in breast cancer, 8% and 1% in prostate cancer, and 4% and 4% in lung cancer, and other cancers, respectively.^{4–6} These cancers are asymptomatic in the very early stage; therefore, careful examination is required. Symptoms of SpCC are back pain, listlessness of the lower limb and cauda equina syndrome.^{7–8} Symptoms of MHC are anorexia, nausea,

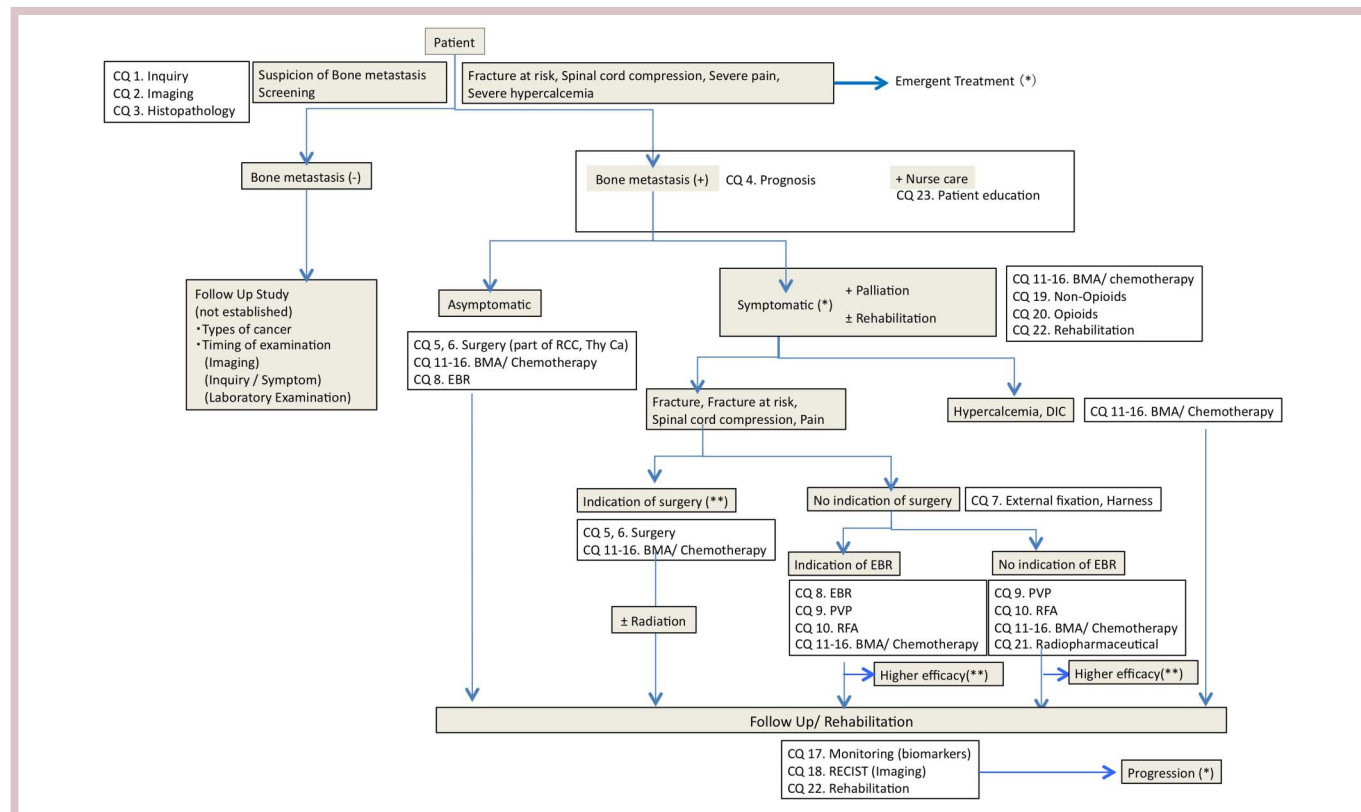


Figure 1 Clinical algorithm of diagnosis and treatment of bone metastasis guideline. BMA, bone-modifying agent; CQ, Clinical Question; DIC, disseminated intravascular coagulation; EBR, external beam radiation; PVP, percutaneous vertebroplasty; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumor; RFA, radiofrequency ablation; thy CA, thyroid cancer.

Box 1 Table Clinical Questions and Answers

- CQ 1. What are the symptoms induced by bone metastasis that necessitate emergent treatment?
A. Spinal cord compression and hypercalcemia need to be treated emergently.
- CQ 2. What kinds of imaging are useful to diagnose bone metastasis?
A. Bone scintigraphy, ¹⁸F-fluorodeoxyglucose positron emission tomography/CT and MRI are useful to diagnose bone metastasis.
- CQ 3. When is pathological examination needed?
A. It is needed when diagnosis is difficult, in primary unknown cancers, or in cases with multiple cancers.
- CQ 4. Does the presence of bone metastasis affect the patient's prognosis?
A. Bone metastasis at diagnosis might affect the prognosis.
- CQ 5. Is surgery beneficial to treat spinal metastasis with spinal cord compression?
A. Surgery is effective for functional improvement.
(Weak, Evidence B)
- CQ 6. Is surgery beneficial to treat long bone metastasis with pathological fracture or those at risk?
A. Surgery is beneficial for pain relief and/or functional improvement.
(Strong, Evidence C)
- CQ 7. Is the use of instrumentation beneficial in bone metastasis?
A. Instruments are beneficial for treatment and prevention of pathological fracture.
(Strong, Evidence C)
- CQ 8. Is external beam radiation beneficial in bone metastasis?
A. External beam radiation is beneficial for relief from pain.
(Strong, Evidence A)
- CQ 9. Is vertebroplasty beneficial in bone metastasis?
A. Vertebroplasty is beneficial for inoperable cases to sooner relieve pain on movement.
(Weak, Evidence C)
- CQ 10. Is ablation is beneficial in bone metastasis?
A. Ablation is beneficial to relieve pain.
(not approved in Japan, Evidence C)
- CQ 11. Are bone-modifying agents (BMAs) beneficial in bone metastasis of lung cancer?
A. Zoledronic acid (ZA) and denosumab (D-mab) are beneficial to SREs, regardless of symptoms.
(Strong, Evidence A)
- CQ 12. Are BMAs beneficial in bone metastasis of breast cancer?
A. ZA, pamidronic acid and D-mab are beneficial in treating SREs.
(Strong, Evidence A)
- CQ 13. Are BMAs beneficial in bone metastasis of prostate cancer?
A. ZA and D-mab are beneficial in treating SREs among castration resistant cases.
(Strong, Evidence A)
- CQ 14. Are BMAs beneficial in bone lesions of multiple myeloma?
A. Bisphosphonates are beneficial in treating SREs.
(Strong, Evidence A)
- CQ 15. Are BMAs beneficial in bone metastasis of the other cancers?
A. BMAs are beneficial in treating SREs of the other cancers.
(Weak, Evidence C)
- CQ 16. What are the adverse events with BMAs to be cautious of?
A. Osteonecrosis of the jaw, renal toxicity, hypocalcaemia and flu-like illness should raise caution.
- CQ 17. What kinds of biomarkers are useful to monitor the effects?
A. No biomarkers are recommended for practice.
- CQ 18. What kinds of imaging are useful to monitor the effects of therapeutic measures to bone metastasis?
A. Osteolytic or mixed bone metastases with soft tissue components can be monitored with CT or MRI.
- CQ 19. Are non-opioids effective to relieve pain of bone metastasis?
A. Non-opioids are effective to relieve pain.
(Strong, Evidence C)
- CQ 20. Are opioids effective to relieve pain of bone metastasis?
A. Opioids are effective to relieve pain.
(Strong, Evidence C)
- CQ 21. Are radiopharmaceuticals effective to relieve pain of bone metastasis?
A. Radiopharmaceuticals are beneficial to relieve pain in valid cases with the other measures.
(Weak, Evidence B).
- CQ 22. Is Rehabilitation beneficial in bone metastasis?
A. Rehabilitation is beneficial to improve activities of daily living and quality of life, and to prevent disuse syndrome.
(Weak, Evidence C).
- CQ 23. Is patient education beneficial in bone metastasis?
A. Patient education is beneficial in bone metastasis.

fatigue, polyuria, muscle weakness, hyporeflexia, confusion, tremor, torpor, etc.⁹

Imaging (CQ 2)

'Bone scintigraphy (BS), ¹⁸F-fluorodeoxyglucose positron emission tomography (PET) and magnetic resonance imaging (MRI) are useful to diagnose bone metastasis'. BS, ¹⁸F-fluorodeoxyglucose PET, and MRI are recommended as practical imaging measures to detect bone metastasis. A meta-analysis of BS combined with single-photon emission CT (SPECT) indicated that the sensitivity was 86% and specificity was 81%.¹⁰ A meta-analysis showed that the sensitivity of PET combined with CT (PET/CT) was 90% and the specificity of this combination was 97%.¹⁰ For cancers with a high risk of metastasis, including breast cancer, PET/CT is recommended in the National Comprehensive Cancer Network (NCCN) guideline.¹¹ PET is better than CT in diagnosing osteolytic lesions; however, when combined with CT, its ability to detect osteoplastic lesions increases.¹² MRI, particularly whole-body MRI, can detect bone metastasis with sensitivity and specificity of 91% and 95%, respectively.¹³ Using diffusion-weighted MRI (DW-MRI), the specificity increases to 96%.¹³ Radiography and CT are useful in evaluating the size of lesions or the rigidity of skeletal structures;¹⁴ sodium ¹⁸F-fluoride has high diagnostic potential and accuracy.¹⁵

Histopathology (CQ 3)

'Histopathology is needed when diagnosis is difficult, and in primary unknown cancers or in cases with multiple cancers'. In many cases where bone metastasis is confirmed based on the patient's clinical course, histopathological analysis is often omitted; however, in case of an unknown primary and ≥ 2 synchronous or metachronous cancers, it is necessary.¹⁶ Tissue materials can be obtained using CT-guided percutaneous needle or open biopsy; aspiration cytology, despite the lower accuracy, is an alternative.^{17 18}

Prognosis (CQ 4)

'Bone metastasis at diagnosis might affect the prognosis'. In the Danish National Patient Registry (DNPR; 1997–2007), the 5-year survival rates of patients with prostate cancer with and without bone metastasis at diagnosis were 3% and 56%, respectively.¹⁹ Among registrants in the Surveillance Epidemiology, and End Results programme in the USA (1999–2005), the HRs for risk of death in patients with prostate cancer with and without SREs were 10.2 and 6.6, respectively.²⁰ In DNPR, the 5-year survival rates of patients with breast cancer with and without bone metastasis at diagnosis were 8.3% and 75.8%, respectively.²¹ Katagiri *et al.*²² proposed a scoring system that correlated with prognosis.

TREATMENTS

Surgery

Metastatic spinal tumour (CQ 5)

'It is weakly suggested that surgery is effective for functional improvement'. Surgery for spinal metastasis is beneficial for tumour resection as well as for relieving pain and improving neurological manifestations. Significant improvement pertaining to walking was observed in patients treated with surgery plus radiation compared with that in patients treated with radiation alone;²³ however, a report by Rades *et al.*²⁴ did not confirm these results. Surgery for spinal metastases because of radiosensitive tumours such as multiple myeloma, malignant lymphoma and leukaemia, should be avoided.^{23–25} Surgery is not recommended in cases where ≥ 48 h are passed since complete paralysis or when prognosis is predicted within 6 months.^{23 26} For spinal metastasis of breast or prostate cancer, hormonal treatment or radiation is the first choice before surgery.^{23 27} Operative methods for spinal metastasis differ according to the sites and sizes of metastases. A posterior approach, decompression by laminectomy and spinal fixation, are the most common procedures. Total *en bloc* spondylectomy may be beneficial when the lesion is single and long survival is expected.²⁶

Metastasis to long bones (CQ 6)

'It is strongly suggested that surgery is beneficial for pain relief and/or functional improvement'. Surgery is beneficial to repair mechanical ruptures, relieve pain, and improve diseased limb function and QOL during pathological fractures or at risk fractures.^{28–30} The outcomes of surgery for at risk fractures are better than those of surgery for pathological fractures in many aspects such as those concerning blood loss, period of hospitalisation and functional recovery.^{31 32} Mirels reported a scoring system for risk of fracture.^{33–35} Linden claimed that axial cortical involvement >30 mm and circumferential cortical involvement $>50\%$ are predictive of fracture.³⁶ Operative methods are divided into two types: internal fixation and prosthesis replacement.

External fixation (CQ 7)

'It is strongly suggested that instruments are beneficial for treatment and prevention of pathological fractures'. Braces are used for various purposes such as relief from pain, and preservation and stabilisation of diseased bone. Braces are appropriate for postoperative fixation. For pathological and at risk fractures, surgery is superior to non-surgical conservative treatment in increasing QOL. Among conservative approaches such as resting and rehabilitation, braces and body casts, braces are best for thoracic and lumbar spinal compression (compression rate $<50\%$) without neurological symptoms.³⁷ Emergently, external fixation using splint and weight-bearing orthoses such as crutches are suitable for long-bone metastasis.

External beam radiotherapy (CQ 8)

'It is strongly suggested that external beam radiation (EBR) is beneficial for relief from pain'. EBR can relieve pain caused by bone metastasis without SpCC or pathological fracture in 59–73% of cases,^{38–40} and neuropathic pain in 53–61% of cases.⁴¹ Dose fractionation is performed using multifractionated radiation (MFR) such as 30 Gy divided into 10 fractions (30 Gy/10 Fr or 20 Gy/5 Fr). Single-dose irradiation (SDI) such as 8 Gy is also performed. In some studies, the effects on pain using either MFR or SDI were identical; pain relief was achieved in 60–73% patients using SDI and in 59–73% patients using MFR.^{38–40} Pain relief was achieved within 3 weeks in half the total number of cases where the treatment was effective. Neuropathic pain was relieved in 53% of patients treated using SDI and in 61% of patients treated using MFR.⁴¹ Regarding the duration of pain relief, there was no significant difference between SDI and MFR; the median time for recurrence was 2.4 months after SDI and 3.7 months after MFR.⁴¹ The average duration of pain relief was 29 weeks after SDI and 30 weeks after MFR.⁴² Additional radiation is performed in 7–8% of MFR patients and in 20–22% of SDI patients.^{38–40} Additional radiation relieved pain in 58% of patients in another study comprising 33–66% of patients in whom the first radiation treatment was not effective.⁴³ Additional SDI and MFR relieved pain in 66–70% and 33–57% of patients, respectively.⁴³ It is not clear whether EBR can completely prevent pathological fracture. The incidence of fracture was identical by both methods (SDI=3.3% vs MFR=3.0%).⁴⁰ Thus, fixation of the damaged cortex of a femoral metastasis >30 mm in longitudinal length is necessary before irradiation.⁴⁴ The frequency of SpCC after EBR is reduced to 2.8–3.0% using SDI, and 1.6–1.9% using MFR.^{39 40}

Vertebroplasty (CQ 9)

'It is weakly suggested that vertebroplasty is beneficial for inoperable cases to sooner relieve pain on movement'. Percutaneous vertebroplasty (PVP) can relieve pain associated with movement of weighted vertebrae or relieve neuropathic pain when surgery is not indicated. Complications such as acute phase of infection, haemorrhagic diathesis and severe heart disease, are contraindicated.⁴⁵ PVP is applicable for radio-resistant patients, and an additive effect is obtained by combining it with radiotherapy. PVP relieves pain within 1–3 days.⁴⁶ Polymethyl methacrylate is commonly used as cement. Extreme care should be taken to not leak cement out of the targeted vertebral body. As the therapeutic effect does not correlate with cement volume, it is recommended that only the minimum amount needed should be used. Balloon kyphoplasty is performed to attempt kyphosis of the diseased vertebra to avoid leakage.⁴⁷

Ablation (CQ 10)

'Ablation is beneficial for pain relief'. Radiofrequency ablation (RFA) is used to kill tumours by heating, using

image-guided needle centesis. RFA is one measure to relieve pain from bone metastasis, based on results from two RCTs.^{47 48} RFA is used to treat resistant patients or patients unresponsive to radiotherapy; however, in Japan, it is not covered by medical insurance. Cryoablation is an alternative method to relieve pain.⁴⁹

Bone modifying agents

Lung cancer (CQ 11)

'It is strongly suggested that zoledronic acid (ZA) and denosumab (D-mab) are beneficial to SREs, regardless of symptoms'. RCTs comparing ZA with placebo that target NSCLC (50% of total participants) and small cell lung cancer (8%) have shown the occurrence rate of SRE treated with ZA to be 38.9% and that with placebo to be 48.0% ($p=0.039$).^{50 51} RCT comparing ZA with D-mab showed that the duration of the first SRE was 16.3 months using ZA and 20.6 months using D-mab (40% were NSCLC).⁵² Non-inferiority of D-mab to ZA is proven ($p=0.06$). For SREs that needed radiotherapy, the grade of pain and dosage of opioids were significantly suppressed in the D-mab group.⁵³ Exploratory analysis of this trial indicated that OS was prolonged in the D-mab group.⁵⁴

Breast cancer (CQ 12)

'It is strongly suggested that ZA, pamidronic acid (PA) and D-mab are beneficial to SREs'. An RCT comparing PA with placebo showed that PA could significantly decrease SREs of breast cancer from 4.0 to 2.5 per person-year. PA was effective with chemotherapy or hormonal treatment.⁵⁵ In the breast cancer subgroup, ZA significantly decreased SREs by 20%.⁵⁶ Improvements in QOL score, progression free survival (PFS) and OS were not achieved. Ibandronate decreased SREs and improved pain and QOL scores.^{57–60} An RCT comparing ZA with D-mab showed that D-mab significantly decreased the first SREs by 18% and the second SREs by 23%.^{61 62} Improvement in QOL score was achieved in 37.1% of the D-mab group and in 31.4% of the ZA group.^{61 62} No improvements were observed in PFS and OS. A meta-analysis showed 8 of 10 papers reporting BPs to significantly reduce SREs (relative risk (RR) = 0.85). ZA significantly reduced SREs compared with PA (RR=0.80).⁶³ D-mab significantly reduced SREs compared with ZA (RR=0.78).

Prostate cancer (CQ13)

'It is strongly suggested that ZA and D-mab are beneficial to SREs of castration resistant cases'. Hormonal treatment is effective in most prostate cancers, regardless of bone metastasis. In many cases, combined androgen blockade with lutenising hormone-releasing hormone analogue, antagonist and a non-steroidal antiandrogen agent, is used.⁶⁴ Prostate cancer is sensitive to hormonal treatment in the first 2 years on average, but finally turns into castration-resistant prostate cancer (CRPC).^{65 66} Clodronate combined with hormonal treatment

prolongs survival compared with placebo (RR=0.77).⁶⁷ The survival benefit of ZA or D-mab with hormonal treatment is controversial. An RCT comparing ZA with placebo against CRPC indicated that the frequency of SREs was 33.2% in the ZA group and 44.2% in the placebo group ($p=0.021$). OS was longer in the ZA group than in the placebo group (546 vs 464 days, $p=0.094$).^{5 68} An RCT comparing D-mab with ZA against CRPC showed that the duration to the first SRE was 20.7 months in the D-mab group and 17.1 months in the ZA group ($p=0.0085$).⁶⁹

Multiple myeloma (CQ 14)

'It is strongly suggested that BPs are beneficial to SREs'. Combination therapy of PA with chemotherapy for bone lesions reduced the occurrence of SREs compared with chemotherapy alone (24% vs 41%, $p<0.001$).⁷⁰ Clodronate with chemotherapy inhibited the progression of osteolytic lesions compared with chemotherapy alone (12% vs 24%, $p=0.026$).⁷¹ An RCT comparing PA with ZA to treat breast cancer and multiple myeloma showed that they had similar effects.⁷² An RCT comparing the first-line treatment using ZA plus chemotherapy with that of clodronate plus chemotherapy showed that SREs were significantly suppressed in the ZA group (HR=0.74, $p=0.0004$).⁷³ A meta-analysis comparing BPs with placebo showed that BPs significantly suppressed pathological fracture of vertebrae (RR=0.74) and occurrence of SREs (RR=0.80), and improved pain (RR=0.75).⁷⁴ A better survival benefit with ZA was achieved compared with clodronate (HR=0.84, $p=0.0118$).⁷³ A meta-analysis comparing all types of BPs to placebo showed that BPs had no survival benefits. However, ZA showed a survival benefit (HR=0.61).⁷⁴ An RCT comparing ZA with D-mab showed that D-mab significantly prolonged the duration to the first SRE (14.4 vs 19.0 months, $p=0.022$).⁷⁵ However, the survival benefit with D-mab was inferior to that with ZA (HR=2.26).

An RCT comparing melphalan plus prednisone (MP) with MP plus bortezomib (VMP) showed that VMP suppressed the progression of bone lesions and decreased the need for radiation.^{76 77}

Other cancers (CQ 15)

'It is weakly suggested that BMAs are beneficial to SREs of the other cancers'. In an RCT comparing ZA with placebo, other cancers such as gastrointestinal cancer accounted for 10% of the total.⁵⁰ Subset analysis showed that ZA had a similar effect on SREs. A meta-analysis of three RCTs comparing ZA with D-mab showed that D-mab significantly suppressed SREs.⁷⁵ No survival benefit of D-mab was observed.

Combination with radiotherapy

There are no meta-analyses of combination treatment with BMAs and radiation; however, >200 retrospective studies have been reported,^{78–82} where radiation with

BPs has been effective. The American Society of Clinical Oncology (ASCO) guideline for bone metastasis of breast cancer recommends radiation with BPs for SREs.^{83 84}

Adverse events (CQ 16)

'Osteonecrosis of the jaw (ONJ), renal toxicity, hypocalcaemia and flu-like illness should be cautious'.

Osteonecrosis of the jaw

The frequency of ONJ induced by BPs varies from 1% to 10%.⁸⁵ D-mab induces ONJ with the same frequency.⁶¹ Longer duration of BP injection increases the risk; the incidence at 4–12 months is 1.5%, whereas that at 27–48 months is 7.7%.⁸⁵ Appropriate oral hygiene decreases ONJ.^{86 87} Patients should maintain good oral hygiene, and have dental examinations and preventive dental treatment prior to initiating therapy.⁸³ Tooth extraction, oral infection and artificial dentures are risk factors.⁸⁸ Extraction should be completed before administration and takes 14–21 days to recover from.⁸⁹

Renal toxicities

The frequency of renal toxicities with ZA is 4.9–44.5%.^{6 51 52 61 69 90–93} However, many of these toxicities remain within grade 1 or 2 and are reversible. Risk factors are older age (>65 years), combination use with non-steroidal anti-inflammatory drugs (NSAIDs) or cisplatin, diabetes mellitus and multiple myeloma. Multiplicity and longer duration (>2 years) increase the risk.⁹³ The median time to occurrence is 4.7–5.4 months.^{94 95} The risk for acute renal failure increases in low creatinine clearance rates (CCR, <60 mL/min).^{52 61} Dose modification according to CCR is recommended. The frequency of renal toxicities with D-mab is 3.3–14.7% for all grades and 0.4% for grades >3.^{52 61 69}

Hypocalcaemia

The frequency of hypocalcaemia with ZA is 3.3–9.0%.^{53 61 69 75 94} The frequency of clinical symptoms or for grades >3 is 1.0–4.7%.^{53 69 74 96} The frequency with D-mab is 1.7–10.8% for all grades and 1.3–5.1% for grades >3.^{53 61 68 75} Administration of BMA without vitamin D and oral calcium elevates the frequency of hypocalcaemia by 5–6 times.^{53 61 68} In case of D-mab, a daily supply of vitamin D (natural form; 400 IU) and oral calcium (500 mg) is necessary. Risk factors are low serum calcium before treatment, and renal dysfunction.^{97 98} The onset is ≤10 days in most cases and early monitoring is important.

Others

Other adverse events include flu-like reactions, which occur within 3 days; their frequencies are 17.7–22.0% with ZA and 8.4–10.4% with D-mab.^{61 68 92} Atypical femoral fractures are rare severe adverse events associated with ZA.⁹⁹

Monitoring of treatment

Biomarkers (CQ 17)

'No biomarkers are suggested for practice'. Broun reported that elevation of type I collagen cross-linked N-telopeptide (NTx) or bone-specific alkaline phosphatase during treatment indicated poor prognosis of lung and prostate cancers with bone metastases.¹⁰⁰ Coleman *et al*¹⁰¹ reported that, in cases with high urine NTx (uNTx), SRE or disease progression risks were 4–6 times higher than those with low uNTx. The prognostic value of uNTx is apparent, but the predictive value for therapeutic effects is not. Longer survival was achieved in cases where uNTx was normalised using ZA compared with cases where uNTx was not normalised (RR=0.52).¹⁰² Clinical events such as death or SREs were preceded by elevation of bone turnover markers (BTMs) in >90% of cases. Inverse phenomena were observed only in 5.6% of breast cancers and 5.9% of prostate cancers.¹⁰³ The ASCO guideline does not recommend measurement of BTMs to monitor BMA effects.⁸⁷

Imaging (CQ 18)

'Osteolytic or mixed bone metastases with soft tissue components can be monitored with CT or MRI'. Evaluation using radiography, BS, or PET is not suitable for bone metastasis, according to the Response Evaluation Criteria in Solid Tumor V.1.1.¹⁰⁴ Osteolytic and mixed lesions can be evaluated by CT or MRI. There are no imaging devices for evaluating osteoplastic lesions. The Prostate Cancer Working Group 2 in the USA set the criteria for progressive disease of osteoplastic new lesions using BS.¹⁰⁵ The bone scan index (BSI) is a quantitative method for detecting possible metastatic lesions as a percentage of total bone quantity. Changes in BSI before and after treatment show better correlation with prognosis than changes in prostate specific antigen (PSA).¹⁰⁶ DW-MRI can measure water diffusion, which reflects cellularity as an apparent diffusion coefficient (ADC).¹⁰⁷ The possibility of ADC to predict tumour response clinically is now under verification.

Others

The patient-reported outcome (PRO) measures a patients' own health condition by self-reporting. PRO has recently been considered to provide a real benefit to patients; for example, McGill-Melzack reported benefits of using the pain intensity scale and brief pain inventory scale.^{108 109}

Palliation

Non-opioids (CQ 19)

'It is strongly suggested that non-opioids are effective to relieve pain'. The WHO has developed a three-step ladder for cancer pain, and non-opioids are the first choice. No RCTs have compared non-opioids on a large scale.^{110 111} Joishy and Walsh¹¹² reported that the dosage of morphine could be reduced by ketorolac. Combined effects of opioids and non-opioids are still

controversial.^{110 111} Other reviews have concluded that acetaminophen, NSAIDs and steroids are effective. Steroids are not analgesics but are effective for reducing pain flare induced by radiation.¹¹³

Opioids (CQ 20)

'It is strongly suggested that opioids are effective to relieve pain'. Many observational studies indicate that opioids are effective for pain of bone metastases.^{114 115} Comparison between the fentanyl patch and codeine-acetaminophen combination indicated that fentanyl had significantly superior effects.¹¹⁶ Bone metastatic pains are divided into two types: continuous pain at rest and breakthrough pain. The treatment strategy differs for each type. A systemic review found that the utility of rescue drugs for breakthrough pain and the dosage should be individually adjusted.¹¹⁷ For neuropathic pain, when not fully relieved by opioids, combination use with adjuvant analgesics should be considered.

Radiopharmaceuticals (CQ 21)

'It is weakly suggested that radiopharmaceuticals are beneficial to relieve pain in valid cases with the other measures'. A meta-analysis showed that radiopharmaceuticals were effective for 1–6 months.¹¹⁸ Two-thirds of patients treated using ⁸⁹Sr showed pain relief.^{119 120} ⁸⁹Sr contributed to reducing the dosage of analgesics and improving patients' QOL.¹¹⁸ In Japan, ¹⁵³Sm and rhenium-186 are not covered by medical insurance. ⁸⁹Sr is particularly effective for prostate cancer because it is highly taken up by osteoplastic lesions as calcium mimetics.^{118 120} In many reports, the effect of ⁸⁹Sr is identical to that of EBR, but the incidences of nausea and vomiting are lower using ⁸⁹Sr.¹¹⁹ The effect of a combination of ⁸⁹Sr and EBR remains controversial.^{118 119} The combination of ⁸⁹Sr and ZA was effective for prostate cancer.¹²¹ An RCT comparing the combination of ⁸⁹Sr and ZA with ⁸⁹Sr alone for asymptomatic bone metastasis of NSCLC showed that the combination reduced the occurrence of SREs and improved OS.¹²² The antitumour effects of ⁸⁹Sr, including reduction of PSA levels or improved survival in prostate cancer, are reported in a few cases.¹²³ ⁸⁹Sr can be administered every 3 months. Reported adverse events include bone marrow suppression; thrombocytopenia is most common (15–50%), but the grade is <2 in most cases.^{118–120} Leucocytopenia is less frequent; however, caution is required when ⁸⁹Sr is combined with chemotherapy. An RCT showed that ²²³Ra significantly increased OS and the time to occurrence of SREs with low toxicities compared with placebo.¹²⁴

Rehabilitation and patient education (CQ 22, 23)

'It is weakly suggested that rehabilitation is beneficial to improve ADL and QOL, and to prevent disuse syndrome'. Rehabilitation is beneficial in terms of providing pain relief, prevention of degeneration, improvement of ADL and QOL, and increased survival. An RCT

comparing treatment plus rehabilitation with treatment alone of symptomatic spinal metastasis showed significant improvements in pain score ($p < 0.001$), dosage of analgesics ($p < 0.001$) and depression status.¹²⁵ Tang retrospectively showed that rehabilitation for spinal metastasis significantly improved the scores of functional independence measures and recovered function.¹²⁶ Resting in bed is good for preventing SREs but leads to reduction of ADL and QOL, and results in disuse syndrome, which can cause sepsis or respiratory failure and increase the risk of death.

'Patient education is beneficial to bone metastasis'. PRO-SELF is an education programme provided in the patient's home and by telephone. An RCT comparing PRO-SELF with normal care showed that knowledge of cancer pain reduced pain scores.^{127–129} A systematic review of educational intervention showed that it could reduce pain scores but could not improve patient's QOL.¹³⁰

CONCLUSION

Diagnosis to treatment for bone metastasis needs various types of measures, specialists and caregivers. Consideration of the status of diseases, as well as of the background of patients, should be taken. For this purpose, a multidisciplinary team is necessary. In treating, multidisciplinary meetings are helpful. To collaborate with other specialists, a guideline describing each specialty field is necessary. The clinical benefits, such as physical or psychological palliation, obtained by the multidisciplinary team approaches, are described in some papers.^{131–133} Further, registration in addition to multidisciplinary team approaches could be advantageous to monitor the therapeutic outcomes according to the guideline.

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