Case Report

Two cases of prostate cancer with disseminated carcinomatosis of the bone marrow treated with novel hormonal agents

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Abbreviations & Acronyms
ALP = alkaline phosphatase
CT = computed tomography
DCBM = disseminated carcinomatosis of the bone marrow
DIC = disseminated intravascular coagulation
LD = lactate dehydrogenase
NHA = novel hormonal agents
OS = overall survival
PCa = prostate cancer
PSA = prostate-specific antigen

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Introduction: Disseminated carcinomatosis of the bone marrow in prostate cancer is rare and has a poor prognosis. Although strong evidence suggests that novel hormonal agents improve the prognosis of metastatic prostate cancer, their effectiveness in cases of disseminated carcinomatosis of the bone marrow remains unclear.

Case presentation: We encountered two cases of prostate cancer with disseminated carcinomatosis of the bone marrow at the time of initial diagnosis. One patient was treated with enzalutamide, abiraterone, docetaxel, cabazitaxel, denosumab, and radium-223 and died 38 months after the initial diagnosis. The other patient was treated with apalutamide and denosumab, and had progression-free survival for 17 months after the initial diagnosis.

Conclusion: These results suggest that novel hormonal agents may improve the prognosis of prostate cancer even in patients with disseminated carcinomatosis of the bone marrow.

Key words: androgen receptor-axis targeted agents, bone marrow involvement, bone marrow metastasis, new hormonal agents, radium-223.

Keynote message

Treatment with novel hormonal agents may improve the outcomes of prostate cancer patients with disseminated carcinomatosis of the bone marrow when compared with those treated with vintage hormonal therapy.

Introduction

DCBM is a condition in which diffuse bone marrow invasion of cancer cells results in leucoerythroblastic anemia, thrombocytopenia, leukopenia, and DIC. DCBM is rare and is usually associated with gastric, breast, lung, and PCa.[1] DCBM in PCa is not mentioned in any of the EAU, NCCN, or Japanese guidelines. Several case reports of DCBM in PCa have been published, but most describe cases treated with vintage hormonal therapies, and the prognosis was poor.[2] It is assumed that NHA improve the prognosis of PCa associated with DCBM; however, this outcome has rarely been reported.

Here, we report two cases of PCa with DCBM treated with NHA.

Case presentation

Case 1: A 66-year-old man with no remarkable medical history presented to our hematology clinic with purpura, thigh pain, and fatigue. A bone marrow biopsy was performed by a hematologist because the complete blood count was notable for the appearance of myelocytes and metamyelocytes, mild anemia with a hemoglobin of 10.9 g/dL, and thrombocytopenia with a platelet count of 33 000/μL; It revealed a PSA- and NKX3.1-positive adenocarcinoma on immunostaining, confirming bone marrow invasion of PCa (Fig. 1a–c). The patient was then referred to our department. Initial laboratory studies revealed elevated levels of PSA (1,

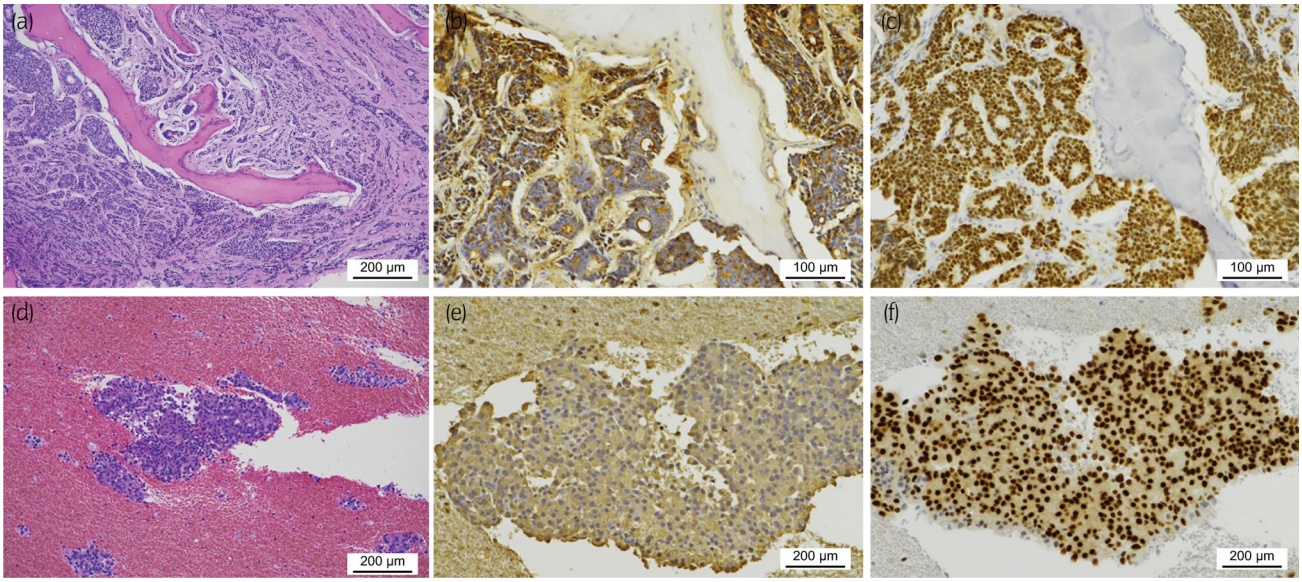

Fig. 1 (a) Hematoxylin and eosin stain of bone marrow biopsy of Case 1. (b) PSA immunostaining of bone marrow biopsy of Case 1. (c) NKX 3.1 immunostaining of bone marrow biopsy of Case 1. (d) Hematoxylin and eosin stain of bone marrow puncture of Case 2. (e) PSA immunostaining of bone marrow puncture of Case 2. (f) NKX 3.1 immunostaining of bone marrow puncture of Case 2.

664 ng/mL), LD (583 IU/L), and ALP (692 IU/L). However, DIC was not observed. A prostate biopsy showed a Gleason score of 4 + 5, Grade Group 5 adenocarcinoma. CT revealed an enlarged unilateral obturator and internal iliac lymph nodes, but no obvious visceral metastases were observed. Bone scintigraphy revealed diffuse bone metastases (Fig. 2). Based on these results, we diagnosed the patient with PCa cT3N1M1b and DCBM.

Treatment was initiated with degarelix and bicalutamide, and the PSA level decreased to 5.08 ng/mL after 4 months. LDH and ALP levels also decreased quickly, anemia and thrombocytopenia improved, and myelocytes and metamyelocytes were not observed in the peripheral blood. However, 2 months later, the patient progressed to metastatic castration-resistant PCa; thus, bicalutamide was changed to enzalutamide, and concomitant treatment with denosumab was initiated. Six courses of radium-223 were administered during the period of enzalutamide treatment, and the PSA level decreased from 25.49 to 1.23 ng/mL. The administration of enzalutamide allowed the patient to remain DCBM-free for 15 months. The administration of radium-223 caused mild leukopenia, which was quickly resolved after the completion of six courses. During the administration of docetaxel, myelocytes and metamyelocytes reappeared in the peripheral blood. The patient was no longer able to receive active treatment and died 38 months after diagnosis (Fig. 2).

Case 2: A 76-year-old man with no remarkable medical history presented to our gastroenterology clinic with anorexia and weight loss. He was referred to our department with a strong suspicion of PCa because of the diffuse and heterogeneous osteosclerosis noted on CT and a remarkably high PSA level (3278 ng/mL). Initial laboratory studies revealed elevated LD (423 IU/L) and ALP (509 IU/L) levels. A complete blood count revealed pancytopenia with leukocyte and platelet counts of 2800 and 60 000/μL, respectively, and hemoglobin of 9.3 g/dL. Myelocytes, metamyelocytes, and erythroblasts were observed in the blood samples. Bone marrow aspiration and biopsy revealed PSA- and NKX3.1-positive adenocarcinoma on immunostaining, confirming the bone marrow invasion of PCa (Fig. 1d–f). A prostate biopsy showed a Gleason score of 5 + 5, Grade Group 5 adenocarcinoma. CT revealed enlargement of the unilateral external iliac and para-aortic lymph nodes. CT also revealed probable bladder and seminal-vesicle invasion of the PCa. Bone scintigraphy revealed diffuse bone metastases (Fig. 3). Based on these results, we diagnosed the patient with PCa cT4N1M1b and DCBM.

Treatment with apalutamide, goserelin acetate, and concomitant denosumab was initiated. LD and ALP levels quickly decreased, and anemia and thrombocytopenia improved. After 6 months, myelocytes, metamyelocytes, and erythroblasts were not observed in the peripheral blood. After 17 months of treatment, the PSA level decreased to 17 ng/mL and CT showed that the primary tumor had shrunk but still had a strong contrast effect and no enlarged lymph nodes. Bone scintigraphy showed that the bone metastases had improved, but many remained (Fig. 3).

Discussion

Minato *et al*. summarized 18 cases of PCa with DCBM at the initial presentation.[2] Docetaxel was administered in one of these cases, but NHA were not, and the median OS was 9 months. Shahait *et al*. retrospectively reviewed 189 metastatic PCa and reported 11 cases of PCa with DCBM at initial presentation.[3] Seven patients received upfront docetaxel or abiraterone, with a median OS of 18.1 months. In Case 1, the patient received enzalutamide, abiraterone, docetaxel, and

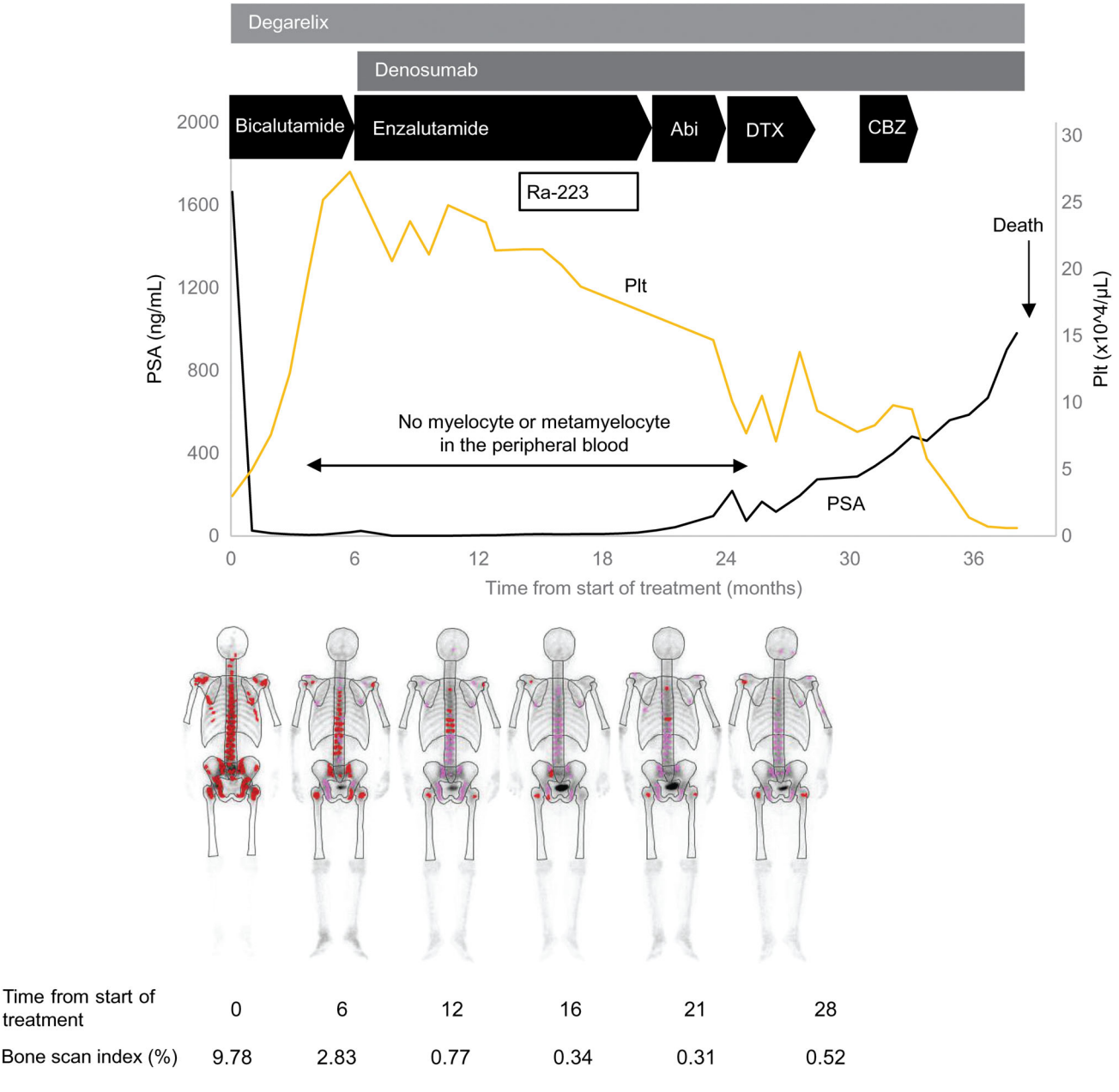

Fig. 2 Bone scintigraphy results and clinical course of Case 1.

cabazitaxel and died 38 months after the initial presentation. In Case 2, apalutamide was administered, and the patient remained progression-free for 17 months. These results suggest that the use of NHA and chemotherapy may prolong the OS of patients with PCa complicated with DCBM.

Lassmann *et al*. calculated the organ dose after six intravenous injections of 0.05 MBq/kg of radium-223 each, using the International Commission on Radiological Protection model for radium[4]; the short-range alpha radiation (<100 μm) of radium-223 was reported to reach the bone marrow at approximately 1.5 Gy.[4] A previous case report described a patient who developed PSA elevation and pancytopenia during radium-223 treatment, leading to a bone-marrow biopsy and diagnosis of DCBM.[5] These results suggest that radium-223 might be less effective in cases with DCBM than in cases without DCBM. In Case 1 of this report, six courses of radium-223 were completed without severe adverse effects, and the disease remained stable. However, it cannot be assumed that radium-223 suppressed DCBM because it was simultaneously administered with enzalutamide.

In conclusion, patients with metastatic PCa with DCBM treated with recent multimodality therapies, including NHA and chemotherapy, may have a better prognosis than those treated with vintage hormonal therapies. However, it should be noted that radium-223 as part of multimodality therapy might be less effective in cases with DCBM than in cases without DCBM.

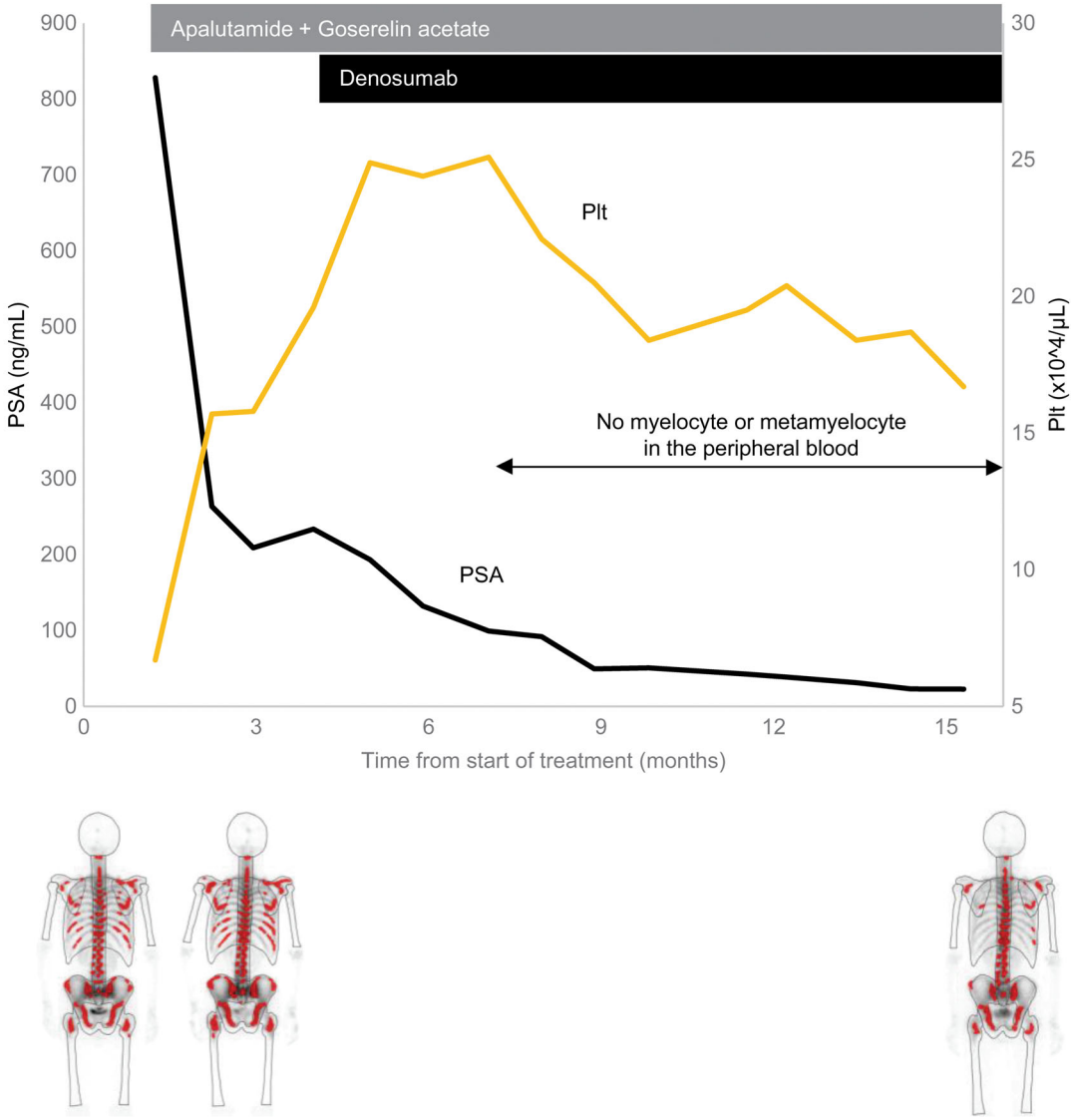

Fig. 3 Bone scintigraphy results and clinical course of Case 2.

Author contributions

Keina Nozaki: Writing – original draft. Hisashi Matsushima: Conceptualization; supervision. Hiyo Obikane: Supervision; writing – review and editing. Ryohei Nishimoto: Writing – review and editing. Ryo Tanaka: Writing – review and editing. Takeru Morishige: Writing – review and editing. Tomoko Masuda: Supervision. Haruki Kume: Supervision.

Conflicts of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Not applicable.

Registry and the Registration No. of the study/trial

Not applicable.

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