



Treatment Management in Patient with a Prostate Cancer Adenocarcinoma Presenting with Disseminated Bone Marrow Carcinomatosis

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ABSTRACT

Bone marrow metastasis is a rare occurrence in castration-sensitive prostate cancer (CSPC). In this article, we discuss the treatment management of a 62-year-old male patient with bone marrow metastasis from prostate cancer. We started treatment with weekly docetaxel (20 mg/m²/day) and zoledronic acid (4 mg/day every 3 weeks) with maximum androgen blockade. After 6 weeks of treatment, his thrombocytopenia resolved, and docetaxel treatment was continued for a total of 8 months. At 12 months after diagnosis, we started enzalutamide therapy for castration-resistant metastatic disease. As a result, it was concluded that a rapid response can be obtained with docetaxel in prostate cancer patients with bone marrow metastasis. This case highlights the rare presentation of bone marrow metastasis in patients with CSPC and the importance of a multimodal approach combining androgen deprivation therapy, chemotherapy, and novel agents to achieve prolonged survival.

Keywords: Bone marrow metastasis; prostate cancer; castration-sensitive

INTRODUCTION

Prostate cancer is the most common cancer in men, following skin cancers.¹ The overall 10-year survival rate in castration-sensitive prostate cancer (CSPC) without metastasis is over 90%. However, despite recent advances in diagnosis and treatment options, the 5-year survival rate for patients with metastatic prostate cancer is approximately 29.3%. The body areas where prostate cancer metastasizes most frequently are bone, lung, and liver. One of the rare sites of metastasis is the bone marrow.^{1,2}

It has been reported that metastasis of prostate cancer to the bone marrow is between 6% and 47.8%.¹⁻³ Bone marrow involvement is often diagnosed in the final stages of castration-resistant metastatic disease. Although it is rare, metastatic castration-sensitive prostate cancer (mCSPC) can be seen as the first presentation. The prognosis of prostate

cancer with bone marrow infiltration in both castration-sensitive and castration-resistant prostate cancer (CRPC) is quite poor.⁴⁻⁹

In this article, we discussed the management of a 62-year-old male patient who was diagnosed with metastatic prostate cancer with bone marrow involvement. The diagnosis was made while being investigated for hematological malignancies due to thrombocytopenia and leukocytosis, as well as conglomerate lymphadenomegaly. The discussion is supported by current literature information

CASE REPORT

A 62-year-old male patient was admitted to the emergency department with complaints of increasing back and low back pain, weakness, and difficulty in walking for the past month. Previously, the patient had been diagnosed with coronary artery

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disease, atrial fibrillation, and hypothyroidism for approximately 5 years, treated with digoxin 1x25 mg/day, carvedilol 1x12.5 mg/day, spironolactone 1x25 mg/day, edoxaban 1x30 mg/day, and levothyroxine 1x100 mcg/day treatment.

In the emergency service, he had limited range of motion and tenderness in the lumbar region. There were no pathological examination findings in other systems. Measurements for blood pressure, heart rate, and body temperature were normal. Since the pathological blood tests performed were glucose 128 mg/dL, urea 58 mg/L, creatinine 1.10 mg/dL, calcium 13 mg/dL, alkaline phosphatase 345 IU/L, lactate dehydrogenase 337 IU/L, hemoglobin 13.4 g/dL, leukocyte count $15.4 \times 10^3/\mu\text{L}$, and platelet count $67 \times 10^3/\mu\text{L}$, it was determined that the patient was to be investigated for hematological malignancy. He was hospitalized in the hematology clinic.

No findings suggestive of leukemia were detected in the peripheral smear. The required serum parathormone level for the differential diagnosis of hypercalcemia was 9.1 pg/mL. In radiological examinations, conglomerate lymph nodes measuring up to 60 mm were detected in the left para-iliac and para-aortocaval regions, conglomerate lymph nodes were found in the right para-esophageal area at the subcarinal level, and a heterogeneous prostate was observed indented to the base of the bladder and increased in size, as detected with computed tomography (CT). In the whole-body scintigraphy taken based on the findings of the skeletal system in CT, increased activity uptake was observed as foci in the entire vertebral column-prominent in the thoracic,⁷ lumbar 1 and 2 vertebrae; in both hemithorax; in the lateral edges of both scapulae; focal in the left iliac wing; and in the left ischium. Bone marrow biopsy was performed to evaluate plasma cell dyscrasia and lymphomas.

Despite the absence of urinary symptoms, the observed prostate-specific antigen (PSA) level was 1850 ng/mL, considering radiological prostate-related findings. For this reason, the prostate was palpated as hard in the rectal examination performed by the urologist, and a transrectal six-core prostate fine-needle aspiration biopsy was performed. The patient, who was diagnosed with prostate adenocarcinoma (Gleason score of 5+5=10), after histopathological examinations revealed metastasis of prostate carcinoma to the bone marrow during biopsy (Figure 1), was taken over by the medical oncology clinic.

After the cardiac evaluation, bicalutamide 1x50 mg/day was started for the first-line treatment of CSPC. One week later, goserelin acetate injection (1x10.8 mg/day) was administered and planned to be administered every 3 months. After obtaining the consent of the patient and his relatives, a weekly dose of 20 mg/m²/day docetaxel, was added to the androgen

deprivation treatment (ADT), and zoledronic acid was added at 4 mg every 3 weeks for bone metastasis and hypercalcemia. Before the first docetaxel treatment, the platelet count was $37 \times 10^3/\mu\text{L}$, while the hemoglobin and leukocyte counts were 9.1 g/dL and $12.6 \times 10^3/\mu\text{L}$, respectively.

Between February 23, 2022, and April 11, 2022, a total of 6 sessions of docetaxel were administered at a dose of 20 mg/m²/day in the hospital. In this process, a total of 2 units of erythrocyte suspension and 4 units of thrombocyte suspension were administered to the patient, along with pain and nutrition management, and hydration. It was observed that the hematological profile returned to normal after the fourth session of weekly docetaxel. At the end of the sixth week, the complete blood count and biochemical tests were completely normal, and the PSA level had decreased to 328 ng/dL. Grade 1 nausea and grade 1 diarrhea were observed only in the third week during the weekly treatments. The patient again declined the bone marrow biopsy. He was

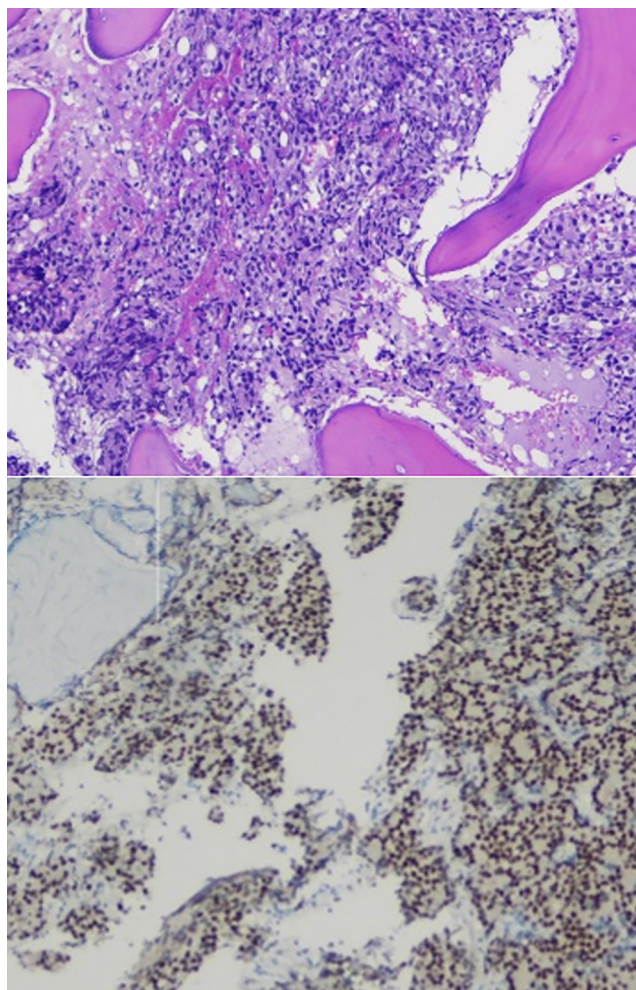


FIGURE 1: Adenocarcinoma infiltration in the form of acinar glandular structures that tend to merge with each other in the intertrabecular spaces (x10; hematoxylin & eosin).

referred to palliative radiotherapy for bone metastases. A total of 30 Gy of radiotherapy was applied to the patient for 10 days on the right and left femoral head, the area above the 12th thoracic vertebra, and the areas below the spina iliaca externa.

Between 30 May 2022 and 7 November 2022, docetaxel treatment at a dose of 75 mg/m² every 3 weeks, was continued together with zoledronic acid and goserelin acetate. After the last chemotherapy, docetaxel treatment was discontinued in the patient whose PSA level was 36.8 ng/dL, and total testosterone level was 0.0250 ng/mL. Grade 1 oral mucositis, grade 1 diarrhea, and grade 1 fatigue were observed once in different courses during the treatments applied every three weeks. Grade 1 peripheral neuropathy developed in the patient starting with the 4th cycle. CT performed 11 months after the first treatment revealed a significant regression in intra-abdominal lymph nodes, with the largest lymph node measuring 11 mm, and a response in bone metastases.

In the control dated December 8, 2022, the levels of PSA and serum total testosterone were measured as 174 ng/dL and 0.0250 ng/dL, respectively. Enzalutamide 160 mg/day was started in combination with goserelin acetate and zoledronic acid (4 mg every four weeks).

At the end of the first month, the PSA level was 82.3 ng/dL, and at the end of the sixth month, it decreased to 6.02 ng/dL. The patient's treatment was continued with zoledronic acid, enzalutamide, and goserelin. Prostate specific membrane antigen (PSMA) positron emission tomography (PET)/CT was planned due to PSA progression observed at the 18th-month. In PET/CT, Gallium-68 PSMA uptake was observed in the prostate and left seminal vesicle area. There were varying levels of pathological PSMA uptake in metastatic lymph nodes in the mediastinum, abdomen, and pelvis, and widespread metastatic sclerotic lesions in the entire vertebral column, sacrum, bilateral humerus, femur bone, and bone marrow areas. Lutetium treatment was planned for the patient with widespread bone metastases. The patient's PSA levels decreased from 4.75 ng/dL to 0.881 ng/dL, while Lutetium and enzalutamide treatment continued. The patient is in the 23rd month of treatment and is still being followed.

DISCUSSION

More limited information is available on the frequency of mCSPC and the treatment of these patients in the English literature.³⁻⁹

In a study published in 2020, it was reported that 8 of 55 solid tumor patients with bone marrow metastases had prostate cancer. It was stated that only two of these eight patients had mCSPC.⁷ The 83-year-old patient presented

with thrombocytopenia, concomitant anemia, whereas the 68-year-old patient was diagnosed with isolated anemia. It was found that the patient with thrombocytopenia was followed with the best supportive treatment and did not receive systemic anti-cancer therapy.⁷

In the literature, recommendations for the treatment of prostate cancer with bone marrow metastases are limited. Most of the case reports or case series available in the literature contain information on the management of bone marrow metastases in mCRPC. It has been reported that these cases were given ADT and zoledronic acid treatment for bone metastasis in the castration-sensitive period. In the treatment of mCRPC with bone marrow metastases, most authors stated that abiraterone or enzalutamide may be appropriate rather than docetaxel because of the risk of myelosuppression.⁹ In contrast, Kunthur⁹ also reported that a patient with mCRPC who had severe pancytopenia was successfully treated with docetaxel chemotherapy. However, there is limited information in the literature regarding the management of bone marrow metastasis treatment in mCSPC.

Two cases of prostate cancer presenting with severe anemia and disseminated intravascular coagulation (DIC) were published by Hiroshige and Eguchi⁵ in 2017. It was stated that in these two cases, an inadequate response was obtained with standard ADT, and an increase in PSA was observed when DIC clinics were repeated. Although the most important differences from our case are deep anemia and DIC clinical picture, we think that discussing the management of both these cases and ours can give important clues to clinicians. Since these two cases had DIC, it was understood that docetaxel, including any systemic anti-cancer drugs, were not added to the ADT treatment. It was observed that denosumab treatment was started for bone metastasis, which was different from our case.⁵ However, Iguchi and Matsuhisa⁴ recommended a combination of bisphosphonates, including zoledronic acid, with anticoagulant treatments and chemotherapies in prostate cancer patients with Disseminated carcinomatosis of the bone marrow. We know that bisphosphonates, including zoledronic acid, not only prevent bone resorption, but also inhibit the release of growth factor from bone to the bone marrow cavity and control the growth of cancer cells. We started zoledronic acid for our patient, both because of hypercalcemia and in accordance with this hypothetical approach.

Docetaxel is a chemotherapeutic in the taxane group that exerts anticancer effects by inhibiting microtubules. A meta-analysis including these three randomized controlled clinical trials (CHAARTED, STAMPEDE and GETUG-AFU15) showed that the addition of docetaxel to ADT in mCSPC resulted in

an absolute improvement of 9% at 4-years [95% confidence interval (CI): 5-14%] as well as improved overall survival (OS) [hazard ratio (HR): 0.77, 95% CI: 0.68-0.87, $p < 0.0001$]. Moreover, significant improvement in progression-free survival (PFS) (HR: 0.64, 95% CI: 0.58-0.70, $p < 0.0001$), including 4-year absolute risk reduction in PFS (95% CI: 12-19%), has been reported.¹⁰ In another meta-analysis, it was reported that the addition of docetaxel was superior in terms of both OS (HR: 0.73, 95% CI: 0.60-0.90, $p = 0.002$) and PFS (HR: 0.63, 95% CI: 0.57-0.70, $p < 0.002$).¹⁰

A meta-analysis of two large, randomized-controlled phase III studies of abiraterone (LATITUDE and STAMPEDE arm-G), which exerts anti-cancer effects by inhibiting CYP17, an enzyme critical for androgen production in testicles, adrenal glands, and prostate tumor tissue, all-causes demonstrated a reduction in mortality (HR: 0.64, 95% CI: 0.56-0.73) in patients with mCSPC.¹⁰ Enzalutamide, another second-generation antiandrogen drug, targets the androgen receptor signaling pathway and competitively inhibits androgen receptor binding. The two randomized-controlled phase III studies investigating the efficacy of enzalutamide combined with ADT in MCSPC are the ENZAMET and ARCHES studies. In the ENZAMET study, ADT with enzalutamide was shown to significantly improve 3-year OS (HR 0.67, 95% CI 0.52-0.86, $p = 0.002$) and PFS (HR: 0.40, 95% CI: 0.33-0.49, $p < 0.001$) compared to ADT plus placebo.¹⁰ The ARCHES study also achieved significant efficacy in both endpoints (HR: 0.66, 95% CI: 0.53-0.81, $p < 0.001$, and HR: 0.39, 95% CI: 0.30-0.50, $p < 0.001$, respectively).¹⁰ Moreover, as demonstrated in the randomized, controlled phase III TITAN study, the combination of apalutamide with ADT which specifically inhibits DNA binding by targeting the ligand-binding domain of the androgen receptor and blocks androgen receptor-mediated transcription, had advantages in both 2-year OS (HR: 0.67, 95% CI: 0.51-0.89, $p = 0.005$) and PFS (HR: 0.48, 95% CI: 0.39-0.60, $p < 0.001$).¹⁰ In more recent studies, multimodal treatment approaches in which docetaxel and abiraterone are given in combination with ADT have also come to the fore, and it has been stated that it provides an advantage in treatment.¹⁰ However, literature on the response status of these three drugs and multimodal approaches in mCSPC with bone marrow metastases remains unclear.

CONCLUSION

As a result, we think that good results can be obtained with docetaxel treatment in prostate cancer with bone marrow

metastasis. This treatment should be supported by blood product transfusions if necessary. Treatment should start with a weekly low dose, then adjust to every 2 or 3 weeks depending on the response.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.T., S.K., R.I.Y., G.P., A.A., Concept: Ö.T., S.K., R.I.Y., G.P., A.A., Design: Ö.T., S.K., R.I.Y., G.P., A.A., Data Collection or Processing: Ö.T., S.K., R.I.Y., G.P., A.A., Analysis or Interpretation: Ö.T., S.K., R.I.Y., G.P., A.A., Literature Search: Ö.T., S.K., R.I.Y., G.P., A.A., Writing: Ö.T., S.K., R.I.Y., G.P., A.A.

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