Progression to bone-marrow carcinomatosis and extraosseous legion during treatment with radium-223 for multiple bone metastases

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Abstract

A 67-year-old man with metastatic prostate cancer presented with progression to castration-resistant prostate cancer. After sequential therapies with flutamide, estramustine phosphate, docetaxel, enzalutamide, and cabazitaxel for castration-resistant prostate cancer, radium-223 was initiated and continued up to 4 cycles. However, concurrently with radiological and clinical progressions, pancytopenia was observed due to bone-marrow carcinomatosis by prostatic adenocarcinoma. This case suggested that radium-223 should be employed at appropriated timing before appearances of extraosseous and bone-marrow lesions in addition to visceral metastasis.

Keywords Bone-marrow carcinomatosis · Prostate cancer · Radium-223

Introduction

Presently, several therapeutic options are available for castration-resistant prostate cancer (CRPC). Radium-223 has shown prolongation of adverse symptoms occurrence as well as survival benefit [1], and accordingly approved for clinical use for symptomatic patients with CRPC carrying bone metastasis, but no visceral metastasis. Here, we report a case who showed cancer progression to bone-marrow carcinomatosis and extraosseous legion during treatment with radium-223.

Case report

The case is 67-year-old man who was referred to a urologist due to elevated serum prostatic-specific antigen (PSA) level of 361 ng/ml. He was diagnosed as prostate cancer (Gleason score, 3 + 4) with multiple bone metastases, and accordingly treated with androgen-deprivation therapy utilizing gonadotropin-releasing hormone antagonist degarelix and antiandrogen bicalutamide (Fig. 1). However, 1 year later, serum PSA level increased up to 13 ng/ml after 1.0 ng/ml as nadir PSA level, and then, flutamide was started instead of bicalutamide. Five months later, since PSA went up to 37 ng/ml and bone pain appeared, estramustine phosphate was started instead of flutamide, which showed no laboratory and clinical improvements. At that time, patient with serum PSA level of 316 ng/ml and symptomatic multiple bone metastases was introduced to our department. Accordingly, docetaxel chemotherapy with prednisolone was started, which showed transient relief of pain and improvement of serum PSA level down to 37 ng/ml. However, since clinical progression and PSA progression up to 180 ng/ml were recognized after 7 cycles of docetaxel chemotherapy, enzalutamide was administered. Although serum PSA level transiently decreased to 13 ng/ml, 6 months later serum PSA level came back to 122 ng/ml. Then, cabazitaxel chemotherapy with prednisolone was initiated. However, despite 2 cycles of cabazitaxel chemotherapy, serum PSA level

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Fig. 1 Clinical course in this case

increased up to 416 ng/ml, with increased bone pain due to multiple bone metastases (Fig. 2), but no visceral metastasis.

At that time, radium-223 administration was started, and continued up to 4 cycles. However, increased bone pain in lumbar and both lower extremities, and increased serum PSA level from 416 ng/ml at pre-treatment to 3737 ng/ml were observed although serum ALP level slightly increased from 3221 U/l at pre-treatment to 3766 U/l. In addition, imaging examination showed increased soft-tissue shadow in pelvic surface of sacrum developing extraosseous lesion with computed tomography (Fig. 2a) and obvious progression of super bone scan with bone scintigraphy (Fig. 2b). Concurrently, pancytopenia (white blood cell count, 3560/ μ l; hemoglobin concentration, 9.1 g/dl; platelet count, 44,000/ μ l) was observed, and therefore, radium-223 administration was stopped. To reveal the cause of pancytopenia, bone-marrow biopsy from ilium was conducted, and showed cancer cells invading bone marrow with positive staining for epithelial markers CAM5.2 and AE1/AE3 (data not shown) as well as PSA (Fig. 3), but negative staining for p63 and CK903 (data not shown), which was diagnosed as bone-marrow carcinomatosis by prostatic adenocarcinoma.

Discussion

In Phase III ALSYMPCA trial enrolling patients with bone-metastasized CRPC without visceral metastasis, radium-223 showed prolonged time to symptomatic skeletal event and

overall survival (OS) with 5.8 and 3.6 months compared to placebo group, respectively [1]. Therefore, radium-223 was approved as first α -ray radionuclide therapy for CRPC with bone metastasis.

Radium is a member of alkaline earth metal homologues as calcium, and captured into the sites with increased bone metabolism such as bone metastases. Radium-223 showed antitumor effects by discharging α -ray characterized with high linear energy transfer and short-emission range of 50–80 μ m within tissues captured, compared with β - and γ -rays. Therefore, high amount of radiation dose to captured tissues can be available, while very small amount of radiation dose is irradiated beyond emission range, contributing to rare serious adverse event [2].

In retrospective study from the United States, it has been reported that there was significant deleterious OS when less than 4-cycle administration compared with 5–6 cycles of radium-223 administration [3]. Since this case could not complete 6 cycles of radium-223 administration due to severe pancytopenia by bone-marrow carcinomatosis, possible adverse effect on bone marrow by radium-223 cannot be excluded. Enough antitumor effect may not be obtained due to insufficient number of treatment. However, we guess that insufficient antitumor effect by radium-223 may be derived mainly from cancer development to extraosseous and bone-marrow lesions. The distances from cortical bone capturing radium-223 to extraosseous and bone-marrow lesions are beyond α -ray reaching distance, and therefore, α -ray cannot reach to

Fig. 2 Radiological evaluation after 4 cycles of radium-223 administration. **a** Computed tomography indicated cancer progression to extraosseous legion. **b** Bone scintigraphy indicated cancer progression to systemic bone legions as presented with super bone scan. White arrows indicate soft-tissue mass in pelvic surface of sacrum developing extraosseous legion

extraosseous and bone-marrow legions. Actually, it was reported that absorbed dose of radiation in bone marrow was 3.7×10^{-7} Sv/Bq [4], which was far less than the dose to exert toxicity as well as antitumor effect by radiation. Accordingly, this case experienced cancer progression to extraosseous and bone-marrow legions, where radium-223 would be ineffective, although several indirect effect such as bystander effect, abscopal effect, and osteoblast-mediated effect might be involved [5–7]. In this case, radium-223 was finally administered after several lines of CRPC treatment such as taxanes and enzalutamide in addition to alternative antiandrogen therapy and estramustine phosphate. Since cancer progression to extraosseous and bone-marrow lesions might occur during radium-223 therapy, earlier administration of radium-223 may result

in different clinical course in this case. Therefore, we should care to utilize radium-223 at appropriate timing, although consensus on treatment position of radium-223 is not determined at present.

So far, the therapeutic effect of radium-223 to extraosseous and bone-marrow lesions has not reported yet. Therefore, further experiences with radium-223 would be required. Currently, clinical trials examining therapeutic outcome with increased administration of radium-223 or combination with other therapeutic agents are underway. In addition, further development of α -ray radionuclide therapy such as PSMA-antibody-based radio isotope directing systemic cancer cells including extraosseous or bone-marrow lesions and visceral metastases would be required [8].

Fig. 3 Pathological finding of bone-marrow biopsy from ilium. Microscopic finding showed prostate cancer cells in bone marrow

Conclusion

In conclusion, we experienced the case presenting cancer progression to extraosseous and bone-marrow lesions despite radium-223 administration, which suggested that radium-223 should be employed at appropriated timing before appearances of extraosseous and bone-marrow lesions in addition to visceral metastasis.

Compliance with ethical standards

Conflict of interest All authors declare no potential conflict of interest to disclose.

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