Normalization of serum PSA level using zoledronic acid on metastatic hormone-refractory prostate cancer resistant to estramustine and betamethasone

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KEY WORDS

hormone-refractory prostate cancer ◗ zoledronic acid ◗ prostate specific antigen

ABSTRACT

We present a 78-year-old male with hormone-refractory prostate cancer (HRPC), who obtained complete long term regression of prostate specific antigen level during zoledronic acid (ZA) therapy. Our case suggests clinical utility of ZA in managing some of HRPC patients.

INTRODUCTION

Many strategies have been studied for treatment of hormone-refractory prostate cancer (HRPC) [1]. However, the management of it is still replete with controversy [1]. We have experienced a patient with HRPC who was treated successfully with zoledronic acid (ZA). This is the second report to demonstrate that ZA application is an effective method for treatment of heavily pretreated metastatic HRPC leading to the decrease of prostate specific antigen (PSA) level to normal range.

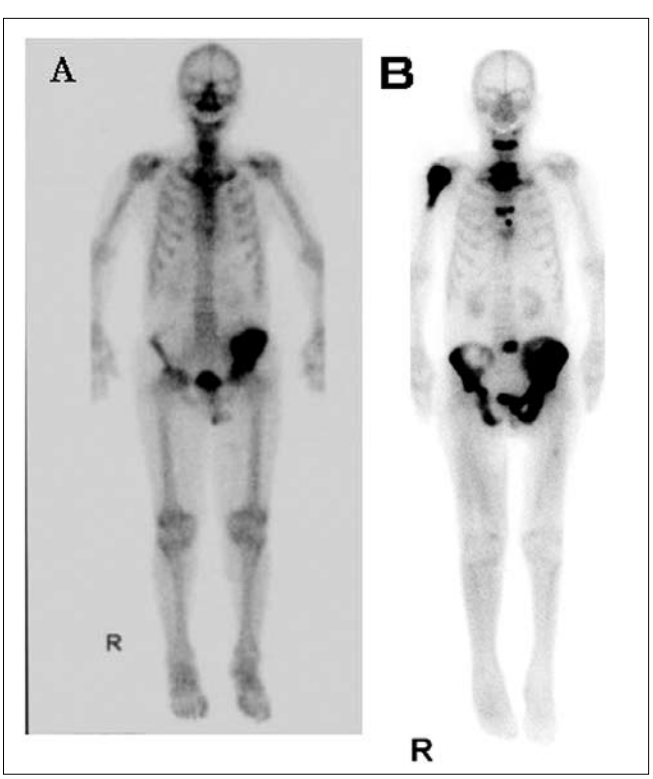

Fig. 1. Bone scan at initiation (A) and at present (B). Aggravation of bone metastasis regardless of normal PSA level.

CASE REPORT

A 78 year-old patient with no significant past medical history was diagnosed with stage IV prostate cancer in 2002 (Fig. 1A). He was initially treated with leuprolide and bicalutamide. Eight months later his clinical state deteriorated along with the increase of prostate specific antigen (PSA) level. Estramustin was administered in 2004 but showed little clinical efficacy as PSA levels continued to rise. They reached 160.4 ng/ml. in 2005 despite an additional administration of betamethasone. In 2007, we started to administer ZA in order to alleviate bone pain. PSA levels decreased from 160.4 ng/ml to 18.4 ng/ml and then to 5.5 ng/ml and subsequently normalized to 0.9 ng/ml. Remission lasted for 6 months and cancer-related symptoms improved significantly (Fig. 2). However, bone scan revealed aggravation of metastatic sites regardless of normal PSA level (Fig. 1B).

DISCUSSION

Despite heavily pretreated metastatic HRPC, ZA therapy appears to be effective and safe in this case. The discrepancy between results of bone scan and PSA level may depend on the point of time the bone scan was performed just before administration of ZA. PSA level itself should not be used as the sole treatment response although previous studies have suggested that certain

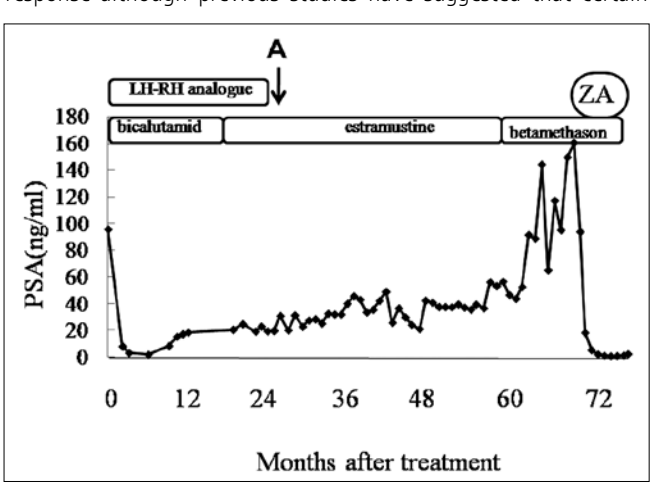

Fig. 2. Serum prostate-specific antigen (PSA) levels plotted at monthly intervals from March 2002 to May 2008. A = surgical castration abbreviation, ZA = Zoledronic Acid.

changes in PSA levels serve as a surrogate endpoint for survival [2]. Bisphosphonate treatment with ZA is widely used as a standard treatment for cancer, including prostate cancer with bone metastases in order to reduce the risk of developing bone complications [3]. It is unclear to what extent the observed anti-tumor effects of ZA *in vivo* are due to a direct cytostatic effect on tumor cells or appear due to the indirect alterations in the bony microenvironment [3]. Our experience and previous clinical report would help to validate the previous experimental research on clinical human levels, although the exact reasons for these responses still need to be determined [4]. It would depend on the fact that the patient had no obvious metastatic sites except for bone tissue [4].

Administration of betamethasone for this case simultaneously with ZA would bring positive results in the patient's condition. The anti-proliferative and apoptotic effects of ZA on myeloma cells in vitro were enhanced by the addition of dexamethasone in experimental models [5].

Previous studies, which already confirmed that ZA therapy prolonged little survival, indicated the actual clinical benefit for HRPC (hormone-refractory prostate cancer) [3, 6]. Evidence on the use of bisphosphonates in HRPC is limited to 10 randomized trials examining five different bisphosphonates in different patient populations. Six of those trials were small, including less than 100 patients. In contrast to other disease sites, in which bisphosphonates have been more extensively evaluated, the limited available evidence in HRPC cancer makes it difficult to derive treatment recommendations for bisphosphonates as a class of agents [3, 6].

Our experience will be an anchor for further clinical exploration, though it is exceptional. Even though systematic information is more reliable than anecdotal information, Enkin discussed the strength of an anecdote, and demonstrated its significance even within the evidence-based paradigm [7]. Bisphosphonates including ZA and chemotherapy show promising effects in the battle against HRPC. However, further definitive clinical research is required to evaluate emerging treatments.

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