

Are Stereotactic Body Radiotherapy and Zoledronic Acid Combination Additive or Synergistic in Bone Metastasis?

SBRT ve Zoledronik Asid Kombinasyonu Kemik Metastaz Tedavisinde Aditif veya Sinerjistik Etki Mi Yapar?

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ABSTRACT

Bone metastasis is an important cause of morbidity and mortality. In today's oncology practice, zoledronic acid (ZA) and Stereotactic Body Radiotherapy (SBRT) have been widely used in the treatment of bone metastases and in the treatment of bone pain reduction. Whether this combined therapy is additive or synergistic is not yet known. There are not enough studies on this subject yet. To better understand the effects of ZA and SBRT combination therapy, prospective studies including more patients are needed.

Keywords: Bone metastasis, SBRT, zoledronic acid

ÖZ

Kemik metastazı önemli bir morbidite ve mortalite nedenidir. Günümüz onkoloji pratiğinde zoledronik asit ve stereotaktik vücut radyoterapisi (SBRT), kemik metastazlarının tedavisi ve kemik ağrıların azaltılması tedavisinde yaygın olarak kullanılmaya başlanılmıştır. Bu kombine tedavinin aditif veya sinerjistik etki yapıp yapmadığı henüz bilinmemektedir. Bu konuda henüz yeterli çalışma bulunmamaktadır. Zoledronik asit ve SBRT kombinasyon tedavisinin etkilerinin daha iyi anlaşılabilmesi için prospektif ve daha çok sayıda hastayı içeren çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kemik metastazı, SBRT, zoledronik asit

INTRODUCTION

Bone metastasis is an important cause of morbidity and mortality. Treatment requires a multidisciplinary approach. Radiotherapy (RT) and bisphosphonates are important treatment options in reducing complications related to bone metastasis. Bisphosphonates are synthetic analogues of pyrophosphates, which facilitate the chelation of calcium ions, and act by inhibiting the mevalonate cycle of osteoclasts (1-3). In a meta-analysis of the efficacy of bisphosphonates in bone metastasis, it has been shown that bisphosphonates are associated with a 15% reduction in skeletal-related events compared with placebo, prolongation in the time to first bone-related event, and in pain and an increase in quality of life (1). In addition, the risk

of developing bone metastases during bisphosphonate treatment has been reported to be less (2).

Zoledronic Acid (ZA), the third generation and containing nitrogen, is the most effective preparation among bisphosphonates. ZA has effects on osteoclast activity as well as cytotoxic, apoptotic, immunomodulatory and antiangiogenic effects. ZA provides a transient decrease in circulating VEGF and bFGF levels, thereby inhibiting antiangiogenic activity and inhibition of bone invasion of tumor cells. It provides direct antitumor action by inhibiting the prenylation of Ras and Ras-related proteins. It also induces apoptosis by performing S-phase cell cycle arrest. ZA is widely used in hypercalcemia, multiple myeloma, bone metastases of tumors such as prostate, breast, and lung cancers associated with malignancy, and bone me-

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tabolism such as osteoporosis, osteopenia, Paget's disease, and osteogenesis imperfecta (2-5).

Direct and indirect antitumor effects of ZA supported by pre-clinical studies are shown. Some *in vitro* studies have demonstrated antiproliferative and cytostatic effects in myeloma, breast cancer, and prostate cancer cell lines (6,7). An AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) study showed a significant increase in a pathological complete response by addition of zoledronic acid to neoadjuvant chemotherapy in patients with locally advanced breast cancer (8). It has been reported that the number of skeletal related events decreases with the addition of bisphosphonates to standard treatment in patients with bone metastasis hormone refractory prostate cancer as in breast cancer patients (9). In all these preclinical and clinical studies, it seems likely that ZA will find its place as an effective agent not only in the treatment of complications, but also in the treatment of prostate, breast, and other cancers.

After ZA showed an additive and synergistic effect in the combination of chemotherapy, combination therapy with RT started to be investigated. Some clinical and preclinical studies have shown that ZA does not only reduce the risk of bone fracture and stimulate osteoclastic remodeling, but also increases immune response and radio sensitivity (3,4,10,11). However, there are limited numbers of clinical studies on this subject. In a phase 1 study planned by Pichon et al., they evaluated the tolerability and efficacy of a Stereotactic Body Radiotherapy (SBRT) and Zoledronate combination in non-compressive vertebral metastases. They applied the SBRT 3 x 9 Gy and zoledronate once a month for a year. Three patients had acute mucosal side effects. None of the patients had late neurological toxicity. They achieved control of the local disease in 94% of patients followed for an average of 19.2 months. As a result, the combination of Zoledronate and SBRT in the treatment of vertebral metastasis was well tolerated and reported that it reduced the rate of vertebral collapse, effectively reduced pain, and provided good local tumor control without late neurological side effects (10). Lu et al. examined the combination of radiofrequency ablation, 125I-seed, zoledronic acid or radiotherapy in patients with spinal metastasis percutaneous vertebroplasty. They emphasized that RT was the most effective way to relieve pain (11).

As a result, in today's oncology practice, zoledronic acid and SBRT have been widely used in the treatment of bone metastases and in the treatment of bone pain reduction. Whether this combined therapy is additive or synergistic is not yet known. There are not enough studies on this subject yet. To better understand the effects of ZA and SBRT combination therapy, prospective studies including more patients are needed.

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