Original Article

Evaluation of the Effects of Ibandronic Acid and Zoledronic Acid on Progression-free Survival in Patients with Bone Metastatic Breast Cancer

İbandronik Asid ve Zoledronik Asidin Kemik Metastazlı Meme Kanserli Hastalardaki Progresyonsuz Sağkalım Üzerindeki Etkilerinin Değerlendirilmesi

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ABSTRACT

Introduction: Bisphosphonates have been reported to limit tumor formation, in addition to inhibition of bone resorption. We evaluated the effect of intravenous zoledronic acid (ZA) and oral/intravenous ibandronic acid (IA) on progression-free survival (PFS), overall survival (OS), and skeletal-related events (SRE) in breast cancer patients with bone metastases.

Materials and methods: The retrospective study included patients with metastatic breast cancer who received ZA or IA treatments for at least three months between 2013 and 2018. Menopausal status, presence of visceral metastases, history of skeletal-related events (fracture, radiotherapy, and operation), de novo bone metastasis, and anticancer treatments were recorded. PFS and OS were calculated for each patient.

Results: There were 44 patients in the ZA group as opposed to 22 patients in the IA oral group and 11 patients in the intravenous IA group. Median PFS was 15 months in the ZA group and 25 months in the IA group (p=0.134). Median OS was 81 months in the IA group and 153 months in the ZA group (p=0.088). No significant difference was found between the groups with regard to history of fracture, radiotherapy, and operation (p=0.606, p=0.295 and p=0.747, respectively). The two-year survival rate was 71.5% in the ZA group and 78.3% in the IA group.

Discussion: ZA and IA have similar efficacy in terms of SRE development, PFS and OS. In the selection of treatment for the treatment of bone metastases in metastatic breast cancer, besides evaluating drug efficacy/side effects, treatment compliance and cost should also be considered.

Keywords: Bone metastasis, ibandronic acid, metastatic breast cancer, overall survival, progression-free survival, zoledronic acid

ÖZET

Giriş: Bisfosfonatların kemik rezorbsiyonu inhibisyonu yanı sıra, tümör oluşumunu sınırlama etkileri bildirilmektedir. Çalışmamızda tek merkezde Zoledronik asid (ZA) intravenöz ve İbandronik asid (İA) oral/intravenöz kullanan hastalardaki progresyonsuz sağkalım (PS), genel sağkalım (GS) ve iskelet ilişkili olayların (İİO) değerlendirilmesi amaçlandı.

Gereç ve yöntemler: 2013-2018 yılları arasında, en az 3 ay ZA ya da İA tedavileri alan metastatik meme kanserli hastalar retrospektif olarak incelendi. Menopoz durumu, visseral metastaz varlığı, İİO öyküsü (kırık, radyoterapi, operasyon), tanı anında kemik metastaz varlığı, kullanılan antikanser tedaviler değerlendirildi. PS ve GS süreleri hesaplandı.

Bulgular: ZA grubunda 44 hasta var iken, İA oral 22 ve intravenöz grubunda 11 hasta vardı. Her iki gruba ait hasta özellikleri birbirine denkti. Çalışmamızda PS, ZA grubunda15 ay, İA grubunda 25 ay idi (p=0.134). GS, ZA grubunda 81 ay, İA 153 ay idi (p=0.088). İİO'lar açısından gruplar

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değerlendirildiğinde; kırık, radyoterapi ve operasyon açısından sırasıyla iki grup arasında fark bulunamadı (sırasıyla p=0.606, p=0.295, p=0.247). 2 yıllık sağkalım oranı ise ZA grubunda %71.5 iken, İA grubunda %78.3 olarak izlendi.
Tartışma: ZA ve IA, İİO gelişimi, PS ve GS açısından benzer etkinliğe sahiptir. Metastatik meme kanserinde kemik metastazlarının tedavisine yönelik tedavi seçiminde ilaç etkinliği/yan etkilerinin değerlendirilmesinin yanı sıra tedaviye uyum ve maliyet de göz önünde bulundurulmalıdır.

Anahtar kelimeler: Zoledronik asid, ibandronik asid, genel sağkalım, progresyonsuz sağkalım, metastatik meme kanseri, kemik metastazı

Introduction

Bone is the most common site of metastasis in many solid tumors, particularly in breast. Bone metastasis, its localization, and tumor burden can lead to skeletal-related events (SREs) that cause serious clinical conditions such as fracture, hypercalcemia, spinal cord compression, and pain [1, 2].

Treatment of breast cancer with bone metastasis shows diversity. Moreover, in patients with a life expectancy of more than three months, the guidelines recommend the use of bisphosphonates in addition to systemic treatment in order to reduce SREs and pain [3, 4].

Zoledronic acid (ZA) and oral/intravenous ibandronic acid (IA) are highly active nitrogen-containing bisphosphonates that increase bone mineralization by inhibiting bone resorption and osteoclast activity. They are also known to inhibit many steps of metastasis such as angiogenesis, invasion, adhesion, and proliferation [5-8]. Skeletal metastasis was developed in 22% of early stage breast cancers and 75% of stage IV breast cancers [9-11]. Additionally, bisphosphonates have been found to be effective in reducing cancer-related bone loss and SREs in breast cancers with bone metastases [12].

We evaluated the effect of ZA and IA on progression-free survival (PFS), overall survival (OS), and skeletal-related events (SRE) in breast cancer patients with bone metastases.

Materials and Methods

The Institutional Review Board waived the need for informed consent given the retrospective nature of the research. The study was conducted in accordance with the principles laid out by the 18th World Medical Assembly (Helsinki, 1964) and all its subsequent amendments (up to 2013) and with the International Society for Pharmaco-epidemiology guidelines for Good Pharmaco-epidemiology Practice and local regulations, including local data protection regulations. The study protocol was approved by the Ethics Committee of reference center.

The study included patients with metastatic breast cancer who applied to Medical Oncology outpatient clinic between 2013 and 2018.

Inclusion criteria were as follows:

1-) Aged over 18 years,

2-) A history of ZA and IA therapies lasting more than three months.

Exclusion criteria were as follows:

1-)Presence of brain metastasis at the beginning of the bisphosphonate therapy,

2-) Presence of a second malignancy,

3-) Absence of a measurable metastasis,

4-) Male gender,

5-) Ongoing steroid or immunosuppressive therapy.

Age, bisphosphonate type, menopausal status, presence of visceral metastases, history of radiotherapy or fracture surgery, presence of metastasis at the time of diagnosis, breast cancer histology, anticancer treatments (hormone therapy/chemotherapy), type of bone metastasis (lytic, sclerotic, lytic+ sclerotic), progression date, date of last follow-up, and date of death were recorded for each patient. PFS was calculated as the time of diagnosis to first progression. OS was calculated as the time of diagnosis to death or last follow-up.

Serum creatinine, total calcium, phosphorus and alkaline phosphatase (ALP) levels were measured both before and after the bisphosphonate treatment using a Beckman Coulter AU5800 autoanalyzer (Beckman Coulter Inc. CA, USA).

Statistical analysis

Data were analyzed using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp.). Categorical variables were compared using Chi-square test and Fisher's Exact test. Normal distribution of continuous variables was assessed using Kolmogorov-Smirnov test. Group means were compared using Wilcoxon signed-rank test. The survival probability was calculated using the Kaplan-Meier method and the factors independently affecting survival time were determined using univariate Cox regression analysis. A p value of <0.05 was considered significant.

Results

Of the 73 patients, 40 (54.8%) were using ZA, 22 (30.1%) were using IA tablets, and 11 (15%) were using IA intravenously (iv). Table 1 presents the demographic and clinical characteristics of the patients. Mean age was 56.0±9.2 years in the ZA group and 54.0±8.9 years in the IA group. Most patients in both groups consisted of non-menopausal patients with hormone receptor (HR)-positive/HER2-negative breast cancer histology. Visceral metastasis was detected in 29 (72.5%) patients in the ZA group and in 21 (63.6%) patients in the IA group. Lytic bone metastases was found in 12.5% (5/40) of the ZA group and 21.2% (7/33) in the IA group. No difference was found between the two groups with regard to the types of bone metastasis (p=0.518).

The median follow-up period and the median duration of drug use was 66.5 (39.8-107.8) months, 28 (11-43) months in the ZA group and respectively 83 (46-124) months, 34 (21.5-51) months in the IA group. No significant difference was found between the two groups with regard to follow-up period and duration of drug use (p=0.197 and p=0.159, respectively).

Table 2 presents the prevalence of SREs in both groups. No significant difference was found between the two groups with regard to the prevalence of fractures, radioteraphy and bone surgery requirement (p=0.606, p=0.295, p=0.247).

In the ZA group, pre-treatment ALP level was 103U/L and post-treatment ALP level increased to 130U/L (p=0.033). In the IA group, pre-treatment ALP level was 85U/L and post-treatment ALP level increased to 93U/L (p=0.072). In the ZA group, creatinine level was 0.62mg/dL before the treatment and increased to 0.74mg/dL after the treatment (p=0.003), while in the IA group creatinine level was 0.6mg/dL prior to the treatment and increased to 0.67mg/dL after the treatment (p=0.284).

A total of 43 patients died during the 5-year follow-up period and the mortality rate was 67.5% (27/40) in the ZA group and 48.5% (16/33) in the IA group. Mean PFS and mean OS was 15 months (95% Confidence Interval [CI]: 11.28-18.71) and 81 months (95% CI=56-106) in ZA users. Respectively 25 months (95% CI=18.23-31.76) and 153 months (95% CI=52.7-253.3) in IA users. No

Table 1. Demographic and clinical characteristics

		ZA n=40	IA n=33	*p**
Age	Mean	56.0±9.2	54.0±8.9	0.404
	< 55 years	18 (45.0%)	19 (57.6%)	
	≥ 55 years	22 (55.0%)	14 (42.4%)	
Menopause	No	32 (80.0%)	24 (72.7%)	0.650
	Yes	8 (20.0%)	9 (27.3%)	
Histology	HR (+) HER-2 (-)	31 (77.5%)	24 (72.7%)	----
	HR (+) HER-2(+)	5 (12.5%)	4 (12.1%)	
	HR (-) HER-2 (-)	2 (5.0%)	-----	
	HR (-) HER-2 (+)	2 (5.0%)	5 (15.2%)	
Solid metastasis	Yes	29 (72.5%)	21 (63.6%)	0.577
	No	11 (27.5%)	12 (36.4%)	
Metastasis at the time of diagnosis	Yes	12 (30.0%)	13 (39.3%)	0.553
	No	28 (70.0%)	20 (60.6%)	
Bone metastasis	Sclerotic	16 (40.0%)	10 (30.3%)	0.518
	Lytic	5 (12.5%)	7 (21.2%)	
	Mixed	19 (47.5%)	16 (48.5%)	
Systemic treatment	<3 cycles of chemotherapy	19 (47.5%)	20 (66.6%)	-----
	≥3 cycles of chemotherapy	17 (42.5%)	13 (39.4%)	
	No chemotherapy	4 (10.0%)	---	
Hormonal therapy	Tamoxifen	5 (12.5%)	6 (18.8%)	-----
	Aromatase Inhibitor	18 (45.0%)	13 (40.6%)	
	Combination (Tmx+AI)	14 (35.0%)	9 (28.1%)	
	No	3 (7.5%)	4 (12.5%)	
Mortality	Yes	27 (67.5%)	16 (48.5%)	0.160
	No	13 (32.5%)	17 (51.5%)	

*Chi-Square Test
ZA: Zoledronic acid, IA: Ibandronic acid, HR: Hormone receptor, Tmx: Tamoxifen, AI; aromatase inhibitors, HER-2; human epidermal growth factor-2
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Table 2. Prevalence of SREs in both groups

		ZA n=40	IA n=33	*p*
Fracture	Yes	13 (%32.5)	8 (%24.2)	0.606*
	No	27 (%67.5)	35 (%75.8)	
Radiotherapy	Yes	27 (%67.5)	26 (%81.2)	0.295*
	No	13 (%32.5)	6 (%18.8)	
Surgical history	Yes	5 (%12.5)	5 (% 15.2)	0.747**
	No	35 (%87.5)	28 (%84.8)	

*Chi-Square Test, **Fisher Exact Test
ZA: Zoledronic acid, IA: Ibandronic acid

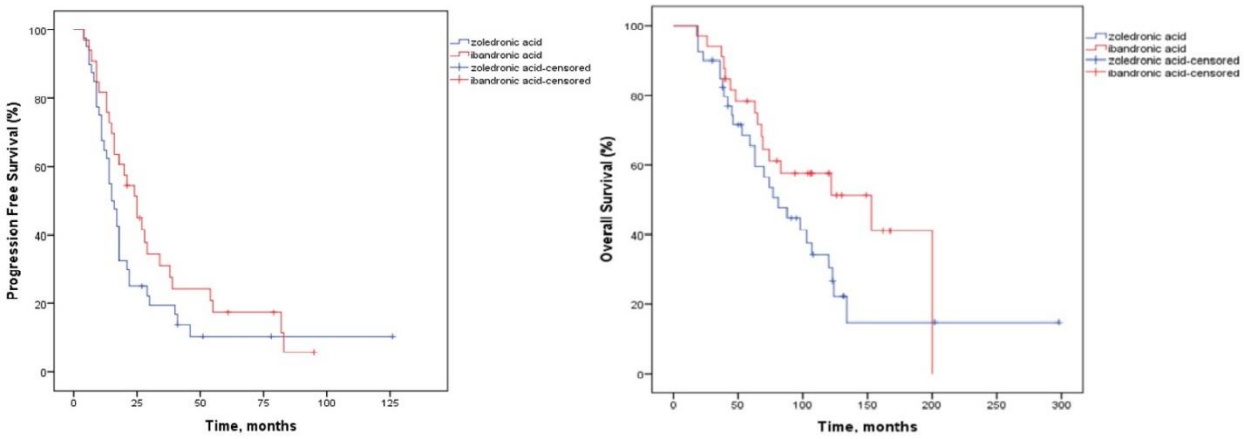

Figure 1. Relationship between ZA and IA use and progression-free survival (PFS) and Overall Survival (OS) time

Table 3. Analysis of independent factors affecting survival

	ZA				IA			
	HR	95% CI		*p*	HR	95% CI		*p*
		Lower	Upper			Lower	Upper	
Age (years)	0.960	0.920	0.999	0.044	1.019	0.957	1.085	0.552
Menopausal status	0.682	0.284	1.640	0.393	1.065	0.333	3.410	0.916
Solid metastasis	2.954	1.101	7.927	**0.031**	2.468	0.695	8.765	0.162
Chemotherapy cycles ≥3 *vs.* <3	2.525	1.023	6.234	**0.045**	0.996	0.350	2.831	0.994
Metastasis at the time of diagnosis	1.983	0.818	4.806	0.130	4.647	1.527	14.139	**0.007**
Fracture	1.484	0.686	3.211	0.316	0.484	0.134	1.749	0.268
Radiotherapy	1.785	0.710	4.490	0.218	1.244	0.349	4.433	0.736
Surgical history	0.563	0.168	1.879	0.350	0.206	0.026	1.629	0.134

HR: hazard ratio, ZA: Zoledronic acid, IA: Ibandronic acid
* Cox regression analysis

significant difference was found between PFS and OS in groups (p=0.134, p=0.088, Figure 1). The two-year survival rate was 71.5% in ZA users and 78.3% in IA users. In the univariate Cox regression analysis, age, solid metastasis and the number of chemotherapy cycles were found to be statistically significant for ZA group and metastasis at the time of diagnosis for IA group (p=0.044, p=0.031, p=0.045 and p=0.007, Table 3). In the multivariate Cox regression analysis, in which the parameters found to be statistically significant for ZA were included in the model, the number of chemotherapy cycles was found to be statistically significant (HR:2.63; CI: 1.05-6.64 & p=0.040).

Discussion

Cost, physician, and patient characteristics (e.g. patient preference, mode of transportation to hospital) play a role in drug selection. The ZICE study compared ZA and IA and reported that oral IA was inferior to ZA in terms of SREs [13]. However, initial SRE development was found to be similar in both groups and IA was associated with a

significantly reduced risk of nephrotoxicity and with insignificantly fewer events of osteonecrosis of the jaw [14]. In our study, no significant difference was found between the two groups with regard to SRE development (Table 2).

Bisphosphonates have the potential to limit tumorigenesis. ZA has been reported to cause rapid and sustainable reduction in circulating tumor cells (CTC) in breast cancer patients. Patients with low CTC levels have been shown to have better PFS [15-18]. Accordingly, the role of bisphosphonates has been evaluated in both metastatic and locally advanced patients and in adjuvant breast cancer patients [19]. Although the addition of bisphosphonates to the standard therapy in metastatic breast cancer reduces the risk of SRE development by 15% and has been associated with delayed SRE development and reduced bone pain, it has been found to have no benefit on OS and PFS [20-22]. Survival in patients with breast cancer can be affected by many factors including histological classification, genetic characteristics, tumor volume, metastasis localization, and patient-related comorbidities. It has also been reported that the median OS after the development of bone metastasis varies 40-79 months depending on the presence of isolated or multiple metastases [10, 23]. In our study, advanced age, increased chemotherapy cycles count and solid metastases in the ZA group and presence of metastases at diagnosis in the IA group adversely affected survival. OS was found longer in IA users compared to ZA users, though no significant difference was found (153 vs. 81 months, p=0.088). Moreover, unlike in the ZICE study, both iv and oral forms of IA were used in our patients. The efficacy of iv and oral ibandronate on osteoporosis was evaluated and found that both forms had similar effects [24]. This finding suggests that there will be no significant difference between iv and oral IA with regard to SRE, PFS, and OS.

Studies have shown that ZA increasing the normalization of osteolytic markers and this normalization was associated with better survival in patients with bone metastases [25,26]. In our study, serum ALP level increased significantly in the ZA group after the treatment (p=0.030). This significant increase could be related to the shorter duration of ZA use. On the other hand, increased ALP concentration is affected by many factors including liver, gallbladder, and kidney diseases.

Our study was limited in several ways. First, it was a single-center retrospective study that evaluated a homogeneous patient group. Due to the retrospective nature of the study, the effect of drugs on pain palliation could not be evaluated. Second, it had a limited number of patients. Finally, bone resorption markers could not be evaluated and thus a comprehensive examination of bone turnover could not be performed.

Conclusion

The survival of breast cancer patients has been significantly improved. Due to their antiresorptive and antitumor effects, bisphosphonates can be used safely both in adjuvant and metastatic breast cancer patients, particularly in high-risk postmenopausal patients. The effectiveness and side effects of both agents are similar. Further comprehensive studies are needed to evaluate the effect of these two agents on patient comfort, survival, and cost-effectiveness.

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