



Therapeutic bone response of breast cancer recurrences on single sm-153 EDTMP treatment (+/- influence of statin intake)

Purpose: Data comparing osteoblastic vs osteolytic recurrences of therapeutic response are still very limited. We aimed to answer this question in 164 female breast cancer patients (including 61 females on statin therapy) suffering from recurrent breast cancer who received a single dose of Sm-153 EDTMP for painful metastatic bone lesions.

Methods: 164 female patients suffered from painful metastatic breast cancer with >1 up to 5 bone lesions, we evaluated the response of recurrences judged by CT as osteoblastic (BL), osteolytic (LY) or mixed (MI) showing up in bone scintigraphy to a single dose of 30 mCi (1.1 GBq) ¹⁵³Sm-EDTMP. 116 females (70.03%) suffered from ductal, 37 (22.56%) from lobular, 10 (6.09%) from mixed and 1 (0.61%) from medullary cancer. Statin used by the 61 female patients were Simvastatin (20 or 40 mg/day orally), Atorvastatin (20 or 40 mg/day orally) and Rosuvastatin (20 mg/day orally).

Results: Bone uptake and pain response did not show any difference between BL-, LY- and MI-recurrences. No correlation of pain response and its duration vs. uptake, type, number and extent of lesions, adhesion molecules (AM) and histology was seen. Out of 164 female breast cancer, females on statins exhibited a significantly (P-value<0.01) more pronounced decrease in adhesion molecules vs. non users.

Conclusion: These findings indicate no significant difference in pain response between the different types of bone recurrences. Whether, the effect of statins on adhesion molecules is a direct drug effect or reflect on antitumoral action as well as, the influence on the extent of recurrences should be examined in prospective studies.

KEYWORDS: therapeutic ▪ bone response ▪ breast cancer ▪ recurrences ▪ sm-153 EDTMP treatment ▪ influence ▪ statins intake.

Introduction

Breast cancer is a major health problem that affects the lives of millions [1]. Almost 75% of all breast cancers occur in postmenopausal women, of which about 80% are hormonal receptor positive [2]. Metastases account for more than 90% in cancer patients [3]. At post mortem examination ~70% of all patients dying due to breast cancer, show evidence of metastatic bone disseminations which in many patients is a chronic painful condition [4]. Bone is considered the common site affected in breast cancer metastases. Bone metastases are usually associated with pathological fractures, spinal cord compression result in immobility, it occur in more than 50% [5]. Bone metastases are interrupting the process of active bone formation by osteoblasts and bone resorption by osteoclasts [6] *via* an organized process involving tumor intravasation & extravasation into surrounding tissue, cell survival, initiation of growth, Tumor vascularization and angiogenesis [7].

Scintigraphically, 48% of bone metastases from breast cancer are purely osteolytic (LY), while 13% are purely osteoblastic (BL) and

38% are mixed osteoblastic and osteolytic [8]. Histologically and biochemically, the two processes occur irrespective of the lytic or blastic radiological appearance [9].

The optimal treatment of bone metastases from breast cancer involves the incorporation of local systemic anti-cancer therapy with bone-targeted agents "bisphosphonates". Treatment is aimed at reducing pain, preventing disability and improving quality of life [10].

Systemic therapy with radionuclides linked to bone avid agents is a promising treatment option for patients with disseminated skeletal metastases, owing to its efficacy, low cost and low toxicity [11]. Sm-153 EDTMP is a promising radiopharmaceutical for the palliation of metastatic bone pain for several cancers, mainly breast and prostate [12,13].

It accumulates in the skeleton by chemisorption of the tetraphosphonate by hydroxyapatite and by the formation of samarium oxide involving oxygen on the hydroxyapatite molecule with minimal accumulation in nonosseous tissues. Skeletal

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uptake was shown to be directly related to the number of metastatic sites [14,15].

Statins are a class of hypocholestermic drugs first marketed in 1987, they are quite commonly used among persons aged 50 years and older [16]. A growing body of laboratory data and experimental evidence suggests that beside the cardiovascular benefit, statins may have chemopreventive potential against cancer at various sites, including colon, lung, breast and prostate [17].

This is a retrospective analysis on 164 female patients suffering from recurrent breast cancer who underwent a single dose of Sm-153 EDTMP therapy for painful metastatic bone lesions.

Aim of the study was to assess if there is a difference in bone uptake and pain response rate of Sm-153 EDTMP between patients with BL, LY or MI recurrences ("±" with or without the influence of statin intake).

■ Treatment design

Sm-153-Lexidronam administration was performed according to the Vienna protocol [18]. The protocol is defined as follows: 30 mci (1.1 GBq) Sm-153 EDTMP is administered intravenously on an outpatient basis. Red and white blood cell as well as platelet count was determined (3 and 6 weeks and immediately before the next treatment respectively). Whole body bone Scintigraphy was performed usually on the next day, anyway, about 20 h after radionuclide application to achieve complete blood clearance, using large field of view double headed γ -camera, LEHR-collimation, energy window 20%, 103 Kev, acquisition mode continuously 15 cm/min, early images (<4 h) showed significantly lower quality.

Methods

1. 164 female patients suffering from breast cancer were included in this study. Their age ranged from 35-77 years as shown in (Table 1). Their tumor histology was the following:

116 (70.03%) ductal, 37 (22.56%) lobular, 10 (6.09%) mixed and 1 (0.61%) medullary.

Statin therapy: Statin used by the 61 female patients were Simvastatin (20 or 40 mg/day orally), Atorvastatin (20 or 40 mg/day orally) and Rosuvastatin (20 mg/day orally).

2. All the patients had metastatic bone pain was assessed clinically and according to WHO Analgesia Scale and the lesions number varied from 1 up to ≤ 5 judged initially by sequential X-ray and/or CT to be verified later by bone scintigraphy.

3. Blood for determination of adhesion molecules was drawn immediately before starting therapy and thereafter at the end (12 weeks) of monitoring on the following scheduled treatment, respectively. Stored plasma was thawed and assayed for ICAM-1, E-selectin and VCAM-1 with a commercially available ELISA according to the manufacturers' instruction (R&D System, Inc., Europe). Standardization was done using a recombinant adhesion molecules provided with the kit. Blood (1:10 anticoagulated with 2% EDTA) was drawn from a non-occluded cubital vein. After sedimentation (<20 minutes) and centrifugation (15 minutes; 1000 \times g; 4°C) plasma samples were frozen at >-70 °C. Sensitivity of the assays was 7 ng/ml for ICAM-1, 2 ng/ml for E-selectin and 100 ng/ml for VCAM-1.

■ Statistical analysis

Date entry and data analysis were done using SPSS version 16 (Statistical Package for Social Science). The data of the patients were retrospectively collected. Continuous variables were summarized as means \pm SD, while categorical variables were summarized as numbers and percentage. Post-treatment data was compared with pre-treatment data (baseline), because the scores changed considerably over the weeks. VAS, analgesic scores were calculated at 7, 8, 9, 10, 11, 12 weeks. Repeated measures analysis was then used to calculate the statistical significance of interval changes in post-therapy

Table 1. Patients characteristics.

	BL	LY	MI
n	86	54	24
Age range (y)	37-73	35-77	41-74
Mean age (y) \pm SD	51.6 \pm 14.3	53.8 \pm 16.1	53.7 \pm 14.7
BL =osteoblastic; LY =osteolytic; MI =mixed; n =number; y=years			

scores. Calculation for significance was done using ANOVA. A p-value<0.01 was considered statistically significant.

Results

Sm-153 EDTMP uptake was not significantly different among the patients with different types of bone recurrences as well as the pain response rate with a very low prevalence of flare occurrence as shown in Table 2.

The rate of pain response among the patients receiving Sm-153 EDTMP did not differ between patients with the different types of bone recurrences, while there was a gradual decline in pain response rates with time to record the highest response at 7 week and the lowest one at 12 week (91.8%, 96.3% and 87.5% *vs.* 77.9%, 81.5% and 66.6%), respectively. Previous relevant studies reported a great variation of pain response rate in relation to the time of therapy among cancer patients with different confirmed primaries [19]. Number and extent of bone lesions had no influence on the findings; furthermore, statin intake and histology did not influence pain response either as shown in Table 3.

In patients already on statin therapy who receiving Sm-153 EDTMP therapy, there was a statistical significant reduction in the values of adhesion molecules *vs.* non-statin users as shown in Table 4. No difference as to the type or the dose of the respective statin could be

detected, probably due to a few numbers in the respective subgroup.

Table 5 describes the effect of the histology of breast cancer on the adhesion molecules in statin users *vs.* non-statin users. There was a statistical significant decline of the adhesion molecules values (p-value<0.01) among all the different histological types of breast cancer among statin users except medullary cancer, where patients number did not allow conclusive analysis.

Discussion

There are several studies documenting the efficacy of Sm-153 EDTMP as a palliative treatment in controlling bone pain in cancer patients with disseminated bone metastases. The initial study of 35 patients was done by Turner et al., including 15 prostate, 10 breast and 10 other cancer patients who received dosimetry-confirmed exposure to 100-280 cGy with Sm-153 EDTMP, showed stabilization or even improvement of bone scans three months after therapy in 15 of 34 evaluable patients. The same group of authors reported that patients who were retreated after hematological recovery showed improvement in overall survival relative to patients who received only a single dose (9 months *vs.* 4 months), they concluded that both the median duration of pain control and survival were greater in patients receiving multiple doses of Sm-153 EDTMP as compared to patients receiving a single dose [20].

Table 2. Uptake and pain response vs. lesion number.

	BL		LY		MI	
Lesions	2-3	4-5	2-3	4-5	2-3	4-5
Uptake	54.2	55.9	53.9	53.7	52.9	54.3
Complete*	51.4	51.0	52.0	51.7	50.0	42.9
Partial*	42.9	43.1	44.0	44.8	40.0	50.0
No*	5.7	5.8	4.0	3.5	10.0	7.1
Flare*	2.9	3.9	8.0	3.4	10.0	7.1
n	35	51	25	29	10	14

values in %; *significant pain response means p< 0.01; n= number

Table 3. Duration of pain response vs. type of bone recurrences.

Wk	BL	LY	MI
Total (n/%)	86/52.4	54/33	24/14.6
*7	79/91.8	52/96.3	21/87.5
8	77/89.5	50/92.6	20/83.3
9	76/88.4	50/92.6	18/75
10	74/86.0	49/90.7	18/75
11	71/82.6	46/85.2	16/66.6
*12	67/77.9	44/81.5	16/66.6

Table 4. Influence of statin treatment on adhesion molecules vs. non statin users.

AM		Statin users(+)						Non statin users(-)					
		BL	Lowering%	LY	Lowering%	MI	Lowering%	BL	Lowering%	LY	Lowering%	MI	Lowering%
ICAM-1	Before	387.3	18.1	376.7	14.0	391.8	20.3	386.4	11.9	377.5	9.3	395.0	
	After	317.2		324.0		312.3		340.6		342.4		347.8	11.9
VCAM-1	Before	324.7	16.8	833.8	17.4	836.5	16.2	826.1	12.7	835.2	14.4	842.7	
	After	686.5		689.0		701.3		721.0		714.8		715.4	15.1
E-selectin	Before	90.2	16.6	88.7	12.5	93.6	21.5	93.4	7.8	90.2	7.5	94.8	9.6
	After	75.2		77.6		73.5		86.1		83.4		85.7	

AM:Adhesion Molecules; Values in ng/ml; prevalues vs. 12 week ± statin use; + :statin users; - : non statin users

Table 5. Influence of statin use and histology on adhesion molecules (change in % vs. prevalue).

Statin use	Medullar	*Mixed	*Lobular	Ductal*	AM
+	22.1	18.5	19.4	18.2	
-	10.6	12.3	9.7	11	ICAM-1
+	14.5	18.8	19.5	17.4	
-	11.6	13.2	14.3	12.6	VCAM-1
+	20.5	18.1	20.3	21.6	
-	8.2	8.6	9.4	7	E-selectin
	1	10	37	116	n

A study performed by Li et al. measured the rate of Sm-153 EDTMP bone uptake using whole-body scintigraphy and analyzed the relationship between bone uptake rate and therapeutic effect in 66 patients with painful bone dissemination, reported statistical significant difference between the complete responder and partial responder groups (t=4.258, P=0.001) as well as between partial responder and non responder groups (t=8.48, P=0.001) [21].

Another study by Vigna et al. calculated the activity dose delivered to the bone surface and red marrow in 20 patients treated with 153-Sm EDTMP, administering a fixed activity per kg (37 MBq/kg). Blood and urinary samples were collected for 24 h post treatment, reported a high bone and marrow activity dose among prostate cancer patients with osteoblastic bone lesions while, in breast cancer with osteolytic or mixed lesions showed no statistical difference in clinical results among them [22].

Bacyzk et al. assumed that high osteoblastic activity allows for incorporation of a large amount of isotope into pathologically changed

osteosclerotic bone matrix, while the efficacy of mixed metastases therapy is inversely related to the increase in the osteolytic component, especially in large foci. Therefore, they concluded that the type and size of metastases and the type of neoplasm are the main factors predicting effectiveness. In general, osteoblastic or mixed metastases have been claimed as an indication for radioisotope therapy, while osteolytic metastases require bisphosphonate treatment as a first line [23].

Hellman et al. also considered that the osteoblastic activity determined by bone scan is the main indication for radionuclide therapy while the osteolytic lesions are the relative contraindication for therapy [24]. On the contrary, in this retrospective analysis we were unable to judge on the efficacy as we depended only on the bone scintigraphy as a functional imaging in detection of the positive bone uptake. We found no significant difference in Sm-153 EDTMP uptake as well as pain response rate among patients with the different types of bone recurrences. In the follow up of the patients over 3 months, there was a decline in pain response rate among BL, LY bone recurrences (91.8%,

96.3% vs. 77.9%, 81.5%) and respectively, with a significant reduction at mixed type (87.5% vs. 66.6%) at 7 and 12 week.

In hypercholesterolaemic post-menopausal women with coronary artery disease suffered from breast cancer, Statins, is the most commonly prescribed class of drug, have demonstrated an added effects beyond lowering cholesterol level including anti-cancer and immunomodulatory properties. Several studies have studied an anti-carcinogenic effect of statins, evidenced by decreasing in cancer incidence and cancer-caused mortality. Clinical trials on statins as part of therapy for cancer have generated interest among the oncologists. Statins have been investigated for a variety of cancers, at early and late stages, alone and in combination with chemotherapeutic agents and radiation therapy [25]. Several promising results have been suggested statin use in hepatocellular carcinoma [26], colorectal cancer [27], and advanced stage of pancreatic cancer [28].

In this study, we reported the non-lipid mechanism of statin in reducing the cellular adhesion molecules, which include the intercellular adhesion molecule (ICAM-1), the vascular cell adhesion molecule (VCAM-1) and E-selectin [29]. In patients without statins, pre values of adhesion molecules were significantly higher compared to the ones on the drug. Sm-153 EDTMP caused a significant decrease in adhesion molecules in both groups of patients,

the extent, however, being more pronounced in patients on statins. We were unable to differentiate if this change, wherever, was a direct effect of statin use or due to an antitumor action.

There was a significant influence of the histology of the breast cancer on the adhesion molecules among statin users vs. non-users (p-value<0.01) except in medullary cancer where only one patient was evaluated.

Conclusion

We found no significant difference in pain response between the different types of bone recurrences in breast cancer patients. Therefore, wherever more than one bone lesion is detected by bone scintigraphy, therapy should be started irrespective of the morphological type of recurrences. Whether, the effect of statins on adhesion molecules is a direct drug effect or reflect on antitumor action as well as, the influence on the extent of recurrences should be examined in prospective studies.

Compliance with ethical standards

There is no financial support. There are no conflicts of interest. This study was approved by the Ethics Commission at the Medical University of Vienna and the Vienna General Hospital (AKH), each patient was explained the details of the procedure, benefits and side effects of therapy and the follow-up protocol and all patients provided written informed consent.

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