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pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en Rhumatologie

Les bisphosphonates utilisés dans le traitement de l'ostéoporose réduisent le risque de rechute et de décès des femmes ménopausées avec cancer du sein RE+

Bisphosphonates reduce the risk of relapse and death of postmenopausal women with ER+ breast cancer

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LISTE DES ABREVIATIONS

WHO	World Health Organisation
DNA	Deoxyribonucleic acid
VDR	Vitamin D Receptor
PTH	Parathyroid hormone
ER	Estrogen receptor
AI	Aromatase inhibitor
HER	Human epidermal growth factor receptor
PR	Progesterone receptor
BMI	Body mass index
HR	Hazard ratio
BMD	Bone mineral density
CTX	C-terminal telopeptide of type I collagen
DFS	Disease-free survival
BCSS	Breast cancer-specific survival
OS	Overall survival
BPs	Bisphosphonates

Plan

RESUME

Introduction : Le pronostic du cancer du sein dépend entre autres de sa taille, de l'envahissement ganglionnaire, de son grade histologique et de l'expression ou non des récepteurs aux estrogènes (RE), à la progestérone (RP) et de la protéine HER. L'objectif de cette étude était d'analyser l'influence des paramètres osseux et des prescriptions de bisphosphonates et de vitamine D sur le devenir du cancer du sein.

Patients et méthodes : Il s'agit d'une étude de cohorte, longitudinale, prospective portant sur 450 femmes avec cancer du sein RE+ initialement localisé. Nous avons analysé (1) les caractéristiques de la tumeur, (2) le statut osseux lors de la prescription des anti-aromatases (fractures, DMO, vitamine D, PTH et CTX sériques) (3) les modalités thérapeutiques (chirurgie, radiothérapie, chimiothérapie, tamoxifène, anti-aromatases, vitamine D, bisphosphonates) et (4) le devenir clinique de la patiente à la date de point (1/07/2015) par analyse multivariée en utilisant un modèle de Cox.

Résultats : Le suivi moyen était de 10,3 ± 3,0 ans. 79 décès et 75 rechutes sont survenus. L'âge moyen au diagnostic était de 61 ans, 30,7% avaient un antécédent de fracture, 16,9% avaient un T-score lombaire ou fémoral ≤ -2,5, la 25(OH) vitamine D était < 50 nmol/L chez 292 patientes (65%). 159 femmes (35,3%) ont été traitées par bisphosphonates pour une ostéoporose pour une durée moyenne de 5 ± 1,7 années. Le risque de rechute ou de décès n'était corrélé ni à la présence de fracture, ni à la densité osseuse. L'âge au diagnostic de cancer (HR=1,03, p=0,05), la taille de la tumeur (HR=1,32, p=0,001) et le nombre de ganglions envahis (HR=1,07, p=0,03), étaient significativement associés au risque de rechute du cancer. La prescription de bisphosphonates était associée, de façon indépendante, à une forte diminution du risque de rechute (HR=0,49, p=0,02). L'âge au diagnostic (HR=1,07, p=0,001) et la carence en 25(OH) vitamine D (HR=1,91, p=0,03) étaient associés à une augmentation du risque de décès, alors que la prescription de bisphosphonates était associée à une diminution du risque de décès global (HR=0,46, p=0,01).

Conclusion : Notre étude montre qu'un traitement par bisphosphonates utilisé pendant 5 ans pour une ostéoporose par des femmes avec un cancer du sein localisé RE+ traité par inhibiteur de l'aromatase diminue le risque de rechute et de décès de 50% à 10 ans.

ABSTRACT

Introduction: risk factors of breast cancer relapse are well known such as large tumor size, lymph node involvement, high-grade tumor, absence of progesterone and estrogen receptors, expression of HER protein. The aim of our study was to analyze the influence of bone parameters and the prescription of bisphosphonate and vitamin D on breast cancer outcome.

Patients and methods: this is a longitudinal and prospective cohort of 450 postmenopausal women with local ER+ breast cancer. For every patient we analyzed (1) tumor characteristics', (2) bone status at the beginning of aromatase inhibitor treatment (fractures, BMD, vitamin D, PTH and CTX) (3) tumor and bone treatments (surgery, radiotherapy, chemotherapy, tamoxifen, aromatase inhibitors, vitamin D, bisphosphonates) and (4) cancer outcome at the date of point (1/07/2015) with Cox model.

Results: mean follow-up was 10.3 ± 3.0 years. 79 women died and 75 had a relapse. Mean age of the women was 61 years, 30.7% had an history of fracture, 16.9% had a lumbar or hip T-score ≤ -2,5. 292 women (65%) had 25(OH) vitamin D concentration < 50 nmol/L. Bisphosphonates were prescribed to 35.3% women for osteoporosis for a mean duration of 5 ± 1.7 years. The risk of relapse or death was not correlated to history of fracture, bone density or CTX. Age at cancer diagnosis (HR=1.03, p=0.05), tumor size (HR=1.32, p=0.001) and the number of lymph nodes involved (HR=1.07, p=0.03) were significantly associated with relapse. Bisphosphonate treatment was significantly associated with a decreased risk of relapse (HR=0.49, p=0.02). Age at cancer diagnosis (HR=1.07, p=0.001) and vitamin D deficiency (HR=1.91, p=0.03) were associated with an increased risk of death. Bisphosphonate treatment was associated with a decreased risk of death (HR=0.46, p=0.01).

Conclusion: our study showed that bisphosphonates using for osteoporosis treatment in women treated by aromatase inhibitors for ER+ breast cancer reduced by 50% relapse and death at 10 years.

INTRODUCTION

Breast cancer is the leading non-skin cancer in women worldwide and a major public health issue[1]. In France 54 062 new cases and 11 913 deaths have been projected in 2015 representing the first cause (18.8%) of cancer deaths according to the National Cancer Institute[2]. Many risk factors of breast cancer are known (age, certain inherited genes, personal and family history of breast cancer, etc.), improving the screening of patients leading to earlier diagnosis and care. Furthermore, its multidisciplinary approach has also significantly improved the prognosis in recent years around the world, combining surgery, radiotherapy, chemotherapy and hormonal therapy, resulting in fewer local or distant recurrences. Thus, the survival rate at 5 years in North America and Europe is currently close to 90%[3]. Risk factors of breast cancer relapse are also well known: large tumor size, lymph node involvement, high-grade tumor, absence of progesterone and estrogen receptors, expression of HER protein, younger age, high body mass index and no physical activity[4].

Bone status is a matter of concern for patients with breast cancer particularly because of the risk of osteoporosis induced by hormonal therapy, mainly aromatase inhibitor. Thus, it is now recommended to assess the risk of osteoporosis of women with breast cancer and to treat them using lifestyle recommendations, vitamin D supplementation and specific treatment such as bisphosphonates in case of history of osteoporotic fracture or low density.

Beyond their effects on bone remodeling in case of osteoporosis, recent studies have reported effects of vitamin D and bisphosphonates on breast cancer outcome. It has been demonstrated in vitro and in vivo anticarcinogenic effect of vitamin D by stimulating or inhibiting at least 290 different genes[5], modulating cell proliferation, cell differentiation, immune function[6] and DNA repair. Its role in several cancer risk/incidence has been shown[7–9], including breast cancer, but is still controversial in the prognosis[10]. To date, most studies have focused on the association between vitamin D concentrations and incidence of breast cancer[7], a few studies have investigated the possible relationship between serum 25(OH) vitamin D concentrations and cancer outcomes, even if many of them reported a significant association, results remained controversial[11,12]. Vitamin D supplementation on breast cancer outcome is still unknown.

Bisphosphonates are used in case of bone metastasis treatment but recent studies[13,14] also suggest an adjuvant effect on breast cancer of bisphosphonates reducing rates of recurrence and death in postmenopausal patients with early-stage breast cancer[15,16]. These studies have been mainly realized outside of the context of osteoporosis.

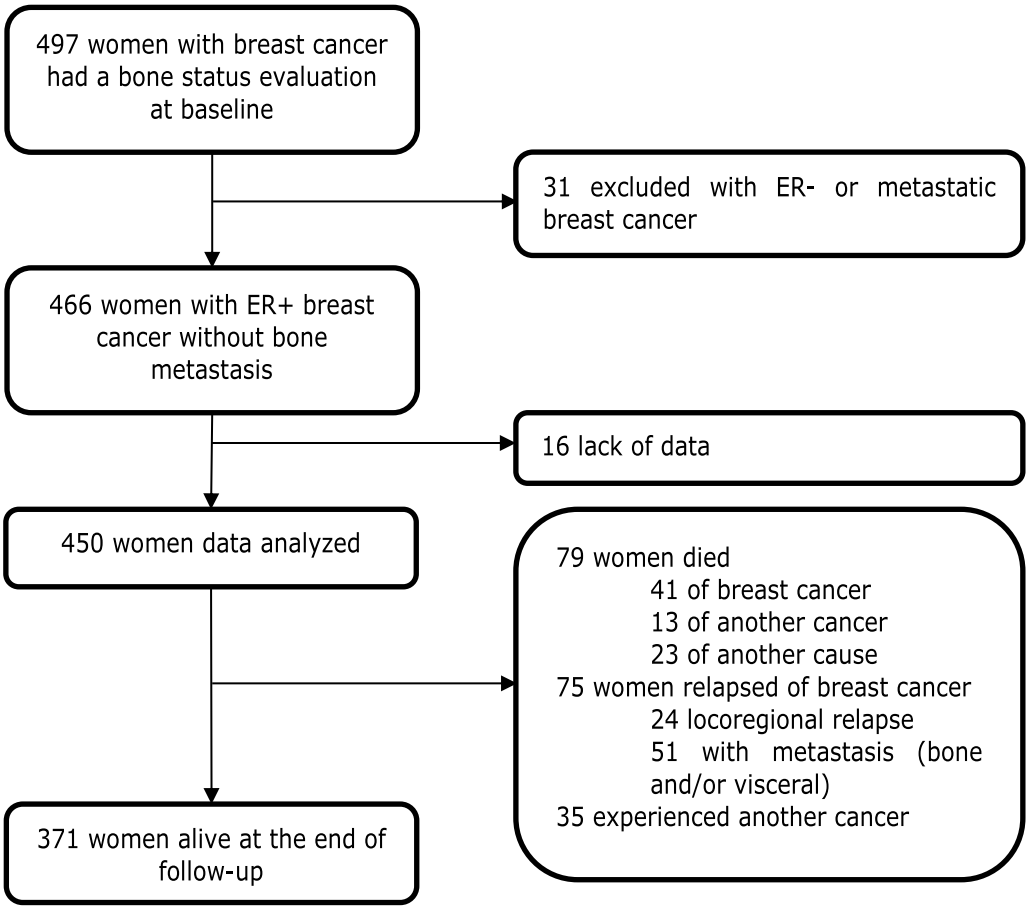
The aim of our study was to analyze, alongside classic risk factors, the effects of bone mineral density, vitamin D and PTH concentrations, vitamin D supplementation and bisphosphonate treatment used for osteoporosis on breast cancer outcome.

PATIENTS AND METHODS

Patients

This prospective, observational and longitudinal study was conducted by both the Department of Rheumatology of the University Hospital of Angers, and the Department of Medical Oncology of the Cancer Institute (institute de Cancérologie de l'Ouest) of Angers. Inclusion period in the cohort was from January 2004 to January 2006. Among 920 consecutive women with breast cancer, 497 consecutive women with ER+ breast cancer had an osteoporosis assessment within the first three months of aromatase inhibitor (AI) therapy. Thirty-one were excluded because of ER- breast cancer or metastasis at the time of bone assessment. Sixteen patients were excluded because of lack of data. Finally, statistical analyzes were performed on 450 postmenopausal women (flow-chart in figure 1).

Figure 1 – Flow chart



Methods

Methods have been already published[17]. All included women had a bone assessment within the first three months of aromatase inhibitor (AI) therapy with (1) an extensive medical history and a physical examination including age, age at onset of menopause, family history of osteoporosis, personal history of fractures, medications, alcohol and tobacco use, physical activity, vitamin D supplementation and calcium food intake (2) a fasting serum sample including calcium, phosphate, albumin, creatinine, 25(OH) vitamin D (Nichols Institute Diagnostics, San Clemente, CA), parathyroid hormone (PTH) (Beckman Coulter, Brea, CA) and C-terminal telopeptide of type I collagen (CTX) was collected. Measurements were performed immediately without freezing (3) a BMD measurement of lumbar spine, femoral neck and total hip using dual energy X-ray absorptiometry (DXA) operating in fan-beam mode (Hologic QDR 4500A densitometer; Hologic Inc., Waltham, MA) (4) anteroposterior and lateral spinal X-ray films.

Treatments and parameters of breast cancer were collected at the same time: tumor size (in cm and TNM), tumor grade (Scarff-Bloom and Richardson (SBR) or Elston and Ellis (EE)), nodal involvement (number of lymph nodes with cancer cells), human epidermal growth factor receptor (HER), progesterone receptor, previous treatments (surgery, chemotherapy, radiotherapy, tamoxifen, aromatase inhibitors).

After this evaluation, women with osteoporosis defined by an history of non-traumatic fracture and/or a T-score ≤ -2.5 at at least one of the bone density measured sites were treated by oral (alendronate 70mg weekly or risedronate 35mg weekly) or intravenous (acid zoledronic 5mg annually) bisphosphonates.

Data about cancer outcome were collected from November 2015 to February 2016: death, death from breast cancer, local relapse, regional relapse and distant relapse. Data were collected by phone calls to general practitioners and reviewing on computer records. Date of point was July 2015.

Endpoints

The main endpoint of this study was to analyze after a 10 years' follow-up, influence of bone parameters collected at aromatase inhibitors therapy initiation (history of fracture, BMD, 25(OH) vitamin D, PTH and CTX concentrations) and prescription of bisphosphonates and vitamin D on outcome of breast cancer.

Statistical analyzes

Statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS release 22.0, IBM corp., Chicago). Bone assessment characteristics were expressed in mean ± one standard deviation or in number of patients with percentage. Characteristics of tumor and treatments were expressed in mean ± one standard deviation or in number of patients with percentage. We analyzed characteristics of patients, tumor and bone assessment according cancer outcome using standardized definitions: relapse (local/regional and distant recurrences), death of breast cancer and death. We also analyzed characteristics of patients treated or not by bisphosphonates. These characteristics were compared between groups using Pearson's chi-2 test or Student t-test, when appropriate; a p-value < 0.05 was considered statistically significant.

We analyzed cancer outcome according vitamin D and PTH concentrations. As there is no cut point in the cancer field, we analyzed 25(OH) vitamin D using standard definition of deficiency (defining as serum concentration ≤ 25 nmol/l) and insufficiency (defining as serum concentration ≤ 50 nmol/l) and PTH concentration defining two categories normal and abnormal (defining mean + one standard deviation).

We then analyzed survival data. Disease-free survival (DFS) was defined as the period from the date of vitamin D measurement to the date of the first locoregional recurrence (breast, chest wall, skin, or lymph nodes), distant metastasis, death from any cause or the date of the last follow-up. Breast cancer-specific survival (BCSS) was defined as the period from the date of vitamin D measurement until the date of breast cancer-related death, death from other cause or the date of the last follow-up. Overall survival (OS) was defined as the period from the date of vitamin D measurement until the

date of death (from any cause) or the date of the last follow-up. The survival curves, by vitamin D and PTH serum concentrations and use of bisphosphonates, were obtained using the Kaplan-Meier method, Log-Rank and Breslow tests were used to compare the survival curves. Cox proportional hazard regression models were used to examine the classical prognostic factors of relapse or death: age at diagnosis (in years), BMI (in kilograms per square meter), tumor size (cm), nodal involvement (n), progesterone receptor status (positive vs. negative), HER status (positive vs. negative) with the use of bisphosphonate therapy, and 25(OH) vitamin D deficiency. P values <0.05 were considered statistically significant.

RESULTS

1. Characteristics of the cohort

We reported cancer outcome of 450 postmenopausal women with ER+ breast cancer and no bone or visceral metastasis at the time of aromatase inhibitor treatment initiation. Mean follow-up from the diagnosis of cancer to the date of point was 10.25 (± 3.02) years. Mean duration between breast cancer diagnosis and bone assessment was 2.2 (± 1.8) years. Baseline characteristics of the breast cancer are presented in table I and results of bone assessment are presented in table II.

Table I. Characteristics of breast cancer and treatment		
Age at the diagnosis, years, mean ± SD		60.7 ± 10.2
Tumor size, n (%)		
	≤ 2 cm	310 (68.9)
	> 2 - ≤ 5 cm	101 (22.4)
	> 5 cm	9 (2.0)
	Missing	30 (6.7)
Tumor grade, n (%)		
	1	104 (23.1)
	2	226 (50.2)
	3	99 (22.0)
	Missing	21(4.7)
Tumor type, n (%)		
	Ductal cancer	364 (80.9)
	Lobular cancer	79 (17.6)
	Tubular cancer	6 (1.3)
	Other type	12 (2.7)
Nodal involvement, n (%)		
	0	256 (56.9)
	1-3	140 (31.1)
	4-9	44 (9.8)
	≥ 10	10 (2.2)
PR status, n (%)		
	positive	368 (81.8)
	negative	76 (16.9)
	Missing	6 (1.3)
HER status, n (%)		
	positive	36 (8)
	negative	414 (92)
Previous chemotherapy, n (%)		
	Yes	251 (55.8)
	Anthracyclines	215 (85.7)
	Mean number of cures ± SD	5.01 ± 1.39

	Docetaxel	82 (32.7)
	Mean number of cures ± SD	3.76 ± 1.39
	Other type	40 (15.9)
	Mean number of cures ± SD	6.35 ± 3.49
	No	199 (44.2)
Previous radiotherapy, n (%)		
		419 (93.1)
		31 (6.9)
Previous tamoxifen therapy, n (%)		
	Yes	182 (40.4)
	Mean duration ± SD, months	35.4 ± 19.3
	No	268 (59.6)

Abbreviations. SD, standard deviation; PR, progesterone receptor; HER, human epidermal growth factor receptor.

Table II. Bone assessment of the 450 women

Variables	Mean ± SD
Age of menopause, years	49.4 ± 4.5
Body mass index, kg/m2	27.1 ± 5.6
Serum creatinine, µmol/l	66.9 ± 37.5
Calcemia, mmol/l	2.44 ± 0.18
Phosphatemia, mmol/l	1.12 ± 0.16
Serum 25(OH) vitamin D, nmol/l	46.21 ± 22.60
Serum parathyroid hormone, pg/ml	35.44 ± 21.19
CTX, ng/ml	0.75 ± 0.36
Sex Steroid Binding Globulin, nmol/l	59.6 ± 32.2
BMD lumbar spine, g/cm2	0.932 ± 0.149
BMD total hip, g/cm2	0.860 ± 0.141
BMD femoral neck, g/cm2	0.707 ± 0.111
	n (%)
T-score ≤ - 2.5 at at least one site	76 (16.9)
≥ 1 fractures at baseline	138 (30.7)
≥ 1 Vertebral fracture	86 (19.1)
≥ 1 Peripheric fracture	77 (17.1)
Hip fracture	6 (1.4)
Vitamin D supplementation after bone assessment	
Yes	302 (67.1)
No	147 (32.7)
Bisphosphonates for osteoporosis after bone assessment	
Yes	159 (35.3)
oral	151 (33.5)
intravenous	19 (4.2)
No	289 (64.2)

Abbreviations. SD, standard deviation; CTX, C-terminal telopeptide of type I collagen; BMD, Bone mineral density.

159 women (35.3%) received bisphosphonates after bone assessment for a mean duration of 5 ± 1.7 years. Characteristics of these patients are described in annex 1. Briefly, women who received bisphosphonates were significantly older (63.4 ± 10.5 vs 59.2 ± 9.8 years; p=0.001) at the diagnosis of breast cancer, had a lower BMI (25.2 ± 4.9 vs 28.1 ± 5.7 kg/m2; p=0.001), a lower BMD at each sites (all p=0.001), and more fractures at the time of bone evaluation (all p=0.001). 13.8% women who received bisphosphonates died, 11.9% experienced a relapse, and 6.9% died of breast cancer. No serious secondary effects due to bisphosphonates (osteonecrosis of the jaw or atypical fracture) have been reported.

2. Cancer outcome - Descriptive analysis

Seventy-nine women (17.6%) died after a mean follow-up of 5.04 (± 2.57) years. Forty-one women (9.1%) died of breast cancer after a mean follow-up of 5.38 (± 2.07) years, and 36 (8.4%) died of other causes. Seventy-five women (16.7%) experienced a breast cancer relapse after a mean follow-up of 4.22 (± 2.78) years consisted in 11 local relapse (2.4%), 13 regional relapse (2.9%) and 51 (11.3%) general relapse with bone or visceral metastasis. Thirty-five (7.8%) women experienced another cancer.

Patients who died, in comparison with patients alive at the end of follow-up, were significantly older at the diagnosis of cancer (66.0 ± 9.7 vs 59.5 ± 10.0 years; p=0.001), had larger tumor (2.2 ± 1.3 vs 1.8 ± 1.1 cm; p=0.007), with a more important nodal involvement (2.3 ± 4.6 vs 1.2 ± 2.5 pathological nodes; p=0.005). They had lower vitamin D concentration (38.15 ± 18.83 vs 47.9 ± 22.98 nmol/l; p=0.001) and higher PTH concentrations (42.74 ± 36.03 vs 33.90 ± 16.08 pg/ml; p=0.001) (Table III).

Table III. Characteristics of patients who died of any cause during the follow-up

Death	no (N = 371)	yes (N = 79)	
Variables	Mean ± SD		*p*
Age at the diagnosis, years	59.5 ± 10.0	66.0 ± 9.7	0.001
Age of menopause, years	49.4 ± 4.5	49.2 ± 4.7	0.704
Body mass index, kg/m2	27.0 ± 5.5	27.4 ± 6.0	0.637
Tumor size, cm	1.8 ± 1.1	2.2 ± 1.3	0.007
Nodal involvement, n	1.2 ± 2.5	2.3 ± 4.6	0.005
Tamoxifen, months	35.8 ± 19.1	33.1 ± 20.6	0.501
Serum 25(OH) vitamin D, nmol/l	47.90 ± 22.98	38.15 ± 18.83	0.001
Serum parathyroid hormone, pg/ml	33.90 ± 16.08	42.74 ± 36.03	0.001
Calcemia, mmol/l	2.43 ± 0.10	2.47 ± 0.36	0.055
CTX, ng/ml	0.75 ± 0.36	0.72 ± 0.37	0.543
Sex Steroid Binding protein, nmol/l	59.10 ± 32.24	62.06 ± 32.16	0.464
BMD lumbar spine, g/cm2	0.931 ± 0.144	0.934 ± 0.176	0.903
BMD femoral neck, g/cm2	0.709 ± 0.111	0.696 ± 0.113	0.356
BMD total hip, g/cm2	0.860 ± 0.138	0.862 ± 0.157	0.924
	n (%)		*p*
T-score ≤ - 2.5 at at least one site	61 (16.4)	15 (19)	0.584
≥ 1 fractures at baseline	109 (29.4)	29 (36.7)	0.200
≥ 1 Vertebral fracture	66 (17.8)	20 (25.3)	0.123
≥ 1 Peripheric fracture	61 (16.4)	16 (20.3)	0.415
Hip fracture	5 (1.3)	1 (1.3)	0.775
Bisphosphonates prescription	137 (37.0)	22 (28.2)	0.140
Positive PR status	307 (82.7)	61 (77.2)	0.141
Positive HER status	29 (7.8)	7 (8.9)	0.757
Previous chemotherapy	209 (56.3)	42 (53.2)	0.607
Tumor grade 1	92 (26.1)	12 (15.8)	0.066
Tumor grade 2	185 (52.4)	41 (53.9)	0.808
Tumor grade 3	76 (21.5)	23 (30.3)	0.102

Abbreviations. SD, standard deviation; CTX, C-terminal telopeptide of type I collagen serum; BMD, Bone mineral density; PR, progesterone receptor; HER, human epidermal growth factor receptor.

Patients who experienced a relapse had a larger tumor (2.5 ± 1.4 vs 1.8 ± 1.1 cm; p=0.001), with a more important nodal involvement (2.4 ± 4.1 vs 1.2 ± 2.7 pathological nodes; p=0.001), had more frequently negative PR breast cancer (25.3 vs 16.8 %; p=0.038) and a higher BMI (28.3 ± 6.4 vs 26.8 ± 5.4 kg/m2; p=0.037) (Table IV).

Table Ⅳ. Characteristics of patients who experienced a relapse of breast cancer

Relapse of breast cancer	no (N = 375)	yes (N = 75)	
Variables	Mean ± SD		*p*
Age at the diagnosis, years	60.5 ± 10.2	61.3 ± 10.4	0.549
Age of menopause, years	49.3 ± 4.6	49.7 ± 4.3	0.519
Body mass index, kg/m2	26.8 ± 5.4	28.3 ± 6.4	0.037
Tumor size, cm	1.8 ± 1.1	2.5 ± 1.4	0.001
Nodal involvment, n	1.2 ± 2.7	2.4 ± 4.1	0.001
Tamoxifen, months	34.5 ± 19.3	39.7 ± 19.4	0.183
Serum 25(OH) vitamin D, nmol/l	47.06 ± 22.92	41.99 ± 20.53	0.076
Serum parathyroid hormone, pg/ml	34.94 ± 21.23	37.93 ± 20.96	0.265
Calcemia, mmol/l	2.44 ± 0.19	2.44 ± 0.11	0.999
CTX, ng/ml	0.76 ± 0.37	0.68 ± 0.31	0.096
Sex Steroid Binding protein, nmol/l	60.02 ± 32.55	57.64 ± 30.60	0.568
BMD lumbar spine, g/cm2	0.929 ± 0.150	0.943 ± 0.146	0.493
BMD femoral neck, g/cm2	0.704 ± 0.109	0.724 ± 0.125	0.155
BMD total hip, g/cm2	0.855 ± 0.136	0.889 ± 0.164	0.056
	n (%)		*p*
T-score ≤ - 2.5 at at least one site	64 (17.1)	12 (16.0)	0.822
≥ 1 fractures at baseline	113 (30.1)	25 (33.3)	0.584
≥ 1 Vertebral fracture	73 (19.5)	13 (17.3)	0.669
≥ 1 Peripheric fracture	61 (16.3)	16 (21.3)	0.289
Hip fracture	4 (1)	2 (2.6)	0.297
Bisphosphonates prescription	140 (37.4)	19 (25.7)	0.054
Positive PR status	312 (83.2)	56 (74.7)	0.038
Positive HER status	27 (7.2)	9 (12.0)	0.163
Previous chemotherapy	203 (54.1)	48 (64.0)	0.117
Tumor grade 1	91 (25.5)	13 (18.1)	0.194
Tumor grade 2	183 (51.3)	43 (59.7)	0.190
Tumor grade 3	83 (23.2)	16 (22.2)	0.851

Abbreviations. SD, standard deviation; CTX, C-terminal telopeptide of type I collagen serum; BMD, Bone mineral density; PR, progesterone receptor; HER, human epidermal growth factor receptor.

Patients who died of breast cancer had a larger tumor (2.6 ± 1.4 vs 1.8 ± 1.1 cm; p=0.001), with a more important nodal involvement (2.3 ± 3.5 vs 1.3 ± 2.9 pathological nodes; p=0.038) (Table V).

Table V. Characteristics of patients who died of breast cancer

Death of breast cancer	no (N = 409)	yes (N = 41)	
Variables	Mean ± SD		*p*
Age at the diagnosis, years	60.5 ± 10.4	62.5 ± 8.7	0.234
Age of menopause, years	49.4 ± 4.5	49.8 ± 4.5	0.572
Body mass index, kg/m2	27.0 ± 5.5	27.8 ± 6.6	0.435
Tumor size, cm	1.8 ± 1.1	2.6 ± 1.4	0.001
Nodal involvment, n	1.3 ± 2.9	2.3 ± 3.5	0.038
Tamoxifen, months	35.2 ± 19.1	38.0 ± 22.4	0.603
Serum 25(OH)vitD, nmol/l	46.61 ± 22.66	42.22 ± 21.90	0.236
Serum parathyroid hormone, pg/ml	35.11 ± 21.07	38.73 ± 22.34	0.297
Calcemia, mmol/l	2.44 ± 0.18	2.44 ± 0.10	0.858
CTX, ng/ml	0.75 ± 0.37	0.67 ± 0.28	0.180
Sex Steroid Binding protein, nmol/l	59.81 ± 32.14	57.77 ± 33.26	0.704
BMD lumbar spine, g/cm2	0.931 ± 0.149	0.935 ± 0.157	0.869
BMD femoral neck, g/cm2	0.705 ± 0.112	0.723 ± 0.107	0.346
BMD total hip, g/cm2	0.858 ± 0.139	0.889 ± 0.164	0.180
	n (%)		*p*
T-score ≤ - 2.5 at at least one site	68 (16.6)	8 (19.5)	0.639
≥ 1 fractures at baseline	127 (31.1)	11 (26.8)	0.577
≥ 1 Vertebral fracture	80 (19.6)	6 (14.6)	0.446
≥ 1 Peripheric fracture	69 (16.9)	8 (19.5)	0.669
Hip fracture	5 (1.2)	1 (2.4)	0.288
Bisphosphonates prescription	148 (36.4)	11 (26.8)	0.225
Positive PR status	338 (83.9)	30 (73.2)	0.083
Positive HER status	31 (7.6)	5 (12.2)	0.300
Previous chemotherapy	224 (54.8)	27 (65.9)	0.174
Tumor grade 1	98 (24.0)	6 (14.6)	0.178
Tumor grade 2	199 (51.3)	27 (65.9)	0.076
Tumor grade 3	91 (23.5)	8 (19.5)	0.570

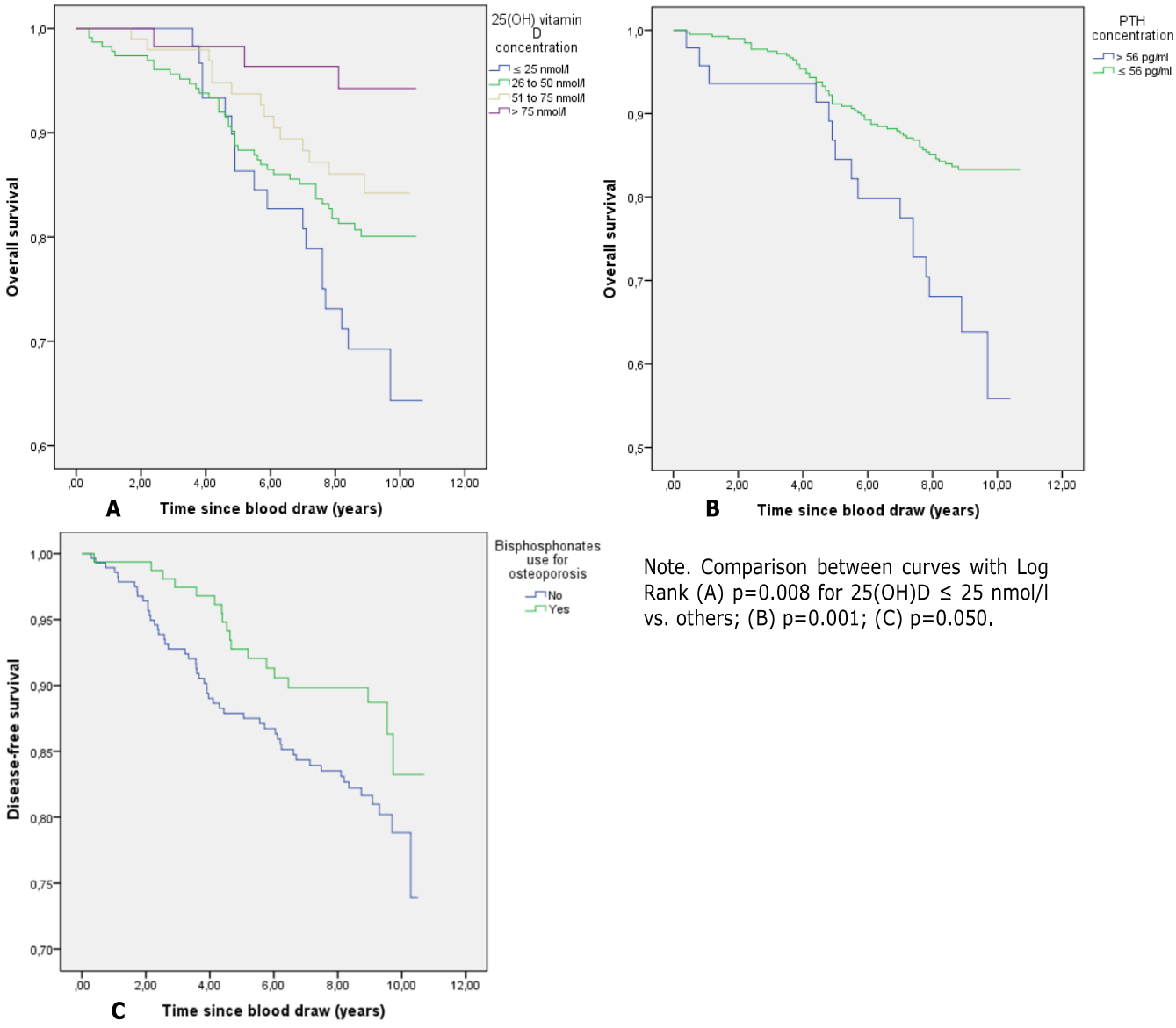
Abbreviations. SD, standard deviation; CTX, C-terminal telopeptide of type I collagen serum; BMD, Bone mineral density; PR, progesterone receptor; HER, human epidermal growth factor receptor.

Cancer outcome according vitamin D and PTH serum concentrations is presented in table in annex 2. Briefly patients with vitamin D deficiency (serum concentration ≤ 25 nmol/l, N = 62) or insufficiency (serum concentration ≤ 50 nmol/l, N = 292) had an increased global mortality and patients with abnormal PTH had an increased risk of relapse, global mortality and breast cancer-specific mortality.

3. Survival curves

The unadjusted association of serum vitamin D and PTH with OS showed that 25(OH) vitamin D deficiency and abnormal PTH were associated with worse prognosis (figure 2).

Survival according bisphosphonates treatment showed that women who had a bisphosphonate had less risk of relapse that still remained significant after vitamin D or tumor size stratification (data not shown). BCSS (p=0.197) and OS (p=0.162) with use of bisphosphonates were not statistically significant. The unadjusted association of vitamin D supplementation with OS, BCSS and DFS did not indicate a statistic association (data not shown).



Note. Comparison between curves with Log Rank (A) p=0.008 for 25(OH)D ≤ 25 nmol/l vs. others; (B) p=0.001; (C) p=0.050.

Figure 17 - Association between 25(OH) vitamin D and PTH concentrations with overall survival (A)(B); Association between use of bisphosphonates for osteoporosis with disease-free survival (C).

4. Parameters associated with death and relapse

In multivariate survival Cox analyzes, age at diagnosis, nodal involvement, 25(OH) vitamin D deficiency and bisphosphonates use were significantly associated with death; age at diagnosis and tumor size, with breast cancer-specific death; and tumor size, nodal involvement and use of bisphosphonates with relapse (Table VI).

Bisphosphonates prescription for osteoporosis was significantly and independently associated with a decreased risk of relapse (HR=0.49, p=0.025) which remained significant in patients with the most serious tumors, tumor size > 2 cm (HR=0.36, p=0.042), at least one pathological node (HR=0.41, p=0.041) or receiving previous chemotherapy (HR=0.29, p=0.013).

Table VI. Multivariate Survival Analysis for prognostic factors of breast cancer.

	Disease-free survival				Breast cancer-specific survival				Overall survival			
Multivariate	HR	95% IC		*p*	HR	95% IC		*p*	HR	95% IC		*p*
Age at the diagnosis	1.03	1.00	1.05	0.054	1.04	1.00	1.08	0.036	1.07	1.04	1.10	0.001
Tumor size (cm)	1.32	1.13	1.55	0.001	1.31	1.07	1.60	0.010	1.12	0.94	1.34	0.193
Nodal involvement	1.07	1.01	1.13	0.029	1.04	0.96	1.13	0.314	1.07	1.00	1.14	0.049
Positive PR status	0.86	0.44	1.68	0.658	0.53	0.24	1.17	0.115	0.57	0.31	1.04	0.067
Positive HER status	1.90	0.86	4.22	0.115	1.48	0.53	4.15	0.457	0.94	0.39	2.30	0.898
BMI	1.03	0.98	1.08	0.252	0.99	0.93	1.05	0.781	0.98	0.93	1.03	0.354
BPs for osteoporosis	0.49	0.26	0.91	0.025	0.45	0.20	1.02	0.056	0.46	0.26	0.84	0.012
Vitamin D deficiency	1.47	0.77	2.79	0.241	2.01	0.93	4.35	0.076	1.91	1.08	3.39	0.027

Abbreviations. PR, progesterone receptor; HER, human epidermal growth factor receptor; BMI, body mass index; BP, bisphosphonates; HR, hazard ratio.

DISCUSSION

In this study, we reported breast cancer outcome after a 10 years' follow-up of 450 women with non-metastatic ER+ breast cancer at the time of bone assessment for aromatase inhibitor initiation. In our study, 16.7% of women experienced a relapse and 17.6% died. Cancer parameters associated with relapse and death in our study were similar to those previously observed in large cohorts of breast cancer, particularly the risk of relapse associated with tumor size (HR=1.32), and nodal involvement (HR=1.07)[18], or the protective effect of the PR expression (risk of death reduced by 47%)[19]. These results suggest that our cohort was adapted to explore new risk factors for relapse and death such as parameters of bone assessment: vitamin D and PTH concentrations, history of fracture, bone mineral density and bisphosphonates used for osteoporosis treatment.

The first and main result of our study was the effect of bisphosphonates on breast cancer outcome. We observed a significantly lower risk of relapse (-51%), breast cancer-specific death (-55%) and all-cause mortality (-54%) in patients who received bisphosphonates for osteoporosis treatment. The principal function of bisphosphonates used in cancer is to prevent skeletal events associated with bone metastasis. Recent studies have shown the potential effect of bisphosphonates used in adjuvant treatment to reduce disease recurrence and metastasis. The Early Breast Cancer Trials Collaborative Group (EBCTCG) has conducted a formal individual patient data meta-analysis of data from 18 766 women involved in 26 randomized trials of adjuvant bisphosphonates for early breast cancer. The majority of these patients received either oral clodronate 1600mg daily or intravenous zoledronic acid 4mg every 6 months or more frequent dosing. For the entire population, bisphosphonates reduced the number of patients with first distant recurrence in bone (RR=0.83; 95%CI 0.73-0.94, p=0.004), but had less clear effects on time to any breast cancer recurrence (RR=0.94; 95%CI 0.87-1.01, p=0.08), distant recurrence (RR=0.92; 95%CI 0.85-0.99, 2p=0.03) or breast cancer mortality (RR=0.91; 95%CI 0.83-0.99, p=0.04). However, in postmenopausal women (n=11 767), bisphosphonates not only improved recurrence in bone (RR=0.72; 95%CI 0.60-0.86, 2p=0.002) but also overall breast cancer recurrence (RR=0.86; 95%CI 0.78-0.94, p=0.002), distant recurrence at

any site (RR=0.82; 95%CI 0.73-0.92, p=0.003) and breast cancer mortality (RR=0.82; 95%CI 0.73-0.93, p=0.002)[16]. The majority of women who received bisphosphonates in the studies of this meta-analysis did not have osteoporosis. Kremer et al., in a pharmaco-epidemiological study based on administrative data of 21 664 women, found lower risk of bone metastasis (HR=0.55) and mortality (HR=0.48) with low-dose oral bisphosphonates used for osteoporosis in a population of postmenopausal women who received bisphosphonates after diagnosis of breast cancer[20]. We did not find a specific lower risk of bone metastasis in our study that could be explain by the poor number of related events observed (only 34 women experienced bone metastasis).

Osteoporosis in postmenopausal women is the consequence of estrogen deficiency which causes high bone turnover. Higher bone turnover is associated with higher rates of growth factors released from bone, which provides a favorable environment for tumor cells adhesion and proliferation[21]. Bisphosphonates, by reducing bone turnover with its antiosteoclastic activity, inhibit release of growth factors from bone which accelerates tumors cells proliferation and maintains the vicious cycle of bone metastasis[22,23], act as prevention of tumor cell adhesion to bone[24], and induce tumor cell apoptosis[25].

Women who received bisphosphonates in our study had less PR positive tumors (76.7% vs. 84.8%, p=0.008) and less previous chemotherapy (47.2% vs. 60.2%, p=0.008), implying breast cancer with a better prognosis which could explain better outcome of women under bisphosphonates. However, considering only women who received chemotherapy, bisphosphonates prescription remained significantly associated with a decreased risk of relapse (HR=0.29, p=0.013).

Treatment of osteoporosis, in addition to bisphosphonates, includes lifestyle recommendations such as physical activity and vitamin D supplementation, which could be potential confounding factors. In our population, 98.1% of women who had a prescription of bisphosphonates had also vitamin D supplementation, and only 32.6% received vitamin D supplementation without bisphosphonates. In our study, we did not observe significant effect of vitamin D supplementation alone on cancer outcome but we cannot exclude a synergistic effect of bisphosphonate and vitamin D supplementation. Furthermore, we did not precisely evaluate physical activity in our study.

A panel of experts has recently recommended that bisphosphonates are considered as part of adjuvant treatment in postmenopausal women for metastasis prevention for 3-5 years associated with vitamin D supplementation and adequate calcium intake[26]. The results of our study confirm recent data and suggest that postmenopausal patients with ER+ breast cancer treated by bisphosphonates for osteoporosis: alendronate 70mg weekly or risedronate 35mg weekly during 5 years or zoledronic acid 5mg annually during 3 years had better outcomes. It is important to note that no serious adverse effects have been reported in our cohort as usual with dose and limited duration of osteoporosis treatment.

The second result of our study was the association between 25(OH) vitamin D concentration and death, in addition to the usual prognostic factors of breast cancer, suggesting a worse prognosis in women with 25(OH) vitamin D deficiency. The existence of a vitamin D biological threshold, between 60 and 80 nmol/l, was described for many diseases such as hip fracture[27], colorectal cancer prevention[28,29], colorectal recurrence[30] and primary prevention of breast cancer in the general population[12,31]. Few studies have examined the link between 25(OH) vitamin D concentration and breast cancer outcomes. Goodwin et al. conducted a prospective cohort of 512 women with early breast cancer with a mean 25(OH) vitamin D at 58.1 ± 23.4 nmol/l. Women in the lower quintile of 25(OH) vitamin D (< 15 nmol/l) had an increased risk of distant recurrence (HR=1.94) and death (HR=1.73) compared to those with concentrations > 72 nmol/l[32]. In the other hand, Jacobs et al. did not find a significant relationship between 25(OH) vitamin D concentration and breast cancer recurrence in a study including 512 cases and 512 controls, but this cohort encompassed 28% of ER- breast cancer, and a lower percentage of women receiving anti estrogen therapy (54.9 vs. 64.5%) in cases[33]. Recent studies showed that breast cancer patients with a more aggressive molecular phenotype (basal-like) and worse prognostic indicators (ER- and triple negative) had lower mean 25(OH) vitamin D concentrations, which may explain why vitamin D deficient breast cancer patients have decreased survival rates[34]. An extended vitamin D deficiency leads to secondary hyperparathyroidism with high PTH concentration. In our study, women with higher PTH

concentration (> 56 pg/ml) had an increased risk of overall and breast cancer-specific death (Log Rank, p=0.001 and 0.008 respectively).

In conclusion, we observed in a homogeneous cohort of postmenopausal women with early ER+ breast cancer treated by aromatase inhibitors that treatment of osteoporosis by bisphosphonate reduces by 50% the risk of relapse and death at 10 years. This beneficial effect is probably also due to lifestyle recommendations such as physical activity and vitamin D supplementation. As previously reported, women with 25(OH) vitamin D deficiency had an increased risk of death. These results confirm data of recent international meta-analysis and underline the necessity to consider bisphosphonates as part of adjuvant treatment in postmenopausal women for metastasis prevention. However, further studies are necessary to determine what happen after bisphosphonates cessation when bone remodeling start again.

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Annex 1. Characteristics of patients who received or not bisphosphonates

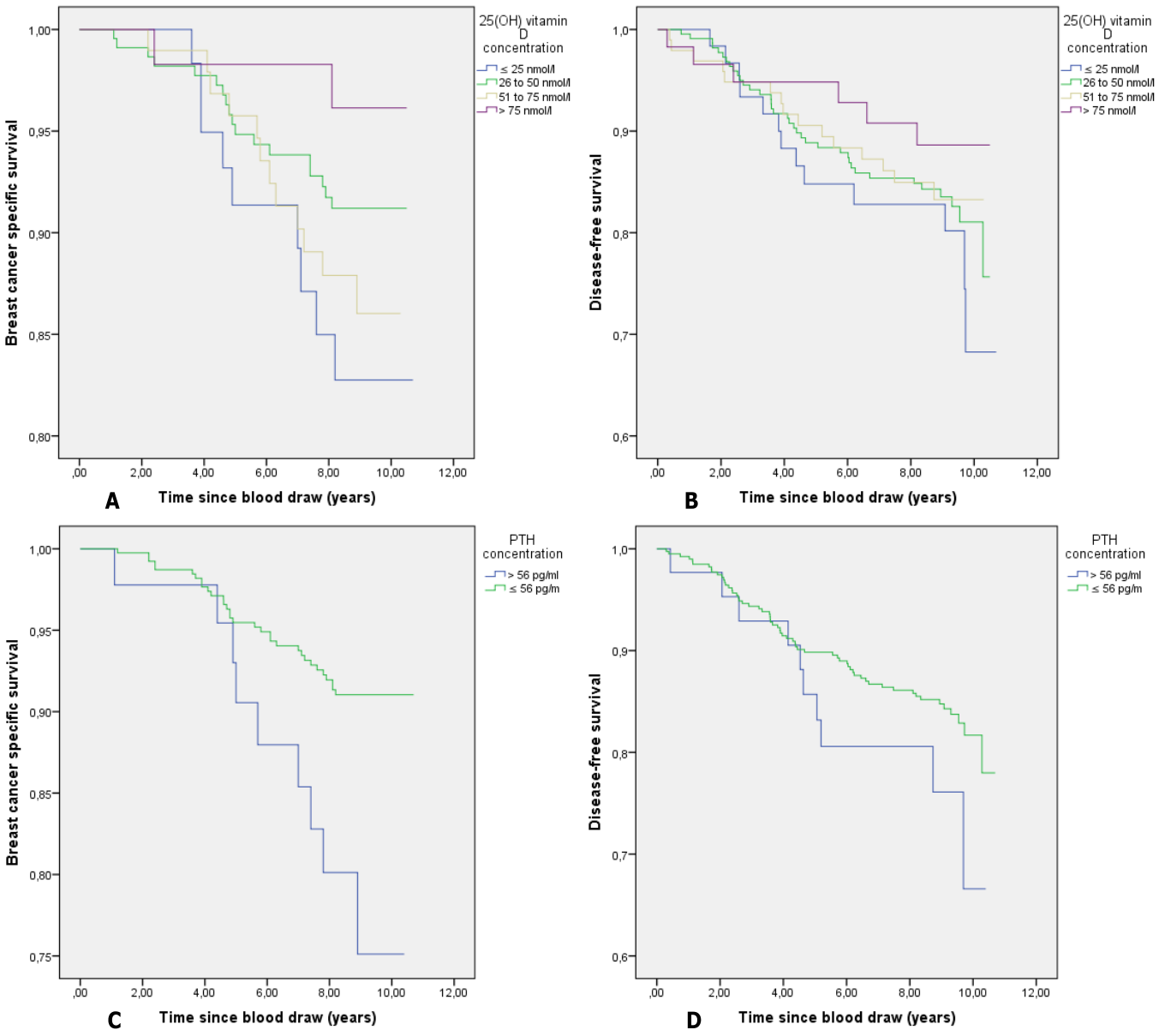
Bisphosphonates	no (N = 289)	yes (N = 159)	
Variables	Mean ± SD		*p*
Age at the diagnosis, years	59.2 ± 9.8	63.4 ± 10.5	0.001
Age of menopause, years	49.6 ± 4.7	49.2 ± 4.1	0.410
Body mass index, kg/m2	28.1 ± 5.7	25.2 ± 4.9	0.001
Tumor size, cm	1.9 ± 1.2	1.8 ± 1.0	0.584
Nodal involvment, n	1.6 ± 3.4	1.1 ± 2.1	0.158
Tamoxifen, months	34.4 ± 18.9	37.5 ± 20.3	0.305
Serum 25(OH) vitamin D, nmol/l	45.57 ± 21.31	47.45 ± 24.91	0.401
Serum parathyroid hormone, pg/ml	35.80 ± 23.60	35.03 ± 16.04	0.713
Calcemia, mmol/l	2.45 ± 0.21	2.42 ± 0.10	0.174
CTX, ng/ml	0.72 ± 0.35	0.79 ± 0.39	0.057
Sex Steroid Binding Globulin, nmol/l	54.32 ± 28.09	69.80 ± 36.92	0.001
BMD lumbar spine, g/cm2	0.996 ± 0.125	0.815 ± 0.117	0.001
BMD femoral neck, g/cm2	0.750 ± 0.098	0.629 ± 0.091	0.001
BMD total hip, g/cm2	0.917 ± 0.126	0.759 ± 0.109	0.001
	n (%)		*P*
T-score ≤ - 2.5 at at least one site	9 (3.1)	67 (42.1)	0.001
≥ 1 fractures at baseline	56 (19.4)	81 (50.9)	0.001
≥ 1 Vertebral fracture	33 (11.4)	53 (33.3)	0.001
≥ 1 Peripheric fracture	24 (8.3)	52 (32.7)	0.001
Hip fracture	1 (0.3)	5 (3.2)	0.009
Positive PR status	245 (84.8)	122 (76.7)	0.008
Positive HER status	19 (6.6)	17 (10.7)	0.126
Previous chemotherapy	174 (60.2)	75 (47.2)	0.008
Tumor grade 1	71 (26.0)	33 (21.4)	0.362
Tumor grade 2	141 (51.6)	83 (53.9)	0.656
Tumor grade 3	61 (22.3)	38 (24.7)	0.585
Relapse of breast cancer	55 (19.0)	19 (11.9)	0.054
Mean duration, years ± SD	4.1 ± 2.8	4.7 ± 2.7	0.376
Mortality by breast cancer	30 (10.4)	11 (6.9)	0.225
Mean duration, years ± SD	5.6 ± 2.1	4.9 ± 2.1	0.381
Global mortality	56 (19.4)	22 (13.8)	0.140
Mean duration, years ± SD	5.3 ± 2.4	4.9 ± 1.9	0.452

Abbreviations. SD, standard deviation; CTX, C-terminal telopeptide of type I collagen serum; BMD, Bone mineral density; PR, progesterone receptor; HER, human epidermal growth factor receptor.

Annex 2. Percentage of relapse, mortality by breath cancer and global mortality according to 25(OH) vitamin D and PTH serum concentrations in 450 women with ER+ breast cancer

25 (OH) vitamin D serum concentration	**Relapse (%)**	**Breast cancer-specific mortality (%)**	**Global mortality (%)**
≤ 25 nmol/l, n = 62	21	14.5	29*
26 to 50 nmol/l, n = 230	17.4	7.8	18.7
51 to 75 nmol/l, n = 98	16.3	12.2	14.3**
> 75 nmol/l, n = 59	10.2	3.4	5.1
PTH serum concentration			
≤ 56 pg/ml, n = 400	15.5§	8§	15.5§
> 56 pg/ml, n = 47	27.7	19.1	34

Note. * $P < 0.05$ for vitamin D ≤ 25 nmol/l vs. > 25 nmol/l. ** $P < 0.05$ for vitamin D ≤ 50 nmol/l vs. > 50 nmol/l. § $P < 0.05$ for PTH comparison.



Note. Comparison between curves with Log Rank. (A) p=0.082, (B) p=0.260 for 25(OH)D ≤ 25 nmol/l vs. others; (C) p=0.008, (D) p=0.174.

Annex 3 - Association between 25(OH) vitamin D and PTH concentrations with breast cancer-specific survival and disease-free survival.

CHATELAIS Jérémy

Les bisphosphonates utilisés dans le traitement de l'ostéoporose réduisent le risque de rechute et de décès des femmes ménopausées avec cancer du sein RE+

RÉSUMÉ

Introduction : Le pronostic du cancer du sein dépend entre autres de sa taille, de l'envahissement ganglionnaire, de son grade histologique et de l'expression ou non des récepteurs aux estrogènes (RE), à la progestérone (RP) et de la protéine HER. L'objectif de cette étude était d'analyser l'influence des paramètres osseux et des prescriptions de bisphosphonates et de vitamine D sur le devenir du cancer du sein.

Patients et méthodes : Il s'agit d'une étude de cohorte, longitudinale, prospective portant sur 450 femmes avec cancer du sein RE+ initialement localisé. Nous avons analysé (1) les caractéristiques de la tumeur, (2) le statut osseux lors de la prescription des anti-aromatases (fractures, DMO, vitamine D, PTH et CTX sériques) (3) les modalités thérapeutiques (chirurgie, radiothérapie, chimiothérapie, tamoxifène, anti-aromatases, vitamine D, bisphosphonates) et (4) le devenir clinique de la patiente à la date de point (1/07/2015) par analyse multivariée en utilisant un modèle de Cox.

Résultats : Le suivi moyen était de 10,3 ± 3,0 ans. 79 décès et 75 rechutes sont survenus. L'âge moyen au diagnostic était de 61 ans, 30,7% avaient un antécédent de fracture, 16,9% avaient un T-score lombaire ou fémoral ≤ -2,5, la 25(OH) vitamine D était < 50 nmol/L chez 292 patientes (65%). 159 femmes (35,3%) ont été traitées par bisphosphonates pour une ostéoporose pour une durée moyenne de 5 ± 1,7 années. Le risque de rechute ou de décès n'était corrélé ni à la présence de fracture, ni à la densité osseuse. L'âge au diagnostic de cancer (HR=1,03, p=0,05), la taille de la tumeur (HR=1,32, p=0,001) et le nombre de ganglions envahis (HR=1,07, p=0,03), étaient significativement associés au risque de rechute du cancer. La prescription de bisphosphonates était associée, de façon indépendante, à une forte diminution du risque de rechute (HR=0,49, p=0,02). L'âge au diagnostic (HR=1,07, p=0,001) et la carence en vitamine D (HR=1,91, p=0,03) étaient associés à une augmentation du risque de décès global, alors que la prescription de bisphosphonates était associée à une diminution du risque de décès global (HR=0,46, p=0,01).

Conclusion : Notre étude montre qu'un traitement par bisphosphonates utilisé pendant 5 ans pour une ostéoporose par des femmes avec un cancer du sein localisé RE+ traité par inhibiteur de l'aromatase diminue le risque de rechute et de décès de 50% à 10 ans.

Mots-clés : 25-hydroxyvitamine D – cancer du sein – bisphosphonates – ostéoporose – anti-aromatase

Bisphosphonates reduce the risk of relapse and death of postmenopausal women with ER+ breast cancer

ABSTRACT

Introduction: risk factors of breast cancer relapse are well known such as large tumor size, lymph node involvement, high-grade tumor, absence of progesterone and estrogen receptors, expression of HER protein. The aim of our study was to analyze the influence of bone parameters and the prescription of bisphosphonate and vitamin D on breast cancer outcome.

Patients and methods: this is a longitudinal and prospective cohort of 450 postmenopausal women with local ER+ breast cancer. For every patient we analyzed (1) tumor characteristics', (2) bone status at the beginning of aromatase inhibitor treatment (fractures, BMD, vitamin D, PTH and CTX) (3) tumor and bone treatments (surgery, radiotherapy, chemotherapy, tamoxifen, aromatase inhibitors, vitamin D, bisphosphonates) and (4) cancer outcome at the date of point (1/07/2015) with Cox model.

Results: mean follow-up was 10.3 ± 3.0 years. 79 women died and 75 had a relapse. Mean age of the women was 61 years, 30.7% had an history of fracture, 16.9% had a lumbar or hip T-score ≤ -2,5. 292 women (65%) had 25(OH) vitamin D concentration < 50 nmol/L. Bisphosphonates were prescribed to 35.3% women for osteoporosis for a mean duration of 5 ± 1.7 years. The risk of relapse or death was not correlated to history of fracture, bone density or CTX. Age at cancer diagnosis (HR=1.03, p=0.05), tumor size (HR=1.32, p=0.001) and the number of lymph nodes involved (HR=1.07, p=0.03) were significantly associated with relapse. Bisphosphonate treatment was significantly associated with a decreased risk of relapse (HR=0.49, p=0.02). Age at cancer diagnosis (HR=1.07, p=0.001) and 25(OH) vitamin D deficiency (HR=1.91, p=0.03) were associated with an increased risk of death. Bisphophonate treatment was associated with a decreased risk of death (HR=0.46, p=0.01).

Conclusion: our study showed that bisphosphonates using for osteoporosis treatment in women treated by aromatase inhibitors for ER+ breast cancer reduced by 50% relapse and death at 10 years.

Keywords: 25-hydroxyvitamin D - breast cancer – bisphosphonates – osteoporosis – aromatase inhibitor

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