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ORIGINAL ARTICLE

Change of influence of prognostic markers on metastasis free interval during and after adjuvant tamoxifen therapy in breast cancer patients

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Summary

Purpose: *To evaluate the influence of molecular biomarkers (estrogen receptor – ER, progesterone receptor - PR, and human epidermal growth factor receptor2 - HER2) and pathological parameters on metastasis free interval (MFI) in adjuvantly tamoxifen-treated breast cancer patients, during different follow up periods (0-2.5 years, 2.5-5 years and 5-12 years).*

Methods: *The study included 113 postmenopausal breast cancer patients with known pathological parameters. Steroid receptors were determined by ligand-binding assay and HER2 amplification status by chromogenic in situ hybridization (CISH).*

Results: *During the first 2.5 years of therapy patients with ER <5 fmol/mg, PR <5 fmol/mg or pT2 (≥2cm) tumors had higher probability of distant metastasis. For the period between 2.5-5 years, analysis of MFI according to pathological parameters and molecular biomarkers, separately, did not show any statistically significant difference. Patients with pT≥2 cm and HER2 amplification had much greater chance of developing distant metastasis when compared to other phenotypes (HER2-negative/pT1, HER2-negative/pT2 and HER2-positive/pT1). Patiens with ER ≥160 fmol/mg and PR ≥45 fmol/mg had good prognosis after 5 years of tamoxifen therapy.*

Conclusion: *Our study indicates that there is a change of influence of the analyzed pathological parameters on MFI, depending on different follow up periods. Steroid receptor status, tumor size and HER2 status (alone or in combination) are significant parameters for the course of disease of postmenopausal ER-positive breast cancer patients, but during different periods of follow up.*

Key words: *breast cancer, HER2, metastasis free interval, resistance, tamoxifen*

Introduction

Tamoxifen represents a standard therapy for patients with ER-positive (detectable) tumors. The effectiveness of tamoxifen is substantiated by a large number of randomized trials [1,2]. Adjuvant tamoxifen is most effective when given in a period of 5 years [2]. After 2-3 years of primary treatment, acquired resistance to tamoxifen therapy is one of the main causes of late recurrence. Mechanisms of this acquired resistance are still unknown. Although ER-positive patients respond well to tamoxifen therapy, disease recurrence could appear early in the treatment (de novo) or later (acquired) [3]. Specific biomarkers such as HER2 and others, could be related to the acquired resistance which appears in this kind of endocrine therapy [4]. Although tamoxifen inhibits the genomic function of ER, its agonistic effect on nongenomic ER pathway and activation of HER2 could be the predominant mechanism of acquired resistance [3,5]. The role of HER2 in tamoxifen resistance has also indisputably proven in a large number of in vitro experiments, showing that tamoxifen-resistant MCF-7 cells have increased levels of HER2 [6,7]. HER2 oncogene has been recognised as an important variable for the assessment of breast cancer prognosis and response to therapy, whether in the adjuvant or metastatic

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setting [8,9].

In this study we evaluated the time-dependent influence of ER, PR, HER2 and standard pathological parameters on MFI during and after adjuvant tamoxifen treatment. Our objective was to determine whether the effect of these parameters on the risk of recurrence varies in different follow up time intervals and the primary endpoint was the development of distant metastasis only.

Methods

One hundred and thirteen postmenopausal patients with primary operable breast carcinoma were included in this study. All of the patients had detectable levels (>0 fmol/mg) of steroid receptors. According to protocols at the time of diagnosis, all of the patients received adjuvant tamoxifen therapy as monotherapy. The course of disease was followed for 12 years, or until emergence of distant metastasis. The study was approved by the Institute's Ethics Committee. Pathological parameters and molecular characteristics were obtained from the patients' medical records and are shown in Table 1. A patient was considered to be postmenopausal if menstruation had ceased for at least 6 months. The patients' age ranged from 43 to 81 years (median 62).

Steroid receptors and HER2 estimations

ER and PR quantitative values were estimated by the classical biochemical method as recommended by the EORTC [10]. The intralaboratory quality assessment of steroid hormone receptor levels was performed periodically following the EORTC recommendations.

HER2 gene amplification was determined using the Zymed's SPoT-Light HER2 CISH™ Kit (San Francisco, California 94080, USA) [11]. CISH staining results were studied using 40x magnification in tumor tissue sections. Tumors without HER2 gene amplification showed 1-2 chromogenic reaction product signals per nucleus, or 2-4 spots in case of chromosomal aneuploidy. HER2 gene amplification typically appeared as nuclear gene copy clusters of >5 gene copies per nucleus.

Statistics

The results were divided into 3 time periods of follow up (0-2.5 years, 2.5-5 years and 5-12 years) in order to determine the probabilities of MFI in these time periods. Kaplan-Meier curves were plotted and then compared using the log-rank test which was used

Table 1. Pathological characteristics of breast carcinomas for the period of the first 2.5 years, between 2.5 and 5 years of tamoxifen therapy and between 5 and 12 years after therapy

Characteristics	*Patients in the first 2.5 years of tamoxifen therapy*		*Patients between 2.5 and 5 years of tamoxifen therapy*		*Patients between 5 and 12 years after tamoxifen therapy*	
	N	%	*N*	%	*N*	%
Total	113	100	89	100	49	100
No recurrence	93	83	74	83	29	59
Recurrence	20	17	15	17	20	41
Tumor size (cm)						
pT1 (<2)	58	51	51	57	28	57
pT2 (≥2)	53	47	36	40	19	38
Unknown	2	2	2	3	2	5
Lymph nodes						
N0	13	11	11	11	4	8
N+	89	78	72	77	44	89
Unknown	11	11	6	12	1	3
Histological type						
IDC	50	44	41	46	24	48
ILC	46	40	42	47	17	34
Rare and mixed	17	16	6	7	8	16
Histological grade						
I	17	15	9	10	6	12
II	77	68	65	73	38	77
III	19	17	15	17	5	11

IDL: invasive ductal carcinoma, ILC invasive infiltrative lobular carcinoma

to determine optimal cutoff values. A p-value <0.05 was considered as statistically significant.

Results

During the first 2.5 years of tamoxifen therapy, follow up was possible for all 113 patients. During that period of time 20 (17%) patients developed distant metastasis. In the period between 2.5 and 5 years of therapy, follow up was possible for 89 patients. Four patients were excluded from analysis due to lack of follow up data by the end of the 5th year. During that period of time 15 (17%) patients developed distant metastasis. After the 5th year none of the patients received any kind of therapy and they were followed until the end of the 12th year. In the period between 5 and 12 years, follow up was possible for 49 patients. During that period of time 20 (41%) patients developed distant metastasis. Twenty-five patients were excluded from analysis due to lack of follow up data by the end of the 12th year. Analysis of MFI according to pathological and molecular parameters showed a statistically significant difference when patients were stratified according to steroid receptors status (cut off: ER=5 fmol/mg, PR=5 fmol/mg) and tumor size (<2 vs ≥2 cm) (Table 2). Other pathological parameters (lymph node status, histological type, histological grade and HER2 status) did not show any statistically significant difference in MFI analysis (Table 2). Combination of different pathological parameters had no influence on MFI (data not shown).

None of the women investigated in the period between 2.5 and 5 years had distant metastasis within the first 2.5 years of the primary diagnosis. During this period, distant metastasis appeared in 17% of the patients (Table 1). Patients were not stratified in low and high risk groups according to ER and PR status in this time period. Pathological parameters alone (Table 3), or in combinations (data not shown) had no effect on MFI, except for combined HER2 status and tumor size (Figure 1). Patients with tumors ≥2 cm and HER2 amplification (HER2-positive/pT2) had significantly more events (occurrence of distant metastasis in 57% of the cases) in this period than other subgroups of patients such as HER2-negative/pT1 (p=0.01), HER2-negative/pT2 (p=0.04) and HER2-positive/pT1 (p=0.003) (Figure 1).

In the period between 5-12 years 41% of the patients developed metastatic disease (Table 1). Analysis of MFI according to steroid receptors status showed statistically significant difference between steroid receptor subgroups when the cut off value was determined for ER (160 fmol/mg) and PR (45 fmol/mg) (Table 4). Patients with lower values of ER and PR had a greater risk of metastatic disease in the period between 5-12 years. There were not any statistically significant results in the probability of MFI according to pathological parameters alone, HER2 status alone or phenotypes consisting of HER2 and pathological parameters together.

Table 2. MFI probabilities according to pathological variables and molecular biomarkers for the period of the first 2.5 years of tamoxifen therapy.

	Patients	*Recurrences*		
Variables	*N*	*N (%)*		*p-value*
Tumor size				0.03
pT1	58	6	(10)	
pT2	53	14	(26)	
Lymph nodes				0.89
N0	13	2	(15)	
N+	89	13	(15)	
Histological type				0.34
IDC	50	7	(14)	
ILC	46	10	(21)	
Histological grade				0.33
I	17	3	(18)	
III	19	6	(32)	
Estrogen receptor* (fmol/mg)				0.002
ER- (<5)	13	6	(46)	
ER+ (≥5)	100	14	(14)	
Progesterone receptor* (fmol/mg)				<0.001
PR- (<5)	22	9	(41)	
PR+ (≥5)	91	11	-12	
HER2 status				0.8
HER2-	82	13	(16)	
HER2+	22	3	(14)	

*cut off values specific for the first 2.5 years of tamoxifen therapy. IDL: invasive ductal carcinoma, ILC: invasive lobular carcinoma, MFI: metastasis free interval

Discussion

Resistance to adjuvant endocrine treatment is a significant clinical problem which results in 20% relapse rate of early breast cancer patients [2]. We

Table 3. MFI probabilities according to pathological variables and molecular biomarkers for the period between 2.5 and 5 years of tamoxifen therapy

	Patients	*Recurrences*	
Variables	*N*	*N (%)*	*p-value*
Tumor size			0.12
pT1	51	6 (12)	
pT2	36	9 (36)	
Lymph nodes			0.11
N0	11	4 (36)	
N+	72	7 (10)	
Histological type			0.9
IDC	41	6 (15)	
ILC	35	5 (14)	
Histological grade			0.51
I	8	1 (13)	
III	15	4 (27)	
HER2 status			0.63
HER2-	65	11 (17)	
HER2+	19	4 (21)	

MFI: metastasis free interval

Table 4. MFI probabilities according to pathological variables and molecular biomarkers for the period between 5 and 12 years after tamoxifen therapy

	Patients	*Recurrences*	
Variables	*N*	*N (%)*	*p-value*
Tumor size			0.6
pT1	28	13 (46)	
pT2	19	7 (36)	
Lymph nodes			0.12
N0	4	0 (0)	
N+	44	19 (43)	
Histological type			0.14
IDC	24	13 (54)	
ILC	17	5 (29)	
Histological grade			0.9
I	6	1 (16)	
III	5	1 (20)	
Estrogen receptor* (fmol/mg)			0.05
ER- (<160)	43	20 (46)	
ER+ (≥160)	6	0 (0)	
Progesterone receptor* (fmol/mg)			0.008
PR- (<45)	33	18 (54)	
PR+(≥45)	16	2 (13)	
HER2 status			0.8
HER2-	38	15 (39)	
HER2+	9	4 (44)	

*Cut off values specific for the period between 5 and 12 years after tamoxifen therapy IDL: invasive ductal carcinoma, ILC: invasive lobular carcinoma, MFI: metastasis free interval

analyzed the influence of pathological parameters on MFI in patients treated with adjuvant tamoxifen in 3 consecutive follow up periods. During the whole follow up period (12 years), metastatic cases increased from 17% (first 2.5 years and 2.5-5 years of therapy) to 41% (5-12 years, without therapy) (Table 1). Many studies have reported that the peak of recurrences during adjuvant tamoxifen therapy happens around 2-2.5 years [12-14]. Our analysis of the first 2.5 years of therapy showed that there is a difference in the influence of pathological and molecular parameters on MFI, compared to later periods, between 2.5-5 and 5-12 years (Tables 2-4). MFI analysis confirmed that steroid receptors status represents an important predictive factor. According to MFI analysis, patients with ER ≥5 fmol/mg or PR ≥5 fmol/mg respond much better to adjuvant tamoxifen therapy. It is indicative that, in patients with ER ≥5 fmol/mg, the frequency of relapse is 14% and in patients with ER<5 fmol/mg this figure is 46%. Similarly, patients with low PR levels (<5 fmol/mg) are at higher risk of recurrence. These findings are in accordance with a similar study that also showed that low-positive ER status (cut off 10-49 fmol/mg) was associated with recurrence within 2.5 years compared with recurrence between 2.5 and 5 years [15]. However, in that study, other

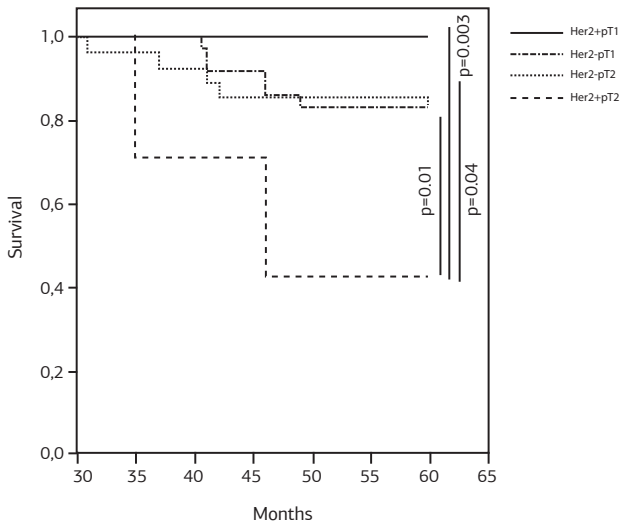

Figure 1. Metastasis free interval as a function of HER2 and pT in patients with breast carcinoma in the period between 2.5 and 5 years of tamoxifen treatment.Analysis showed statistically significant differences between HER2+ pT1 and HER2+ pT2, HER2- pT1 and HER2+ pT2, HER2- pT2 and HER2+ pT2.

pathological variables were not predictive of early recurrence. This contrasts our study because according to our results, besides steroid receptors, the size of tumor is a significant predictive factor, indicating that patients with tumors ≥2 cm are at greater risk for recurrence.

Defining high risk groups in the period between 2.5 and 5 years of therapy is very important, because alternative types of therapy may be more effective [16-18]. During this period of time amplification of HER2 gene in tumors ≥2 cm defines a group of patients with a much greater risk of recurrence. HER2 is considered to be the main reason for failure of endocrine therapy, due to its role in a complex cascade which includes cell proliferation, survival, migration, adhesion and differentiation. HER2 function is essential for a series of normal cellular processes, but it takes part in aberrant development and growth of tumor cells as well [19]. Another study showed that decreased antagonistic properties of tamoxifen, increased agonistic activity and increased sensitivity to estradiol can be caused by upregulation of HER2 and downstream protein kinases [17]. Nevertheless, our study showed that HER2 amplification exerts its effect on the emergence of distant metastasis later during tamoxifen treatment, rather than during first 2.5 years of therapy. In this context, late recurrences can be caused by long estrogen deprivation caused by tamoxifen. This can lead to acquired resistance that is a consequence of activation of dormant signaling pathways including upregulation of growth factor signaling pathways [4,20].

Since HER2 and tumor size are better determinants for MFI during 2.5-5 years (Table 3) and steroid receptor status loses its significance for defining subgroups of patients at risk for recurrence, this indicates that after initial treatment with tamoxifen, therapy should be modified. Other types of endocrine therapy could be more effective in HER2 - positive patients, because ER deprivation affects both nuclear and membranous ER [20,21].

The use of tamoxifen beyond 5 years is still questionable. International guidelines do not recommend tamoxifen treatment longer than 5 years, except in the context of a clinical trial [22]. According to NSABP, B-14 and other trials, tamoxifen therapy after the 5th year offers no benefit to the patients. This is consistent with the finding that the agonist activity of tamoxifen becomes dominant with time and promotes tumor growth [23,24]. According to Kennecke et al. 15% of breast cancer postmenopausal ER-positive patients develop metastasis 6-10 years after diagnosis [25]. Particularly in endocrine-responsive disease, the majority of all breast cancer recurrences and deaths occur after the completion of 5 years of adjuvant tamoxifen [26]. This is consistent with our results regarding a tendency for increasing incidence of relapse after tamoxifen therapy. In the period between 5-12 years after therapy 41% of the patients developed metastatic disease (Table 1). Review of the relevant literature in patients receiving prolonged or late adjuvant endocrine therapy indicated that prolonged adjuvant letrozole reduced the risk of distant metastases by 40% [27]. One of the current questions is which patients can benefit from prolonged adjuvant hormonal therapy, which can successfully replace tamoxifen after 5 years. Prolonged adjuvant aromatase inhibitor therapy should be started within 3 months of finishing tamoxifen therapy, and evidence supports its use for at least 4 years, showing increasing benefit with longer treatment duration. For example, in the MA-17 trial, letrozole given for 5 years after 5 years of tamoxifen improved disease free survival which included substantial reduction in the rate of distant metastasis [18]. Letrozole is also effective even after a longer time period following completion of tamoxifen therapy.

There are conflicting results regarding long-term influence of prognostic factors on survival of breast cancer patients. According to some authors, the impact of traditional prognostic factors in breast cancer persists in the long run, regardless of treatment modality and treatment duration [28]. Another study showed that the effects on the risk of relapse (or death) of most prognostic factors are time-limited in primary breast cancer [29]. Their effect decreased over the years and after long term follow up patients that survived were free of the impact of a poor initial prognostic factor. However, this is questionable, because distinct factors may be a cause for late recurrences. According to our results, standard clinicopathological parameters, alone or in combination, were not significant for prognosis in the period after 5 years of tamoxifen therapy. Yet, some molecular features, such as steroid receptors, could have prolonged effect, even after 5 years of tamoxifen therapy. According to MFI analysis, patients with high levels of ER (≥160 fmol/mg) or PR (≥45 fmol/mg) had longer MFI, even after 5 years of follow up (Table 4). This way, quantitative levels of steroid receptors continue to influence the course of disease even after the end of tamoxifen therapy. Moreover, in the period 5-12 years, in the subgroup of patients with

ER ≥160 fmol/mg there was no recurrence at all (0%), in contrast to the subgroup with ER <160 fmol/mg (46% patients with recurrence) (Table 4). Cut off values for steroid receptors vary in different follow up periods and continue to contribute to better defining high/low risk subgroups. However, the reason for a change (increase) of steroid receptors' effective cut off values remains unknown. This could be somehow a consequence of previous treatment that perhaps blocked ER for a long period and caused feedback that resulted in increase of prognostically relevant levels. These findings confirm the significance of some tumor characteristics that determine its biology even after a long time from initial diagnosis, indicating the necessity to change therapy. Switching to other types of endocrine therapy for estrogen deprivation after 5 years can extend the period without recurrence. Therefore, analysis of molecular features of the tumor can assist in the selection of subgroups of patients which can benefit from combinations of novel targeted agents. But surely, other randomized trials are needed to reevaluate the long-term endocrine therapeutic strategy for ER-positive patients.

The patients were undertreated in our study according to the current guidelines, mortality rates were quite low. Therefore, the treatment modalities applied might not actually be undertreatment. Future randomized studies targeting these patients are needed to determine an optimum treatment algorithm.

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