Docetaxel first-line therapy in HER2-negative advanced breast cancer: a cohort study in patients with prospectively determined HER2 status

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Docetaxel is one of the most active cytotoxic drugs against breast cancer, but data are lacking on specific activity in molecularly selected subgroups. This retrospective study was aimed at assessing the outcome and prognostic factors for survival of patients with HER2-negative tumors receiving first-line docetaxel-based chemotherapy for advanced breast cancer (ABC). The medical charts of all 162 patients with prospectively proven HER2-negative ABC and having received docetaxel as first-line chemotherapy for metastatic disease at our institution were retrospectively reviewed with special emphasis on docetaxel efficacy. Potential prognostic factors were sought using multivariate analysis. Median progression-free survival (PFS) was 12 months (95% confidence interval 9.7–14.8) and median overall survival (OS) was 34.9 months (95% confidence interval 28.1–52.1). Hormone receptor (HR) status was the strongest prognostic factor in the univariate analysis for both PFS [hazard ratio = 0.23; *P* = 0.00000063] and OS (hazard ratio = 0.35; *P* = 0.0000079). After multivariate analysis, only three independent variables for PFS (HR-positive tumor, no prior adjuvant/neoadjuvant chemotherapy, and isolated bone metastases) and two for OS (HR-positive tumor and isolated bone metastases) remained predictive of a favorable outcome. HER2-negative, HR-positive ABC patients have a relatively good prognostic after docetaxel-containing first-line therapy. The subset of HER2-negative, HR-negative (triple-negative) has a very poor outcome, and innovative therapies are eagerly awaited for these patients. *Anti-Cancer Drugs* 20:946–952

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Introduction

Docetaxel is one of the most active single chemotherapy drugs against breast cancer. Since its first introduction in the clinic almost 15 years ago, it has been incorporated at all breast cancer stages, from the adjuvant/neoadjuvant setting to second-line for metastatic disease and has become a gold standard [1–3].

Although a large body of data is available on docetaxel activity in metastatic breast cancer, most of these results come from molecularly unselected populations. However, current management of metastatic breast cancer is no longer uniform, but rather based on molecular typing, including at least estrogen receptor (ER)/progesterone receptor (PgR) and HER2 status. In addition, gene expression profiling, using DNA microarray, has established molecular phenotypes of breast cancer with distinctly different gene expression patterns, that is, luminal, basal-like, HER2 overexpressing, and normal-like that are associated with different clinical phenotypes and outcomes [4].

HER2 gene amplification and/or protein overexpression occurs in approximately 20% of breast cancers and has been shown to be correlated with hormone receptor (HR) negativity, resistance to hormone therapy, high histological grade and higher chemosensitivity, and is also a strong independent poor prognosis factor [5–7]. However, the introduction of targeted anti-HER2 therapy, namely trastuzumab, in the treatment of patients with HER2-positive breast cancer has considerably improved the outcome of this subset [8,9].

The luminal subtype is correlated to HER2-negative, HR-positive cancers, whereas the basal-like subtype is

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correlated to the HER2-negative, ER and PgR), 'triple-negative' phenotype [4,10,11]. These two subtypes, covering almost all HER2-negative tumors, have been identified as the most frequent molecular subtypes of breast cancer [12,13]. Triple-negative tumors have been recently identified as having a particularly poor prognosis [14–16], and their treatment can only rely on cytotoxic chemotherapy.

Although convergent data strongly suggest that anthracycline-based regimen provide more benefit than non-anthracycline-based regimens, especially in patients with HER2-overexpressing tumors, specific data concerning docetaxel efficacy according to molecular subtypes defined by HR and HER2 status are lacking or contradictory [3,17,18]. However, clinical data in metastatic disease seem to indicate that neither HR nor HER2 status can predict taxane sensitivity [19,20]. We have, therefore, undertaken this retrospective study in our institution with the following objectives: to assess the outcome of patients with prospectively defined HER2-negative advanced breast cancer (ABC) receiving first-line docetaxel treatment, and to identify prognostic factors for survival, specifically focusing on the HR status.

Patients and methods

Study objectives

The study objective was to assess the outcome and detect prognostic factors of HER2-negative ABC patients receiving a first-line docetaxel-based chemotherapy regimen.

Patient selection

Among histologically proven ABC patients treated at our institution between 1997 and 2005, 363 were prospectively tested for HER2 expression, mainly from 2002 onwards (see flow diagram in Fig. 1). The HER2 negativity was determined at diagnostic in the primary tumor of all patients and defined as immunohistochemistry (IHC; HercepTest, Dako, Carpinteria, California, USA) 0 or 1+ or IHC 2+ and fluorescence in-situ hybridization negativity. As far as possible, the HER2 status was also determined at the metastatic level in 132 of the 363 patients (36%). In this case, only patients with HER2-negative tissues in both primary and metastases were considered HER2-negative. Two hundred and thirty-seven (65% of tested patients) had HER2-negative ABC. Among them, the medical records of all 162 patients (68%) treated with first-line docetaxel-based chemotherapy in the routine practice were selected retrospectively and reviewed. This study was approved by local institutional review board.

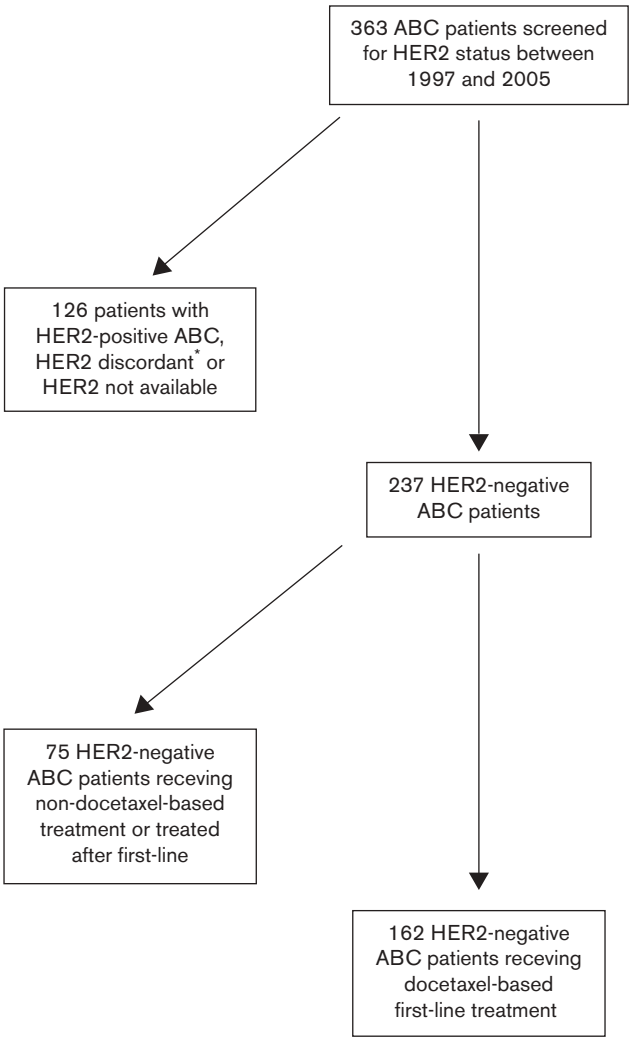
Assessment

Metastatic relapse was detected by routine follow-up, including clinical exam, CA 15-3 dosage, and standard imaging methods (chest radiographs, abdominal ultrasound, thoracic and abdominal computed tomography scan, bone scan). Therefore, patient population included both symptomatic and asymptomatic patients.

After metastasis diagnosis, routine tumor evaluation using appropriate imaging methods (clinical status, computed tomography scan, MRI, or bone scan) was performed every three cycles until the last cycle of chemotherapy, and then every 3 months until progression.

Patient characteristics at baseline, type of docetaxel-containing regimen used, tumor response according the WHO criteria, date of progression or death, and date of, and state at, the last follow-up from docetaxel initiation were collected by local physicians. The breast cancer institutional review board approved and validated all the data entered in the database.

Fig. 1



Flow diagram of the advanced breast cancer (ABC) cohort selection. [a]Patients with discordant HER2 status between primary and metastatic tissue, when available, were not included in the analysis.

Statistical methods

Data analysis was descriptive and performed using the R software, version 2.7.1. (*http://CRAN.R-project.org*) and SAS software, version 9.1 (SAS Institute Inc., Cary, North Carolina, USA). Quantitative data were described by the median value and ranges, and categorical data by the numbers in each category and corresponding percentages. Survival estimations were calculated using the Kaplan–Meier method. Overall survival (OS) and progression-free survival (PFS) were defined by the time between the start of docetaxel treatment and death (OS) or disease progression or death, whichever occurs first (PFS). Data were censored at the last follow-up in the absence of event.

Univariate correlations with baseline parameters were calculated for PFS and OS using the Wald's test. All variables with a P value ≤ 0.10 in the univariate analysis were entered in a Cox proportional hazard model, using a stepwise backward procedure. Only variables with a P value ≤ 0.05 in this multivariate analysis were considered as independent prognostic factors.

Results

Patients

The characteristics of the primary disease were the following: pT1-T2 and pT3-T4 diseases were observed in 85 (52%) and 49 (30%) patients, respectively whereas pT stage was not evaluable in 28 patients (18%); 98 and 36 patients had node-positive (60%) and node-negative diseases (22%), respectively whereas pN stage was not known in 28 patients (18%). Conservative surgery was performed in 84 patients (52%), whereas radical mastectomy was performed in 78 patients (48%). One hundred and two (66%) patients had received neoadjuvant/adjuvant chemotherapy, mostly including an anthracycline (88%). Only three patients had been exposed to taxane earlier. Sixty-two (38%) patients had received adjuvant hormonal therapy (58 of them by tamoxifen). Adjuvant radiotherapy had been administered to 147 patients (90%).

The baseline characteristics of the patients on metastasis diagnosis are summarized in Table 1. The median age was 51 years and the median disease-free interval (DFI) was 26 months. Approximately, one half of the patients had a high-grade 3 histology and 45.7% had visceral metastases. The majority of the patients (64.8%) had bone metastases and approximately 30% had bone deposits as the unique metastatic site. The HR status was unknown in only one patient, positive (ER-positive and/or PgR-positive) in 82.6% of the evaluable patients, and negative in 17.4% (ER-negative and PgR-negative).

Table 1 Characteristics of the patients ($N=162$)

Age (years)	
Median (range)	51 (24–75)
DFI (months)	
Median (range)	26.0 (0–310)
≤ 24 months	75 (46.6%)
>24 months	86 (53.4%)
NA	1
Histology	
Ductal	122 (81.3%)
Lobular	22 (14.7%)
Ductal and lobular	6 (4.0%)
NA	12
Histological grade ($N=141$)	
1	16 (11.3%)
2	49 (34.8%)
3	76 (53.9%)
NA	21
Metastases	
Median number of site (range)	1.5 (1–5)
≥ 3	36 (22.2%)
Visceral[a]	74 (45.7%)
Bone	105 (64.8%)
Bone only	48 (29.6%)
Liver	50 (30.9%)
Hormone receptor status	
ER and/or PgR-positive	133 (82.6%)
ER-positive	129 (80.1%)
PgR-positive	108 (67.1%)
NA	1
Prior adjuvant/neoadjuvant chemotherapy	
Any	107 (66.0%)
Anthracycline	95 (58.6%)
Taxane plus anthracycline	3 (1.9%)

DFI, disease-free interval, time from first diagnosis to first occurrence of relapse; ER, estrogen receptor; NA, not available; PgR, progesterone receptor.
[a]Liver, lung, or brain metastases.

First-line regimens

Eighty-two (50.6%) patients were given docetaxel of 75–100 mg/m^2 every 3 weeks as a single agent for metastatic disease, whereas 80 (49.4%) patients received a docetaxel-based combination regimen. The vast majority (74) of these patients were given anthracycline (combination epirubicin 75–100 mg/m^2 day 1 plus docetaxel 75 mg/m^2 day 1, every 3 weeks), six of them received docetaxel 75 mg/m^2 day 1 plus capecitabine 1800 mg/m^2/day days 1–14, every 3 weeks. Chemotherapy was scheduled to be administered for six to nine cycles. In case of anthracycline-based combination, epirubicin was stopped at a cumulative dose of epirubicin or equivalent of 900 mg/m^2. At least three cycles of chemotherapy were administered in 152 patients (94%), and at least six cycles were delivered in 96 patients (59%). Young, responding patients with good performance status and oligometastatic disease were offered high-dose alkylating agents plus autologous hematopoietic stem cell support as consolidation (39 patients, 24%). Primary hormonal therapy for metastatic disease in HR-positive patients was not systematically used before chemotherapy. However, hormonal therapy (tamoxifen or aromatase inhibitors) was offered to HR-positive patients as maintenance strategy to 96 patients (59%), mainly aromatase inhibitors (78 patients, 82%) or antiesotrogens (18 patients, 18%). No patients received bevacizumab.

Efficacy and prognostic factors

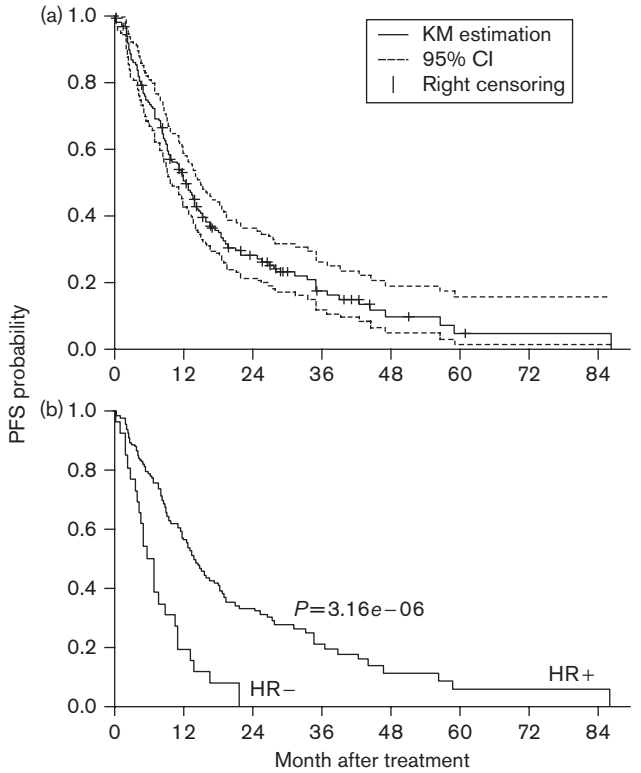
Response rate according to WHO criteria was not reliable in this retrospective study, as a large number of patients

were not measurable on treatment initiation. Nevertheless, disease progression on primary evaluation was reported in only 24 patients (15%).

With a median follow-up of 32.7 months [95% confidence interval (CI): 28.8–40], the median PFS was 12 months (95% CI: 9.7–14.8) and the median OS 34.9 months (95% CI: 28.1–52.1) (Fig. 2a and Fig. 3a).

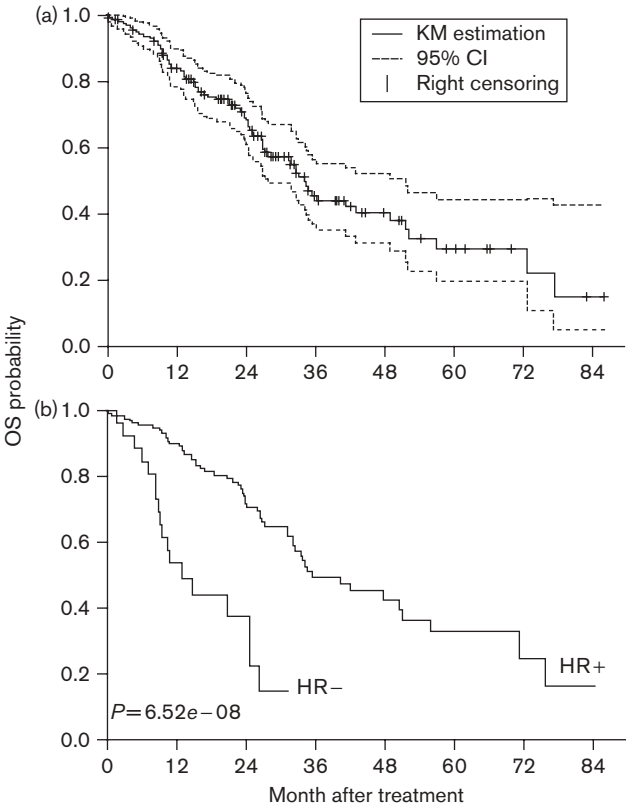
The HR status was the strongest prognostic factor in the univariate analysis for both PFS and OS (Table 2). The risk of death was decreased by 77% and the risk of disease progression or death by 65% in patients with HR-positive tumors compared with HR-negative tumors ($P = 6.3 \times 10^{-7}$ and 7.9×10^{-6}, respectively). This difference is illustrated in Fig. 2b and Fig. 3b, showing highly significant different PFS ($P = 3.16 \times 10^{-6}$) and OS (6.52×10^{-8}) according to the HR status. The estimated 2-year PFS was 33.2% for patients with HR-positive tumors, versus 0% for patients with HR-negative tumors. The estimated 2-year OS was 76.2% for patients with HR-positive tumors and 37.8% for patients with HR-negative tumors.

Fig. 2



Progression-free survival (PFS). CI, confidence interval; ER+, estrogen receptor-positive; ER−, estrogen receptor-negative; HR+, hormone receptor-positive; HR−, hormone receptor-negative; KM, Kaplan–Meier; PgR+, progesterone receptor-positive; PgR−, progesterone receptor-negative.

Fig. 3



Overall survival (OS). CI, confidence interval; ER+, estrogen receptor-positive; ER−, estrogen receptor-negative; HR+, hormone receptor-positive; HR−, hormone receptor-negative; KM, Kaplan–Meier; PgR+, progesterone receptor-positive; PgR−, progesterone receptor-negative.

The following variables with a P value ≤ 0.10 in the univariate analysis were entered in the Cox model: HR (positive/negative), bone metastasis only (yes/no), visceral metastasis (yes/no), adjuvant/neoadjuvant chemotherapy (yes/no), histological grade (1–2/3), docetaxel regimen (single agent/combination), and DFI (≤ 24/> 24 months) for PFS; and HR, DFI, histological grade, visceral metastasis, bone metastasis only, and liver metastasis for OS. After multivariate analysis (Table 3), only three independent variables for PFS (HR-positive tumor, no prior adjuvant/neoadjuvant chemotherapy, and isolated bone metastases) and two for OS (HR-positive tumor and isolated bone metastases) remained predictive of a favorable outcome. Notably, docetaxel monotherapy that was weakly correlated with a shorter PFS compared with combination therapy in the univariate analysis, no longer remained significant in the multivariate analysis.

Table 4 shows an exploratory analysis of baseline characteristics of the patients according to their HR status. The patient profiles are strikingly different across subsets and patients with HR-negative tumors had a

Table 2 Univariate analysis

	N	Hazard ratio (95% CI)	*P* value
Progression-free survival			
Hormone receptor-positive	161	0.354 (0.22–0.56)	0.0000079
Bone metastasis only	162	0.471 (0.31–0.72)	0.00055
Visceral metastasis	162	1.77 (1.24–2.51)	0.0015
Adjuvant/neoadjuvant CT	162	1.78 (1.2–2.63)	0.0038
Bone metastasis	162	0.599 (0.42–0.86)	0.0054
Time from breast cancer diagnosis (continuous variable)	162	0.996 (0.99–1)	0.027
Histological grade (1–2 vs. 3)	141	1.52 (1.025–2.244)	0.037
Single agent docetaxel	162	1.43 (1–2.06)	0.049
Histological grade (1 vs. 2–3)	141	1.74 (0.948–3.206)	0.074
DFI >24 months	161	0.739 (0.52–1.05)	0.092
Liver metastasis	162	1.3 (0.9–1.88)	0.16
Number of metastases (continuous variable)	162	1.09 (0.92–1.29)	0.30
Age at metastasis diagnosis >45 years	162	0.913 (0.616–1.355)	0.65
Number of metastatic sites ≥ 3	162	0.978 (0.64–1.49)	0.92
Overall survival			
Hormone receptor-positive	161	0.234 (0.13–0.41)	0.00000063
DFI >24 months	161	0.486 (0.3–0.78)	0.0028
Histological grade (1–2 vs. 3)	141	1.95 (1.187–3.206)	0.0084
Visceral metastasis	162	1.88 (1.17–3.04)	0.0094
Time from breast cancer diagnosis (continuous variable)	162	0.992 (0.99–1)	0.010
Bone metastasis only	162	0.537 (0.3–0.97)	0.038
Liver metastasis	162	1.59 (0.99–2.54)	0.053
Bone metastasis	162	0.633 (0.4–1.01)	0.054
Histological grade (1 vs. 2–3)	141	2.15 (0.924–5.024)	0.076
Adjuvant/neoadjuvant CT	162	1.43 (0.87–2.34)	0.16
Single agent docetaxel	162	1.31 (0.82–2.09)	0.26
Age at metastasis diagnosis >45	162	1.22 (0.724–2.057)	0.45
Number of metastatic sites ≥ 3	162	0.824 (0.47–1.44)	0.49
Number of metastases (continuous variable)	162	1.06 (0.85–1.33)	0.59

CI, confidence interval; CT, chemotherapy; DFI, disease-free interval.

higher incidence of other unfavorable prognostic factors than patients with HR-positive tumors (DFI ≤ 24 months, histoprognostic grade 3, visceral metastases, and inflammatory cancer). In contrast, only 1.3% of patient with HR-negative tumors had bone-only metastases, which is an independent, good prognosis factor. Notably, triple-negative tumors had almost exclusive ductal histology.

Discussion

The unfavorable prognostic significance of HER2 amplification/overexpression in breast cancer was well established, but can be partially reverted by HER2-targeted therapy. Indeed HER2-positive ABC patients treated with trastuzumab could paradoxically achieve a similar, or even better, outcome than patients with HER2-negative tumors [9,21].

In contrast, few studies have been specifically carried out in patients with selected HER2-negative tumors. Their prognostic factors and optimal therapy have, therefore, been poorly explored.

Table 3 Multivariate analysis

	Hazard ratio (95% CI)	*P* value
Progression-free survival (*N*=139)		
Hormone receptor status		
Negative	1	
Positive	0.381 (0.226–0.641)	0.00028
Adjuvant/neoadjuvant chemotherapy		
No	1	
Yes	1.79 (1.157–2.755)	0.0088
Bone metastasis only		
No	1	
Yes	0.576 (0.380–0.874)	0.0095
Overall survival (*N*=139)		
Hormone receptor status		
Negative	1	
Positive	0.284 (0.151–0.535)	0.00010
Bone metastasis only		
No	1	
Yes	0.588 (0.351–0.984)	0.043

CI, confidence interval.

Table 4 Baseline characteristics according to hormone receptor status (*N*=161)

	ER and PgR-negative (*N*=28)	ER and/or PgR-positive (*N*=133)
Age (years)		
Median (range)	50.5 (33–66)	52.0 (24–75)
DFI (months)		
Median (range)	12.8 (0–161.9)	29.1 (0–310)
≤ 24 months	22 (78.6%)	54 (40.6%)
Histology		
Ductal	24 (92.3%)	97 (78.9%)
Lobular	1 (3.8%)	21 (17.1%)
Ductal and lobular	1 (3.8%)	5 (4.1%)
NA	2	10
Grade		
1	0	16 (13.8%)
2	3 (12.5%)	45 (38.8%)
3	21 (87.5%)	55 (47.4%)
NA	4	17
Inflammatory		
Yes	8 (28.6%)	18 (13.5%)
Metastases		
Median number (range)	2 (0–5)	1 (0–5)
Visceral	20 (71.4%)	53 (39.8%)
Liver	11 (39.3%)	38 (28.6%)
Lung	11 (39.3%)	27 (20.3%)
Bone	10 (35.7%)	97 (72.9%)
Bone only	1 (3.6%)	47 (35.3%)
Adjuvant/neoadjuvant chemotherapy		
Yes	20 (71.4%)	86 (64.7%)

DFI, disease-free interval; ER, estrogen receptor; PgR, progesterone receptor; NA, not available.

In our series of 162 patients with HER2-negative ABC receiving a first-line docetaxel regimen, the median PFS (12 months) and OS (35 months) were relatively long, but very similar to median time to progression (11.7 months) and median OS (31.2 months) reported in patients with HER2-overexpressing ABC given first-line docetaxel plus trastuzumab [22]. These data, consistent with other reports [21], illustrate the fact that the historical favorable prognostic of HER2-negative tumors could become clinically irrelevant in the trastuzumab era.

Whether taxane-based strategies have contributed to improve the outcome of metastatic breast cancer patients

remains controversial in the whole population and is even unknown in patients with HER2-negative tumors. These compounds generated a great deal of enthusiasm in the early 1990s, when they showed a lack of cross-resistance with anthracyclines in ABC. However, among the 12 randomized trials comparing head-to-head taxanes with anthracyclines as single agents, or evaluating anthracycline–taxane combinations, only two trials showed the incorporation of a taxane in front-line therapy associated with a significant OS prolongation. Yet, both published meta-analyses focusing on this issue [23–25] have contradictory conclusions about first-line taxane impact on overall survival. This discrepancy may be related to the comparator used, either any non-taxane-based regimen [23] or anthracycline-based regimens only [24,25]. Owing to the retrospective and noncomparative nature of our study, it does not provide any new insight into the impact of docetaxel on efficacy in HER2-negative patients. It has been suggested that HER2 amplification and ER negativity could be predictive of taxane response [26]. However, clinical studies in the metastatic setting have not confirmed this finding [19,20]. Our results show poor outcomes of triple-negative patients despite early docetaxel exposure.

Our multivariate analysis showed that the most powerful independent prognostic factor was the expression of HR, for both PFS and OS. The relatively good prognostic of the whole HER2-negative population is, in fact, limited to the subpopulation of patients whose tumor expresses ER and/or PgR (corresponding to the luminal molecular subtype). Patients with triple-negative tumors (corresponding to the basal-like subtype) represent only 17.4% of the whole HER2-negative population, but have a very poor prognosis with median PFS of less than 7 months and OS of nearly 12 months and no patient free of progression 2 years after docetaxel initiation. Notably, the PFS was close to, and the OS even worse than, those observed in HER2-positive patients receiving docetaxel without trastuzumab (6.1 months and 22.7 months, respectively) [22]. Our data are consistent with those recently reported by Largillier *et al.* [27] in a large population of ABC patients, in which few patients had a known HER2 status. They also found in this general population that, irrespective of HER2 overexpression, HR status and metastatic site were among the most powerful independent prognostic factors for survival, and that DFI did not remain an independent factor in the multivariate analysis. Interestingly, the HER2 status was determined in only 19% of patients and a similar population of 155 patients was HER2-negative. The median survival of 36 months of this subset was very similar to that observed in our series.

Whether the well-recognized adverse outcome of the triple-negative population is related to intrinsic aggressiveness, the lack of effective targeted therapy, or both is not fully understood. In our series, the triple-negative population had an increased incidence of other poor prognostic factors, such as short DFI, high-grade histology, and visceral metastases, consistent with earlier descriptions of basal-like breast cancer [14]. Younger age, reported in this subset in the literature [15], was not evident in our series. A recent PET scan study in HER2-negative tumors also suggested that triple-negative tumors have a more aggressive biology than double-negative tumors [16]. In contrast, the triple-negative population may be very close in terms of characteristics and outcome to the 'double-negative' one (HR-negative; HER2-positive), suggesting that both the poor prognosis and tumor aggressiveness of the triple-negative subset could be mainly related to the lack of HR expression, regardless of the HER2 status [4,28]. In contrast, the HR-positive, HER2-negative (luminal) subtype could be a particularly good prognostic subset. In this subset, modern taxane-based cytotoxic and hormonal strategies may achieve relatively long median PFS and OS and provide a robust basis upon which further progresses can be built. Among other explanations, these patients may have tumors that are more sensitive to hormone therapy than those with HR-positive, HER2-positive tumors, because HER2 overexpression remains a predictive factor of hormone therapy failure, even in the trastuzumab era [29].

Conclusion

Our study confirms the heterogeneity of the population with HER2-negative metastatic breast cancer, mainly based on the HR status. The triple-negative subset has a particularly poor outcome and few available therapeutic options. The intrinsic aggressive behavior of triple-negative tumors may be similar to that of HER2-overexpressing tumors before trastuzumab. Innovative therapies are eagerly awaited for patients with triple-negative tumors and could deeply modify their natural history as well [30].

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