Ten years of experience with weekly chemotherapy in metastatic breast cancer patients: multivariate analysis of prognostic factors

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Weekly chemotherapy administration represents an emerging option for the treatment of metastatic breast cancer. In order to identify clinical and biological prognostic factors for outcome, we performed a multivariate analysis in a 10-year experience of weekly chemotherapy for metastatic breast cancer patients. The original databases of phase II trials of metastatic breast cancer patients who had undergone first-line weekly chemotherapy were collected. Clinical and biological covariables were screened for a possible relationship with time to progression and overall survival in a Cox model. From 1990 to 2003, 184 patients were enrolled in three consecutive phase II studies, to evaluate activity and tolerability of weekly epirubicin with lonidamine or vinorelbine or paclitaxel. All patients were evaluable for clinical variables; histological samples were available in 40 patients. At a median follow-up of 24 months, median time to progression was 9 months (95% confidence interval 8–10) and median overall survival was 34 months (95% confidence interval 24–42). Independent variables were response (hazard ratio 2.34, $P<0.0001$), receptor status (hazard ratio 1.62, $P=0.01$) and performance status (hazard ratio 2.31, $P<0.0001$) for time to progression, and response (hazard ratio 1.86, $P=0.005$), performance status (hazard ratio 2.81, $P<0.0001$), dominant metastatic site (hazard ratio 2.27, $P<0.0001$) and enrollment period (hazard ratio 2.51, $P=0.001$) for overall survival. Although no biological factors were entered into the Cox model owing to the small sample size, some subpopulations showed a negative trend in survival. In our series of patients who had undergone weekly chemotherapy for metastatic breast cancer, independent prognostic factors for survival improvement were responders, performance status 0–1, nonvisceral dominant metastatic site and enrollment period. A greater sample population is needed to extensively screen for biological prognostic factors. ***Anti-Cancer Drugs*** **17:1193–1200 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Breast carcinoma is the second most frequent cause of cancer-related death in women in the USA [1]. Despite the improvements achieved in the overall outcome of breast cancer patients, metastatic spread is still frequent. Indeed, up to 60% of the patients will ultimately develop distant metastases. The treatment of advanced breast cancer is still complex and, in part, controversial, as there is still no universally accepted therapy. Conventional treatments, however, have no curative impact on advanced disease, with a median survival of about 2 years after evidence of metastases [2].

Although anthracyclines (doxorubicin and epirubicin) still play a major role in the treatment of advanced breast cancer, new active drugs such as the taxanes (paclitaxel and docetaxel), vinorelbine and gemcitabine have become available in the recent years.

Randomized clinical trials and meta-analyses have shown that polychemotherapy is better than monochemotherapy, and that taxane–anthracycline-based chemotherapy improves time to progression (TTP) over nontaxane-based chemotherapy in the first-line setting [3,4]. Furthermore, chemotherapy has been demonstrated to affect survival over time, in particular, as second-line treatment [5,6].

In order to improve the effectiveness of chemotherapy by drug dose intensification, several attempts to optimize the administration of antiblastics have been designed,

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such as the dose-dense and weekly strategy [7,8]; unfortunately, the impact on late outcome of these different modalities in large series has never clearly been evaluated in metastatic disease.

From a theoretical perspective, the exposure to more sustained antineoplastic administration should inhibit tumor regrowth between cycles and decrease the onset on chemotherapy-resistant cancer clones [7]. Concerning adjuvant setting, randomized evidence suggests that (i) a dose reduction higher than a threshold level is detrimental for disease-free survival, (ii) a 'more-dense' regimen improves survival over a 'less-dense' treatment and (iii) a dose-dense schedule improves survival when compared with a conventional 3-weekly schedule [9–11]. Less randomized evidence is available for weekly strategy, even if weekly paclitaxel has recently demonstrated higher activity than a 3-weekly schedule in both metastatic and locally advanced disease [12,13].

In clinical practice, the treatment choice is determined by clinical, and rarely by biological (with the exception of the epidermal growth factor), prognostic factors identified in multiple randomized trials. Regarding weekly chemotherapy, no large trials are available to screen for specific prognostic factors [14].

In order to clarify which factors independently affect outcome in patients who have undergone first-line weekly chemotherapy for metastatic breast cancer (MBC), we performed a multivariate analysis of a retrospective monoinstitutional database of phase II studies in the past 10 years.

Patients and methods

Inclusion criteria

All patients who entered into phase II trials designed to evaluate activity and toxicity of weekly schedule of anthracycline-based chemotherapy for previously untreated MBC between 1990 and 2003 were considered eligible.

Entry criteria for these studies were histological proof of primary breast cancer with at least one bidimensionally measurable or evaluable metastatic lesion, life expectancy ≥ 3 months, age between 18 and 75 years, performance status (PS) (Eastern Cooperative Oncology Group scale) ≤ 2. Other requirements were adequate bone marrow function (absolute neutrophil count $\geq 2.0 \times 10^3$/dl, platelet count $\geq 100 \times 10^3$/dl; hemoglobin ≥ 9 g/l), adequate liver function (bilirubin concentration ≤ 1.5 times the upper normal limit, aspartate aminotransferase and alanine aminotransferase ≤ 1.5 times the upper normal limit), adequate renal function (creatinine concentration ≤ 1.5 mg/dl, blood urea nitrogen < 50 mg/dl) and cardiac function. Patients should not have received any chemotherapy for the metastatic setting and could have received anthracycline as adjuvant treatment if administered at least 12 months before metastatic disease. Treatment had to start at least 4 weeks after the end of any previous treatment. All patients had to provide informed consent.

Treatment plan

Patients were required to be treated with a sustained, continuous weekly chemotherapy for 24 weeks without planned interruption, in the absence of disease progression. After 12 weeks of therapy, patients were reevaluated for response according to World Health Organization criteria [15]. Each of the single-center staff had to review and confirm the response evaluation. Radiological evaluation included chest radiograph, head, chest and abdomen-computed tomography scan, radionuclide bone scan and bone magnetic resonance imaging; responses needed to be confirmed after 4 weeks. All patients who received at least one chemotherapy infusion were included in the toxicity evaluation. Complete blood count and blood chemistry tests were evaluated prior to each treatment. Patients were assessed every week for toxicity according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Antibodies and immunohistochemistry

Breast carcinomas were stained with anti-Fas and anti-FasL monoclonal antibodies (clone GM30 and clone 5D1, respectively; Novocastra Laboratories, UCS Diagnostic, Rome, Italy) and anti–vascular endothelial growth factor (clone JH121; UCS) [16,17]. Immunohistochemistry staining was carried out on 5-μm sections, harvested on SuperFrost Plus slides (Menzel-Glaser, Braunschweig, Germany). The deparaffinized and rehydrated sections, pretreated in a thermostatic bath at 96°C for 40 min in 10 mmol/l citrate buffer (pH 6 for anti-Fas and FasL monoclonal antibodies, and pH 8 for anti-vascular endothelial growth factor (VEGF) monoclonal antibody), were incubated with reagents for 60 min at room temperature. The reactions were visualized using a streptavidin–biotin immunoperoxidase system (LSAB 2 kit; DakoCytomation, Milan, Italy) and 3-amino-9-ethylcarbazole solution (DakoCytomation) as chromogenic substrate. Sections were then counterstained with Mayer hematoxylin and mounted in aqueous mounting medium (Glycergel; DakoCytomation). All of the immunostained slides were analyzed and scored independently by two investigators (M.M., F.N.). Estrogen and progesterone receptors were assayed immunohistochemically on formalin-fixed paraffin-embedded tumors using commercially available antibodies (ER1D5 and 1A6; Immunotech, UCS). Patients were considered to be hormonal-receptor-positive if they expressed at least one of the two subclasses (estrogen and progesterone receptors). HER-2 protein expression was evaluated using the polyclonal antibody A0485 purchased from

DakoCytomation. HER-2 was considered overexpressed only when at least 10% of the neoplastic cells displayed an intense staining of the entire plasma membrane (++/+++ score).

Statistics

The objective of this analysis was to screen for independent prognostic factors for TTP and overall survival (OS) in a multivariate analysis. The original phase II studies were all designed according to the Simon two-step method design [18], and TTP and OS were analyzed by the Kaplan–Meier method [19]. Original databases from each single phase II trial were pooled together, and the response and survival analyses were carried out following an intention-to-treat assignment. At the univariate analysis, responses were compared with χ^2 test and survivals by log-rank determination. Cox's multivariate proportional hazard model was used to assess the impact of known prognostic factors. The cutoff *P*-values to enter in or to be removed from the model were set to 0.05 and 0.10, respectively. Tested covariates were hormonal receptor status (positive plus unknown versus negative), adjuvant chemotherapy, anthracycline-based adjuvant chemotherapy, PS (according to Eastern Cooperative Oncology Group), age (cutoff: 50), disease-free interval (cutoff: 24 months), menopausal status, number of metastatic sites, response with chemotherapy (responders versus nonresponders), paclitaxel chemotherapy and enrollment time (1990–1993 versus 1994–1999 versus 1999–2001). Available biological covariates were immuno-histochemical HER-2, Fas, FasL and VEGF overexpression. Statistical analyses were performed using the SPSS version 11 package (Chicago, Illinois, US) for Windows.

Results

Patient characteristics

From 1990 to 2001, 184 MBC patients overall entered three consecutive phase II studies with anthracycline-based weekly chemotherapy. Patient characteristics are listed in Table 1. Patients underwent the following weekly chemotherapy for 24 consecutive weeks in the absence of disease progression: epirubicin 25 mg/m^2/week intravenous bolus, plus lonidamine (i.e. monochemotherapy, EL, 400 mg/day orally), vinorelbine 25 mg/m^2/week, intravenous bolus (EN), or paclitaxel 80 mg/m^2/week intravenous bolus (EP) [20–22]. Median age was 55 years (range 29–77) and median disease-free interval was 38 months (range 0–309 months). Fifty-eight percent of patients had hormonal positive receptors, while hormonal receptor status in 21% was unknown. Owing to various clinical behaviors along all the enrollment years, significant differences in certain patient features were found. Unknown hormonal receptor status rate was significantly higher in the first two phase II studies (conducted from 1990 to 1999) than in the last trial ($P < 0.0001$) (Table 1). This is likely due to the different availability of specific technical devices for the receptor determination over all 13 years. The number of patients receiving adjuvant chemotherapy is significantly higher in the last two studies (1994–2001) when compared with the first one (conducted from 1990 to 1993) ($P < 0.0001$) and the number of patients receiving anthracyclines in the adjuvant setting is significantly higher in the last trial (conducted from 1999 to 2001) ($P < 0.0001$) (Table 1). This trend reflects the changes in clinical practice and treatment guidelines that occurred during the 1990s. Forty patients had histological samples available for multivariate analysis looking at biological prognostic factors.

Table 1 Patient characteristics

	EL (*n*/%)	EN (*n*/%)	EP (*n*/%)	Total (*n*/%)
Hormonal receptors				
positive	25/41	28/48.3	54/83.1	107/58.2
negative	13/21.3	17/29.3	8/12.3	38/20.7
unknown	23/37.7	13/22.4	3/4.6	39/21.2
Adjuvant chemotherapy				
anthracyclines	1/1.6	5/8.6	17/26.2	23/12.5
no anthracyclines	21/34.4	35/60.3	29/44.6	85/46.2
no treatment	39/63.9	18/31	19/29.2	76/41.3
Performance status (ECOG)				
0	33/54.1	27/46.6	53/81.5	113/61.4
1	18/29.5	20/34.5	11/16.9	49/26.6
2–3	10/16.4	11/19	1/1.5	22/12
Menopausal status				
pre	13/21.3	9/15.5	14/21.5	36/19.6
post	48/78.7	49/84.5	51/78.5	148/80.4
Disease-free survival (median)				
<24 months	21/34.4	16/27.6	21/32.3	58/31.5
>24 months	40/65.6	42/72.4	44/67.7	126/68.5
Dominant metastatic sites				
bone	19/31.1	14/24.1	21/32.3	54/29.3
liver	13/21.3	12/20.7	15/23	40/21.7
nodes	14/23	8/13.8	11/16.9	33/17.9
lung	6/9.8	4/6.9	12/18.4	21/11.4
skin	6/9.8	8/13.8	1/1.5	15/8.2
pleura	1/1.6	8/13.8	–/–	9/4.9
omentum	–/–	2/3.4	2/3.1	4/2.2
other soft tissue	2/3.3	1/1.7	1/1.5	2/1.1
breast	–/–	–/–	2/3.1	2/1.1
pancreas	–/–	1/1.7	–/–	1/<1
No. of metastatic sites				
1	28/45.9	27/46.6	29/44.6	84/45.7
2	26/42.6	22/37.9	24/36.9	72/39.1
>2	7/11.5	9/14.5	12/18.5	28/15.2

EL, epirubicin + lonidomine; EN, epirubicin + vinorelbine; EP, epirubicin + paclitaxel; ECOG, Eastern Cooperative Oncology Group.

Activity

Concerning the main end-point of the phase II studies, overall 33 patients obtained complete response [17.9%, 95% confidence interval (CI) 12.0–23.0] and 97 obtained partial response (52.7%, 95% CI 45.5–60.0), for an overall response rate of 70.6% (95% CI 64.1–77.2). Thirty-five patients had stable disease (19%, 95% CI 13.3–24.7), while 19 underwent progression (10.3%, 95% CI 7.0–14.7). No significant difference in responses was

found between the three regimens ($P = 0.26$), whereas a significant difference in progression rate in favor of polychemotherapy was detected (EL 27.9% versus EN 1.7% and EP 1.5%, $P < 0.001$). Although not significant, a trend in responses in favor of patients with visceral metastases ($P = 0.08$) and with less than two metastatic sites ($P = 0.09$) was found.

Survival analysis

Clinical factors

At a median follow-up of 24 months (range 1–115), overall median TTP and OS were 9 (95% CI 8–10) and 34 months (95% CI 26–42), respectively.

At the multivariate analysis, responders [hazard ratio (HR) 2.34, 95% CI 1.67–3.27, $P < 0.0001$], positive/unknown hormonal receptor (HR 1.62, 95% CI 1.12–2.34, $P = 0.01$) and PS 0–1 (HR 2.31, 95% CI 1.45–3.66, $P < 0.0001$) status are independent prognostic factors for TTP improvement (Table 2). Unadjusted TTP curves for responder status are shown in Fig. 1.

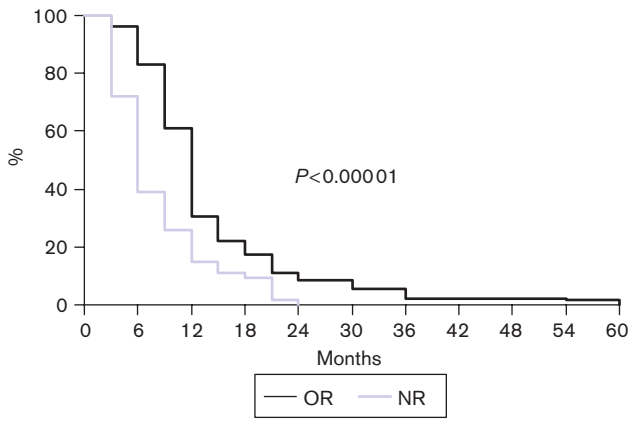
At the multivariate analysis, responders (HR 1.86, 95% CI 1.21–2.87, $P = 0.005$), PS 0–1 (HR 2.81, 95% CI 1.67–4.72, $P < 0.0001$), nonvisceral dominant metastatic site (HR 2.27, 95% CI 1.51–3.39, $P < 0.0001$) and enrollment time (HR 2.51, 95% CI 1.36–4.62, $P = 0.001$) are independent prognostic factors for OS improvement (Table 3). Unadjusted OS curves for variables are shown in Figs 2–5.

Table 2 Multivariate analysis (TTP)

	HR	95% CI	*P*
Responders (NR versus OR)	2.34	1.67–3.27	<0.0001
Hormonal receptor (negative versus positive/unknown)	1.62	1.12–2.34	0.01
PS (2–3 versus 0–1)	2.31	1.45–3.66	<0.0001

TTP, time to progression; HR, hazard ratio; CI, confidence interval; NR, nonresponders; OR, overall responders; PS, performance status.

Fig. 1



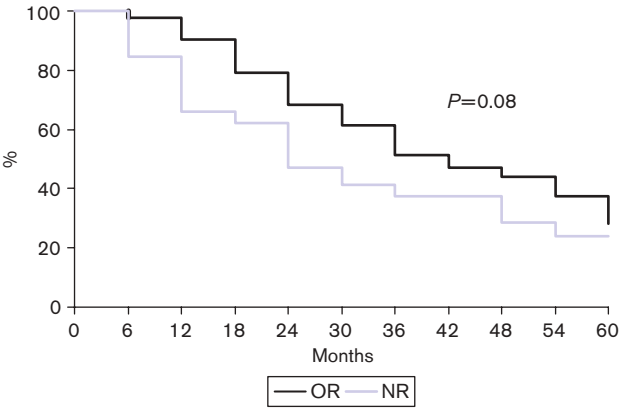
Unadjusted time to progression curve for responders status. OR, overall responders; NR, nonresponders.

Table 3 Multivariate analysis (OS)

	HR	95% CI	*P*
Responders (NR versus OR)	1.86	1.21–2.87	0.005
PS (2–3 versus 0–1)	2.81	1.67–4.72	<0.0001
Dominant metastatic site (visceral versus nonvisceral)	2.27	1.51–3.39	<0.0001
Enrollment period (1990–1999 versus 1999–2001)	2.51	1.36–4.62	0.001

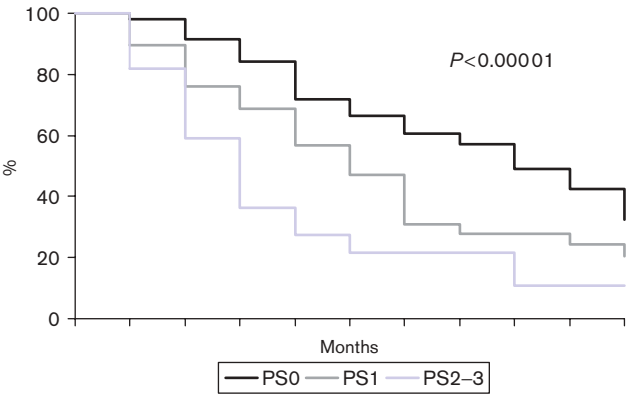
OS, overall survival; HR, hazard ratio; CI, confidence interval; NR, nonresponders; OR, overall responders; PS, performance status.

Fig. 2



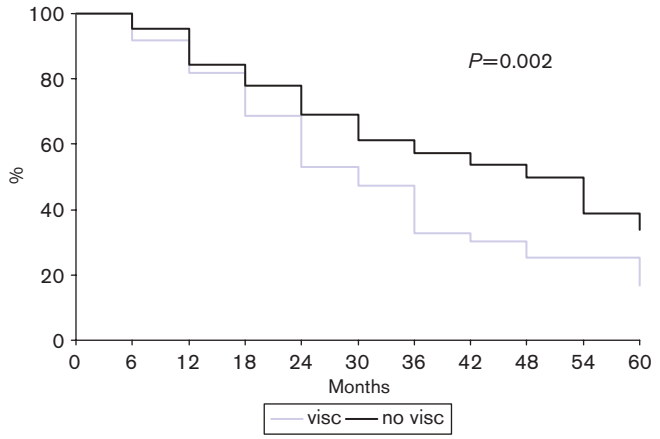
Unadjusted overall survival curve for responders status. OR, overall responders; NR, nonresponders.

Fig. 3



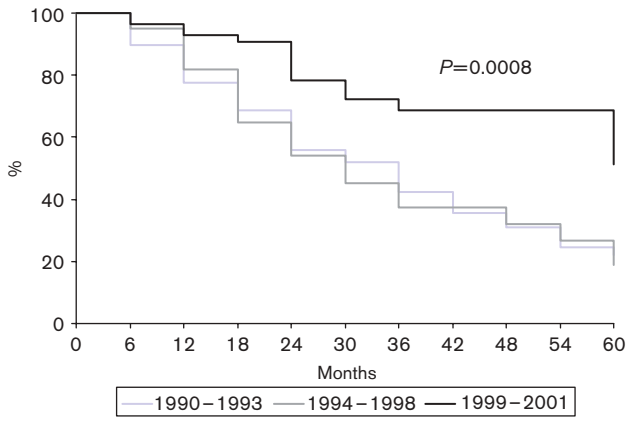
Unadjusted overall survival curve Eastern Cooperative Oncology Group performance status (PS).

Fig. 4



Unadjusted overall survival curve for metastatic site. visc, visceral metastatic site; no visc, nonvisceral metastatic site.

Fig. 5



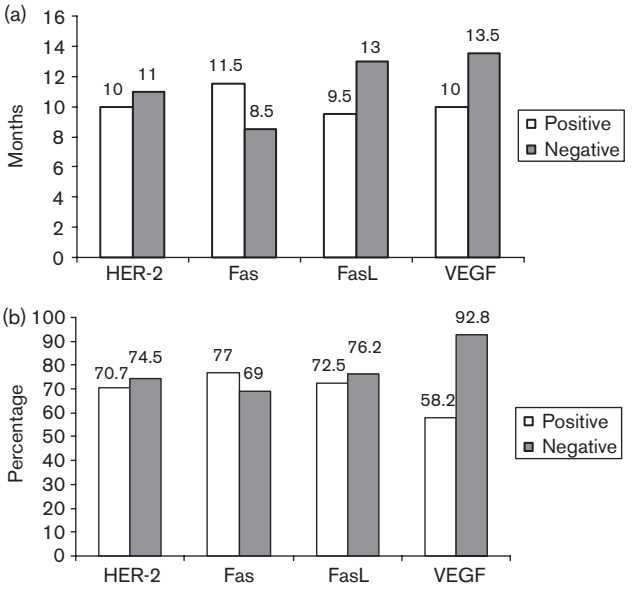
Unadjusted overall survival curve for enrollment period.

Biological factors

Forty patients were evaluated. Median follow-up was 25 months (range 3–91), median TTP 11 months (95% CI 8–14) and median OS 47 months (95% CI 25–79).

Probably owing to the small sample size, none of the supposed prognostic factors were entered into the multivariate model for TTP and OS. Regarding the apoptosis pathway, univariate analysis shows a trend in favor of patients overexpressing Fas for a longer TTP and 2-year OS. Conversely, those patients overexpressing FasL demonstrated a shorter TTP (Fig. 6a) and OS (Fig. 6b). When approaching the angiogenesis pathway, patients with a low VEGF score seem to have a better TTP (Fig. 6a) and OS (Fig. 6b). The Fas^{-}/Fas^{+} phenotype, when compared with the other profiles, seems to be detrimental in both TTP and OS.

Fig. 6



(a) Unadjusted median time to progression curve (months) for biological factors. (b) Unadjusted 2-year overall survival curve (%) for biological factors. VEGF, vascular endothelial growth factor.

Discussion

MBC patients represent a highly heterogeneous setting of the disease, because of different prognostic and clinical behavior linked to both patient characteristics (i.e. PS, age, comorbidities and menopausal status) and disease factors (hormonal and growth factor receptor status, stage and grading) [14]. Although median OS is 24–36 months, some subgroups benefit most from treatment. In the last 20 years, a survival improvement has been observed, thanks to new drugs development as well [3,4,23,24]. From these perspectives, the drug delivery optimization developed through the exploration of different schedules is a new emerging option [8].

Paclitaxel has become the most studied drug for weekly administration, as preclinical and clinical evidence has shown important new viewpoints [25]; while the 'laboratory bench' had suggested proapoptotic and neo-angiogenetic pathways involved in weekly paclitaxel mechanism of action [26,27], the 'patient bed' demonstrated higher activity and efficacy for such a schedule when compared with 3-weekly administration in both the advanced and neo-adjuvant treatment setting [12,13]. On a sustained weekly basis, paclitaxel is able to increase the dose intensity as in the dose-dense approach, but the exploited cytotoxicity did not seem to be related only to this, but rather to the increased sustained administration that involves appealing pathways different from the 3-weekly schedule. This theory is actually demonstrated in

the direct comparison with a 3-weekly regimen with the same dose intensity [13].

The property of being easily and safely administered on a sustained weekly basis, and also providing an increased dose intensity at the same time, seems peculiar to paclitaxel and is not shared by all drugs; indeed, we have previously demonstrated that the sustained administration of weekly docetaxel did not provide significant dose-intensity increase and, moreover, the expected toxicities appeared at a threshold level [28]. The chemotherapy intensification provided by both dose-dense and weekly schedule becomes possible with the concurrent use of hematopoietic growth factors such as granulocyte-colony stimulating factors (G-CSF) [29]. The maintenance of the continuous sustained frequency obtained with G-CSF support is crucial for the activity of weekly paclitaxel, rather than for avoiding hematological toxicity, which is supposed to be mild in such a regimen [30,31]. A previous report demonstrated that a less-intensive G-CSF administration modulated on growth factor half-life, chemotherapeutics pharmacokinetics and bone marrow function is as active as a classical schedule in breast cancer in avoiding toxicity and dose-intensity maintenance [32]. In the same direction, we have previously demonstrated that a 2-day G-CSF administration is able to reduce neutropenia and maintain dose intensity in a sustained weekly schedule as well; a one-unit delay per month translates into a 25% reduction in dose intensity [33].

Besides, the best treatment choice in MBC is required to be correctly determined through an appropriate prognosis estimation. Indeed, all variables that influence the disease management have been determined based upon data from randomized trials and meta-analyses concerning 3-weekly chemotherapy approaches [3,34]. Under weekly chemotherapy emerging in the recent years owing to positive results in two randomized trials [8,12,13], multivariate analyses aimed at the identification of independent variables for survival are needed. With this intent, our analysis has been performed to screen for prognostic factors for outcome through a retrospective database of first-line weekly chemotherapy for MBC. Moreover, our study population has to be considered as one of the largest samples in the literature concerning weekly chemotherapy for breast cancer.

Although retrospective and based upon selected patients (as it is supposed to be for phase II studies), the multivariate analysis shows that the prognostic factors panel for outcome overlaps that well known for conventional treatment. This should strengthen the reliability of our analysis, also considering all significant biases in patient characteristics (i.e. hormonal receptor status, adjuvant chemotherapy and enrollment period). In particular, independent variables are response, hormonal receptor status and PS for TTP (Table 2), and response, PS, dominant metastatic site and enrollment period for OS (Table 3). Some issues need to be explored using these data. The relationship between response and survival is controversial, while in tumors such as colorectal cancer, some evidence has been provided [35]. Besides, large series, although retrospective, have demonstrated that patients showing a response had a longer survival than those not responding to treatment [36]. Moreover, Greenberg *et al.* [36] showed that complete response seems to be a prerequisite for longer survival. In our retrospective analysis, patients who responded were 56% more likely to prolong their OS when compared with nonresponders. The issue regarding response as a surrogate end-point for survival has recently been handled by Bruzzi *et al.* [37] in individual patient data meta-analysis exploring this topic across randomized trials comparing dose-dense versus conventional chemotherapy. That analysis conducted in more than 2100 patients, when adjusted in the multivariate model, did not reveal any independent relationship between response and survival [37]. In the absence of prognostic analysis performed upon multiple randomized trials exploring the weekly issue, the unique evidence that weekly paclitaxel would improve response in MBC over 3-weekly paclitaxel is provided by the CALGB 9840 randomized trial [12]. Anyway, OS should not be considered as the primary end-point in first-line setting, owing to the impact on survival provided by polychemotherapy with new drugs in second-line treatment [38]. In our analysis, PS significantly affects both TTP and OS; a prospective analysis looking at this particular issue, which is crucial for example in lung cancer, should be performed, at least to save patients with a poor prognosis who are not likely to benefit from chemotherapy after second-line treatment. Moreover, in our series, patients with minimal disease (single nonvisceral metastases) are likely to live longer than patients with multiple visceral involvement. Actually, we are not able to clearly understand whether those patients would also benefit from weekly chemotherapy; we can generate the hypothesis that seeking a major response in these patients (with a less-toxic but more active optimized schedule such as weekly paclitaxel) could have an impact on survival [12,13]. The significant benefit in OS provided by paclitaxel-based chemotherapy overlaps that seen in patients treated in the period 1999–2001; although these two subgroups almost analyze the same group of patients, we are actually not able to distinguish which of these independent factors plays the major role in improving survival. The very same effect is seen in the series recently published by Bruzzi *et al.* [37], in which the time cohort instead of type of chemotherapy was an independent factor for survival [37]. Nevertheless, the impact of time period on survival needs to be considered independently by the achieved advances in chemotherapy for MBC [23,24].

Screening for unknown prognostic factors between new biological features is also required; although the definition of targeted therapy is restricted to those drugs (such as trastuzumab) directed to a specific well-defined receptor, some standard chemotherapeutics could be customized on a specific mechanism of action, if this pathway is understood. For these reasons, if a specific drug in a certain schedule (such as weekly paclitaxel) affects a specific tool in cancer cell growth, the identification of targets involved in the same mechanism could be useful in the selection of those patients who would benefit more from that particular treatment. So, it may be possible to 'tailor' a classical chemotherapeutic treatment starting from a biological platform. With this intent, we looked for biological indicators that are supposed to be involved in the weekly paclitaxel mechanism of action as well. In particular, the apoptotic process regulated by the Fas system and the angiogenetic pathway driven by the VEGF cascade could be preferentially involved in the peculiar weekly schedule mechanism of action [26,37]. Although no significant results are available, the trends found confirm those reported in the literature; in particular, the $Fas^{-}/FasL^{+}$ phenotype seems to confer a detrimental prognosis [16]. The small sample size does not allow us to draw any conclusion, although we strongly believe that screening patients for biological features is helpful not only for new targeted drugs, but also for the optimization of 'older' chemotherapeutic agents.

Although all the limitations of a retrospective analysis need to be considered, in particular in a selected population over a large period, our report represents one of the largest series of MBC patients who have undergone weekly chemotherapy. Moreover, it provides indications about prognostic factors for patients to whom this schedule is offered; a relevant suggestion about tools to investigate in order to choose the drug (and the schedule) on a biological basis is given. The identification of clinical and biological prognostic factors in a larger population of patients treated with weekly chemotherapy enrolled in phase III trials is needed.

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