Weekly Non-pegylated Liposomal Doxorubicin Chemotherapy in Heavily Pre-treated Patients with Metastatic Breast Cancer

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Abstract. *Background: Due to its low cardiac toxicity, non-pegylated liposomal doxorubicin (NPLD) may represent an attractive therapeutic option as salvage therapy for patients with metastatic breast cancer who have already received anthracycline-based chemotherapy. Patients and Methods: We retrospectively reviewed 47 consecutive patients with metastatic breast cancer treated with NPLD at our Institution between 2008 and 2012. Patients received weekly NPLD at a dose of 20 mg/m^2 i.v. until disease progression or unacceptable toxicity. Results: Nine patients (19.1%) achieved a partial response and 11 (23.4%) had stable disease, with a disease control rate of 42.6%; 27 patients (57.4%) had progressive disease. The median progression-free survival and overall survival were 2.7 and 11.5 months, respectively. Grade 3 and 4 adverse events did not occur. No cardiac events were observed. Conclusion: Weekly NPLD represents a safe and effective therapy and may be considered a new therapeutic option for heavily pre-treated patients with metastatic breast cancer.*

For advanced breast cancer, multiple, sequential lines of treatment are frequently administered. The choice of therapeutic regimens usually follows accepted guidelines (1, 2) but also requires consideration of individual factors, not least the correct timing in stopping the administration of any anticancer therapy.

Anthracyclines and taxanes are crucial in the treatment of metastatic breast cancer (3), but due to their extensive use in neoadjuvant and adjuvant setting, their indication in patients with metastatic disease is currently limited. In fact, despite their potential activity, anthracyclines are not considered for use in pre-treatment of patients with metastatic breast cancer who have already received an anthracycline-based chemotherapy because of the risk of dose-cumulative cardiotoxicity (4, 5). On the other hand, previous data support taxane re-challenge after first-line therapy when the disease-free interval is at least one year (6). However, considering the existence of many other available options and of significant toxicity concerns, especially myelosuppression, this is considered a less appealing option.

The most consistent data on therapy for patients with metastatic breast cancer previously treated with anthracyclines and taxanes concern monotherapies approved for use in the late-line setting, such as capecitabine, vinorelbine, platinum-based treatments and, more recently, eribulin and nab-paclitaxel (7). There are no data to support an optimal sequence of these therapies and very few agents as monotherapy in the metastatic setting have so far demonstrated a benefit on overall survival (OS) (8, 9). Currently, two other important challenges for oncologists lie in the choice of the most adequate treatment for patients pre-treated with at least three regimens, after anthracyclines and taxanes, and the best approach for elderly patients and those with multiple morbidities. In these settings, in order to achieve anthracycline efficacy, liposomal anthracycline formulations may represent an attractive opportunity for treatment, especially because of their profile of low cardiac toxicity. Two different liposomal doxorubicin formulations are currently used in clinical practice: non-pegylated liposomal doxorubicin (NPLD) and pegylated liposomal doxorubicin. The former results from the encapsulation of doxorubicin within a macromolecular vector, the liposome. Compared to doxorubicin, NPLD provides similar anti-tumour efficacy, with significantly reduced cardiotoxicity, which leads to an improvement of its therapeutic index (10).

Based on the study of Batist *et al.* (11), NPLD has been approved in Europe as first-line treatment for metastatic breast cancer after treatment with anthracyclines in combination with cyclophosphamide. It has been shown to

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be effective and significantly less cardiotoxic than doxorubicin, but a higher incidence of grade 4 neutropenia has been reported (11). Also in the study of Mrozek *et al*., where NPLD was administered in combination with docetaxel, grade 3-4 non-haematological and haematological side-effects occurred (12). Bernardi *et al*. reported data from a prospective study of 20 patients with metastatic breast cancer, previously exposed to conventional anthracyclines, treated with NPLD as a single agent at a dose of 60 mg/m2 every three weeks (13). In this study, there was a clinical benefit of 35%, but grade 3-4 haematological toxicity occurred in 35% of patients and three of them had congestive heart failure.

Considering these reported toxicities and in order to minimize all side-effects as much as possible, we decided to investigate the role of weekly NPLD in a setting of heavily pre-treated patients with metastatic breast cancer. In some cases, for patients who otherwise would have had very few therapeutic options, weekly NPLD was used as salvage therapy.

Patients and Methods

We performed a systematic retrospective analysis of all 47 consecutive patients with metastatic or locally advanced breast cancer treated at the Humanitas Cancer Center (Rozzano-Milan) with weekly NPLD between 2008 and 2012. All patients provided written informed consent. All data were collected from clinical files and recorded in an-ad hoc database maintained at our Institution. Demographic/clinical parameters analyzed for each patient were: age, performance status (PS) assessed according to the Eastern Cooperative Group (ECOG) scale, sites of metastatic disease, oestrogen (ER) and progesterone receptor (PgR) status, c-erbB2 (HER-2) status, previous taxane and anthracycline exposure, number and type of previous chemo-immunotherapies and endocrine treatments.

Responses were assessed according to both radiological and clinical evaluations and graded according to standard RECIST criteria (14). We also analyzed the palliation of cancer-related symptoms during treatment with weekly NPLD.

Treatment schedule. NPLD (Myocet®, The Liposome Company, Elan Corp., Princeton, NJ, USA) was administered intravenously on an outpatient basis, with a weekly schedule, at a dose of 20 mg/m^2 over 2 h. The drug was administered until disease progression or unacceptable toxicity occurred.

Objectives and statistical analyses. The principal aim of this analysis was to assess the activity of weekly NPLD in terms of disease control rate, which is the proportion of patients with complete response (CR), partial response (PR) and disease stabilization (SD). Moreover, we aimed to evaluate the benefit on prognosis in terms of progression-free survival (PFS) and OS. PFS was calculated from the beginning of treatment to disease progression or death, whichever occurred first, or to the last visit for patients alive and with no evidence of disease progression. OS was calculated from the beginning of treatment until the date of last contact or death (any cause). Duration of response was calculated from the first evidence of PR or SD to disease progression or death.

All patients underwent physical examination and side-effect evaluation prior to each treatment administration. Toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (15).

Data are summarized as frequencies and percentages, or as the median and range. Associations between categorical data were estimated by using the continuity-adjusted Chi-square or the Fisher exact test, when appropriate. Differences between medians were evaluated by the Wilcoxon *t*-test.

Survival curves were estimated using the Kaplan–Meier method and differences between groups were evaluated by using the log-rank test. Hazard ratios with their corresponding 95% confidence intervals (95% CI) were calculated using the Cox proportional hazard regression model. Statistical significance was set at <0.05 for each analysis. All statistical analyses were carried out using the statistical software R (http://www.r-project.org/).

Results

Among 47 patients treated with weekly NPLD, 45 (96%) had metastatic disease and two patients had locally advanced breast cancer. Baseline patients characteristics and previous treatments administered are summarized in Table I.

Hormonal receptor status was positive in 31 (66%), while HER-2 was positive in nine (19.1%) cases. Two patients had locally advanced breast cancer and 41 (87%) had visceral disease, most of them with three or more sites of metastases; in four cases (8.5%) stable brain metastases were present. At the beginning of the treatment with weekly NPLD, 38 patients (80%) had a PS 0-2 and 9 (19%) had a PS of 3.

Three patients were chemonaïve; 36 (77%) had already received anthracycline chemotherapy, 26 (72%) of whom in an adjuvant setting and 10 (28%) for metastatic disease; 30 patients (64%) had already been treated with taxanes. Five patients (10.6%) received weekly NPLD as second-line treatment, and six (13%) as third-line, while 33 patients (70%) received it after three or more regimens of chemotherapy for metastatic disease. The median number of treatments prior to weekly NPLD was three (range: 0-6). Weekly NPLD was used as first- or second-line treatment in three and five patients, respectively, because of their old age/relevant comorbidities.

Activity and efficacy. Out of the 47 patients, nine (19.1%) achieved PR, and 11 (23.4%) SD for at least two months, with a global disease control rate (PR+ SD) of 42.6%. Out of the three chemonaive patients, two had PR and one had PD. Among the other seven responders, two were receiving NPLD as second-line therapy, 1 as third-line, 4 as fourth-line or more. Three (33.3%) out of the nine (19.1%) responding patients had been pre-treated with anthracyclines.

Out of the nine patients with HER-2-positive disease, six (66.6%) presented PD, two (22.2%) SD and one achieved PR

Table I. *Baseline characteristics of the patients.*

Characteristic	N	%
All patients	47	100
Median age, years (range)	60.5 (34.9-91.3)	
Histology		
Ductal	35	74.5
Lobular	4	8.5
Other	8	17
Hormone receptor status		
ER and/or PgR positive	31	66
ER and PgR negative	10	21.3
Unknown	6	12.7
HER-2 status		
Positive	9	19.1
Negative	27	57.5
Unknown	11	23.4
ECOG PS		
0	5	10.6
1	14	29.8
2	19	40.4
3	9	19.1
No. of metastatic sites		
Median (range)	2.9 (1-6)	
Visceral	41	87.2
Bone	29	61.7
Brain	4	8.5
No. of chemotherapy lines before NPLD		
Median (range)	3 (0-6)	
0	3	6
1	5	11
2	6	13
≥3	33	70
Chemo-immunotherapy before NPLD	44	93.6
Anthracycline	36	81.8
Taxane	30	68.1
Capecitabine	40	90.9
Vinorelbine	38	86.3
Gemcitabine	15	34.0
Oral cyclophosphamide and methotrexate	9	20.4
Platinum-based	5	11.3
Trastuzumab	9	20.4
No. of prior endocrine therapies for metastatic disease		
Median (range)	1.6 (0-4)	
0	14	29.8
1	10	21.3
2	9	19.1
≥3	14	29.8

ER: Estrogen receptor, PgR: progesterone receptor, HER-2: c-erbB2, NPLD: non-pegylated liposomal doxorubicin, ECOG: Eastern Cooperative Oncology Group, PS: performance status.

(11.1%). All six triple-negative patients presented PD. In 19 cases (40%), a clinical improvement of tumour-related symptoms was reported, independently of response.

Table II. *Association between treatment response and clinicopathological characteristics.*

	Response		
	PR/SD N(%)	PD N(%)	*p*-Value
All patients	20 (42.6)	27 (57.5)	
Age, years			0.310
≤60 years	17 (47.2)	19 (52.8)	
>60 years	3 (27.3)	8 (72.7)	
ER/PgR			
ER and/or PgR positive	15 (48.4)	16 (51.6)	0.059
ER and PgR negative	1 (10.0)	9 (90.0)	
HER-2			
Positive	3 (33.3)	6 (66.7)	1.00
Negative	11 (40.7)	16 (59.3)	
ECOG PS			
0-1	9 (50.0)	9 (50.0)	0.513
2-3	10 (35.7)	18 (64.3)	
Chemotherapies lines			
≤3	12 (41.4)	17 (58.6)	1.00
>3	8 (44.4)	10(55.6)	

Er: Estrogen receptors, PgR: progesterone receptors, HER-2: c-erbB2, PR: partial response, SD: stable disease, PD: progressive disease, ECOG: Eastern Cooperative Oncology Group, PS: performance status.

The association between treatment response and clinical/pathological characteristics is reported in Table II. In the univariate analysis, only hormonal receptor status had a possible association with disease response, however, this was not statistically significant (p=0.059).

Kaplan–Meier curves for PFS and OS are shown in Figure 1. PFS was 2.7 months and OS was 11.5 months. Considering responding patients, we observed improved PFS, with a gain of about two months *versus* patients not responding (4.3 *vs*. 2.0 months; p=<0.001). Patients not responding to weekly NPLD had a median OS of 9.5 months *versus* 13.6 of responders (p=0.080), as shown in Figure 2.

These results were confirmed in the multivariable model: HR ER/PgR$^+$ *vs*. ER/PgR$^-$=3.3, (95% CI=1.5-7.7, p=0.004), HR PR/SD *vs*. PD=3.5, (95% CI=1.4-8.5, p=0.007). PFS and OS stratified for baseline characteristics of the patients are shown in Table III.

At the beginning of weekly NPLD, 10 patients (21.3%) had impairment of liver function due to progressive disease: alteration of transaminases or bilirubin was classified as grade 1 in seven and grade 2 in three patients. In these last three cases, weekly NPLD was used as salvage therapy. All of these patients experienced an improvement in liver function (from grade 2 to grade 1) and thus were fit to receive subsequent treatments: two patients had paclitaxel, and one paclitaxel followed by vinorelbine. Furthermore, two patients started the treatment with pancytopenia/anemia due to medullary invasion but recovered after NPLD.

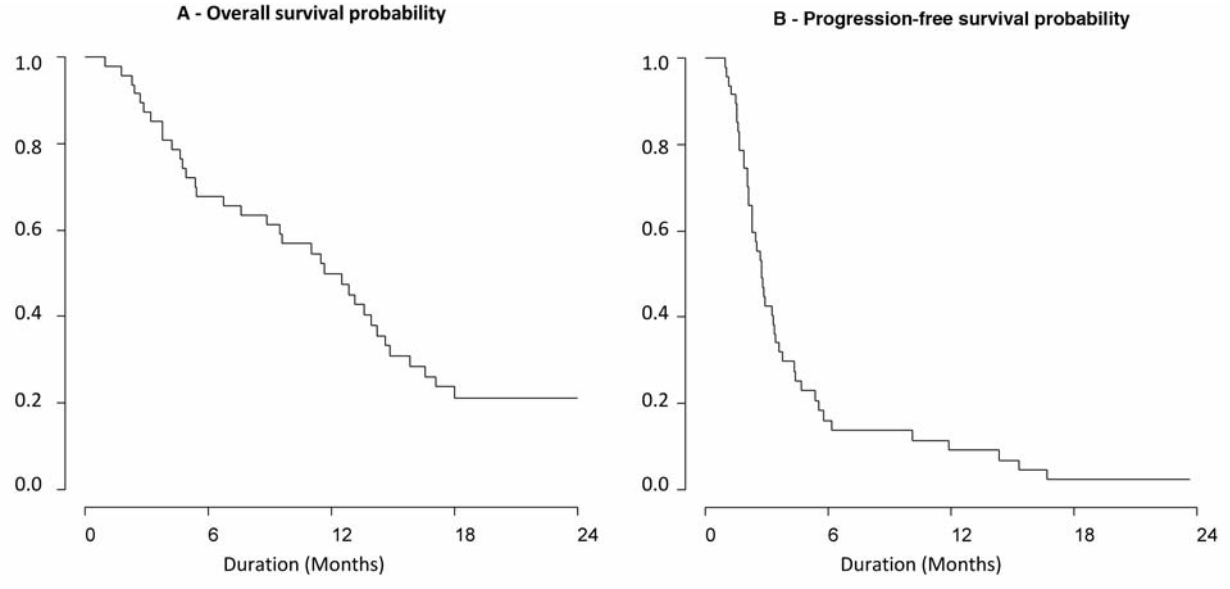

Figure 1. *Kaplan-Meier curve of overall (A) and progression-free (B) survival.*

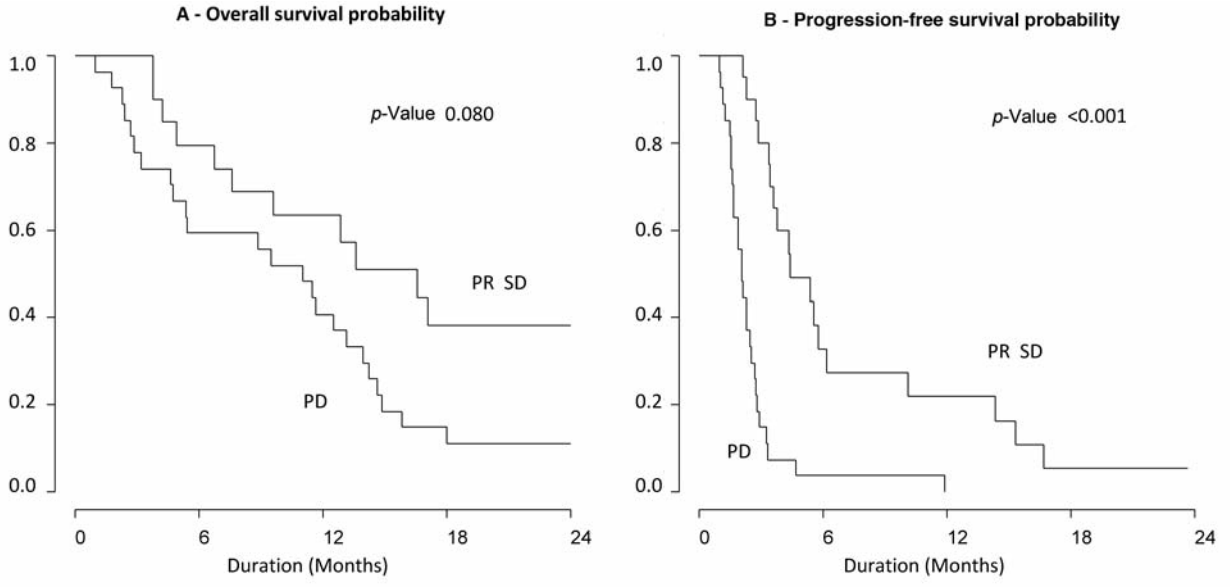

Figure 2. *Kaplan-Meier curve of overall (A) and progression-free (B) survival stratified by treatment response.*

Treatment compliance and toxicity. A total of 411 weekly NPLD treatment administrations were performed, for a median of eight weeks per patient (range=4-18). Grade 3 and 4 adverse events did not occur. Grade 2 neutropenia was observed in two patients, grade 1 in one patient. Five patients had grade 2 non-haematological toxicity (asthenia, mucositis, abdominal pain or nausea). No cardiac events were recorded.

Discussion

Longer survival, better-tolerated treatments, and several new active drugs mean that most women with metastatic breast cancer will potentially undergo multiple lines of chemotherapy. Indeed, oncologists usually treat women with metastatic breast cancer with an average of four to five lines

Table III. *Progression-free survival (PFS) and overall survival (OS) stratified by baseline characteristics of the patients.*

	Median PFS (months)	*p*-Value	Median OS (months)	*p*-Value
All patients	2.7		11.5	
Age, years		0.572		0.612
≤60 ys	2.8		12.5	
>60 ys	2.1		4.7	
ER/PgR		<0.001		0.147
ER and/or PgR positive	2.9		11.7	
ER and PgR negative	1.6		4.7	
HER-2		0.404		0.336
Positive	2.0		5.4	
Negative	2.5		11.5	
ECOG PS		0.960		0.741
0-1	2.3		9.6	
2-3	2.8		11.0	
Chemotherapy lines		0.865		0.908
≤3	2.7		12.5	
>3	2.8		9.5	

ER: Estrogen receptor, PgR: progesterone receptor, HER-2: c-erbB2, ECOG: Eastern Cooperative Oncology Group, PS: performance status, PR: partial response, SD: stable disease, PD: progressive disease.

of chemotherapy, using different regimens after anthracyclines and taxanes. The main issue is how to manage patients already exposed to multiple lines of therapy, with poor performance status, advanced age or with initial impairment of hepatic function but who still deserve more than palliative care alone.

The decision to administer further chemotherapy in this setting of patients is extremely complex because its aim is to obtain a tumour reduction and improvement of neoplasia-related symptoms minimizing chemotherapy-related toxicities at the same time. By treating patients who otherwise would have had very few therapeutic options with weekly NPLD, we obtained a disease control rate of 42.6% (19.1% PR and 23.4% SD) and an improvement of neoplasia-related symptoms in 40% of patients. Weekly NPLD was prescribed before the introduction into clinical practice of new chemotherapeutic agents such as eribulin mesylate, a non-taxane inhibitor of microtubule dynamics with a novel mode of action. Eribulin achieved a 10% response rate in two phase II studies of pre-treated patients with metastatic breast cancer, refractory to anthracycline and taxane agents after two or more other treatment lines (16, 17). In the EMBRACE study, 762 women with advanced breast cancer, who had received between two and five previous chemotherapy regimens, were randomly assigned to eribulin or physician's treatment choice (either monotherapy or supportive care) (9). In this study, the objective response rate was 12% in the eribulin arm in comparison with 5% in the arm of physician's treatment choice, with a prolongation of median survival from 10.6 to 13.1 months; the reported PFS was 3.7 months.

It is noteworthy that using weekly NPLD we achieved similar results to those with eribulin in terms of response rate, PFS and OS (which were 2.7 and 11.5 months, respectively), even if our patients were less accurately selected, reflecting daily clinical practice outside of clinical trials. Moreover, in our population, nine patients (19%) had a PS of 3, 10 (21%) had impairment of hepatic function, four had brain metastases and two had pancytopenia/anemia, while in the eribulin study, all patients had a PS of 0-2, adequate liver and bone marrow function, and no brain metastases were reported at enrolment (9).

Notably, in our population, among those who were in poor condition, three patients had a grade 2 compromised liver function which improved over time for all of them (from grade 2 to 1). Furthermore, two patients had pancytopenia/anemia, but recovered after weekly NPLD. Their improvements were so marked that they were able to receive other lines of treatment, as did other responders.

From the multivariate analysis perspective, patients who achieved PR or SD during the treatment with weekly NPLD *versus* those who progressed had a statistically significant improvement in PFS (p=<0.001) and in OS, although the latter was not statistically significant (p=0.080).

An important limitation of our study is the small sample size, which does not allow us to assuredly confirm the efficacy of weekly NPLD in specific subsets, such as those with HER-2-positive or triple-negative disease, even if the drug seems to be effective in HER-2-positive and in anthracycline-pretreated patients.

It should be noted that compared to eribulin and other chemotherapeutic treatments, such as platinum-based chemotherapy, gemcitabine, and nab-paclitaxel (7) the favourable disease control obtained with weekly NPLD in our series of patients was free of grade 3-4 haematological and non-haematological toxicities. Weekly NPLD led to a low incidence of grade 3-4 events, similar to those seen with capecitabine. The toxicity profile we observed is definitely safer than that reported for non-pegylated liposomal doxorubicin when given as single agent at a dose of 60 mg/m^2 every three weeks or in association with other drugs (18).

In our series, 40% of patients reported an important improvement of neoplasia-related symptoms while the drug was administered. This may be correlated with the timing of treatment. As a matter of fact, a weekly administration allows the physician to monitor and modulate all palliative care that can be provided together with curative treatments (steroids, antalgic therapy, *etc.*), thus improving the patient's quality of life.

A consistent number of recent pre-clinical and clinical studies support the notion that giving chemotherapy more frequently (daily, weekly or twice weekly) and at a dose

lower than the maximum-tolerated dose (MTD) can have a potentially antiangiogenic activity compared to their cyclic administration (19-21). Furthermore, recent publications on the *in vitro* activity of taxanes and vinca alkaloids at chronic, low-dose exposure, which resulted in inhibition of vessel formation and tumour growth (22, 23), support the concept that the more frequent pace of administration is crucial in conferring efficacy to this schedule of chemotherapy. Weekly paclitaxel also appeared to be more active than standard 3-weekly administration in both the preoperative (24) and metastatic (25) settings.

More and more often, weekly low-dose or metronomic therapy is the method of choice for patients for whom a long-term stabilization of metastatic disease is the main purpose, as supported by other reported experiences. In fact, it has been recently shown that metronomic administration of pegylated liposomal doxorubicin and NPLD is a feasible and active treatment for patients with pre-treated metastatic breast cancer, with a very low toxicity profile (26, 27).

According to the results of the present study, weekly NPLD could represent a very safe treatment, providing the benefit of a metronomic regimen associated with the efficacy of an anthracycline. Taking into account the high number of previous regimens, NPLD is an effective treatment, particularly suitable as salvage therapy for heavily pretreated patients with metastatic breast cancer, including those who have already received anthracyclines. Further studies in larger cohorts of patients are recommended to confirm these data.

Conflicts of Interest

None.

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