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Non-pegylated liposomal doxorubicin in combination with cyclophosphamide or docetaxel as first-line therapy in metastatic breast cancer: a retrospective analysis

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ABSTRACT

Aims and background. Anthracyclines such as doxorubicin play a central role in the management of advanced breast cancer. Unfortunately, the clinical benefits of anthracyclines are limited by cardiotoxicity that can lead to the development of potentially fatal congestive heart failure. In order to limit anthracycline-related cardiotoxicity, liposomal formulations of doxorubicin have been developed. This retrospective analysis evaluated the experience obtained with non-pegylated liposomal doxorubicin as first-line therapy in 34 patients with metastatic breast cancer.

Methods. Patients received non-pegylated liposomal doxorubicin in combination with either cyclophosphamide (n = 14) or docetaxel (n = 20) for up to eight cycles, and efficacy and safety were assessed according to standard criteria.

Results. The overall response rate was 71%. The median progression-free survival was 8 months in patients receiving non-pegylated liposomal doxorubicin plus cyclophosphamide and 13.8 months in those receiving non-pegylated liposomal doxorubicin plus docetaxel ($P = 0.2$). The most commonly observed toxicities were grade 1-2 leucopenia, alopecia, nausea and vomiting; no grade 3-4 toxicities were observed. Overall, three patients (9%) experienced grade 1 cardiac toxicity.

Conclusions. Our results support the use of non-pegylated liposomal doxorubicin as an alternative to conventional doxorubicin formulations in combination regimens for the first-line therapy of metastatic breast cancer.

Introduction

Anthracyclines such as doxorubicin play a central role in the management of advanced breast cancer. Treatment with anthracycline-containing regimens results in significant improvements in response rates and time to progression, compared with non-anthracycline regimens[1-3], and approximately 20% of patients in whom a complete response is achieved remain in remission after 10 years[4]. Combination regimens containing anthracyclines and taxanes currently represent the most active therapies available for advanced breast cancer, although the optimum combination in terms of efficacy and toxicity remains to be determined[5].

Unfortunately, the clinical benefits of anthracyclines are limited by cardiotoxicity that can lead to the development of potentially fatal congestive heart failure. Whereas this was originally outweighed by the potential benefits of treatment in patients who were at high risk of death in the short term, the improvements in survival achieved with modern regimens have made anthracycline cardiotoxicity a major concern[6]. Since the cardiotoxicity is cumulative and dose-dependent[7-9], it may be neces-

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sary to discontinue treatment in patients who could otherwise continue to benefit.

In order to limit anthracycline-related cardiotoxicity, liposomal formulations of doxorubicin have been developed. Liposomes are restricted to the vascular space at tissues with tight capillary junctions, such as the heart, but readily enter tissues where capillary junctions are disrupted by tumor growth or inflammation[10]. As a result, such formulations should deliver drug preferentially to tumor sites, thereby reducing the risk of toxic effects in the heart[11]. In randomized trials, treatment with non-pegylated liposomal doxorubicin (Myocet®, Cephalon Inc.) in patients with metastatic breast cancer resulted in comparable antitumor efficacy to conventional formulations but was associated with significantly less cardiotoxicity[12-14]. Furthermore, a Cochrane review of these studies found that non-pegylated liposomal doxorubicin was associated with a lower incidence of other major toxicities than conventional doxorubicin[15].

This paper reports a retrospective analysis of our experience with non-pegylated liposomal doxorubicin, combined with either cyclophosphamide or docetaxel, as first-line therapy in patients with metastatic breast cancer.

Material and methods

The study was a retrospective analysis of patients with metastatic breast cancer receiving first-line treatment with non-pegylated liposomal doxorubicin at a single center in Italy.

Patients

Patients were eligible for inclusion in the analysis if they were over 18 years of age and had confirmed metastatic breast cancer and a Karnovsky performance status of greater than 70%. All patients were required to have normal bone marrow reserve (granulocytes >2000/mm^3, platelets >150,000/mm^3, hemoglobin >10 g/dl), renal function (creatinine clearance >50 ml/min) and liver function (bilirubin <2 mg/dl), and a left ventricular ejection fraction (LVEF) above 50% as measured by echography. Previous adjuvant therapy with anthracyclines was allowed up to a total dose of doxorubicin ≤300 mg/m^2 or epirubicin ≤450 mg/m^2.

Patients were excluded if they had a history of active angina, myocardial infarction, or other cardiovascular disease, contraindications to the use of corticosteroids, or active infections. Written informed consent was obtained from every patient before starting treatment.

Treatment

Non-pegylated liposomal doxorubicin was given by intravenous infusion over 1 h in combination with either cyclophosphamide, 600 mg/m^2 by intravenous infusion, or docetaxel, 75 mg/m^2 by intravenous infusion. The doxorubicin dose was 50 mg/m^2 when administered with docetaxel and 60 mg/m^2 when administered with cyclophosphamide. All treatments were given on day 1 of 21-day cycles. Patients showing a major response or stable disease after the first three courses continued treatment up to a maximum of eight courses; patients with progressive disease underwent second-line chemotherapy.

Treatment was delayed for seven days if grade 3-4 hematological toxicity were present on day 21 of any cycle. Patients with grade 1 thrombocytopenia or grade 1-2 neutropenia could receive full-dose chemotherapy with concomitant steroids or a single dose of subcutaneous pegfilgrastim, 6 mg, respectively. Patients with hemoglobin concentrations between 10 and 11 g/dl received concomitant human erythropoietin. Chemotherapy was delayed and supportive therapy given in patients with grade 3-4 neutropenia, grade 2-4 thrombocytopenia, or hemoglobin concentrations below 10 g/dl. A dose reduction of 25% of Myocet® was provided in case of grade 3-4 nonhematological toxicity.

Prophylactic treatment in patients receiving non-pegylated liposomal doxorubicin plus docetaxel consisted of prednisone, 25 mg, and dexchlorpheniramine maleate, 6 mg, on the day before chemotherapy and the day of chemotherapy, with dexamethasone, 8 mg, on the day of treatment. Prophylaxis with HCl inhibitors and anti-emetic treatment with 5-HT$_3$ antagonists was also permitted.

Assessments

Baseline assessments included a complete medical history and physical examination, clinical laboratory evaluation, determination of performance status score, measurement of LVEF by echocardiography, computed tomography of the chest and abdomen or ultrasound imaging of the abdomen, bone scan and skeletal radiographs if necessary. Complete hematological and clinical chemistry evaluations, toxicity assessments, recording of adverse events, and physical examination were performed every 3 weeks, before the start of the next treatment cycle. Cardiac ultrasound monitoring was performed every three cycles.

Tumor response was evaluated by radiography every three cycles. Efficacy and toxicity were evaluated according to World Health Organization (WHO) criteria[16]. The response to treatment was classified as a complete response, partial response, or stable disease, according to standard criteria[17]. The duration of response was calculated as the time from the first confirmation of response to radiologically documented progression; time to progression was calculated as the time from the start of treatment to the date of objectively documented progression.

Statistical analysis

Time-to-event curves were constructed using the Kaplan-Meier technique and compared by logrank tests. Statistical results were considered significant at $P < 0.05$. All statistical tests were performed using SAS software.

Results

A total of 34 patients were treated between February 2003 and December 2004. Of these, 20 received non-pegylated liposomal doxorubicin plus docetaxel and 14 received non-pegylated liposomal doxorubicin plus cyclophosphamide. Overall, in the adjuvant setting, 15 patients (44%) received hormonal therapy and 22 patients (65%) had radiation therapy. Adjuvant chemotherapy was administered to 50% of patients, including doxorubicin in 7 patients (21%) with a median cumulative dose of 240 mg/m^2. Baseline demographic characteristics of the patients are summarized in Table 1. All patients were assessable for efficacy and safety.

Table 1 - Patient characteristics

	NPL doxorubicin + cyclophosphamide n = 14	NPL doxorubicin + docetaxel n = 20
Age (yr), mean (range)	54 (39-70)	48.2 (25-64)
Postmenopausal	7 (50)	11 (55)
Adjuvant chemotherapy	6 (43)	11 (55)
Adjuvant anthracyclines	2 (14)	5 (25)
Previous hormonal therapy	6 (43)	9 (45)
Adjuvant Radiotherapy	12 (86)	10 (50)
Right breast radiotherapy	8 (58)	8 (40)
Left breast radiotherapy	4 (28)	2 (10)
HER2 receptor status		
Positive	2 (14)	3 (15)
Negative	6 (43)	9 (45)
Unknown	6 (43)	8 (40)
Estrogen receptor status		
Positive	6 (43)	9 (45)
Negative	6 (43)	8 (40)
Unknown	2 (14)	3 (15)
Progesterone receptor status		
Positive	5 (36)	7 (35)
Negative	7 (50)	10 (50)
Unknown	2 (14)	3 (15)
Sites of metastasis		
Lung	3 (21)	4 (20)
Liver	1 (7)	3 (15)
Bone	1 (7)	2 (10)
≥2 sites	8 (58)	11 (55)
Not available	1 (7)	0 (0)

NPL, non-pegylated liposomal. In parenthesis, percentage.

Efficacy

The mean number of cycles per patient was 5 (range, 4-8). A total of 9 patients (64.4%) receiving non-pegylated liposomal doxorubicin plus cyclophosphamide achieved a response, of whom 3 (21.5%) achieved a partial response and 6 (42.9%) showed stable disease. In the group receiving non-pegylated liposomal doxorubicin plus docetaxel, 15 patients (75%) achieved a response: 7 (35%) achieved a partial response and 8 (40%) showed stable disease. Progressive disease occurred in 5 patients (35.6%) receiving non-pegylated liposomal doxorubicin plus cyclophosphamide and in 5 (25%) of those receiving non-pegylated liposomal doxorubicin plus docetaxel. The median progression-free survival was 8 months in patients receiving non-pegylated liposomal doxorubicin plus cyclophosphamide and 13.8 months in those receiving non-pegylated liposomal doxorubicin plus docetaxel. There was no significant difference in progression-free survival between the groups ($P = 0.2$). After a median follow-up of 15.5 months (range, 3-46), 13 patients had died of progression of disease and 21 patients were alive, 5 of whom were still in response.

Safety

The principal adverse events occurring during the study are summarized in Table 2. The most commonly observed toxicities were grade 1-2 leukopenia, alopecia, nausea and vomiting. No grade 3-4 toxicities were observed. Palmar-plantar erythrodysesthesia (hand-foot syndrome) occurred in 2 patients (10%) receiving non-pegylated liposomal doxorubicin plus docetaxel. In both cases, it resolved within 2 weeks.

Overall, 3 patients (9%) developed grade 1 cardiac toxicity. All these patients received doxorubicin in the adjuvant setting (240 mg/m^2). No patient received adjuvant trastuzumab and radiotherapy. One patient receiving non-pegylated liposomal doxorubicin plus cyclophosphamide had an asymptomatic decrease of 15 units in her LVEF to 50% at a doxorubicin cumulative dose of 540 mg/m^2. Two patients treated with non-pegylated liposomal doxorubicin plus docetaxel experienced an asymptomatic decline of resting LVEF of ≥10% but <20% of baseline value, at a cumulative doxorubicin dose of 600 mg/m^2 and 480 mg/m^2, respectively.

Discussion

The results of this retrospective analysis support the evidence from phase III randomized studies[12-14] that non-pegylated liposomal doxorubicin offers comparable antitumour efficacy to conventional doxorubicin formulations and a favorable safety profile in the first-line therapy of metastatic breast cancer. Although no patient experienced a complete response, the overall response rates achieved in these patients were higher

Table 2 - Hematological and non-hematological toxicities

Toxicity	NPL doxorubicin + cyclophosphamide n = 14	NPL doxorubicin + docetaxel n = 20	Total n = 34
Hematological			
Grade 1-2 leucopenia	10 (71)	12 (60)	22 (65)
Grade 1-2 anemia	2 (14)	8 (40)	10 (29)
Grade 1-2 thrombocytopenia	0 (0)	3 (15)	3 (9)
Non-hematological			
Nausea/vomiting	7 (50)	12 (60)	19 (56)
Alopecia	5 (36)	5 (25)	10 (29)
Mucositis	1 (7)	5 (25)	6 (18)
Diarrhea	0 (0)	2 (10)	2 (6)
Cardiac toxicity	1 (7)	2 (10)	3 (9)
Palmar-plantar erythrodysesthesia	0 (0)	2 (10)	2 (6)
Elevated transaminases	0 (0)	2 (10)	2 (6)
Hypersensitivity reactions	0 (0)	1 (5)	1 (3)

NPL, non-pegylated liposomal. In parenthesis, percentage.

than those in previous studies with non-pegylated liposomal doxorubicin in combination with cyclophosphamide[12,13] and in a study comparing non-pegylated liposomal doxorubicin plus cyclophosphamide with epirubicin plus cyclophosphamide[18]. The median progression-free survival in these patients was comparable with that achieved in previous studies[12-14,18], which also showed that the duration of survival in patients treated with non-pegylated liposomal doxorubicin is comparable with that achievable with conventional doxorubicin or epirubicin.

The number of patients included in the present analysis was too small to allow comparisons between the taxane-containing and non-taxane regimens. However, previous studies have failed to show significant advantages with taxane-containing regimens in terms of progression-free or overall survival[19-21], although some[13,19] have reported higher response rates with taxane regimens than with non-taxane-containing regimens.

Both treatment regimens were well tolerated in the present study, with no grade 3-4 toxicities. The most common adverse event was neutropenia, a finding which is consistent with previous experience in trials with doxorubicin[12,13]. Available evidence suggests that the incidence of hematological toxicity is lower with non-pegylated liposomal doxorubicin than with conventional doxorubicin formulations[12,13,15].

The incidence of cardiac damage may be further diminished by the addition of dexrazoxane, a cardioprotectant, to anthracycline-containing regimens[22,23]. A series of phase II and III studies have shown that Myocet®, both as a single agent or in combination with other drugs, is effective and safe in patients with breast cancer with an associated reduction in incidence and severity of cardiac events[12,13,24,25].

In conclusion, the potential to use doxorubicin for a longer period of time may benefit a number of patients. The present analysis supports the use of non-pegylated liposomal doxorubicin as an alternative to conventional doxorubicin formulation in combination regimens as first-line therapy in patients with metastatic breast cancer.

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