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Primary Chemotherapy with Epirubicin and Vinorelbine in Women with Locally Advanced Breast Cancer

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Abstract. *Background: To assess the activity and toxicity of primary chemotherapy with epirubicin (60 mg/m^2 every other week) and vinorelbine (25 mg/m^2, weekly) plus granulocyte colony-stimulating factor (G-CSF) for 12 weeks, in patients with locally advanced breast cancer in a multicenter setting. Patients and Methods: Patients with stage IIIA or IIIB breast cancer, not older than 70, were eligible. A two-stage phase II design was applied. Response was assessed clinically, instrumentally and pathologically. Results: Out of 48 enrolled patients, 87.5% received all planned cycles, with a median dose-intensity of 30 mg/m^2/week for epirubicin and 23.8 mg/m^2/week for vinorelbine. A clinical or instrumental objective response was reached in 42 patients (87.5%, exact 95% CI: 74.7-95.3); significant downstaging was reached in all but one patient; 6 cases had a pathological complete response in the breast, and 2 cases in the lymph nodes too (pathological complete response rate 4.2%, exact 95% CI: 0.5-14.2); a further 2 patients had only microscopic cancer foci at pathological examination of the breast. Radiological tests underestimated the treatment effect on the breast. Toxicity was mild, neutropenia being the most frequent (grade 3-4 in 47% of patients), but never complicated with fever or sepsis. Mild constipation (≤grade 2) occurred in 35% of patients. Moderate to severe asthenia occurred in 12% of 6 patients. No cardiac toxicity was reported. At 3 years, disease-free survival was 68% and overall survival 81%. Conclusion: Primary chemotherapy with epirubicin every other week, weekly vinorelbine and G-CSF support is highly active and well tolerated in patients with locally advanced breast cancer.*

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Locally advanced breast cancer includes a heterogeneous group of neoplasms (stages IIIA and IIIB), representing roughly 10% of all primary breast cancers (1). Prognosis is poor after treatment with surgery and/or radiotherapy, the 5-year survival rate being less than 20%. With locoregional therapy alone, systemic metastases generally develop rapidly, indicating that most of the patients already have micrometastases at presentation. For these reasons, primary chemotherapy has become the treatment of choice for inoperable patients (2) and is also currently proposed as a possible therapeutic strategy in patients with operable breast cancer (3). Preoperative chemotherapy leads to a significant reduction in tumor size and improves the rate and the cosmetic results of breast conservative surgery. Another aim of preoperative chemotherapy is to improve systemic control of the disease by eradicating distant micrometastases. In fact, chemotherapy, administered to laboratory animals before surgery, has proved to decrease the proliferation of neoplastic cells and to suppress cancer growth (4).

The response of the primary tumor represents a relevant prognostic factor as well as an important test of chemosensitivity *in vivo*, since it provides direct information on clinical efficacy regarding the administered drugs. The first studies on primary chemotherapy, carried out with anthracycline-based regimens, in the treatment of locally advanced breast cancer, showed objective response rates between 47% and 86%, with clinical complete responses between 8% and 23% and pathological complete responses in 8-10% of the patients (5-9). The combination of

anthracyclines with new drugs, such as taxanes and vinorelbine, has led to an increase in objective responses (77-93%) and clinical (20-48%) or pathological (5-28%) complete responses (10-14).

Vinorelbine has proved to be very active as a single agent and in combination in advanced breast cancer as first-line (15-22) and second-line therapy (23-25). We showed that the dose intensity of vinorelbine could be increased by giving the drug without interruption in weekly doses of 25 mg/m^2 and concurrently using the granulocyte colony-stimulating factor (G-CSF). With such a schedule, an objective response rate of 52.5% was obtained in 40 heavily pretreated patients (25). Despite the increased dose intensity achieved, vinorelbine toxicity, never exceeded grade 2 and neurological toxicity, assessed clinically and electromyographically, was likewise mild and completely reversible (26). Moreover, in a previous study, we had demonstrated the activity and tolerability of the combination of epirubicin and vinorelbine plus G-CSF in a weekly schedule. A 77% objective response rate was obtained in 52 previously untreated patients, with 19% complete response. The median response duration and time to progression were both 10 months; median survival was 31 months; toxicity was acceptable (22).

Thus, a multicenter phase II study was planned to test the activity and safety of an intensive epirubicin and weekly vinorelbine schedule plus G-CSF as neoadjuvant treatment in locally advanced breast cancer.

Patients and Methods

Eligibility criteria were: cytologically confirmed locally advanced non-inflammatory breast cancer (T3 or T4 or T2 with major diameter ≥3 cm), measurable disease (at least one lesion measuring ≥2cm x 2 cm), no previous treatment for breast cancer, age ≤70 years, and ECOG performance status ≤2. Other requirements were: adequate bone marrow function (hemoglobin ≥9 g/dl, white blood cell count ≥ 3500 mm^3 with neutrophils ≥2000 mm^3, platelet count ≥100,000 mm^3 and hemoglobin ≥10/g/dl); normal liver and renal function (bilirubin, GOT, GPT, ALP and serum creatinine not higher than 1.25 times the upper limit of the normal value); no history of angina, myocardial infarction, left bundle branch block, or congestive hearh failure; left ventricular ejection fraction (LVEF) ≥50% (measured with nuclear or ultrasonic methods); written informed consent.

Before entering the study, each patient underwent a physical examination, complete biochemistry (including tumor markers) and blood cell count, ECG and LVEF measurement, bilateral mammography, chest X-ray, bone scan, abdominal and axillary ultrasound, and cytological or histological confirmation of diagnosis. Clinical assessment of the tumor lesions had to be repeated every two cycles; instrumental restaging was planned after completion of the whole treatment course (6 cycles). Blood count and platelet tests were repeated weekly, complete biochemical screening plus EKG were carried out every four weeks, and LVEF was re-assessed before surgery.

One cycle included administration of epirubicin on day 1, as an *i.v.* bolus of 60 mg/m^2, and vinorelbine on days 1 and 8, as a 10-min *i.v.* infusion of 25 mg/m^2/week in 50 ml of normal saline. There was no interval between cycles (*i.e.* the second cycle started on day 15); overall, 6 cycles were planned, corresponding to 12 weeks of treatment. G-CSF at the dose of 150 μg/m^2 *s.c.*, on days 2, 4, 9 and 11 of each cycle, was included in the treatment schedule. Emesis was prevented with 8 mg of ondansentron given *i.v.* before chemotherapy plus 8 mg of dexamethasone administered *i.v.* after the vinorelbine infusion. Surgery was planned two weeks after the discontinuation of chemotherapy. The choice of the surgical treatment depended on the individual centers participating in the study. After surgery, six cycles of adjuvant (postoperative) CMF were delivered to all women. Breast irradiation was administered at the end of adjuvant chemotherapy in patients with conservative surgery. Treatment with tamoxifen (20 mg/die for 5 consecutive years) was also planned after adjuvant CMF in all women, except for premenopausal patients with negative receptors.

Toxicity was assessed according to WHO criteria (27). Asthenia and myalgia (treatment- and G-CSF-related) were graded as absent, mild, moderate or severe. No dose reductions were made for toxicity. For hematological toxicity of grade 2 or more, treatment was interrupted until the WBC count was restored to 2500/mm^3 and the neutrophil count was higher than 1500 mm^3. With non-hematological toxicity in excess of grade 2, treatment was suspended until recovery to WHO grade 0 criteria. For WHO grade ≥ 2 cardiac toxicity, treatment was withdrawn. All patients receiving at least one administration of chemotherapy were considered evaluable for safety.

Clinical assessment of tumor shrinkage was done every two cycles. At the end of the treatment, before surgery, a complete clinical and instrumental restaging was planned. Clinical objective response was used as the main outcome measure, assessed by measuring the reduction in the product of the two largest diameters. Complete response was defined as a complete disappearence of all evidence of disease. Partial response was defined as a 50% or greater reduction in the sum of products of the perpendicular diameters of all measurable masses. No change was defined as a less than 50% regression and no more than 25% increase in the sum of the products of the perpendicular diameters of all the tumor masses. Progressive disease was defined as an increase ≥ 25% in the product of the two largest diameters or the appearance of a new disease manifestation, locally or in distant anatomic sites (28).

The one-sample multiple testing procedure for phase II trials, described by Fleming (29), was used with the following parameters: minimum acceptable response rate (p_0) of 0.30, auspicated response rate (p_1) of 0.50, two steps planned, type I error (α) of 0.037, type II error of 0.08. Under these conditions, the first test was planned after 30 patients had been treated; if 16 or more repsonses were obtained, the trial could be closed and the treatment defined interesting for further phase III testing; if less than 16 but more than 9 responses were obtained, 30 more patients had to be enrolled. The second test was eventually planned after the treatment of 60 patients; at least 26 responses were required to define the treatment as active and worthy of entering a phase III evaluation.

The dose intensity (mg/m^2/week) was calculated for the two drugs as described by Hryniuk (30). Progression-free survival was calculated as the time elapsed from the date of enrollment to the date of local recurrence, or distant metastasis or death without

Table I. *Patient characteristics.*

No. of patients:	48
Age, years:	
Median	48.5
Range	31-70
Performance status (ECOG):	
0	45 (94%)
1	3 (6%)
Menopausal status:	
Premenopausal	24 (50%)
Postmenopausal	24 (50%)
Stage:	
III_A	21 (44%)
III_B	27 (56%)
Primary tumor:	
T_3	21 (44%)
T_4	27 (56%)
Lymph nodes:	
N_0	8 (17%)
N_1	32 (67%)
N_2	8 (17%)
Tumor size (cm)	
Median	8
Range	(4-18)

Table II. *Post-treatment characteristics of tumor.*

Pathological stage:	
0	2 (4%)
I	7 (14%)
IIA	26 (54%)
IIB	12 (25%)
Pathological T category:	
pT0	6 (12%)
pT1	25 (52%)
pT1mic	3 (6%)
pT1a	1 (2%)
pT1b	4 (8%)
pT1c	17 (35%)
pT2	14 (29%)
pT3	2 (4%)
pT4	1 (2%)
Number of metastatic nodes:	
0	15 (31%)
1-3	15 (31%)
4-9	10 (21%)
≥10	8 (16%)
Estrogen receptors:	
Positive	18 (37%)
Negative	24 (50%)
Unknown	6 (12%)

recurrence, whichever occurred first. Overall survival was calculated as the interval between the date of enrollment and the date of death or last follow-up information for alive patients. Progression-free and overall survival were calculated according to the Kaplan-Meier method (31).

Results

Between January 1997 and January 1998, the first 30 patients were enrolled. At clinical assessment, there were 9 complete and 19 partial responses and 2 stable disease. Thus, the study was closed with a positive outcome. Thereafter, participating centers decided to continue the enrollment, in view of the highly positive results and to increase the precision of activity estimates. The enrollment was closed as of August 1998, with 48 patients enrolled. Results are reported for the whole group of patients, with a median age of 48.5 years (range 31-70). Patient characteristics are given in Table I.

Forty-two patients (87.5%) received the 6 planned cycles, 3 received 5 and 3 received 4 cycles. Overall, 279 cycles were given. Treatment was delayed because of hematological toxicity in 30 courses (11%) and for unrelated causes in 6 cases (2%). The administered dose intensity was 30 mg/m^2 per week for epirubicin and 23.8 mg/m^2 week for vinorelbine, representing 100% and 95.8% of the theoretical dose, respectively.

Combining clinical and radiological (mammography and ultrasound) assessment, 42 patients showed an objective response (87.5%, exact 95% CI: 74.7-95.3) that was complete in 14 (29.2%, exact 95% CI: 17.0-44.1). Comparing clinical stage before and after treatment, a downstaging was observed in all but one patients. Thirty-five (72.9%) post-treatment cases were considered as candidate for surgery *ab initio* (*i.e.* up to stage IIA).

All patients underwent surgery, that was conservative (quadrantectomy) in 7 cases (14.6%). Among 14 patients for which clinical examination suggested a complete response (29.2%, exact 95% CL: 17.0-44.1), 6 cases resulted as pathological complete response in the breast, in 2 cases with concurrent complete response in the axilla (pathological complete response rate 4.2%, exact 95% CL: 0.5-14.2); a further 2 patients had only microscopic cancer foci at pathological examination of the breast. Radiological tests tended to underestimate the treatment effect on the breast and never suggested complete response. The pathological tumor stage and number of metastatic nodes assessed at pathology after definitive surgery are summarized in Table II.

Table III. *Worst WHO grade of toxicity per patient and per cycle.*

	Per patient (n=48)				Per cycle (n =270)			
	G1	G2	G3	G4	G1	G2	G3	G4
Neutropenia	7 (14%)	12 (25%)	20 (41%)	3 (6%)	32 (12%)	43 (16%)	28 (10%)	6 (2%)
Anemia	21 (43%)	10 (20%)	3 (6%)	-	74 (27%)	19 (7%)	6 (2%)	-
Thrombocytopenia	-	1 (2%)	-	-	4 (1%)	2 (1%)	-	-
Nausea/vomiting	23 (47%)	10 (20%)	1 (2%)	-	106 (39%)	26 (10%)	1 (<1%)	-
Mucositis	8 (16%)	3 (6%)	-	-	16 (6%)	4 (1%)	-	-
Constipation	12 (25%)	5 (10%)	-	-	45 (16%)	10 (4%)	-	-
Diarrhea	1 (2%)	1 (2%)	-	-	1 (<1%)	2 (1%)	-	-
Neuropathy	3 (6%)	-	-	-	6 (2%)	-	-	-
Fatigue	22 (45%)	5 (10%)	1 (2%)	-	89 (33%)	15 (5%)	1 (<1%)	-
Phlebitis	2 (4%)	5 (10%)	1 (2%)	-	9 (3%)	4 (1%)	2 (1%)	-
Alopecia	-	17 (35%)	31 (65%)	-				

All patients were assessed for toxicity. Out of 279 administered cycles, toxicity information were available for 270 and is summarized in Table III. Neutropenia was the most frequent toxicity and was severe (grade 3-4) in 47% of patients; however, there were no episodes of febrile neutropenia or neutropenic sepsis. Anemia reached grade 3 in 6% of patients; thrombocytopenia was reported in 1 patient only. Non-hematological toxicity was mild. Only 1 patient suffered grade 3 vomiting despite antiemetic therapy; mild constipation (≤ grade 2) occurred in 35% of patients. Moderate to severe asthenia occurred in 6 patients (12%). Grade 2 and 3 alopecia was seen in all patients. Alteration of the left ventricular ejection fraction was never observed.

After a 39-month (range, 14-83) median follow-up of alive patients, 20 (41.7%) suffered progression of disease, median disease-free survival was 46 months and the probability of being event-free after 3 years was 0.68. In addition, 14 (29.2%) patients died, 2 because of car accidents; the median survival was 76 months and probability of being alive after 3 years was 0.84 (Figure 1).

Discussion

Primary chemotherapy is part of the multidisciplinary treatment for locally advanced breast cancer. The aims of primary chemotherapy are to reduce the tumor mass, to allow surgery and to act on micrometastasis. At the moment, there is no standard chemotherapeutic regimen, but anthracyclines represent the main drug in several combinations. Epirubicin and vinorelbine are two very active drugs in the treatment of breast cancer. The significant efficacy of the combination in metastatic disease (20-22) has led to the use of the two drugs for locally advanced cancer.

In the present study, the association of epirubicin and vinorelbine, in a weekly schedule with G-CSF, resulted active and safe in a group of patients with stage IIIA and IIIB breast cancer. Despite the unfavorable baseline characteristics of the enrolled patients (initial median tumor size of 8 cm with clinically positive lymph nodes in 84% of patients), we obtained a high rate of clinical remission (87.5% including both partial and complete and 29.2% including only complete clinical responses). This result was significantly better than the minimum requirements used for the study plan, and was reinforced by the fact that no patients had disease progression during treatment and only 3 had stable disease. Two patients had a complete pathological response (4.2%) both in the breast and the axilla, but a further 4 patients had pathological remission in the breast for an overall rate of pathological response in the breast of 12.5%; in addition, a further 2 patients had only microscopic cancer foci following the treatment.

The present data compare well with the results obtained with other drugs and schedules in the treatment of locally advanced breast cancer. Moliterni *et al.* (12), in a group of 32 patients with locally advanced breast cancer treated with adriamycin and paclitaxel, obtained 31% clinical complete response, 9.3% (3/32) pathological complete response and 28.1% (9 patients) residual disease of ≤ 2 cm. Von Minkwitz *et al.* (14) treated 42 patients, 20 with stage IIIA and IIIB disease, with the combination of docetaxel and doxorubicin. Clinically complete responses were reported in 33% of all patients, with 5% pathological complete responses. More recently, with a combination of epirubicin and docetaxel, de Matteis *et al.* reported a 77% clinical response rate and 13% pathological complete responses out of 30 patients with large operable or locally advanced breast cancer (32).

Assessment of response after neoadjuvant treatment of locally advanced breast cancer is a complex issue. In this series, clinical examination overestimated the treatment effect, considering that only 6 out of 14 patients who were defined as complete responders had a pathological complete remission in the breast and only 2 also had complete remission in the axillary nodes. On the other hand,

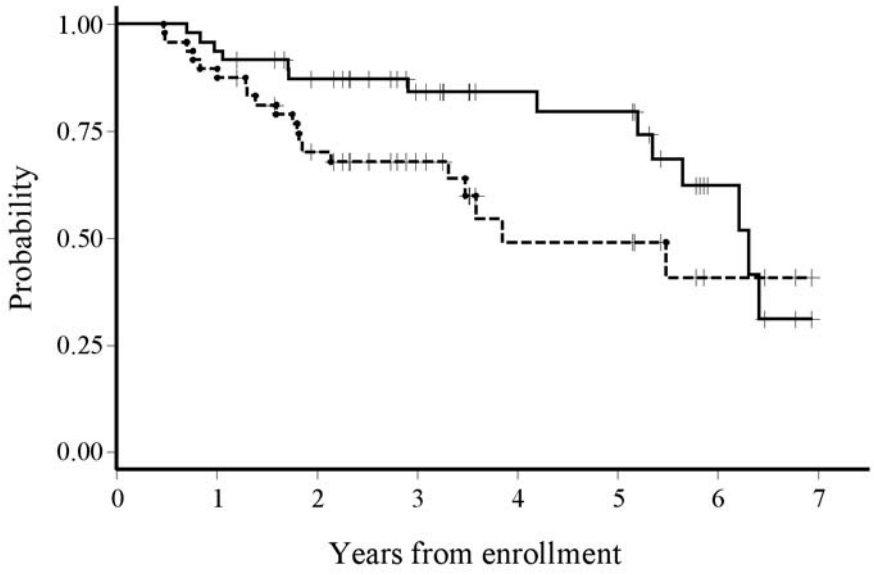

Figure 1. *Kaplan-Meier estimated disease-free survival (dashed line) and overall survival (solid line) curves. Crosses indicate censoring times.*

mammography and US combined underestimated the treatment effect, considering that in no cases did they suggest complete remission either in the breast or the axilla. More recent techniques, such as MRI and PET, could prove much more useful in this field (33, 34).

As regards toxicity, the schedule adopted in this trial was well tolerated. Thanks to the use of G-CSF, severe grade 4 neutropenia was experienced by only 6% of patients, and was never complicated by fever or infection. Anemia was manageable and thrombocytopenia negligible. All other toxicities were almost never severe, with grade 3 vomiting and fatigue in 1 patient only. No signs of cardiac toxicity were reported.

Weekly administration allows clinical application of the dose-density theory (35), with the more frequent dosing made possible by the concurrent use of hematopoietic growth factors such as G-CSF. A dose-dense weekly schedule assures that more drug is given per unit of time, resulting in the death of a greater number of cancer cells. In addition, the theoretical superiority of dose-density may be related to the temporal limits imposed on regrowth between cycles (36, 37).

Several issues are still pending regarding weekly administration of primary chemotherapy in breast cancer: the impact of new drugs, duration of treatment, effect on disease-free and overall survival, and impact on subsequent adjuvant chemotherapy. As for the latter point, the combination of epirubicin and vinorelbine, which we found active and safe in the present study, allows the planning of non cross-resistant taxane-based treatments in the adjuvant setting. Based on this rationale, a pilot study of neoadjuvant epirubicin plus vinorelbine plus G-CSF, followed by surgery and adjuvant weekly paclitaxel plus 5-fluorouracil, is ongoing.

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