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First-line Chemotherapy with Fluorouracil-Epirubicin-Navelbine (FEN) Combination in Advanced Breast Cancer

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Abstract. *Background: A phase II study was carried out to determine the safety and efficacy of the combination of vinorelbine, epirubicin and 5-fluorouracil (FEN) as first-line chemotherapy in advanced breast cancer (BC). Patients and Methods: Thirty-four women with advanced BC, aged 32-75 years (median 59), previously untreated for recurrence, were enrolled in the study. The treatment consisted of fluorouracil 600 mg/m^2 on day 1, epirubicin 75 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8, every 3 weeks, up to a maximum of 9 cycles. Results: The efficacy appeared favourable with 18 objective responses (3 complete and 15 partial) and 9 disease stabilizations, giving an overall response rate of 53% (95% CI: 36-70). The median progression-free and overall survival was 6 and 18 months, respectively (95% CI: 4.8-7.8 and 16.2-22.2, respectively). Toxicity was acceptable; the main grade 3/4 toxicity was alopecia in 94% of patients, neutropenia in 44% and less frequently gastrointestinal toxicity (9%), anaemia (6%), mucositis (6%), thrombocytopenia (3%) and diarrhoea (3%). No treatment-related death occurred. Conclusion: Our results suggest that FEN, as first-line chemotherapy, is an active and well-tolerated treatment for patients with advanced breast cancer.*

Breast cancer (BC) is one of the most common malignancies and a major health problem worldwide (1-4). Although generally sensitive to initial treatment, resistance emerges as the disease progresses. First-line chemotherapy for advanced BC has been a field of ongoing controversy (5). Research is focusing on active, highly effective, yet better tolerated regimens.

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Navelbine (vinorelbine) is a semi-synthetic vinca alkaloid, acting by mitotic inhibition; it is one of the most active agents in BC, with a single- agent response rate in first- and second-line treatment of 40-50% and 30-40%, respectively (6-10). Epirubicin is one of the most active drugs against advanced BC, actually established as a major component of adjuvant chemotherapy for BC. Fluorouracil (5-FU) is an antimetabolite that has also been long known for its activity in advanced BC.

Many phase II and III trials have been conducted combining navelbine with anthracyclines, yielding objective response rates and survival exceeding 70% and 20 months, respectively (11-15). Also, navelbine has been combined with 5-FU in several phase I and II trials in advanced BC with encouraging results (16-20).

Based on the established activity and safety of the 5-FU, epirubicin and cyclophosphamide (FEC) regimen, the present study substituted epirubicin for doxorubicin, to decrease cardiac toxicity, and navelbine for cyclophosphamide. The combination of these agents seems reasonable, since they are known to have important single-agent activity in BC, different mechanisms of action and, apart from myelosuppression, no major overlapping toxicities.

The current phase II study was planned to investigate the safety and efficacy of the above combination (FEN) as first-line chemotherapy in advanced breast cancer.

Patients and Methods

Study design. The study was designed and conducted at a single hospital oncology center, between November 1996 and December 1997. Female patients with advanced BC received FEN. Independent Institutional Ethics Committee approval was obtained before enrolment of each patient into the study, which was performed in accordance with the Declaration of Helsinki, its subsequent amendments and applicable regulatory requirements. Written informed consent was obtained from all patients prior to study entry.

Patients. Thirty-four female patients, 18 years of age or older, with histologically or cytologically confirmed recurrent locoregional

and/or metastatic advanced BC, were eligible for enrolment. Patients were required to have measurable or assessable disease according to World Health Organization (WHO) criteria and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

Patients were excluded if they presented any contraindication for treatment with FEN. Women of childbearing potential were required to maintain effective contraception. Pregnant and/or lactating women were excluded, as were patients receiving any of the investigated drugs within 1 month before trial entry. Patients with any uncontrolled serious illness, uncontrolled central nervous system (CNS) metastases, or invasive malignancy besides BC were also excluded. Patients treated with adjuvant chemotherapy or radiotherapy earlier were included, as well as women treated with hormonal therapy, but no other prior systemic chemotherapy was allowed.

Study treatment. The patients received 600 mg/m^2 5-FU on day 1 every 21 days, as a bolus *i.v.* infusion; 75 mg/m^2 epirubicin on day 1 every 21 days, given as a 5-min *i.v.* infusion diluted in 50 ml of normal saline; 25 mg/m^2 navelbine on days 1 and 8 every 3 weeks, as a 5-min *i.v.* infusion diluted in 100 ml of normal saline. The patients were fully informed of the treatments they were receiving and necessary precautions and advisory information were given. Initially, the treatment was planned for up to a maximum of 9 cycles, depending on previous exposure to anthracyclines in the adjuvant setting.

Safety and efficacy analysis. A full medical history was obtained for all patients at study entry. Physical examination, vital signs, performance status, body weight, haematology and blood chemistry were performed at entry and immediately prior to each FEN administration. The supervising clinician assessed the objective tumour response according to WHO criteria. Safety was determined from changes in vital signs, physical findings and laboratory test results, as well as by questioning the patient with respect to unusual or unexpected signs or symptoms. LVEF and cardiac function were determined regularly either by echocardiography or by MUGA scan. Adverse events were graded according to the National Cancer Institute common toxicity criteria (NCI-CTC, version 2.0). Patients were withdrawn from the study if they developed a LVEF value of <40% or an absolute decrease in LVEF of >15%, or New York Heart Association (NYHA) Class III or IV cardiac dysfunction, or experienced a life-threatening, infusion-related reaction to the first or subsequent doses of FEN.

Statistics. Survival analysis (disease-free and overall) was performed by constructing Kaplan-Meier PFS (progression-free survival) and OS (overall survival) curves (21), where differences between curves were evaluated by the log-rank test. PFS time (months) was defined as the time-interval between the date of surgery and the date of identification of recurrent or metastatic disease. OS time (months) was defined as the time-interval between the date of surgery and the date of death.

Results

Demographics, disease characteristics and patient disposition. The baseline patient demographic information is summarized in Table I. A total of 34 female patients with a median age of 59 years (range 32–75 years) and recurrent locoregional and/or metastatic BC were enrolled. All 34 patients were treated first-line (prior adjuvant chemotherapy allowed), among which 12 (35%) patients had previously received cyclophosphamide-methotrexate-5'-fluorouracil (CMF)-based adjuvant chemotherapy and 17 (50%) had received anthracycline(AC)-based chemotherapy (Table II). Twenty-eight patients had been previously treated with radiotherapy, 27 in the adjuvant setting and 1 for metastatic disease (Table II). Twenty-three patients had been previously treated with hormonal therapy, all in the adjuvant setting (Table II). In addition, 7 (20%) of the patients were premenopausal, 6 (18%) perimenopausal and 21 (62%) postmenopausal (Table II).

Table I. *Patient characteristics.*

Characteristic	No. of patients (%)
Number of patients registered	34
Gender	
Female	34 (100)
Male	0 (0)
Age (years)	
Median	59
Range	32-75
Menopausal status	
Premenopausal	7 (20)
Perimenopausal	6 (18)
Postmenopausal	21 (62)
Histology	
Ductal	29 (85)
Lobular	5 (15)
ECOG performance status	
0	19 (56)
1	13 (38)
2	2 (6)

Treatment results. A total of 206 cycles were administered (range 2–9, median 5.5). Treatment discontinuation was necessary in 11/34 (33%) patients due to either progression of the disease (8; 24%) or toxic side-effects (3; 9%) (Table III). The relative dose intensity delivered for epirubicin, navelbine and 5-FU was 92.5%, 93.6% and 92.1%, respectively.

Safety. Mainly grade 1/2 haematological and non-haematological adverse events occurred, appearing in 32/34 patients. There were 17 (50%), 10 (29%) and 3 (9%) episodes of grade 1/2 neutropenia, anaemia and thrombocytopenia, respectively, during the administration of 206 cycles. Grade 1/2 non-haematological events consisted of gastric and skin toxicity, alopecia, mucositis, diarrhoea and cardiac dysfunction, that appeared in 20 (59%), 12 (35%), 2 (6%), 8 (24%), 3 (9%) and 3 (9%) patients, respectively.

Table II. *Disease recurrence and pretreatment characteristics.*

Characteristic	No. of patients (%)
Disease recurrence	
Local recurrence	10 (29)
Soft tissue metastasis	12 (35)
Bone metastasis	15 (44)
Lung metastasis	12 (35)
Liver metastasis	16 (47)
CNS metastasis	2 (6)
Number of metastatic sites	
1	14 (41)
2	17 (50)
3	3 (9)
Prior adjuvant chemotherapy	
CMF-based	12 (35)
Anthracyclines (AC)	17 (50)
Prior radiotherapy	
Adjuvant	27 (79)
Metastatic	1 (3)
Prior hormonotherapy	
Adjuvant	23 (68)
Metastatic	0 (0)

Table III. *Treatment interruptions and complications.*

Causes of interruption	No. of patients (%)
Progression	8 (24)
Toxicity	3 (9)
Deaths	3 (9)

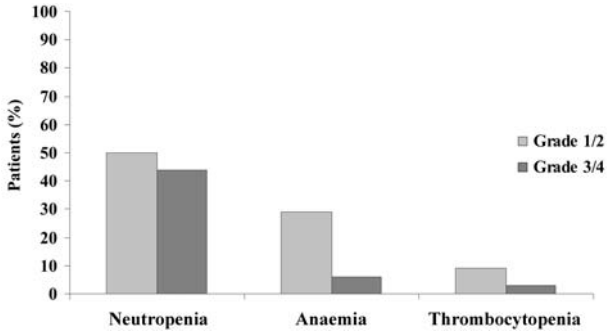

Figure 1. *Non-haematological adverse events (all grades).*

The main dose-limiting adverse effect was grade 3/4 neutropenia, which was seen in 15/34 (44%) patients. Grade 3/4 alopecia appeared in 32/34 patients (94%). In addition, in 3/34 patients (9%) cardiac toxicity occurred. The non-haematological and haematological adverse events are summarized in Figures 1 and 2, respectively.

At the time of analysis, 31 out of 34 patients (91%) had died, attaining an average overall survival rate of 17.4 months (95% CI 14.4-20.3; median=18 months). Of 3 patients alive at the time of analysis, 1 had shown complete response (CR) after 6 cycles, while the other 2 showed partial response (PR) after 9 cycles; all 3 had completed the planned treatment.

Efficacy. The median progression-free survival for all patients was 6 months (Figure 3), whereas the median overall survival for all patients was 18 months (95% CI of the mean: 16.2-22.2) (Figure 4). The clinical responses, evaluated after ≥2 cycles of treatment, are shown in Table IV. There were 18 clinical responses (3 CR, 15 PR) and 9 disease stabilizations, yielding an overall response rate of 53% (95% CI of the mean: 36-70). Complete and partial response was seen in 1/10 (10%) and 3/10 (30%) patients, respectively, with local recurrence and in 3/33 (9%) and 15/33 (45%) cases, respectively, with distant metastasis. The median time to progression in patients showing CR, PR and stable disease (SD) was 13, 9 and 4 months, respectively, (Figure 5), whereas the average time to progression in patients that showed recurrence was 6.12 months (95% CI 4.61-7.62; median=6 months). The overall survival time in patients showing CR, PR and SD was 36, 24 and 14 months, respectively (Figure 6).

Discussion

Advanced BC is heterogenous in terms of its course and chemosensitivity. Moreover, to date there is no gold standard chemotherapy regimen. Therefore, any research concerning the clinical evaluation of new regimens and new combinations, that will maximize tumour response and minimize the toxicity of the treatment, is valuable.

In this phase II study, designed in 1996, the safety and efficacy of the FEN regimen was assessed in patients with advanced BC, as first-line chemotherapy. Previous studies had shown that a combination of navelbine with either anthracyclines or fluorouracil was very well-tolerated and highly active in the treatment of BC (11-19). Spielmann *et al.* (11) reported a high response rate by combining doxorubicin and navelbine in previously untreated BC. Yet, since 5-fluorouracil enhances the antitumour activity of navelbine, Guler *et al.* in 2000 (22), then Elomaa *et al.* in 2003 (23) and, more recently, Berruti *et al.* in 2005 (24), also carried out clinical trials, testing the tolerability and efficacy of this three-drug regimen, with various schedules.

In our study, the main haematological and non-haematological toxicities were grade 1/2, in 32/34 patients.

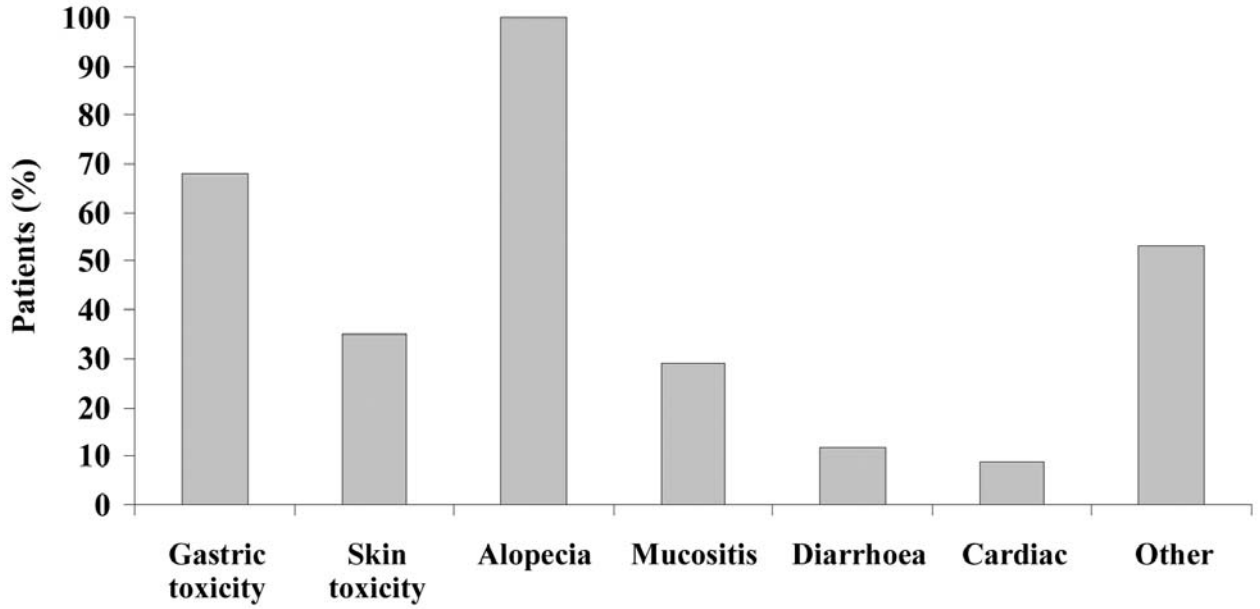

Figure 2. *Grade 3/4 haematological adverse events.*

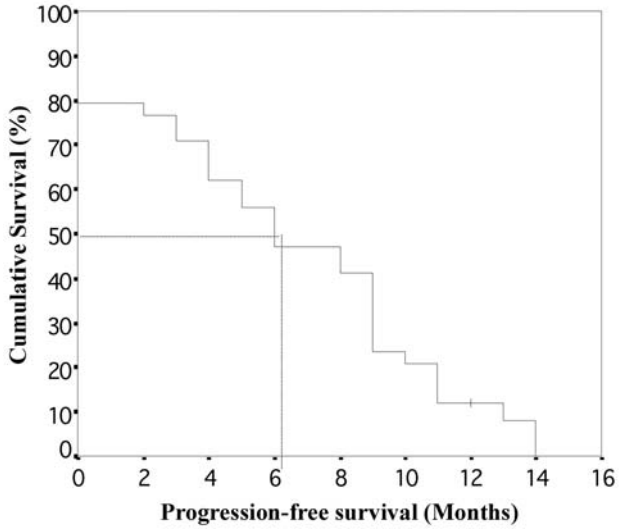

Figure 3. *Kaplan -Meier progression-free survival curves in whole study population.*

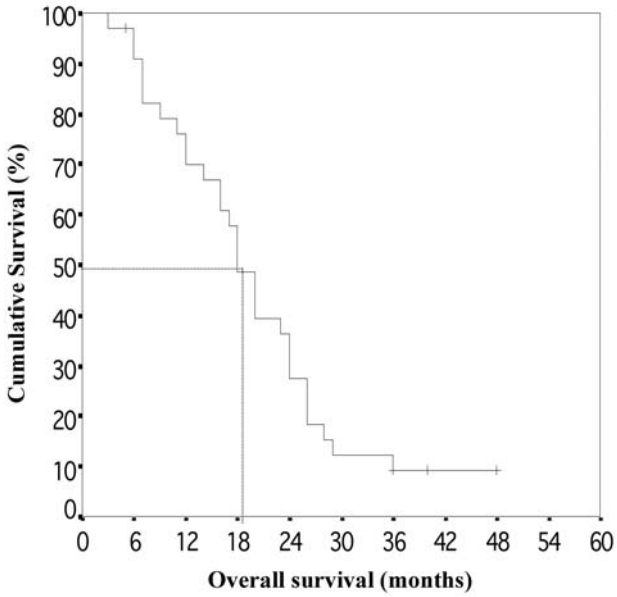

Figure 4. *Kaplan -Meier overall survival curves in whole study population.*

Grade 3/4 toxicity included mainly neutropenia and alopecia and, for a minority of patients, anaemia, thrombocytopenia, gastrointestinal, mucositis and diarrhoea. It is noteworthy that only 3 cases of cardiac dysfunction (grade 1/2) occurred, 1 of them in a patient treated with adjuvant anthracycline-based chemotherapy. Therefore, the toxicity of this regimen was acceptable and similar to that described in the study of Berruti *et al.* (24), but lower than that reported by Elomaa *et al.* (23).

Eighteen of our patients responded objectively, including 3 patients with CR and 15 with PR, yielding an overall response rate of 53%, which is lower than that of other phase II trials using the same combination (22-24). This discrepancy could be attributed to different patient populations, as well as different treatment schedules and doses. Patients enrolled in our study had significant tumour burden, most of them with visceral metastasis and 2 or more

Table IV. *Clinical response and survival (n=34).*

Response	No. of patients	% of patients
Overall response	18	53 (CI: 36-70)
Complete response	3	9
Partial response	15	44
Stable disease	9	26
Disease progression	7	21
Median (months)	Mean; 95% CI	
Time to progression	6	6.3 (4.8-7.8)
Overall survival	18	19.2 (16.2-22.2)

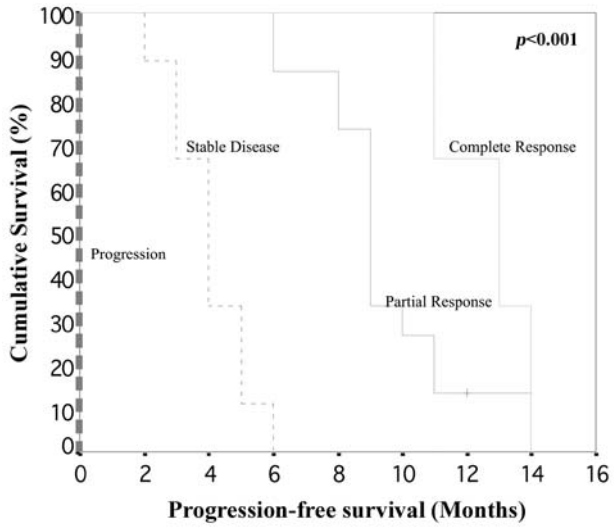

Figure 5. *Progression-free survival regarding the clinical response to the therapy.*

metastatic sites (Table II), therefore representing a dismal prognosis population. Moreover, the study of Berruti *et al.* (24) included only anthracycline-naïve patients, whereas 50% of our patients had been exposed to anthracyclines in the adjuvant setting.

Finally, given the at least equivalent results of studies using epirubicin or doxorubicin and navelbine combinations (11, 12, 14, 15), one might speculate that fluorouracil offers a minor contribution to the combination and could possibly be omitted, minimizing additional toxicity. However, this issue should be assessed in larger studies.

In conclusion, the results of this study suggest that the FEN combination is an active and well-tolerated first-line chemotherapeutic regimen and, therefore, a good option for the treatment of women with advanced BC. Further study of this combination regimen is required to establish its role in advanced BC.

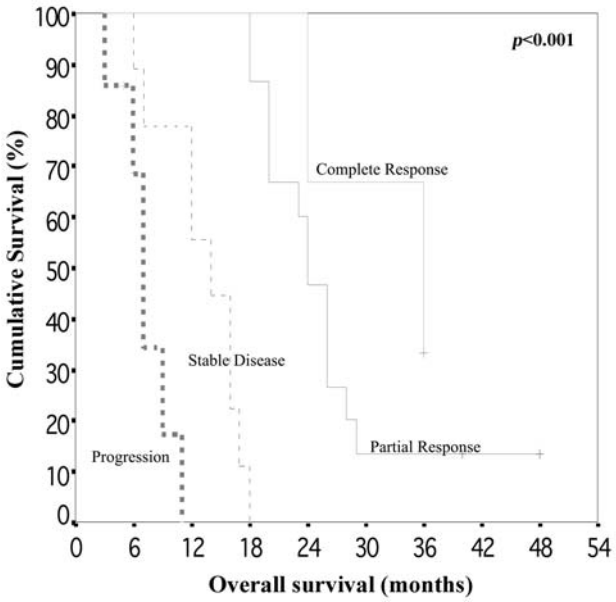

Figure 6. *Overall survival regarding the clinical response to the therapy.*

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