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Combination regimen of epirubicin, vinorelbine and 5-fluorouracil continuous infusion as first-line chemotherapy in anthracycline-naïve metastatic breast cancer patients

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Abstract

We investigated the activity and toxicity of a combination of vinorelbine 25 mg/m^2 on days 1 and 15; epirubicin 25 mg/m^2 on days 1, 8, 15; and 5-fluorouracil continuous infusion at 200 mg/m^2 every day, administered as first-line chemotherapy in anthracycline-naïve metastatic breast cancer patients. Fifty-three patients entered the study. Cycles were repeated every 28 days. Objective response was 60% by World Health Organisation (WHO) criteria and 63% by Response Evaluation Criteria in Solid Tumours (RECIST). The median time to progression was 12.7 months (17.6 months in responders) and the median survival duration was 32.9 months. The dose-limiting toxicity was leucopenia (grade 3/4 in 36% of patients). Grade 3/4 non-haematological toxicities included mucositis in 11% of patients, skin and cardiac toxicity in 4% and 2%, respectively. The combination of vinorelbine, epirubicin and 5-fluorouracil continuous infusion was found to be an active and manageable first-line regimen for metastatic breast cancer patients.

Keywords: Breast cancer; Metastatic disease; Epirubicin; Vinorelbine; 5-Fluorouracil

1. Introduction

Breast cancer is the most commonly diagnosed cancer and ranks first among the causes of cancer-related deaths in Italian women [1]. Despite at least three decades of research with combination regimens, the

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treatment of metastatic breast disease remains challenging, since the great majority of patients continue to die from their disease [2]. Anthracyclines are widely recognised as the most active drugs in the management of patients with metastatic disease [3]. New chemotherapeutic options such as the taxanes and vinorelbine are also substantially active [2]. Compared with standard anthracycline-based chemotherapy, combination therapies incorporating both taxanes and anthracyclines have demonstrated the potential to improve outcomes for patients with metastatic breast cancer [2,4–6]. Vinorelbine is a semi-synthetic vinca alkaloid that blocks the formation of the mitotic spindle apparatus at the metaphase by inhibiting microtubule assembly [7]. The combination of vinorelbine with anthracyclines has been evaluated in a number of phase II trials [8–10].For the most part, this combination has been found to be very active, with an overall response rate of between 50% and 76%. Even though vinorelbine plus doxorubicin failed to demonstrate greater efficacy over doxorubicin alone in a relatively small phase III trial [11], the combination of vinorelbine plus anthracycline deserves further investigation. Fluoropyrimidines, and 5-fluorouracil (5-FU) in particular, have been in use for over 40 years to treat numerous solid tumours, including breast cancer [12]. 5-fluorouracil is an S-phase-specific agent with a short serum half-life of 10–20 min, making it active only against a small proportion of tumour cells in the S phase when administered via short intravenous (i.v.) bolus injection [13]. However, when it is given over an extended period of time, the resulting greater number of actively dividing cells exposed to the drug supports the use of 5-fluorouracil as a continuous infusion. Moreover, due to the altered plasma concentration profile, large cumulative 5-fluorouracil doses administered after continuous infusion are better tolerated than bolus injections [13]. The moderate myelotoxicity of infusional 5-fluorouracil allows its combination with other myelotoxic agents. The therapeutic activity of the combination of 5-fluorouracil with vinorelbine or epirubicin plus/minus other chemotherapeutic drugs in metastatic breast cancer has been widely tested and high response rates have been obtained [12–19]. In a phase II trial conducted by our group, bi-weekly vinorelbine associated with protracted 5-fluorouracil infusion was found to be extremely active as a second- or third-line approach in advanced breast cancer patients previously treated with anthracyclines [20]. In view of these encouraging results, we tested this combination in association with epirubicin as first-line treatment in advanced breast cancer patients not previously submitted to anthracyclines in adjuvant setting. The primary aim of the study was to evaluate the activity of the combination regimen; the secondary aim was to assess toxicity, time to progression and overall survival.

2. Patients and methods

2.1. Patients

Women, 18 years of age or older, were eligible for the study if they had histologically-confirmed advanced breast cancer and disease assessable according to the World Health Organization (WHO) criteria of disease response [21]. Other eligibility criteria included good performance status (WHO grade 0–1), adequate bone marrow reserve (white blood cell (WBC) count $\geq 3.5 \times 10^9$cells/l, platelets $\geq 100 \times 10^9$cells/l), adequate hepatic and renal function (hepatic enzymes and bilirubin $< 2\times$ upper limit of normal, serum creatinine within normal limits), and an estimated life expectancy of at least 12 weeks. Patients were excluded who presented with non-malignant systemic disease or conditions that precluded them from receiving study therapy, or with central nervous system (CNS) metastases or second primary malignancies (except *in situ* carcinoma of the cervix or adequately treated basal cell carcinoma of the skin), or who had used any investigational agent 1 month before enrolment. Prior systemic chemotherapy for advanced disease and prior exposure to epirubicin or vinorelbine were not allowed, but one line of endocrine therapy was allowed. The study was approved by the local ethics committee. Written informed consent was obtained from all patients before starting treatment.

2.2. Treatment schedule

Treatment consisted of vinorelbine (Navelbine; Pierre Fabre Pharma, Milan, Italy) 25 mg/m^2 on days 1 and 15 every 28 days given as a 10 min infusion in 100 ml saline solution; epirubicin (Farmorubicina; Pharmacia, Milan, Italy) 25 mg/m^2 on days 1, 8, and 15 every 28 days given as a bolus injection diluted in normal saline solution; 5-fluorouracil given as a protracted continuous infusion without any interruption, at a daily dose of 200 mg/m^2 using an elastomeric pump. All patients had a central venous access. All drugs were administered on an outpatient basis. Dose modifications were performed as follows: in case of myelosuppression, if the WBC count was $\leqslant 2.5 \times 10^9$ cells/l and/or the platelet count was $<100 \times 10^9$ cells/l, then 5-fluorouracil was continued, but either epirubicin or vinorelbine was omitted. If the blood count had recovered after 1 week, vinorelbine and/or epirubicin were then administered at full dose. If the blood count had not recovered, then either vinorelbine or epirubicin was further omitted, and the dose of both drugs was subsequently reduced by 25%. In the event of hand and foot syndrome, for mild-to-moderate palmoplantar erythema, patients continued 5-fluorouracil; for severe palmoplantar erythema with blistering and desquamation, 5-fluorouracil was interrupted until the erythema resolved. For WHO grade 1

or 2 diarrhoea, antidiarrhoeal agents were prescribed; for persistent diarrhoea, 5-fluorouracil but not vinorelbine and epirubicin was discontinued for 1 week. In patients with grade 2 mucositis, infusional fluorouracil was stopped for 1 week; for grade 3/4 mucositis, 5-fluorouracil was withdrawn until recovery and restarted at a 25% reduction in dosage. Vinorelbine and epirubicin doses were delayed for 1 week in case of grade 2 neurotoxicity; in the event of grade 3 neurotoxicity, vinorelbine was reduced by 50% in subsequent cycles.

Relative dose intensity was defined as the actual weekly doses of vinorelbine, epirubicin and 5-fluorouracil at the end of treatment divided by the planned weekly dose. Supportive care could include blood transfusion and administration of analgesics, antiemetics and growth factors, as appropriate. The prophylactic use of granulocyte-colony stimulating factor (G-CSF) to maintain dose intensity was not permitted.

2.3. Assessment of response and toxicity

Pretreatment evaluation included medical history and physical examination, complete blood cell count, serum chemistries, liver function tests, electrocardiogram (ECG), echocardiography, tumour marker evaluation (CA 15-3) and staging studies appropriate to define the extent of metastatic disease, including chest X-ray, abdominal ultrasonography, thoracic and/or abdominal computed tomography scanning, and bone scanning. Clinical monitoring was performed once weekly, and complete blood cell counts, serum electrolytes, and liver function tests were performed every 2 weeks. Toxicity was evaluated according to the WHO criteria [21].

Antitumour activity was evaluated every 3 months on all measurable lesions; all patients were scheduled for at least a 2-month treatment in order to be eligible for the assessment of tumour response. In patients with tumour response or stable disease, the treatment was planned to be continued for up to 6 months; thereafter, maintenance or no therapy was based on the clinician's choice. After the completion of the treatment plan, the patients were monitored every 3 months.

Tumour response was classified by either WHO criteria [21] or Response Evaluation Criteria in Solid Tumours (RECIST) criteria [22]. All deaths and treatment discontinuations were considered as treatment failures. Time to progression was calculated from the beginning of cytotoxic chemotherapy until the date of objective evidence of progressive disease. Survival was dated from the first day of treatment until death or was censored on the date of the last follow-up appointment.

2.4. Statistical analysis

The primary study end-point was the assessment of the response rate (intent-to-treat analysis). According to the optimal two-stage phase II study design of Simon [23], the sample size was assessed in order to refuse response rates $\leqslant 40\%$ (p0) and to provide a statistical power of 80% in assessing the activity of the regimen as a 60% response rate. The upper limit for the first-stage drug rejection was 8 responses of the first consecutive 16 patients, the upper limit of the second-stage rejection was 23 responses of the 46 consecutively enrolled patients. Since both WHO and RECIST criteria were employed to assess disease response, the trial was planned to end when at least 46 cases assessable with the two response criteria had been consecutively enrolled. Response duration and survival were assessed using Kaplan–Meier survival curves. A 2-sided significance of the 5% level was applied to all tests. All statistical analyses were performed using the Statistica for Windows software program.

3. Results

From January 2000 to April 2002, 53 consecutive patients potentially assessable by WHO response criteria were entered the study. Forty-six were also potentially assessable by RECIST criteria. The demographic data, sites of metastatic tumour, and prior therapies are listed in Table 1. Two registered patients did not meet the inclusion criteria due to PS=3 and primary lung adenocarcinoma erroneously interpreted as lung metastasis. According to the intent-to-treat, both patients were considered in the analysis. Twenty-four patients (45%) had one metastatic site and 29 (55%) had multiple metastases involving two or more organ systems. Predominant visceral sites were found in 43 patients (81%), while predominant bone and soft tissue sites were found in 9 (17%) and 1 (2%), respectively.

3.1. Treatment activity

The best responses recorded for each patient are listed in Table 2. All registered patients were assessed for response including 1 ineligible patient with primary lung cancer and 2 early deaths: 1 for heart congestive failure and 1 for acute respiratory failure. These 3 patients were considered as failures. According to the WHO criteria, an objective regression was recorded in 32 of 53 women (60%, 95% Confidence Interval 47–74%), of which 5 (9%) attained a complete clinical response. The corresponding treatment activity evaluated by RECIST criteria was 29 out of 46 assessable cases that attained a disease response (63%, 95% CI 49–77%), of which 5 (11%) attained a complete clinical response. The distribution of responses according to the disease site is listed in Table 3. Overall response was slightly higher in patients with multiple disease sites (66%) than those with only one disease site (54%). At

Table 1
Patient characteristics

Characteristics	Patients ($N = 53$)
Age (years)	
Median (range)	58.9 (30.4–75.8)
Post-menopause	49 (92%)
Performance status[a]	
0	39 (74%)
1	13 (25%)
2	0
3	1 (2%)
Oestrogen receptor status	
Positive	32 (60%)
Unknown	1 (2%)
Negative	20 (38%)
Disease-free interval (months)	52.2 (0–211.3)
Previous treatments	
Surgery	45 (85%)
Radiation therapy	24 (45%)
Adjuvant chemotherapy	29 (55%)
Previous endocrine therapy:	
Adjuvant	28 (53%)
Advanced disease	7 (13%)
Disease sites	
Skin/lymph nodes	16 (30%)
Bone	26 (49%)
Lung	24 (45%)
Liver	22 (42%)
Other	4 (8%)
Number of sites of disease	
1	24 (45%)
2	22 (42%)
3	5 (9%)
4	2 (4%)

[a] Eastern Cooperative Oncology Group (ECOG) scale.

Table 2
Treatment activity

	WHO criteria Patients ($N = 53$)	RECIST criteria Patients ($N = 46$)
Other tumour	1 (2%)	1 (2%)
Death	2 (4%)	2 (4%)
Progressive disease (PD)	5 (9%)	5 (11%)
Stable disease (SD)	13 (25%)	9 (20%)
Partial response (PR)	27 (51%)	24 (52%)
Complete response (CR)	5 (9%)	5 (11%)
Overall response	32 (60%)	29 (63%)
(95% Confidence Interval)	(47–74%)	(49–77%)

WHO, World Health Organisation; RECIST, Response Evaluation Criteria in Solid Tumours.

the last follow-up appointment (November 30, 2003), 44 patients (83%) showed disease progression and 23 (43%) had died. Median time to progression (TTP) and overall survival of the entire group were 12.7 and 32.9 months, respectively, in the 53 patients assessable by WHO response and 10.9 and 31.5 months, respectively, in the 46 patients evaluable by the RECIST criteria. Median TTP in patients achieving a disease response was 17.6 months in the patient population assessed according to WHO criteria and 15.9 months in the patient population assessed according to RECIST criteria.

Table 3
Disease response according to sites of disease (WHO)

Disease site	CR	PR	SD	PD
Skin/Lymph ($N = 16$)	7 (44%)	4 (25%)	4 (25%)	1 (6%)
Bone ($N = 26$)	2 (8%)	7 (27%)	16 (62%)	1 (4%)
Lung ($N = 24$)	8 (33%)	8 (33%)	5 (21%)	3 (13%)
Liver ($N = 22$)	3 (14%)	8 (36%)	8 (36%)	3 (14%)

3.2. Toxicity

A total of 280 cycles of therapy were administered (median, 6 cycles; range, 1–6). Associated side-effects are reported in Table 4. Leucopenia was the most frequent severe toxicity (grade 3–4 in 36% of patients). Anaemia was frequent, but generally mild (grade 3 in 1 patient only). Only two patients developed grade 3 thrombocytopenia. Gastrointestinal toxicities included grade 3 mucositis in 11% of patients and grade 3 hepatic toxicity in 2%. Two patients developed grade 3 asthenia. It is noteworthy that 68% of patients did not develop alopecia. In a total of 14 patients (26%), 33 courses (11%) were delayed 1 week, and 11 courses (5%) [10 patients (19%)] were delayed 2 weeks due to haematological toxicity. The dose of epirubicin was reduced or omitted in 30 patients (57%) [83 courses (30%)], while the doses of vinorelbine and 5-fluorouracil were reduced or omitted in 27 patients (51%) [62 courses (22%)] and in 29 (55%) [78 courses (28%)], respectively. Leucopenia was the most frequent cause of dose reduction/omission of the three drugs. 5-Fluorouracil was reduced/omitted in 5 patients (9%) [18 courses (6%)] due to mucositis, in 4 (8%) [6 courses (2%)] due to skin toxicity, and in 7 (13%) [10 courses (4%)] due to problems with the central venous access (delay in catheter positioning in 2 patients and catheter infection or thrombosis in 5). Thirty-seven patients (70%) finished the treatment plan (6 cycles), 4 (8%) received 5 cycles, 3 (6%) received 4 cycles, 8 (15%) received 3 cycles, and 1 (2%) received 1 cycle.

Dose intensity was calculated for each patient and for each drug. The median dose intensity for vinorelbine was 10.3 mg/week (82% of planned dose), the median

Table 4
Toxicity in Patients ($N = 53$)

Grade	0	1	2	3	4
Leucopenia	11 (21%)	9 (17%)	14 (26%)	15 (28%)	4 (8%)
Anaemia	19 (36%)	22 (42%)	11 (21%)	1 (2%)	0
Thrombocytopenia	50 (94%)	1 (2%)	0	2 (4%)	0
Nausea/vomiting	28 (53%)	13 (25%)	11 (21%)	1 (2%)	0
Diarrhoea	48 (91%)	3 (6%)	2 (4%)	0	0
Mucositis	31 (58%)	13 (25%)	3 (6%)	6 (11%)	0
Hepatic	51 (96%)	0	1 (2%)	1 (2%)	0
Myalgias	49 (92%)	4 (8%)	0	0	0
Fever	51 (96%)	0	1 (2%)	1 (2%)	0
Asthenia	27 (51%)	14 (26%)	10 (19%)	2 (4%)	0
Neurological	48 (91%)	4 (8%)	1 (2%)	0	0
Cardiac	51 (96%)	1 (2%)	0	0	1 (2%)
Skin	42 (79%)	2 (4%)	7 (13%)	2 (4%)	0
Alopecia	36 (68%)	4 (8%)	4 (8%)	9 (17%)	0

No patients had lung or bladder toxicity.

Table 5
Published studies of protracted 5-fluorouracil or capecitabine-containing schemes

Author [Ref.]	Year	N° pts	Drugs	RR%	TTP (mo)	OS (mo)
Jones [14]	1994	43	5FU+EPX+CDDP	84	12	15
Gabra [15]	1996	56	DOX+5FU	76	10	13
Eisen [16]	1998	RND 62	5FU+EPX+CPM	69	9	13
	1998	RND 34	5FU+EPX+CDDP	68	8	10
Pierga [13]	1998	RND 131	5FU (bolus)+DOX+CPM	54	14	23
	1998	RND 127	5FU (c.i.)+DOX+CPM	53	12	21
Recchia [17]	2001	28	5FU+EPX+CPM	75	13	27.7
De Boer [18]	2002	27	EPX+CPM+5FU±G-CSF	~70	~11.3	~18.8
Venturini [12]	2003	67	CAP+DTX+EPX	82	TE	TE
Humphreys [19]	2004	51	DTX+EPX+5FU	64	9.5	17.5
Present study	2004	53	EPX+VNB+5FU	60	12.7	32.9

RR= response rate; TTP=time to progression; OS=overall survival; mo=months; 5FU=5-fluorouracil; EPX=epirubicin; CDDP=cisplatin; DOX=doxorubicin; CPM=cyclophosphamide; G-CSF=granulocyte colony-stimulating factor; CAP=capecitabine; DTX=docetaxel; VNB=vinorelbine; RND=random; c.i.=continuous infusion; TE=too early; pts, patients.

dose intensity of epirubicin was 15.6 mg/week (83%), and the median dose intensity of 5-fluorouracil was 1173.9 mg/week (84%).

4. Discussion

There is a general consensus that anthracyclines are the preferred first therapeutic option in advanced breast cancer patients not previously submitted to these drugs in adjuvant setting and in patients with newly-diagnosed metastatic disease as well. In a recent meta-analysis of randomised trials of first-line treatments, anthracycline combination regimens were shown to be better than anthracyclines alone [24]. What constitutes the best anthracycline-based combination regimen is a matter of clinical research. Since chemotherapy in most metastatic breast cancer is administered with palliative intent, it is essential to balance the reduction in tumour burden and tumour-associated symptoms with the drug-related toxicity. In a previous study conducted by our cooperative group, bi-weekly vinorelbine associated with continuous 5-fluorouracil infusion was found to be very well tolerated and highly active in a subgroup of heavily pretreated patients [20]. Moreover, the responses obtained were durable. Building on these results, the present study assessed the addition of epirubicin to this combination regimen. Since weekly epirubicin may be better tolerated than the every 3 week administration [25,26], epirubicin was administered on a sustained weekly schedule.

Our results suggest that vinorelbine, epirubicin and 5-fluorouracil combination treatment has a high antitumoral activity in anthracycline-naïve patients, as indicated by the overall response rate, median time to progression (TTP) and overall survival. However, It should be noted that the response rate reported in this study was similar to that obtained in our previous trial with vinorelbine and 5-fluorouracil alone [20]. On the basis of these results, one could speculate that the "dogma" of using an anthracycline as first-line therapy in metastatic breast cancer might be questionable after the

recent introduction of new active drugs. A randomised trial is mandatory to address this issue.

This study was designed when the new RECIST criteria for response were proposed to replace the WHO criteria. Both response criteria were therefore employed to assess treatment activity. Since the RECIST criteria are more restrictive than the WHO criteria (e.g., patients with bone metastases alone are admitted on WHO criteria, but not on RECIST criteria), the number of enrolled cases eligible for WHO response exceeded by 13% the number of enrolled cases eligible for RECIST response. The overall response rate was quite similar in patients eligible on the WHO criteria versus those on RECIST criteria, thus confirming previous observations [22].

The 60% response rate recorded in this trial based on the WHO criteria (63% on the RECIST criteria) lies within the range of response rates reported for standard combinations commonly used against metastatic breast cancer. The therapeutic activity of this regimen was not influenced by adverse prognostic factors such as predominant visceral disease or multiple metastatic sites. It is noteworthy that the clinical response was durable. The TTP of responding patients eligible on WHO criteria (17.6 months on average vs 15.9 months in those eligible on RECIST criteria) is amongst the longest ever published. Similarly, the median survival (32.9 months) is impressive [27]. The good patient performance status and the absence of previous chemotherapy treatment in almost half of the patient population (45%) [28] could have favourably influenced the outcome of the present series. However, such favourable characteristics are offset by the predominance of visceral disease (over 75% of our patients), a finding commonly associated with an adverse prognosis [29].

As concerns treatment tolerability, leucopenia was the most frequent and dose-limiting side-effect associated with this regimen. WHO grade 3 or 4 WBC toxicity occurred in 36% of patients; it was generally brief and was never complicated by septicaemia. Since the prophylactic use of G-CSF was not permitted, leucopenia caused frequent reduction/omission, particularly of epirubicin and vinorelbine. The frequency of bone marrow depression observed here does not differ from that reported in other phase II studies testing the association of epirubicin and vinorelbine [9–11]. This suggests that 5-fluorouracil may have influenced this side-effect only marginally. Although 5-fluorouracil was less frequently reduced due to haematological toxicity, the doses needed to be adjusted because of mucositis, central venous catheter complications, and, less frequently, because of hand and foot syndrome. One toxic death occurred due to acute cardiac toxicity. Other treatment-related toxicities were clinically unremarkable. It is noteworthy that the incidence of grade 2/3 alopecia (25%) was consistently lower than expected [30]. This is attributable to the administration of epirubicin on a weekly schedule. In a randomised phase II trial, 31% of patients receiving weekly epirubicin at 25 mg/m^2 developed alopecia toxicity versus 82% of those given epirubicin every 4 weeks [26].

The combination of anthracyclines and taxanes has been the most widely explored regimen in recent years [2,3]. In general, very high response rates (up to 90%) have been reported in phase II trials, but the activity of these regimens (54–67% response rate) in phase III studies did not differ from that reported in this study [7]. We provided a table of first-line polichemotherapy regimens with protracted infusion of fluorouracil or capecitabine + an anthracycline ± other drugs in metastatic breast cancer (Table 5). On the, whole these regimens reported high activity (response rate $\geq$ 60% in most of them) and relative long TTP. These data may provide a rationale for designing a phase III trial comparing one of these infusional schemes against the most promising taxane-containing regimen.

In conclusion, the association of epirubicin, vinorelbine and infusional 5-fluorouracil shows favourable activity and toxicity profiles and may provide a suitable therapeutic option in advanced breast cancer patients not pre-treated with anthracyclines. Although we were unable to consistently deliver the planned full dose in all patients, the activity of this combination was significant and the responses obtained were durable. Whether 5-fluorouracil could augment the benefit to the association of epirubicin and vinorelbine needs to be addressed in a randomised clinical trial.

Conflict of interest statement

The authors disclose no financial and personal relationships with the drug companies producing the drugs used in the present study.

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