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Original article

Infusional ECarboF in patients with advanced breast cancer: A very active and well-tolerated out-patient regimen

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Summary

We performed a trial using the combination of epirubicin 50 mg/m^2/day 1, carboplatinum AUC 5/day 1 and continuous 5-fluorouracil (5-FU) 200 mg/m^2/day (every 4 weeks for 6 months) to confirm the efficacy and low toxicity profile of this regimen in breast cancer. In 51 patients with metastatic (n = 33) or locally advanced (n = 18) breast cancer the overall response rate was 86% (95% confidence interval (95% CI): 73%–94%): 94% in locally advanced and 81% metastatic disease. Grade 3–4 toxicity was low: 4% of patients presented with febrile neutropenia, 16% with severe palmar-plantar syndrome, 10% with Port-a-cath thrombosis.

This study confirms the high efficacy of infusional 5-FU-based regimens and justifies further research into novel promising oral 5-FU derivatives.

Key words: breast cancer, carboplatinum, chemotherapy, continuous 5-fluorouracil

Introduction

Conventional polychemotherapy regimens induce response rates of 50%–60% in stage III and IV breast cancer [1]. Such regimens often include 5-fluorouracil (5-FU), which is commonly administered as a bolus. Continuous infusion 5-FU helps to overcome its short half-life, and can give response rates of 30% even in heavily pre-treated patients with metastatic breast cancer [2, 3]. Administered in continuous infusion, 5-FU has been successfully combined with cisplatinum, possibly because of a synergistic interaction [4–6]. Furthermore the Royal Marsden Hospital (London) has demonstrated considerable activity for the combination of epirubicin, cisplatinum and continuous infusion 5-FU in the treatment of breast cancer [5–8]. More recently carboplatinum has been substituted for the cisplatinum, allowing for outpatient treatment, reducing the risk of serious emesis, nephrotoxicity and neurotoxicity [7]. However, the efficacy demonstrated in phase II studies conducted in tertiary referral centers does not always survive translation to less specialized units; therefore, a confirmatory trial of the combination of epirubicin (E), carboplatinum, and infusional 5-FU was performed in two general hospitals in Switzerland.

Patients and methods

Patients

Patients referred to the oncology division of two general hospitals in Switzerland (Hôpital Cantonal Universitaire de Genève, Hôpital Régional de Sion) with histologically or cytologically documented locally advanced/inflammatory breast cancer (LABC) or metastatic breast cancer (MBC) were considered for this study. The criteria for LABC were those defined by Haagensen and Stout [9]. Inflammatory breast cancer was defined as a T_4 lesion with diffuse brawny induration of the skin with an erysipeloide edge [10]. Patients with LABC were considered eligible if they had received no previous therapy, whereas patients with metastatic disease could have received prior endocrine therapy but no chemotherapy for metastatic disease.

Additional inclusion criteria were age < 70, World Health Organization (WHO) [11] performance status 0–2, adequate haematological, renal and liver function (i.e., WBC counts > 3.0 × 10^9/l, platelet count > 100 × 10^9/l, creatinine clearance > 60 ml/min, bilirubin < 1.25 × upper normal limit, hepatic enzymes < 2 × normal upper limit), at least one measurable lesion (at least 10 × 10 mm in diameter) and ability to manage an indwelling intravenous catheter. Patients with cerebral metastasis were eligible for inclusion provided there was no major neurologic deficit. The protocol was approved by local Ethics Committee.

Treatment

A Port-a-cath was inserted into the subclavian vein to allow the continuous delivery of infusional 5-FU 200 mg/m^2/day for six months, using a seven day infusor device (Baxter 7 days infusor: ref: 2C1082KJ, Irvine, USA). which was replaced weekly. Epirubicin (50 mg/m^2) and carboplatinum (given at AUC 5, over one hour) were given every four weeks for six courses. The carboplatinum dose administered was calculated as 5 × (GFR + 25) (as per Calvert [12]) using a GFR (glomerular filtration rate) estimated according to the Cockroft & Gault formula:

$$\text{GFR} = \frac{1.1 \times (140 - \text{age}) \times \text{weight}}{\text{serum creatinine } (\mu\text{mol/l})}$$

Routine antiemetics (dexamethasone 10 mg and HT3 antagonists) were administered 30 minutes before the epirubicin and carboplatinum.

Table 1. Patient characteristics.

	Metastatic	Locally advanced
Number of patients	33	18
Age (years)		
Median	55	53
Range	29–69	31–69
Performance status		
0	19	16
1	11	2
2	3	0
Menstrual status		
Pre	9	10
Post	24	8
Site of disease		
Local	13	18
Breast	8	16
Regional nodes	8	14
Chest wall	2	1
Distant		
Soft tissue/distant nodes	17	
Bone	13	
Lung	6	
Liver	16	
Other	2	
Hormonal receptors		
ER+	18/28	9/16
PR+	14/26	10/16
Previous adjuvant chemotherapy	12	
Previous endocrine treatment	10	0
Interval between diagnosis and metastasis (months)	30	
Range	3.5–109	

Antiseptic mouthwash and nystatin (4 times per day) were used in order to decrease the risk of oral mucositis. Patients were started on warfarin (1 mg/day p.o.) since this compound has been shown to decrease the risk of thrombosis associated with an indwelling line [13].

For patients with locally advanced breast cancer (LABC), loco-regional treatment was performed on completion of chemotherapy. Whenever possible, this consisted of surgery (tumorectomy or radical mastectomy + axillary dissection) followed by radiotherapy to the breast (or chest wall after mastectomy) and regional lymph node areas. On completion of chemotherapy, all patients with potentially hormone-sensitive disease (estrogen receptor or progesterone receptor positive tumors $\geq 10\%$ by immunohistochemistry) were given hormonal therapy. For patients with LABC, hormonotherapy consisted of tamoxifen (20 mg/day) for five years whereas for those patients with metastatic disease, tamoxifen or aromatase inhibitors were given, depending on prior therapy, until progression.

Assessment of response and toxicity

Initial staging included clinical examination, blood tests according to inclusion criteria, liver ultrasound or abdominal computed tomographic scan, chest X-rays, bone scan scintigraphy and bone X-rays on hot spots.

Toxicity was assessed according to WHO criteria [11]. Patients had a physical examination, a full blood count, blood chemistry (renal and liver tests) before each cycle. A full blood count was repeated on day 8 and 14.

Port-a-cath thrombosis grade 3 was defined as requiring hospitalization and grade 4 as life threatening thrombosis. Port-a-cath infection grade 3 was defined as requiring hospitalization for i.v. antibiotics and grade 4 requiring removal of line.

Response was assessed according to WHO criteria [11] after every two cycles, and on completion of treatment (or discontinuation). Partial and complete responses were confirmed after one month. Patients were then monitored at two month intervals.

Dose modifications

In case of leucopenia $< 3.0 \times 10^9/l$, thrombocytopenia $< 100 \times 10^9/l$, on day 1 of each subsequent cycle 5-FU was continued but carboplatinum and epirubicin were delayed for one week. If after one week, the blood count had not recovered, treatment was delayed a further week and a dose reduction was undertaken: epirubicin and 5-FU were reduced by 25% and carboplatinum to AUC 4. If low blood count lasted for more than 2 weeks, epirubicin and 5-FU were reduced by 50% and carboplatinum to AUC 3.

For mild to moderate palmo-plantar syndrome (dryness: grade 1, erythema with pain: grade 2), the 5-FU was continued with the addition of pyridoxine (50 mg orally 3 td). For severe palmo-plantar syndrome (erythema with blistering and desquamation: grade 3) pyridoxine was started and 5-FU withheld until healing occurred. Then 5-FU was restarted at 25% dose reduction and pyridoxine continued throughout the treatment. For WHO grade 3 or 4 mucositis or persistent diarrhoea, 5-FU was discontinued for one week and restarted at a 25% dose reduction. Epirubicin was also subsequently given at a 25% dose reduction.

Statistical considerations

This was an open-ended phase II study, with a planned minimum recruitment of 50 patients so that the 95% confidence interval would be $\pm 25\%$ for an anticipated response rate of 85%. Time to progression and survival were calculated using the Kaplan–Meier method, with time to progression defined as the time elapsed between the start of treatment and the date of progression or the date of last evaluation.

Results

Patient characteristics

Between January 1996 and July 1998, 51 eligible patients were registered in this study. Forty-two were treated in Geneva and nine in Sion. Patient characteristics are listed in Table 1. The median age was 53 years (range 29–69). Nineteen patients were pre-menopausal and thirty-two were peri- or post-menopausal. Eighteen (35%) patients had LABC and thirty-three (65%) had metastatic disease: seventeen at diagnosis and sixteen had relapsed after a median time of thirty months (range 3.5–109) following primary treatment. Twelve patients with metastatic disease had received prior adjuvant chemotherapy: cyclophosphamide, methotrexate, 5-FU (CMF) in two; chlorambucil, methotrexate, 5-FU (LMF) in one; adriamycin, cyclophosphamide (AC) in three; cyclophosphamide, adriamycin, 5-FU (CAF) in one; cyclophosphamide, epirubicin, 5 FU (CEF) in two; AC + CMF in three. Ten patients had been previously given endocrine therapy for metastatic disease before entering the study.

All patients were assessable for response and toxicity, except one, who received only one week of treatment. She could not tolerate the seven-day infusor for psychological reasons.

Table 2. Response.

	Metastatic, *n* (%)	Locally advanced, *n* (%)
Number of patients	32	18
CR	5 (16)	5 (28)
PR	21 (66)	12 (67)
OR	26 (81)	17 (94)
SD	6 (19)	1 (6)
PD	0 (–)	0 (–)

Abbreviations: CR – complete response; PR – partial response; OR – overall response; SD – stable disease; PD – progressive disease.

Table 3. Toxicity, worst score for any course of treatment (expressed as number of patients having had that score).

	WHO grade 1–2, *n* (%)	WHO grade 3–4, *n* (%)
Anaemia	37 (74)	8 (16)
Neutropenia	9 (18)	38 (76)
Thrombocytopenia	15 (30)	21 (42)
Infection	8 (16)	2 (4)
Emesis	27 (54)	9 (18)
Stomatitis	19 (38)	3 (6)
Plantar-palmar syndrome	12 (24)	8 (16)
Alopecia	13 (26)	32 (64)
Port-a-cath thrombosis	2 (4)	5 (10)
Port-a-cath infection	0 (–)	0 (–)
Diarrhoea	8 (16)	1 (2)

Response

The overall response rate was 86% (43 of 50 patients) (95% confidence interval (95% CI): 73%–94%). LABC patients achieved a 94% response rate: 5 (28%) had a clinical complete response (CR), while 12 (67%) had a partial response (PR). One had stable disease (SD). Metastatic patients had a 81% response rate: 5 (16%) had a CR, 21 (66%) had a PR. Six had a SD (Table 2). Seven of the twelve patients who previously received adjuvant chemotherapy achieved a 58% response rate (95% CI: 28%–85%), while 19 of the 21 chemotherapy-naïve patients achieved 90% response rate (95% CI: 70%–99%).

Median follow-up was 22 months. One- and two-year survival rates were 94% (95% CI: 81%–98%) and 69% (95% CI: 47%–83%) respectively (Figure 1). One- and two-year time to progression (TTP) rates were 65% (95% CI: 49%–77%) and 44% (95% CI: 24%–61%), respectively (Figure 2). In LABC patients, one- and two-year survival rates were 100%, TTP rates were 94% and 70%, respectively. In metastatic patients one- and two year survival rates were lower at 90% and 50%, respectively; TTP rates were 47% and 28%, respectively (Figures 1 and 2). In LABC patients median TTP was not reached; in metastatic patients median TTP was 11 months.

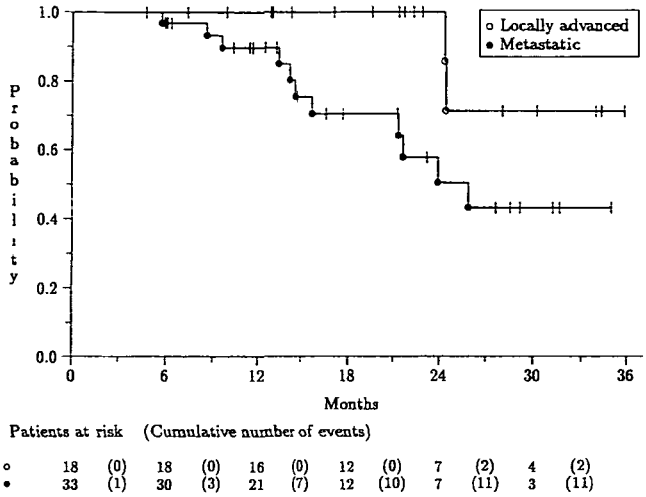

Figure 1. Overall survival of 51 breast cancer patients treated with EcarboF regimen; • – overall survival of 33 metastatic breast cancer patients; o – overall survival of 18 locally advanced breast cancer patients.

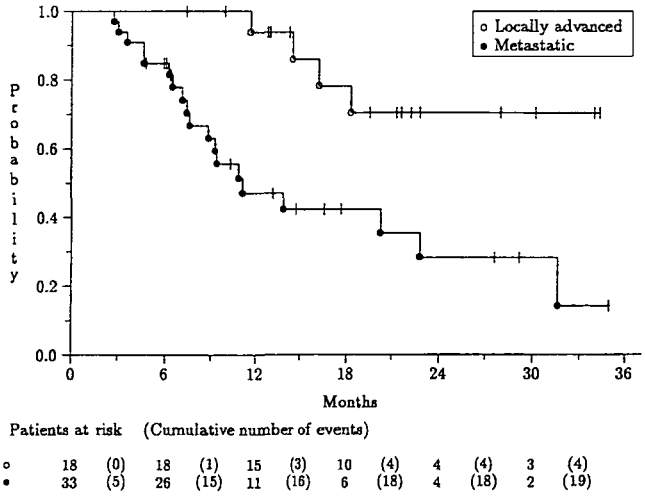

Figure 2. Time to first event for 51 breast cancer patients treated with EcarboF regimen; • – time to first event for 33 metastatic breast cancer patients; o – time to first event for 18 locally advanced breast cancer patients.

Toxicity

Details of toxicity are listed in Table 3. Although neutropenia grade 3–4 was observed in 76% of the patients, febrile neutropenia occurred in only 4%. Thrombocytopenia grade 3–4 occurred in 42% of the patients, but no platelet transfusions were required and no haemorrhagic episodes were observed. In MBC compared to LABC, anaemia and neutropenia rates were comparable. Nausea and vomiting grade 3–4 were seen in 18% of the patients, severe stomatitis in only three patients and diarrhoea in one. Severe palmo-plantar syndrome was observed in 16%. No port-a-cath infection occurred and only five (10%) grade 3 thromboses were observed. Thirty-two patients had alopecia that required wearing a wig. One patient experienced an anaphylactic reaction during first injection of bolus

epirubicin, where in subsequent cycles mitoxantrone was substitued for the epirubicin.

Dose reductions and treatment delays

Treatment was delayed in 14 patients (28%). 5-FU dosage was reduced in 23 patients (46%) because of palmar-plantar syndrome (7 patients), stomatitis (4 patients) and neutropenia or thrombocytopenia (12 patients). The 32 patients who completed at least 6 chemotherapy cycles had a mean and median total dose of 50 g of 5-FU administered (range 25–71 g; first and third quartile: 42–55 g).

Eighteen patients stopped their treatment early. The treatment was interrupted in five for toxicity (Port-a-cath thrombosis in 2; early and severe palmar-plantar toxicity in 1; thrombocytopenia: grade 3; severe asthenia associated with a psychological depression in one). Another five patients stopped treatment early because of progressive disease following an initial response. In seven additional patients treatment was stopped early by the physician (one patient was in CR, she received a total of four cycles; two patients were in partial remission (PR) they received five cycles; in four patients there was no change (NC), they received three, four and two of them five cycles). One metastatic patient who had PR returned to her home country after four cycles of treatment and hence was lost to follow-up.

Discussion

This study conducted in two general hospitals, confirms the high response rate with the EcarboF regimen previously reported from a tertiary care hospital [7]. For patients with metastatic disease, the response rate was similar in the two studies, with 81% overall response including 16% CR in our study and 17% CR in the Royal Marsden Hospital (RMH) trial. In LABC patients the response rate was 94% and 81%, respectively. As in the British trial we report few clinically relevant toxic episodes. The rate of febrile neutropenia was 4% in this study and 11% in the RMH trial. We report no severe central line infection compared to a 6%–17% infection rate in the RMH study. The use of a Port-a-cath instead of a Hickman line may account for this difference. The rate of severe central line thrombosis requiring hospitalization was 10%, but without any life threatening episodes. This is similar to the rate reported across a number of studies conducted at the RMH with infusional 5-FU delivered through a Hickman line [5–8, 14]. Interestingly, the rate of Port-a-cath thrombosis in the literature seems similar whether chemotherapy is administered as a bolus or as a continuous infusion: 8.1% among 132 patients receiving various bolus chemotherapy regimens and 4.7% among 149 patients who received infusional chemotherapy [15, 16].

Chemotherapy is given with palliative intent in metastatic breast cancer, and therefore optimal management requires a balance between activity and tolerability. In this regard, infusional 5-FU-based regimens have a favorable therapeutic index: in terms of efficacy, the phase II results obtained in a number of centers demonstrate that this approach is associated with response rates of 70% to 80% [5, 7, 8] suggesting activity similar to regimens containing anthracycline & taxane combinations [17]. However, with paclitaxel–doxorubicin combination the risk of cardiotoxicity is a concern [18], whereas with docetaxel–anthracycline combinations without G-CSF the rate of febrile neutropenia episodes is high at around 10% [19] per cycle or 38% of patients [20].

Considering the high response rate of ECarboF regimen observed in LABC and MBC, there is a strong argument to evaluate infusional 5-FU-based regimens in the adjuvant setting. The TOPIC trial, now closed to recruitment, is a randomized UK multicentre study, which compared six cycles of neoadjuvant EcisF with standard AC (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2) in patients with large operable primary breast cancer (tumor diameter $\geqslant 3$ cm). With over 400 patients randomized, this trial is expected to report in the near future and will give the first direct data comparing infusional 5-FU chemotherapy with standard bolus treatment in the adjuvant setting. A phase I trial, conducted by the EORTC, testing escalating doses of EcycloF in LABC has been completed (manuscript in press) and will be followed by a phase III trial.

The future of continuous 5-FU based chemotherapy is likely to lie with the new oral 5-FU derivatives, since they appear to mimic the beneficial pharmacokinetics of infusional 5-FU without the cost and potential morbidity of an indwelling Hickman line or Port-a-cath. Recently, encouraging results have been reported in patients with advanced upper gastrointestinal tract carcinoma treated with a regimen where, in the original EcisF, the infusional 5-FU was replaced by UFT, an orally available mixture of tegafur plus uracil (a competitive inhibitor of 5-FU catabolism) [21]. Capecitabine is another promising 5-FU pro-drug, currently being tested in combination with bolus epirubicin and cyclophosphamide in an EORTC study for patients with locally advanced/inflammatory breast carcinoma (CEX study).

In conclusion this study confirms the previously reported high response rate and low toxicity profile of EcarboF regimen. The future developments of this type of continuous infusion 5-FU based chemotherapy are expected to involve the use of new oral 5-FU derivatives.

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