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Cyclophosphamide, Epirubicin, High-dose Folinic Acid and 5-Fluorouracil (Super-FEC) as First-line Chemotherapy for Advanced Breast Cancer: Preliminary Results

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Abstract—*Forty patients with metastatic breast cancer were treated with a new combination regimen consisting of cyclophosphamide, epirubicin, high-dose folinic acid and 5-fluorouracil (super-FEC). A major objective response was observed in 32 patients (80%). Among these, 11 patients (27%) experienced a complete remission.*

The median duration of response was 10+ and 12+ months for CR and PR, respectively. The most common side-effect was oral mucositis (Grade III = nine patients; grade IV = two patients), while haematological toxicity was virtually absent. Considering the high-risk characteristics of the vast majority of the enrolled patients (75% had dominant visceral disease), these preliminary results suggest that super-FEC has a powerful activity in poor-prognosis metastatic breast cancer with an acceptable degree of toxicity.

INTRODUCTION

COMBINATION CHEMOTHERAPY for advanced breast cancer (ABC) reproducibly induces tumour response in 50–80% of patients, the majority of whom experience a palliation of disease-related symptoms [1]. However, major improvements concerning complete response rate, duration of response, median survival, quality of life and, finally, cure, remain to be achieved. As recently stated by Aisner *et al.* [2] '. . . chemotherapy has not eliminated metastatic disease . . . and new chemotherapy approaches are clearly necessary'.

High-dose chemotherapy with or without autologous bone-marrow transplant [3–7] alternating non-cross resistant regimens [8, 9] as well as hormonal synchronization before chemotherapy [10] still represent experimental procedures which often produce conflicting results [11].

A new area of study dealing with the attempts to improve the therapeutic results in ABC and other solid tumours is represented by the biochemical modulation of anticancer agents, mainly of 5-fluorouracil (5-FU). Some experimental and clinical studies have suggested that the therapeutic activity of 5-FU should be enhanced by increasing endogenous reduced folate pools *in vivo* [12–14].

Recently, two randomized trials have shown an interesting response rate (RR) superiority of the combination of 5-FU with high-dose folinic acid (HDFA) over 5-FU alone in advanced colorectal cancer [15, 16]. We previously demonstrated that HDFA + 5-FU has considerable activity as a salvage regimen for advanced and mainly refractory breast cancer [17–19]. After our first report, Doroshow *et al.* [20] and Allegra *et al.* at the NCI, Bethesda [21] provided further data outlining the potential usefulness of this regimen in ABC. Moreover, Fine *et al.* reported an impressive activity by utilizing HDFA + 5-FU as first line treatment in 25 evaluable patients: one CR and 11 PR were achieved for an overall response rate of 48% [22].

These encouraging results led us to combine HDFA + 5-FU with epirubicin (E) and cyclophosphamide (C), two among the most active single drugs in ABC, in an attempt to develop a new combination regimen as first-line chemotherapy in high-risk ABC patients. We report here the preliminary results of our experience.

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MATERIALS AND METHODS

Since June 1986, 40 consecutive patients with ABC entered the present study according to the following eligibility criteria: measurable disease, performance status (ECOG) ≤3, total WBC count ≥4000/mm, platelet count ≥100,000/mm, serum creatinine ≤1.5 mg/dl, serum bilirubin ≤2 mg/dl, no previous chemotherapy for metastatic disease. Patients with lytic bone lesions and/or soft tissue disease as the only metastatic sites were admitted to the study if: oestrogen receptor (ER) negative and/or with a disease-free interval <12 months and/or after the failure of hormonal therapies.

Measurable disease was assessed with chest X-ray and tomography for lung metastases, with CT scan for brain localization and by ultrasound for intra-abdominal disease (liver and uterus). Bone metastases were evaluated with X-ray, while breast masses were measured on mammography. Direct clinical measurement was employed for skin lesions and for metastatic nodes. Cytologically proven malignant pleural effusions were considered as evaluable, unmeasurable disease and followed by serial chest X-ray and periodical cytological evaluations.

The same techniques were utilized for response analysis.

Oral informed consent was required before entry into the study.

The characteristics of the patient population are shown in Table 1. The treatment consisted of: C 600 mg/m^2 i.v. day 1, E 60 mg/m^2 i.v. day 1, HDFA 200 mg/m^2 i.v. days 1–5, 5-FU 370 mg/m^2 i.v. days 1–5, repeated every 28 days. Dose modification for individual treatment cycles was as follows: C and E were reduced by 25% for a WBC count ≤3500 mm^3 but >2500/mm^3 and/or for a platelet count ≤100,000/mm^3 but >75,000/mm^3. 5-FU was reduced to 340 mg/m^2 only if oral mucositis and/or diarrhoea grade III–IV occcurred. E was administered at a dose of 50 mg/m^2 for each first individual cycle only. All patients underwent allopurinol mouthwashes to prevent oral mucositis, as described by Clark and Slevin [23]. In the absence of progressive disease (PD), a total of 10 cycles was delivered to each patient, then patients were followed without any form of maintenance therapy until PD occurred.

Table 1. Patient characteristics

Entered	40
Evaluable	40
Median age in years	50 (35–66)
Median performance status (ECOG)	2 (0–3)
Median disease-free interval in months	25 (0–120)
Menopausal status:	
pre	15
post	25
ER status:	
positive	9
negative	14
unknown	17
Dominant site of disease:	
visceral	30
soft tissue	1
osseous	9
Prior systemic therapy:	
adjuvant chemotherapy (CMF)	24
hormonal therapy	14
No. of organ systems involved	
1	18
2	13
≥3	9

Range in brackets.

The first evaluation of response took place after at least two cycles and WHO criteria were used for the response and toxicity evaluation [24].

Duration of response was calculated starting from the first day of therapy or from the time when it was first recorded for partial (PR) and complete (CR) remission, respectively.

Survival was calculated from the beginning of the present programme of therapy.

RESULTS

Response data

All the 40 entered patients were evaluable for both response and toxicity. Eleven (27.5%) patients obtained a CR and 21 (52.5%) reached a PR, for an overall RR of 32 out 40 (80%) with a 95% C.I. between 68% and 92%. Response according to metastatic sites, ER status and number of involved sites is shown in Tables 2 and 3. Neither failure of previous adjuvant CMF nor performance status significantly influenced the likelihood of response, while patients with only one site of disease achieved a significantly better CR rate than patients with two

Table 2. Response according to metastatic site

	CR	PR	NC	PD	RR (%)
Nodes	6/11	5/11	—	—	100
Breast	1/3	2/3	—	—	100
Liver	6/15	4/15	2/15	3/15	66
Lung	8/18	7/18	1/18	2/18	83
Pleura	3/4	—	—	1/4	75
Bone	3/15	2/15	8/15	2/15	33
Skin	2/3	1/3	—	—	100
Brain	—	2/2	—	—	100
Uterus	—	1/1	—		100

CR = complete remission, PR = partial remission, NC = no change, PD = progressive disease, RR = response rate (unless otherwise specified, the table numbers refer to the absolute number of patients).

Table 3. Response according to ER status, No. of organ systems involved and dominant site of disease

	ER status			No. of OSI			DMS		
	ER+	ER−	ER?	1	2	3	V	O	ST
CR	5/9	3/14	3/17	8/18	1/13	2/9	10/30	—	1/1
PR	4/9	8/14	9/17	4/18	11/13	6/9	14/30	7/9	—
NC	—	1/14	2/17	3/18	—	—	2/30	1/9	—
PD	—	2/14	3/17	3/18	1/13	1/9	4/30	1/9	—
RR (%)	100	78	70	66	92	88	80	77	100

ER? = Oestrogen receptor unknown; OSI = organ system involved; DMS = dominant metastatic site; V = visceral; O = osseous; ST = soft tissue.

or more sites of disease (44% vs. 13% $P < 0.05$). Among the 30 patients with visceral disease, 10 CR and 14 PR (RR = 80%) were seen. It is noteworthy that three out four patients with concomitant liver and lung metastases responded (two CR and one PR), as did the two patients with CNS involvement (two PR).

The median duration of response was 10+ (range: 6+ to 20+) months and 12+ (6+ to 18+) months for CR and PR patients, respectively. The responders' median survival time was 18+ months (7–28+).

Three patients achieved a stabilization of the disease (NC) (median time to disease progression 5 months, median survival 7 months), while five progressed (median survival 4 months). One patient experienced a life-threatening toxicity (grade IV oral mucositis and diarrhoea), and consequently refused further therapy after the third cycle, while in CR of nodal metastases. The remission lasted 9 months and now the patient was followed for survival analysis only.

Toxicity

A total of 320 cycles was administered (77% on an outpatient basis), with a median of eight (3–10) for each patient. All the 40 patients had completed the therapy. The degrees of toxicity are outlined in Table 3. In spite of a median WBC nadir of 1100/mm^3 (range 300–3100), calculated in only 28 out 40 patients because of practical problems, grade III or IV haematological toxicity was never encountered. All patients experienced grade II–III alopecia; 28 patients (70%) had some degree of nausea and/or vomiting. Relevant oral mucositis was reported in 11 patients (27%) with nine and two patients experiencing grade III and IV toxicity, respectively. In addition, three patients had grade III and one grade IV diarrhoea. Eight patients developed a dry skin rash, whereas four patients had refractory conjunctivitis. Neither drug-related death nor any form of cardiac toxicity were observed.

DISCUSSION

The combination of HDFA and 5-FU is currently under active investigation in an increasingly broader spectrum of solid tumours [25, 26]. We combined this regimen with C and E, encouraged by the different pattern of toxicity of these two drugs (mainly haematological) if compared with HDFA + 5-FU (mainly mucositis and diarrhoea). The response rate of 80% (with 27% CR), achieved by the present regimen, suggests a powerful activity of this combination in high-risk, multistational metastatic breast cancer. The poor prognosis of the vast majority of our patients is clearly outlined in Table 1 (75% had visceral involvement, 55% had two or

Table 4. Toxicity of the treatment

	WHO grade			
	I (%)	II (%)	III (%)	IV (%)
Anaemia	2(5)	1(2.5)	—	—
Leukopenia	4(10)	2(5)	—	—
Thrombocytopenia	—	—	—	—
Oral mucositis	—	9(22.5)	9(22.5)	2(5)
Diarrhoea	—	9(22.5)	3(7.5)	1(2.5)
Alopecia	—	11(27.5)	29(72.5)	—
Skin*	—	8(20)	—	—
Nausea/vomiting	5(12.5)	23(57.5)	—	—

*Dry skin rash.

more metastatic sites and also the few patients with only bone or soft tissues metastases were selected according to the quite strict criteria mentioned above).

Nevertheless, a very satisfactory activity was recorded even in patients with a high-burden disease and with 'sanctuary' localizations (CNS metastases). Moreover, haematological toxicity was virtually absent in spite of a total 5-FU dose of 1850 mg/m^2 for each cycle, considerably higher than that usually employed in conventional CAF or FAC regimens.

This observation might be due to the three drug-free weeks between consecutive cycles, but, in our opinion, an interference of HDFA with the haematological toxicity caused by C, E and 5-FU could not be excluded *a priori* and possibly deserves further evaluation. As expected, major side-effects were represented by oral mucositis and diarrhoea; however, only one patient suffered from grade IV toxicity and refused further therapy.

We chose to deliver 10 cycles of chemotherapy both to reach a quite safe total E dose (590 mg/m^2) and because much data suggested that treatment beyond few months after the maximal tumour shrinkage failed to increase response and survival duration [27, 28]. A longer follow-up of our study will provide interesting findings concerning the duration of response, overall survival, time to treatment failure, duration of unmaintained remissions and patterns of progression.

The real contribution of HDFA to both the therapeutic activity and the toxicity of our regimen should be assessed only in a randomized trial comparing super-FEC with the same regimen without HDFA. Nevertheless, the super-FEC regimen seems to compare quite favourably with other recently reported aggressive protocols for ABC.

Hortobagyi *et al.* reported the results of a randomized study comparing high-dose FAC vs. standard FAC [5]. High-dose chemotherapy was administered in protected environment units with a complex prophylactic antibiotic regimen. Among 32 evaluable patients in the high-dose FAC regimen, eight CR (25%) and 17 PR (53%) were achieved for an overall RR of 78%, (not statistically different from standard FAC: CR = 22%, RR = 78%). The median duration of response was 11 months and median survival 20 months in the high-dose group. Moreover, toxicity was substantial; 16 out 32 patients experienced a severe oral mucositis and virtually all developed a grade IV haematological toxicity, with 24 episodes of fever of unknown origin in the protected environment group.

Another aggressive Adriamycin®-containing regimen (PM-FAC) was utilized by Mortimer *et al.* in a group of 42 evaluable patients with oestrogen receptor-negative ABC [7]. Eleven CR (26%) and 21 PR for an overall RR of 76% were documented. The median duration of response and the median survival were 7 and 13 months, respectively. Severe or life-threatening toxicity (mainly stomatitis and leukopenia) was universal, with two drug-related deaths.

Finally, Tormey *et al.* utilized a nine-drug intensive regimen in association with consolidation radiotherapy in 23 patients with ABC. Despite a very high response rate (91%), this study failed to prolong the median duration of survival (24 months) beyond the historical data [29].

Clearly, a major failing of current chemotherapy regimens in ABC is the very low CR rate achieved. To affect 'cure' of ABC, regimens producing higher CR must be developed. From this point of view, our regimen might seem quite unsatisfactory but, once again, our patients' characteristics must be firmly kept in mind. Perhaps patients with visceral disease but with a lower tumour burden might achieve a substantially better CR rate. In addition, the role of consolidation radiotherapy on sites of previously bulky disease, as showed by others [29, 30], as well as a cautious escalation of E dosage (up to 75 mg/m^2) in selected cases might enhance the activity of our regimen with a still acceptable degree of toxicity.

In conclusion, the use of HDFA + 5-FU-based regimens in ABC is still in its infancy. However, the sound biochemical rationale supporting this combination, as well as the encouraging clinical results reported so far, make all efforts to improve its therapeutic index a major challenge for the near future.

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