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New Anthracycline Analogs in Advanced Breast Cancer

VALERIA BONFANTE,* LAURA FERRARI,* CRISTINA BRAMBILLA,* ANNA ROSSI,* FABRIZIO VILLANI,† FLAVIO CRIPPA,‡ PINUCCIA VALAGUSSA* and GIANNI BONADONNA*

**Division of Medical Oncology, Istituto Nazionale Tumori, Via Venezian, 1, Milan 20133, Italy; †Division of Cardiology, and ‡Division of Nuclear Medicine, Istituto Nazionale Tumori, Via Venezian, 1, Milan 20133, Italy*

Abstract—*To test the activity and toxicity of new anthracycline analogs, a series of Phase II disease-oriented studies were performed in women with advanced breast cancer previously untreated with doxorubicin. All drugs were administered every* 3 weeks, *and the doses in* mg/m^2 *were as follows: doxorubicin and epirubicin* 75 *i.v., esorubicin* 35 *i.v., idarubicin* 13 *i.v. and* 45 *p.o. When epirubicin was tested vs doxorubicin, both response rate* (13 *of* 21 *or* 62% vs 11 *of* 21 *or* 52%) *and median response duration* (11 months *vs* 13 months) *were comparable. In* 24 *patients, esorubicin yielded complete plus partial response in* 21% *with a median duration of* 15 months. *In* 27 *patients given idarubicin intravenously the response rate was* 11% *for* 4 months *and the corresponding findings when the drug was administered orally to* 25 *women were* 24% *for* 8 months. *Acute toxic manifestations were lower following treatment with all three analogs compared to doxorubicin. Cardiac toxicity, as documented by echocardiography, systolic time interval and left ventricular ejection fraction was virtually absent following therapy with epirubicin and idarubicin. After a median cumulative dose of* 600 mg/m^2 *for doxorubicin-treated women there was a significant fall in LVEF compared to basal values. Similar findings were observed after a median cumulative dose of* 210 mg/m^2 *for esorubicin. We conclude that epirubicin is as effective as doxorubicin but comparatively less toxic when administered at the same dose schedule. At the doses and schedules utilized in this study, esorubicin and idarubicin resulted less active in breast cancer.*

INTRODUCTION

DOXORUBICIN (DX) is one of the most useful chemotherapeutic agents available and the single most effective drug for the palliative treatment of advanced breast cancer. As documented in innumerable publications, its prolonged administration is limited by the development of myocardial damage. Cardiomyopathy is a delayed type of toxicity being related to the cumulative dose of doxorubicin, and almost always becomes symptomatic when the total drug dose exceeds 600 mg/m^2. Among the early side-effects, reversible myelosuppression, in particular neutropenia, is the most frequently observed finding and is dose-limiting. Vomiting and hair loss occur in the vast majority of patients when the single dose exceeds 25 mg/m^2.

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Reprint Requests to Dr. Gianni Bonadonna, Istituto Nazionale Tumori, Via Venezian, 1 Milan 20133, Italy.

In the search for new anthracycline analogs, the Farmitalia Carlo Erba, Milan, Italy, has launched during the last decade a large scale laboratory and clinical program. By modifications of daunorubicin (DNR) and DX molecules in position 4 of the chromophore or in position 4′ of the aminosugar [1–4], three new compounds underwent preclinical evaluation and early clinical trials. Chronologically, they are the following: (a) 4′ epidoxorubicin (epirubicin) obtained from DX by epimerization of the hydroxylic group at position 4 of the sugar moiety [2]; (b) 4-demethoxydaunorubicin (idarubicin) obtained drom DNR by sostitution of the C–4 methoxyl group in the ring D of the aglycon moiety with an hydrogen atom [3]; (c) 4′-deoxy doxorubicin (esorubicin) derived from doxorubicin by removing the hydroxylic group in position 4′ of the aminosugar [4]. The first Phase I studies for all three analogs were started at the Milan Cancer Institute [5–7] and rapidly extended to many other research institutions in the U.S.A. [8–10] and Europe [11–14]. The initial findings

were promising and indicated a lower acute toxicity of the analogs compared to doxorubicin. Considering the established efficacy of doxorubicin in breast cancer, from 1982 we tested the three new anthracyclines in women with advanced stages of this disease. The scope of these Phase II-oriented trials was to better define the therapeutic index of the analogs utilizing as reference point the parent compound doxorubicin.

PATIENTS AND METHODS

Patient selection

The criteria for eligibility were as follows: histological evidence of locally advanced or metastatic breast carcinoma, no prior treatment with anthracyclines, measurable or evaluable lesions assessable by physical and/or radiological examination, age below 75 yr, Karnofsky index ≥ 60, peripheral leukocyte count $\geq 4000/mm^3$, platelet count $\geq 100{,}000/mm^3$, hepatic and renal function tests within normal limits. Women with left ventricular ejection fraction (LVEF) of less than 50% by radionuclide angiograms at rest as well as patients with a history of prior myocardial infarction or cardiac arrhythmias were excluded.

Treatment plans

Initially, a randomized Phase II study was activated to evaluate the antitumor activity and toxicity of doxorubicin and epirubicin in a patient population selected on the above mentioned criteria. Patients were stratified according to the site of dominant lesion and randomization was performed using the method of random permuted blocks of length four. Patients were allocated to receive either drug at the dose of 75 mg/m^2 by bolus intravenous injection. In the absence of tumor progression, courses were repeated every 3 weeks, not to exceed the cumulative dose of 600 mg/m^2, i.e. for approx. eight courses of either drug.

After reaching the maximum cumulative dose, possible further treatments were decided on individual basis.

Subsequently, different Phase II-oriented trials were activated to evaluate the antitumor activity and toxicity of esorubicin and idarubicin on patient populations whose eligibility criteria remained unchanged. Esorubicin was administered intravenously at the dose of 35 mg/m^2, while the doses of idarubicin were 13 mg/m^2 when given intravenously and 45 mg/m^2 when given by mouth, respectively. In the absence of tumor progression, both drugs were administered every 3 weeks for six cycles. Further treatment was then decided on an individual basis and in seven patients showing progressive tumor shrinkage after partial remission of at least 50% treatment was continued with the same drug for two to four additional courses (median 3).

Patients were informed about the potential side-effects of all drugs and the protocol designs were approved in advance by the Institute's Committee on Clinical Investigation.

Pretreatment and follow-up studies

Baseline studies included complete physical examination with measurement in centimeters of all neoplastic lesions whenever technically feasible; röentgenogram of skull, spine, pelvis and upper third of femurs, or bone scan; echotomography in the presence of hepatomegaly or abnormal liver function tests; complete hemogram and biochemical profile. Physical examination and complete blood count were repeated every 3 weeks, i.e. before each drug course. Dose reduction of drugs were planned for leukocyte count ranging from 3800 to $2500/mm^3$ and for platelet count ranging from 100,000 to $75{,}000/mm^3$. For lower values, drugs were temporarily discontinued. Radiological studies were systematically repeated every 3 months or whenever indicated by individual clinical situations. Serial electrocardiograms were recorded before each treatment cycle; left ventricular systolic time intervals (PEP/LVET ratio) utilizing the technique of Weissler [15], echocardiograms to assess the minor axis shortening (MAS) [16], and radionuclide angiocardiography to determine the LVEF at rest [17] were recorded before therapy, after the third cycle and at the end of treatment.

Response evaluation

Patients were considered evaluable only if a minimum of two cycles of either drug therapy were administered. Response was evaluated following anthracycline treatment alone and categorized according to the standard WHO criteria [18]. The duration of response, calculated in months from the start of chemotherapy to the date of documented progressive disease, was computed only for patients receiving the assigned anthracycline treatment either alone or followed by local irradiation to the sites of initial disease in patients presenting with locally advanced breast cancer. Responsive patients who received further systemic treatment once anthracycline administration was discontinued when approaching the maximum cumulative dose were excluded from the analysis of remission duration.

RESULTS

Main patient characteristics are summarized in Table 1. A total of 125 women all treated on ambulatory basis were considered eligible for the various studies. In 7 patients only a single drug course could be administered. In the epirubicin

Table 1. *Main patient characteristics*

	Doxorubicin	Epirubicin	Esorubicin	Idarubicin i.v.	Idarubicin p.o.
Eligible	21	23	25	28	28
Evaluable	21	21	24	27	25
Median age (range)	51 (28–69)	53 (31–64)	48 (33–69)	53 (33–74)	52 (32–73)
Disease presentation					
Locally advanced	5	7	10	14	12
Metastatic	16	14	14	13	13
Dominant lesion					
Soft tissue	7	8	11	16	15
Skeleton	6	6	4	3	3
Viscera	8	7	9	8	7
Prior systemic therapy					
None	8	10	17	15	12
Endocrine	–	1	2	2	–
CMF	13	10	5	10	13

Table 2. *Treatment response*

	Doxorubicin		Epirubicin		Esorubicin		Idarubicin i.v.		Idarubicin p.o.	
	No.	%	No.	%	No.	%	No.	%	No.	%
Complete response	4/21	19	2/21	9.5	2/24	8.5	0/27	0	0/25	0
Partial response ≥ 50	7/21	33	11/21	52	3/24	12.5	3/27	11	6/25	24
Complete + partial response (evaluable patients)	11/21	52	13/21	62	5/24	21	3/27	11	6/25	24
Complete + partial response (all patients)	11/21	52	13/23	56.5	5/25	20	3/28	11	6/28	21
Median duration in months										
Response		13		11		15		4		8
Survival		20		16		>12		>8		>9
Follow up		29		28		17		13		12

series one patient died of rapidly progressive disease 10 days after the first drug administration and the other patient refused to continue treatment. The remaining 5 women were lost to follow up. Therefore, a total of 118 patients were evaluable for treatment response and they all were off treatment at the time of present analysis. Median age was over 50 yr in all series but in the esorubicin subgroup, and only 14 women were older than 60 yr (doxorubicin 1, epirubicin 3, esorubicin 2 and idarubicin 4 for each route of administration). Postoperative radiotherapy to the left chest wall was delivered to a total of 13 patients (doxorubicin 1, epirubicin 4, esorubicin 1, intravenous idarubicin 4, oral idarubicin 3). Disease presentation was almost equally distributed between locally advanced and metastatic disease but in the series given doxorubicin and epirubicin. In the present series, pulmonary metastases represented the most frequent site of documented visceral involvement. Prior endocrine therapy consisted mainly of tamoxifen, while prior chemotherapy consisted only of CMF (cyclophosphamide, methotrexate and fluorouracil).

Treatment response

The therapeutic results are reported in Tables 2 and 3. Doxorubicin was able to induce complete (CR) or partial remission (PR) in 11 of 21 women or 52% while the response rate after epirubicin was 62% (13 of 21 patients). Frequency of CR was 19% after doxorubicin and 9.5% after epirubicin. As far as the other anthracyclines were concerned, the response rate was 21% after esorubicin, 11% after intravenous idarubicin and 24% after oral idarubicin, respectively. CR was documented in only 8.5% of women given esorubicin. Eleven of 38 responders (doxorubicin 3, epirubicin 4, esorubicin 1, intravenous idarubicin 1 and oral idarubicin 2) were given further systemic therapy after anthracycline discontinuation. CMF chemotherapy was administered to 6 women and additive

Table 3. Treatment response related to disease extent and prior chemotherapy

	Doxorubicin		Epirubicin		Esorubicin		Idarubicin i.v.		Idarubicin p.o.	
	No.	%	No.	%	No.	%	No.	%	No.	%
Dominant lesion										
Soft tissue	5/7	71	6/8	75	2/11	18	1/16	6	5/15	33
Skeleton	3/6	50	3/6	50	0/4	0	1/3	33	0/3	0
Viscera	3/8	37	4/7	57	3/9	33	1/8	12	1/7	14
Prior chemotherapy										
No	6/8	75	8/11	73	5/19	26	2/17	12	4/12	33
Yes	5/13	38	5/10	50	0/5	0	1/10	10	2/13	15

endocrine therapy to the remaining 5 patients.

Median duration of response in women given only anthracycline treatment either alone or followed by local–regional radiotherapy was almost superimposable between doxorubicin, epirubicin and esorubicin, ranging from 11 to 15 months (Table 2), and was longer than median remission duration after either intravenous (4 months) or oral idarubicin (8 months). At the time of present analysis, median overall survival was 20 and 16 months, respectively, for the first two drugs. For esorubicin and idarubicin, median survival was not yet reached. However, median follow-up observation was shorter because these Phase II studies were activated only later (Table 2).

The higher degree of antitumor activity of doxorubicin and epirubicin compared to the two other anthracyclines studied is also evident when disease extent and prior treatment are considered (Table 3). In fact, approximately three fourths of women presenting with soft tissue involvement showed objective tumor shrinkage; partial recalcification of osteolytic metastases or disappearance of pathologic uptake in bone scintiscan was documented in 50% of women, while pulmonary metastases regressed in 3 of 8 women given doxorubicin and in 4 of 7 given epirubicin. The comparative limited activity of either esorubicin or idarubicin is particularly striking at the level of soft tissue disease where response rate ranged between 6 and 33%. In addition, also in women without previous exposure to other cytotoxic drugs the response rate was ranging between 12 and 33% (Table 3).

Acute toxicity

The comparative incidence of immediate and early toxicity is summarized in Table 4. Frequency of vomiting was particularly low after intravenous idarubicin (26%) compared to doxorubicin (72%). Oral mucositis was recorded in 43% of women after doxorubicin, while its incidence was ranging between 11 and 21% for the three other analogs. Hair loss occurred in approx. 50% of patients after esorubicin and idarubicin while, at the doses utilized, it was observed in almost all patients given either doxorubicin or epirubicin.

Complete blood counts with platelets were performed every 3 weeks. Platelet fall below 100,000/mm^3 was never documented. Leukocyte fall requiring either dose reduction or temporary treatment discontinuation was documented in only 7% of epirubicin cycles, while it was ranging between 13 and 18% for the other analogs (Table 4). It is worth noting that in no instance a leukocyte fall below 1000/mm^3 was recorded. No patient developed infections related to severe leukopenia,

Table 4. Percent comparative acute toxicity

	Doxorubicin	Epirubicin	Esorubicin	Idarubicin i.v.	Idarubicin p.o.
Vomiting*	71	53	50	26	72
Mucositis*	43	19	12	11	21
Alopecia*	100	100	58	41	54
Leukocytes fall					
Requiring dose reduction**	15	4	5	10	7
Requiring treatment delay**	3	3	8	5	10

* Per cent of patients.
** Per cent of cycles.

Table 5. Comparative cardiac evaluation

Drug		Median dose (mg/m²)	PEP/LVET	MAS	LVEF
			mean values ± SE		
Doxorubicin	basal		.333 ± .02	32.9 ± 2.31	70.75 ± 2.27
(8 pts)	after	600	.383 ± .02	29.3 ± 1.68	59.87 ± 2.05
					P < 0.01*
Epirubicin	basal		.344 ± .013	33.6 ± 1.69	69.12 ± 2.29
(8 pts)	after	600	.341 ± 0.027	32.5 ± 1.87	64.12 ± 2.91
Esorubicin	basal		.300 ± 0.009	31.0 ± 0.96	71.4 ± 1.91
(15 pts)	after	210	.330 ± 0.011	30.9 ± 1.29	66.3 ± 1.55
					P < 0.05*
Idarubicin iv	basal		.301 ± 0.013	31.4 ± 1.65	68.1 ± 1.33
(10 pts)	after	55	.300 ± 0.014	32.5 ± 1.40	64.6 ± 1.30
Idarubicin po	basal		.301 ± 0.017	30.3 ± 2.29	68.6 ± 1.50
(8 pts)	after	200	.333 ± 0.021	29.1 ± 2.55	68.1 ± 2.58

* Student's *t*-test on paired samples.

nor hepatic or renal dysfunction related to drug administration was documented.

Cardiac toxicity

Table 5 compares the modification of PEP/LVET ratio, MAS and LVEF in patients for whom all three parameters were simultaneously reassessed at the end of drug therapy. The number of evaluable patients as well as the median cumulative doses for each analog are reported. Comparing pre- and post-treatment values, the only significant differences observed were in the LVEF mean values after either doxorubicin ($P < 0.01$) and esorubicin ($P < 0.05$). It is also worth stressing that in the 16 patients who received a median dose of 600 mg/m² of either doxorubicin or epirubicin there were no significant differences between the mean post-treatment values of the two drugs.

With the exception of two women started on doxorubicin, no other patient in these series showed symptoms and signs of cardiac failure during the follow-up. As detailed elsewhere [19], the two patients given doxorubicin developed symptoms and signs of left ventricular failure, 6 and 14 months from drug discontinuation, respectively, after a cumulative dose of 562 and 580 mg/m². In one patient a fall in the LVEF to 37% was aggravated by recurrent bilateral neoplastic effusion. The other patient was previously irradiated with 5000 rad to the left hemithorax more than 3 yr before doxorubicin treatment. At the time of present analysis, both patients remained alive and improved on digitalis.

DISCUSSION

The results of our Phase II trials testing three anthracycline analogs in advanced breast cancer will be discussed from the point of view of comparative acute and delayed toxicity as well as antitumor activity.

As far as acute toxic manifestations were concerned, vomiting, mucositis, hair loss and leukopenia were documented in a consistently lesser incidence compared to doxorubicin. With the intravenous dose schedules utilized, epirubicin appeared the least myelotoxic analog. A lesser incidence of leukopenia following epirubicin vs doxorubicin was also observed by other investigators [20–22]. Esorubicin and idarubicin were the drugs associated with the minimum incidence of mucositis. When given intravenously, idarubicin induced mild vomiting in about one fourth of patients. Frequency of vomiting was about 50% with the other two analogs and about 70% with doxorubicin. While in our experience the incidence of vomiting following oral idarubicin was 72%, other authors [9, 23] by delivering the total dose in 3–5 days reported a much less incidence (8–17%) of this side effect. In the present study, the incidence of hair loss was the same for doxorubicin and epirubicin, but practically all other research groups have reported a comparative less incidence of alopecia following epirubicin when this drug was administered with the same dose schedule as doxorubicin [5, 20, 24]. The incidence of alopecia was decreased by about 50% after esorubicin and idarubicin, and for the latter drug the frequency of this side effect was not related to the route of administration.

Concerning myocardial damage, at comparable cumulative drug dose there was no significant difference in the incidence of laboratory cardiotoxicity between epirubicin and doxorubicin. However, compared to basal values we noticed a more evident degree of laboratory changes following

doxorubicin, particularly as far as LVEF was concerned, and in addition two women given doxorubicin developed symptoms and signs of cardiac damage. Similar findings, indicating that epirubicin is less cardiotoxic than doxorubicin, were reported by other authors [20, 21, 25]. Cardiac evaluation for the other two analogs failed at present to detect important laboratory changes with the cumulative doses utilized. However, it should be pointed out that in the present study we observed a decline in the LVEF following esorubicin (median cumulative dose 210 mg/m^2). Our findings are similar to those observed by other investigators [26, 27].

Present results confirm that epirubicin is an active drug in advanced breast cancer and its antitumor activity appears superimposable in terms of response rate, duration and survival to that of doxorubicin. In fact, with the response rate observed in 21 patients we could confirm that epirubicin was at least as active as the chosen rate (50%), with the probability of false positivity being at most 0.2 [28]. This finding is important considering that the analog was found to induce less acute and delayed toxicity compared to the parent compound. Although active in breast cancer, esorubicin and idarubicin appear in our experience to be definitely inferior to doxorubicin and epirubicin. It is worthy of note that the experience of Memorial Hospital with esorubicin in previously treated breast cancer was totally negative [26]. In fact, utilizing the initial dose of 25 mg/m^2 every 3 weeks, none of the 20 patients showed major therapeutic response.

We conclude that among the three anthracycline derivatives tested in advanced breast cancer, only epirubicin may replace doxorubicin in future trials as well as in current clinical practice since the analog showed comparable treatment activity with less toxicity.

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