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CLINICAL TRIAL REPORT

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Cisplatin, epirubicin, and lonidamine combination regimen as first-line chemotherapy for metastatic breast cancer: a pilot study

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Abstract We assessed the activity and tolerability of a cisplatin, epirubicin, and lonidamine combination regimen as first-line chemotherapy in 28 advanced breast cancer patients. The schedule of treatment was as follows: 60 mg/m^2 epirubicin followed by 40 mg/m^2 cisplatin given on days 1 and 2 every 21 days, with 450 mg lonidamine being given per os (three tablets) on days of chemotherapy administration and in the period intervening between one cycle and the next. Patients received a median of 5 (range 1–6) cycles. Overall, 22 patients were evaluable for response and 28, for toxicity. Four patients refused to continue the treatment after the first course, one was lost to follow-up, and one died due to toxicity (septic shock). The incidence of grade 3/4 nausea and vomiting was found to be greater than that expected with epirubicin and lonidamine alone. The addition of cisplatin resulted in an increase in platelet and hemoglobin toxicities, whereas the WBC toxicity did not differ from that expected with epirubicin and lonidamine. The hematological toxicity was found to be cumulative, leading to treatment delay in about 50% of patients at the fifth and sixth courses. The activity of this cytotoxic regimen was noteworthy, with the overall response rate being 81.8% (31.8% complete responses and 50.0% partial responses) in evaluable patients. This response rate decreased to 64.2% when all registered patients were included according to an intent-to-treat analysis. In conclusion, the association of cisplatin, epirubicin, and lonidamine given on the schedule described herein, appears to be very active but substantially toxic. We are now testing this combination in a randomized comparison, with the cisplatin dose being reduced to 30 mg/m^2 given on days 1 and 2.

Key words Cisplatin · Epirubicin · Lonidamine · Advanced breast cancer · Toxicity

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Introduction

Anthracyclines are widely recognised as the most active drugs in breast cancer patients, with response rates ranging from 40% to 60% in advanced disease [1]. Although it is not often used in the treatment of metastatic breast carcinoma, single-agent cisplatin has led to response rates of 47% in previously untreated patients [2] and to those ranging between 54% and 78% when combined with anthracycline-containing schemes [3–5]. Cisplatin has a number of potential advantages for the treatment of advanced breast cancer patients in combination with anthracyclines: (1) at present there is no known mechanism of cross-resistance between the two agents, (2) patients generally have had no prior exposure to cisplatin in the adjuvant setting, and (3) the combination of these two chemotherapeutic drugs has been found active in other malignancies such as ovarian cancer [6], gastric cancer [7], and urothelial carcinoma [8].

Table 1 Patients' characteristics (*DFI* disease-free interval, *PS* performance status)

Entered		28
Evaluable		22 (78.5%)
Age (years)	Median	55.5
	Range	35–65
DFI	0	2 (7.1%)
	≤2 years	4 (14.2%)
	>2 years	22 (78.5%)
PS	0	5 (17.8%)
	1	18 (64.4%)
	2	3 (10.7%)
	3	2 (7.1%)
Premenopause		5 (17.8%)
Postmenopause		23 (82.2%)
Receptor status	ER+	10 (35.7%)
	ER–	8 (28.6%)
	Unknown	10 (35.7%)
	PgR+	11 (39.3%)
	Pgr–	7 (25.0%)
	Unknown	10 (35.7%)
Prior treatments	Surgery	27 (96.4%)
	Radiation	12 (42.8%)
	Adiuv chem	23 (82.1%)
	ADM+CMF	1 (3.6%)
	FEC	1 (3.6%)
	CMF	21 (75.4%)
Cycles (*n*)	1 cycle	1 (4.3%)
	5 cycles	1 (4.3%)
	6 cycles	10 (43.6%)
	8 cycles	9 (39.2%)
	10 cycles	1 (4.3%)
	12 cycles	1 (4.3%)
Adiuvant endocrine therapy TAM		6 (21.4%)
Endocrine therapy for advanced disease		5 (17.8%)
TAM		3 (10.7%)
LHRH-A		1 (3.6%)
LHRH+MPA		1 (3.6%)
Disease sites	Skin/nodes	6 (21.4%)
	Bone	8 (28.5%)
	Lung	15 (53.5%)
	Liver	10 (35.7%)
	Others	2 (7.1%)
Sites of disease (*n*)	1 site	19 (65.1%)
	2 sites	8 (28.0%)
	3 sites	2 (7.1%)
	4 sites	1 (3.6%)

Lonidamine, [1-(2,4 dichlorophenyl)methyl]-1H-indazole-3-carboxylic acid (LND), is a nonconventional anticancer drug that has no direct effect on cellular DNA, RNA, or protein synthesis but strongly inhibits energy metabolism [9, 10]. The compound has been shown to reduce oxygen consumption and glycolytic activity on tumor cells. Ben-Horin et al. [11] have suggested that the major metabolic effects produced by LND are inhibition of lactate transport and its accumulation, resulting in intracellular acidification. LND also causes early structural and functional modifications on cell membranes as well as the cytoskeleton of cancer cells [12]. Given its peculiar mechanism of action and unique spectrum of toxicity, LND appears to be an ideal candidate for combination with chemotherapy. Experimental studies have demonstrated the ability of LND to increase the cell-killing effect of anticancer drugs, including alkylating agents [13, 14] and anthracyclines [15, 16]. In addition, a complete reversal of doxorubicin resistance has been obtained after combined exposure to LND in a multidrug-resistant breast-cancer cell line [17, 18]. The potentiating effect of LND on cisplatin or epirubicin has been confirmed in phase II and phase III clinical trials involving breast cancer [19–23] or ovarian cancer patients [24–26].

The ability of LND to modulate the cytotoxic activity of cisplatin associated with epirubicin was recently investigated in two human breast-cancer cell lines (MCF7 and T47D), and a superadditive effect was observed [27]. We therefore designed a phase II study to assess the in vivo activity and toxicity of a cisplatin, epirubicin, and lonidamine combination scheme in advanced breast cancer patients.

Patients and methods

A total of 28 patients were eligible for this trial, and their characteristics are shown in Table 1. All patients had histologically proven breast cancer and metastatic disease. Eligibility criteria included an age of <75 years, a performance status of ≤2 (WHO scale), and progressive disease with measurable lesions. Patients could have had prior (adjuvant) chemotherapy (CMF) and/or hormonal therapy and/or radiation therapy. One line of endocrine therapy for metastatic disease for up to 4 weeks prior to study inclusion was also permitted. Blood counts and blood chemistry values had to be within normal limits (WBC $>4\times10^9$/l, platelets 100×10^9/l, creatinine <1.3 mg/dl, bilirubin <1.5 mg/dl). Informed consent was obtained from each patient according to the standard procedures of the respective participating institutions. Exclusion criteria were the following: active angina pectoris, congestive heart failure, previous myocardial infarction, impaired ventricular ejection fraction, previous radiation therapy to the only measurable site of disease, more than one line of endocrine therapy for advanced disease, brain metastases or leptomeningeal disease, osteoblastic bone metastases, ascites and/or pleural effusions as the only indicators of advanced disease, and the presence of concomitant cancers.

Treatment consisted of epirubicin (EPI, Farmorubicina; Pharmacia & Upjohn, Milan, Italy) given at 60 mg/m^2 by slow intravenous push on days 1 and 2, cisplatin (CDDP, Platamine; Pharmacia & Upjohn, Milan, Italy) given at 40 mg/m^2 by 1-h intravenous infusion on days 1 and 2, and lonidamine (Doridamina; Angelini ACRAF, Rome, Italy) given as one 150-mg tablet three times a day. Both cisplatin and epirubicin infusions were repeated every 21 days, whereas lonidamine was given continuously until the end of the cytotoxic treatment.

Recommended treatment modifications for hematological toxicities were as follows: a 1-week delay was introduced if granulocyte counts were <1,500/μl (or WBC counts were <3,000/μl) and/or platelet counts were <100,000/μl on day 21; after 1 week, if hematology parameters did not recover, a dose reduction of 50% was applied when granulocyte counts ranged between 1,000 and 1,500/μl (or WBC counts ranged from 2,000 to 3,000/μl) and/or platelet counts ranged between 75,000 and 100,000/μl. In the case of lower hematology values the following week a further 1-week delay was required. Patients went off study if the delay exceeded 4 weeks. Delays and dose reductions were also required for grade ≥3 stomatitis and renal impairment (creatinine ≥1.8 mg/dl).

Response was evaluated after three treatment cycles, or earlier if clinically indicated because of suspected progressive disease. All patients receiving at least two chemotherapy cycles were considered assessable for response. According to the UICC [28], a complete

Table 2 WHO toxicity[a]

	WHO 0	WHO 1	WHO 2	WHO 3	WHO 4
Naus/vom 28 pts	1 (3.5%)	2 (7.1%)	10 (35.8%)	13 (46.5%)	2 (7.1%)
Stomatitis 28 pts	10 (35.8%)	5 (17.8%)	9 (32.2%)	3 (10.7%)	1 (3.5%)
Diarrhea 28 pts	21 (75%)	4 (14.3%)	3 (10.7%)		
Liver 28 pts	27 (96.4%)	1 (3.5%)			
Neurotoxicity 28 pts	26 (92.9%)	2 (7.1%)			
Fever 28 pts	20 (71.5%)	3 (10.7%)	5 (17.8%)		
Cardiac 28 pts	26 (93.0%)	1 (3.5%)	–	1 (3.5%)	
Alopecia 28 pts	2 (7.1%)	1 (3.5%)	7 (25%)	15 (53.7%)	3 (10.7%)
Myalgias 28 pts	11 (39.3%)	10 (35.8%)	6 (21.4%)	1 (3.5%)	
Asthenia 28 pts	6 (21.4%)	8 (28.7%)	9 (32.2%)	4 (14.2%)	1 (3.5%)
WBC 28 pts	16 (57.4%)	4 (14.2%)	4 (14.2%)	1 (3.5%)	3 (10.7%)
Nadir WBC 21 pts	2 (9.5%)	2 (9.5%)	3 (14.2%)	5 (23.9%)	9 (42.9%)
Plts 28 pts	21 (75%)	1 (3.5%)	4 (14.4%)		2 (7.1%)
Nadir Plts 21 pts	5 (23.9%)	3 (14.2%)	3 (14.2%)	3 (14.2%)	7 (33.5%)
Hgb 28 pts	8 (28.6%)	4 (14.2%)	8 (28.6%)	6 (21.5%)	2 (7.1%)

[a] For each patient the most severe instance of toxicity is taken into account

response (CR) was defined as the complete disappearance of all clinically detectable soft-tissue and visceral malignant disease as measured by physical examination or radiography studies and the complete recalcification of all osteolytic lesions for at least 4 weeks. A partial response (PR) was characterized as a decrease of ≥50% in the sum of the products of the two longest perpendicular diameters of all measurable lesions and ≥50% recalcification of osteolytic lesions that lasted at least 4 weeks. Progressive disease (PD) was defined as an increase of at least 25% in the size of measurable lesions or the development of new lesions. Toxicity was assessed according to WHO criteria [28]. Patients attaining a CR were allowed to stop the treatment after one more cycle, whereas those showing a PR or stable disease (SD) continued the treatment for a maximum of six cycles.

Time to progression, defined as the time from the start of treatment until disease progression, was estimated using the Kaplan-Meier method. Statistical analysis was performed on an IBM compatible personal computer using SPSS PC software [29].

Results

Patients

Between January 1994 and September 1995, 28 women were entered in this study. Two young women with a performance status (PS) of 3 for mobility impairment as a consequence of diffuse bone metastases were included in the study, as the investigators felt that they would have tolerated the treatment scheme at full doses. Most patients were postmenopausal and had received prior chemotherapy in the adjuvant setting. Previous adjuvant chemotherapy consisted of cyclophosphamide, methotrexate, and fluorouracil (CMF) combination regimens in 21 patients; 2 patients had received an anthracycline. Most patients had received between six and eight cycles of adjuvant treatment; the schedule and dose intensity of single agents were not always specified. Adjuvant endocrine therapy had been given to six patients and consisted of tamoxifen. Among the five patients treated with first-line endocrine therapy for advanced disease, three received tamoxifen and two received luteinizing hormone-releasing hormone analogs (LHRH-A) combined or not combined with medroxyprogesterone acetate. Patients were subjected to a median of 4 (range 1–6) cycles, for a total of 124 courses.

Table 3 Response to treatment

Intent to treat:				
CR			7/28 (25.0%)	
PR			11/28 (39.2%)	
SD			1/28 (3.5%)	
PD			3/28 (10.7%)	
CR + PR			18/28 (64.2%)	
Evaluable only:				
CR			7/22 (31.8%)	
PR			11/22 (50.0%)	
SD			1/28 (4.5%)	
PD			3/28 (13.6%)	
CR + PR			18/22 (81.8%)	
Sites of disease:	CR	PR	SD	PD
Liver	4/8	2/8	–	2/8
Lung	4/12	5/12	2/12	1/12
Skin-nodes	2/3	1/3		
Bone	–	3/5	1/5	1/5

Treatment toxicity

All patients were assessable for toxicity. The worst grades recorded for each patient for common toxicities are listed in Table 2. Grade 3–4 nausea and vomiting occurred in 15 patients (53.6%) for a total of 30 courses (25.0%); grade 3–4 stomatitis, in 4 patients (14.2%; 7 courses, 5.8%); and asthenia and myalgias worse than or equal to grade 2, in 14 patients (50.0%; 39 courses, 31.4%) and in 7 cases (25.0%; 26 courses, 21.6%), respectively. No patient developed renal toxicity. With regard to hematological toxicity, 4 (14.2%) patients developed grade 3–4 leukopenia (11 courses, 9.1%) before the administration of the next CDDP and EPI cycle. Corresponding grade 3–4 thrombocytopenia and anemia at recycle were recorded in 2 (7.1%) and 8 (28.6%) cases [5 and 15 courses (4.1% and 12.4%)], respectively. Leukopenia and thrombocytopenia at nadir were the most relevant side effects, occurring in 14 (66.8%) and 10 (47.7%) evaluable cases, respectively, and in 35 (36.5%) and 17 (17.6%) courses, respectively. A clear tendency toward reductions in both WBC and platelet counts at nadir was observed with increasing numbers of courses delivered. The hematological toxicity was responsible for a case of septic shock, leading to the death of the patient.

Treatment delivered

A total of 17 patients ended the treatment plan, whereas 11 patients stopped the treatment early due to toxicity (4 cases), refusal (5 cases), early disease progression (1 case), and toxic death (1 case). Chemotherapy was withdrawn in six patients before the first response evaluation. Reduced doses of epirubicin and cisplatin were given to 3 (10.6%) and 4 (13.7%) patients for a total of 5 (4.1%) and 6 (4.9%) cycles, respectively, due to leukopenia and thrombocytopenia. In all, 21 patients tolerated the planned daily dose of LND (450 mg), 5 patients (29 EPI+CDDP cycles) assumed a daily LND dose of 300 mg, 1 patient (2 cycles) received a daily dose of 150 mg, and 1 patient did not tolerate LND at all. Asthenia and myalgias were the reasons leading to LND reduction or withdrawal. Treatment was delayed for 1 week in 19 courses (15.8%) in 8 patients (28.5%) and for 2 weeks in 8 courses (6.5%) in 7 patients (25.0%). Reasons for treatment delay were hematological toxicity in 7 patients (25.0%), associated or not associated with fever, and patient refusal in 8 cases (28.5%). The proportion of patients delaying treatment was higher at the fifth and sixth courses (53% and 47%) with respect to the second, third, and fourth courses (28%, 24%, and 16%, respectively).

Treatment activity

Of the 28 patients enrolled in the study, 6 were not evaluable for response because of toxicity (2 cases) and patient refusal (4 cases). According to the intent-to-treat procedure, 7/28 patients attained a CR (25.0%) and 11/28 showed a PR (39.2%), for an overall response rate of 64.2% (95% confidence interval 46.1–82.3%). In all, 1 of 28 patients (3.5%) developed SD and 3/28 (10.7%), PD. The corresponding response rates pertaining to evaluable patients only were CR 7/22 (31.8%), PR 11/22 (50.0%), SD 1/22 (4.5%), and PD 3/22 (13.6%), for an overall response rate of 81.8% (95% confidence interval 65.1–98.3%; Table 3). As determined by disease site, the greatest response rate was observed in liver metastases: 6 of 8 evaluable patients. The last follow-up examination was performed in April 1997, when the disease of 23 patients had progressed. The median time to progression was 12 months overall (range 0–28 months) and 15 months in responding patients (range 4–28 months).

Discussion

A variety of new therapeutic strategies continues to evolve from in vitro work attempting to manipulate pharmacologically the biochemical homeostasis of cancer cells [30]. Anthracyclines are the most active drugs for breast cancer, but, despite the high response rate obtained with varying aggressive combinations and dose intensity [1], their role in the treatment of advanced disease is only palliative. The search for new drug combinations and the introduction of biochemical modulators are of particular interest in attempts to improve anthracyclines' efficacy. Our group recently conducted a phase III trial, showing that LND significantly enhanced epirubicin activity in advanced breast cancer patients [22].

Following the interesting in vitro results showing a potentiating effect of LND on both CDDP and EPI cytotoxicity in breast-cancer cell lines [27], we designed the present study in advanced breast cancer patients, in which cisplatin at 80 mg/m^2 was associated with the EPI+LND scheme. With respect to the previous trial [22], LND

administration was reduced from a planned dose of 600 mg/day (four tablets) to 450 mg/day (three tablets). The results obtained clearly show that this three-drug combination is highly active, with a response being obtained in more than 80% of evaluable patients The median time to progression of 15 months observed in responding patients is noteworthy, particularly considering that one-third of them had liver involvement. When all registered patients were evaluated according to an intent-to-treat analysis, the response rate fell to about 65% and the possible superiority of this scheme over EPI+LND alone appeared to be less evident. The reason for the discrepancy between registered and evaluable patients is the elevated and somewhat unexpected toxicity of this combination scheme, leading to treatment discontinuation, to patient refusal, and to one toxic death.

The addition of cisplatin led to an increase in gastrointestinal and hematological toxicity. Grade 3/4 nausea and vomiting, indeed, has been reported in about 15% of patients receiving EPI+LND [22], and this rate appears to be lower than the corresponding 53% obtained in the present study. 5-Hydroxytryptamine ($5HT_3$) antagonists [31] have been employed to counteract gastrointestinal toxicity in all centers, but the association of these antiemetic drugs with steroids has been used by only a few institutions and this may partially account for the scarce control of this side effect. The WBC toxicity encountered in the present study did not differ from that reported for EPI+LND, but a greater incidence of platelet and Hb toxicity was observed. Hematological toxicity appeared to be cumulative, leading to treatment delay in about 50% of patients at the fifth and sixth chemotherapy courses.

When patients were stratified according to disease site, an elevated response rate was observed in patients with liver involvement, further supporting the previous findings of two randomized studies [22, 23] that reported a greater response rate in liver metastases in patients treated with anthracyclines plus LND in comparison with those receiving anthracyclines alone.

In conclusion, the association of EPI with CDDP and LND on the schedule used in the present study appears to be very active but substantially toxic. This regimen, with the CDDP dose being reduced to 60 mg/m^2, is being tested against EPI alone, EPI+LND, and EPI+CDDP in a randomized study with a factorial design.

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