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Cisplatin and epirubicin plus oral lonidamine as first-line treatment for metastatic breast cancer: a phase II study of the Southern Italy Oncology Group (GOIM)

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Lonidamine (LND) is a unique antineoplastic drug derived from indazole-3-carboxylic acid which inhibits oxygen consumption and aerobic glycolysis, interfering with energy metabolism of neoplastic cells. LND has been experimentally shown to potentiate the cytotoxic effects of epirubicin (EPI) in human breast cancer cell lines, cisplatin activity in both platinum-sensitive and -resistant human ovarian carcinoma cell lines, and EPI antineoplastic activity in some recent phase III trials carried out in advanced breast cancer. A multicenter phase II trial was carried out with the combination of cisplatin 60 mg/m^2, EPI 100 mg/m^2 and LND 450 mg/day p.o. in three refracted doses/day starting 2 days before cisplatin and EPI (day −2 and −1), stopping 2 days after chemotherapy (day 0, +1 and +2). Thirty patients with metastatic breast cancer were enrolled into the study. Twenty-nine patients were evaluable for objective response. The overall response rate accordingly to an intent-to-treat analysis was 73% (95% CL 54–88%). Four patients achieved complete response (13%; 95% CL 4–31%) with a median duration of 9.5 months (range 4–16) and 18 patients had partial response (60%; 95% CL 41–77%) with a median duration of 9.8 months. Stable disease was obtained in five cases (17%) and progressive disease was recorded in three patients. One patient died of progressive cancer before restaging. The overall median survival of the whole series of patients was 14+ months. The most frequent toxicities were represented by gastrointestinal and hematological side effects. The combination of cisplatin + EPI plus oral LND is active against metastatic breast carcinoma. The antineoplastic activity of the cisplatin + EPI + LND regimen is as high as that reported for more aggressive regimens such as the fluorouracil + doxorubicin + cyclophosphamide combinations without an increase in toxic effects.

Key words: Breast cancer, cisplatin, epirubicin, lonidamine.

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Introduction

To date front-line polychemotherapy is able to induce objective response rates as high as 90% in selected studies carried out on advanced breast cancer patients at their first diagnosis of metastatic disease.[1] These figures are somewhat lower in other studies carried out on less selected series of patients with metastatic breast cancer even if treated with aggressive polychemotherapeutic regimens.[2–4] However, despite some impressive tumor regression, all patients affected by metastatic breast cancer carry a dismal prognosis since they will eventually show progressive disease at pre-existing tumoral sites or the appearance of new metastases.[1–3] Therefore, the search for new active chemotherapeutic combinations still represents one of the major goals for medical oncologists.

Anthracyclines are certainly the most active class of antineoplastic agents currently available for the treatment of metastatic breast cancer.[5] Preclinical investigations have shown that anthracycline drugs display a steep dose-response curve, which strongly supports clinical data on acute leukemias and bone sarcomas suggesting that higher doses of anthracycline are associated with a higher complete response rate and improved survival.[6–9] These data are also supported by the studies of Hryniuk[10] and Tannock *et al.*[11] who showed that an increased dose intensity of antineoplastic drugs is associated with a better response rate and an increased quality of life. These observations have also been partially confirmed by studies on metastatic breast cancer treated with high-dose epirubicin (EPI), i.e. the less cardiotoxic 4′-epimer of doxorubicin.[12–14] For these reasons several regimens containing high-dose EPI have been tested against

metastatic breast cancer with the aim of improving clinical results and reducing toxicity.

Although cisplatin has been associated with a low response rate (below 10%) in initial phase II trials on heavily pretreated patients,[15,16] subsequent clinical investigations have demonstrated that cisplatin has significant antineoplastic activity when employed as first-line chemotherapy against metastatic breast carcinoma.[17-19] In fact cisplatin is able to induce a nearly 30% overall response rate even if observed tumor regressions were mostly partial and short lived, usually in the range of 3-4 months.[18,19]

Lonidamine (LND) is a unique antineoplastic drug derived from indazole-3-carboxylic acid which inhibits cellular oxygen consumption and aerobic glycolysis, interfering with energy metabolism of neoplastic cells.[20,21] LND has been experimentally shown to potentiate the cytotoxic effects of radiation,[21,22] aklylating agents,[23] EPI in human breast cancer cell lines,[24] and cisplatin activity in both platinum-sensitive and -resistant human ovarian carcinoma cell lines.[25,26] On the clinical side, single-agent LND has been demonstrated to yield a 15% response rate in metastatic breast cancer,[27,28] and to induce the recovery of sensitivity to cisplatin in previously treated patients with ovarian and breast carcinoma.[29,30] Potentiation of EPI antineoplastic activity by LND has also been demonstrated by some recent phase III trials carried out in advanced breast cancer.[31,32]

According to the above reported rationale, we carried out a multicenter phase II trial with the combination of cisplatin and EPI plus oral LND in a small series of patients with metastatic breast cancer at first recurrence. In this paper we report such clinical experience concerning the activity and toxicity of this regimen.

Materials and methods

Entry criteria

After informed consent, 30 patients with histologically confirmed metastatic breast carcinoma were enrolled in the study. Prior to the entry, patients had to fulfil all the following eligibility criteria: measurable disease according to the WHO criteria outside of previous irradiation fields;[33] age 18-70 years; ECOG performance status ≤ 2; life expectancy >3 months; adequate bone marrow function (WBC $>4\ 000/mm^3$; PTL $>120\ 000/mm^3$; serum bilirubin ≤ 1.2 mg% and serum transaminases less than two times the normal value; serum creatine ≤ 1.2 mg%, BUN ≤ 50 mg%, and creatine clearance >60 ml/min; no major ECG abnormalities or altered cardiac function at ecocardiography; absence of brain metastases; absence of a second malignancy with the exception of adequately managed *in situ* uterine carcinoma and/or cutaneous basal call carcinoma; medical history negative for severe or uncontrolled cardiovascular, renal, liver, metabolic or infectious diseases. Geographical accessibility to the cancer centers was preferred in order to avoid difficulty in managing toxicity of chemotherapy or in assuring correct follow-up. Patients were not considered eligible if blastic bone lesions were the only sign of disease or if severe pleural or peritoneal effusions were present. Previous adjuvant chemotherapy was accepted but the treatment had to be stopped at least 12 months before entry into the study. In the case of previous chemotherapy with anthracyclines, the total cumulative dose of previously delivered EPI had to be 400 mg/m^2 or less. Previous hormonotherapy was allowed but it had to be discontinued at least 4 weeks before starting chemotherapy.

Staging procedures

Before starting chemotherapy, patients were extensively staged with medical history, physical examination, ECG, abdominal sonogram, ^{99}Tc bone scan, standard chest X-ray, mammography, and routine hematological and serum chemistry tests. CT scan and bone X-rays were employed as needed. Most of these procedures were also employed for the assessment of objective response. It is noteworthy that cardiological evaluation of the ECG and left ventricular ejection fraction (LVEF) was mandatory before enrolment into the study. Monitoring of LVEF was performed every two cycles.

Treatment plan

The treatment plan consisted of: (i) cisplatin (Platamine®; Pharmacia-Upjohn, Milan, Italy) 60 mg/m^2 diluted in 500 cm^3 of normal saline and given as a 1 h infusion with a standard pre- and posthydration protocol with kCl 20 mEq and $MgSO_2$ plus forced diuresis with 250 cm^3 of 18% manitol on day 1; (ii) EPI (Farmorubicina®; Pharmacia-Upjohn) 100 mg/m^2 diluted in 100 cm^3 of normal saline and given as an i.v. bolus on day 1; and LND (Doridamina®; Angelini, Rome, Italy) 450 mg/day p.o. in three refracted doses/day starting 2 days before cisplatin and EPI (day -2 and -1), stopping 2 days after chemotherapy (day 0, +1 and +2). Investigators were free of employing

cardioprotection with dexrazoxane 1000 mg/m^2 in 250 cm^3 of ringer lactate over 30 min infusion before administration of EPI.[34] Antiemetic therapy consisted of anti-HT_3 agents given i.v. 15 min before starting chemotherapy. Methylpredisolone 125 mg i.v. was routinely given as part of the antiemetic protocol.

Chemotherapeutic treatment was repeated every 3 weeks for three cycles before patients were re-staged to assess objective response. Duration of chemotherapy was dependent on pattern and severity of toxicity and type of objective response achieved. Patients showing complete regression, partial remission or stabilization were given a further three cycles if unacceptable toxicity was absent. Patients with remission after six cycles were given a further two cycles depending on the investigator's decision, toxicity pattern and cardiac function. On the other hand, patients showing progressive disease were given a second-line chemotherapy if required.

Response assessment and statistics

Clinical data were centrally collected at the Service of Chemotherapy of the University of Palermo. Toxicity and objective response were evaluated according to the WHO criteria.[33] Briefly, complete response (CR) was defined as the complete disappearance of all signs of disease for at least 4 weeks; partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the major perpendicular diameters of all measurable lesions for at least 4 weeks without the appearance of any new metastatic deposit; stabilization (SD) as a less than 50% decrease or less than 25% increase in the size of tumoral deposits; and progressive disease (PD) as the appearance of new metastatic sites and/or a greater than 25% increase in the size of pre-existing tumoral lesions.

Objective responses were reported as their relative rates with 95% confidence limits (95% CL). Length of objective response was calculated from the first day of chemotherapy until the date of documented progression or last follow-up. Survival was calculated from the day of registration into the study until death or last follow-up. Univariate analysis of the duration of response and survival was calculated employing the product-limit estimate of Kaplan-Meier.

Side effects

Toxicity was reported according to the WHO.[33] In case of grade 4 toxicity, with the exception of leukopenia and alopecia, chemotherapy was discontinued and patients were put off-study. If at day 21 (i.e. before every cycle) neutrophils and platelets were less than 2000/mm^3 and 120 000/mm^3, respectively, treatment was delayed for 1 week. Patients without complete recovery within 2 weeks from the planned day of recycling were given chemotherapy with a 50% reduction on the dose of EPI. Treatment was definitively withheld if LFEF fell by more than 15% below the patient's own baseline during chemotherapy.

Results

Patient population

Thirty patients with metastatic breast cancer were enrolled into the study. Clinical and demographic characteristics are depicted in Table 1. Briefly, enrolled patients had a median age of 60 years with a median performance status according to the Karnofsky Index of 90. Two-thirds of patients were postmenopausal at entry. Hormonal status was unknown in 30% of cases, positive in 37% and negative in 33%. Most patients had previously received surgery (83%), seven adjuvant

Table 1. Patient characteristics

No. of enrolled patients	30 (100%)
Median age (range)	60 (40–71)
Median PS	90
Menopausal status	
premenopausal	9 (30%)
postmenopausal	21 (70%)
Hormone receptors	
positive	11 (37%)
negative	10 (33%)
unknown	9 (30%)
Previous treatments	
surgery	25 (83%)
radiotherapy	7 (23%)
chemotherapy	23 (77%)
hormontherapy	15 (50%)
Dominant site of disease	
viscera	18 (60%)
bone	6 (20%)
soft tissue	6 (20%)
Sites of disease	
bone	15 (50%)
node	12 (40%)
liver	8 (27%)
lung	4 (13%)
breast	5 (17%)
skin	2 (7%)
Number of involved sites	
single	11 (37%)
multiple	19 (63%)

radiotherapy (23%), 15 adjuvant hormonal therapy with tamoxifen and 23 adjuvant chemotherapy. Of the latter group, 13 patients had received EPI (75–90 mg/m^2/cycles for three or four cycles plus CMF 1 + 8 i.v. for four cycles as adjuvant chemotherapy to surgery. Most patients (63%) had multiple sites of disease at entry. Five patients had advanced locoregional disease with distant metastases at entry, but they were free of any previous therapy. The majority of patients had visceral lesions as the dominant site of disease. Sites of disease included bone in half of cases, node in 40% of patients, liver in 27%, and lung, skin and breast in about 15%. Sixty-three percent of patients had multiple metastases.

Objective response and survival

Twenty-nine patients were evaluable for objective response: one patient had clinically progressive disease before re-staging after the third cycle of chemotherapy. Nevertheless, this patient was considered as progressive disease since all patients were included in an intent-to-treat analysis. The overall response rate was 73% (95% CL 54–88%). Four patients achieved CR (13%; 95% CL 4–31%) with a median duration of 9.5+ months (range 4–16 months) and 18 patients had PR (60%; 95% CL 41–77%) with a median duration of 9.8 months. SD was obtained in five cases (17%) and it lasted a median of 4.5 months. PD was recorded in three patients. After a median follow-up of 11 months, the overall median survival of the whole series of patients was 14.0+ months. Objective responses were recorded both at visceral and bone sites.

Toxicity

Chemotherapeutic treatment with cisplatin + EPI + LND was generally quite well tolerated. No toxic deaths were recorded. The most frequent toxicites were represented by gastrointestinal and hematological side effects. The main toxic effects are depicted in Table 2. Grade 3–4 leukopenia was observed in 40% of patients but significant episodes of febrile neutropenia were limted (five patients). Grade 3 thrombocytopenia was seen in 7% of cases. Anemia was recorded in more than half of the patients, although a grade 3 decrease in hemoglobin was recorded in 7% of cases. Myalgias were recorded in 19 patients (63%), although in most cases they were mild and tolerable. All patients suffered from complete alopecia. Renal toxicity was minimal.

Table 2. Toxicity

Type of toxicity	WHO grade			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
leukopenia	9 (30%)	6 (20%)	10 (33%)	5 (17%)
PTL	5 (17%)	7 (23%)	2 (7%)	0
anemia	8 (40%)	6 (20%)	2 (7%)	0
Gastrointestinal				
nausea/vomiting	11 (37%)	9 (30%)	5 (17%)	0
stomatis	7 (23%)	6 (20%)	5 (17%)	0
diarrhea	3 (10%)	2 (7%)	0	0
Musculo-cutaneous				
alopecia	0	0	30 (100%)	0
myalgias	11 (37%)	5 (17%)	3 (10%)	0

Discussion

In the last decade attempts to improve the clinical outcome of patients with advanced breast cancer have included the use of conventional agents at higher doses, with growth factors and hematological support or the combination of standard chemotherapy with potentiating drugs. These aim at increasing the activity of old drugs and overcoming resistance.[2,3,13,23]

The use of LND as a potentiator of epidoxorubicin and cisplatin antineoplastic activity is based on the results of preclinical investigation carried out *in vitro*,[25,26] and of clinical trials demonstrating that LND is able to improve EPI activity in metastatic breast cancer and to induce recovery of sensitivity to cisplatin in patients with cisplatin-resistant advanced ovarian carcinoma.[18,19]

Based on this rationale, the Southern Italy Oncology Group carried out this phase II trial with such a combination in a small series of patients with metastatic breast cancer at their first metastatic recurrence. The overall tolerance to this combination regimen has been acceptable. Toxicities, mainly hematological and gastrointestinal adverse effects, were largely expected, even if anemia was reported at an unexpected high frequency. Myelotoxicity on red cells has also been stressed in other trials employing high-dose epirubicin and may be related to the repeated use of anthracycline drugs in high doses in combination with alkylators.[2,3] Clinically assessed CR rate was significant (13%) but not outstanding as reported with a similar combination of LND + cisplatin + EPI by other authors.[35] The 73% overall objective response rate achieved in the present study is, however, significant, and is almost identical to response rates reported by our cooperative group in two previous phase II trials employing increasing

doses of anthracycline in combination with cyclophosphamide and 5-fluorouracil with folinic acid.[2,3] These latter regimens were very aggressive and required the routine use of granulocyte colony stimulating factor to protect patients from potentially life-threatening myelosuppression.

The overall response rate achieved with the combination of cisplatin + EPI + LND is certainly higher than that expected with EPI alone, even if employed at high doses. Although such an observation should be confirmed by a prospective randomized phase III trial, these preliminary data suggest a potentiation effect of LND on cisplatin + EPI, even if the degree of activity of such a combination, at least in terms of median duration of duration and survival, is not superior to that reported in other phase II trials with other combinations.

In conclusion, the combination of cisplatin + EPI plus oral LND is active, at least in terms of overall response rate, against metastatic breast carcinoma. The relative impact of LND on the combination of cisplatin and EPI is beyond the aims and possibilities of this phase II study, and could deserve a prospective randomized phase III trial. However, the antineoplastic activity of the cisplatin + EPI + LND regimen is as high as that reported for more aggressive regimens such as the fluorouracil + doxorubicin + cyclophosphamide combinations without an increase in toxic effects.

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