Breast Cancer Research and Treatment **56:** 233–237, 1999.

Report

Weekly epirubicin plus lonidamine in advanced breast carcinoma

Cecilia Nisticò[1], Carlo Garufi[1], Michele Milella[2], Anna Maria D'Ottavio[1], Angela Vaccaro[1], Alessandra Fabi[2], and Edmondo Terzoli[1]
[1]*Service of Complementary Medical Oncology, and* [2]*Division of Medical Oncology I, Regina Elena Cancer Institute, Rome, Italy*

Key words: advanced breast cancer, epirubicin, lonidamine, weekly schedule

Summary

Lonidamine has been demonstrated to potentiate the cytotoxic activity of several antineoplastic drugs, for example anthracyclines. Moreover, epirubicin is considered one of the most active drugs in advanced breast cancer, although optimal dose and schedule remains to be defined.

In the present study we have treated 51 patients with advanced breast cancer with a combination of lonidamine (450 mg/day orally from day 1 throughout treatment) and epirubicin (25 mg/m^2 IV) administered according to a weekly schedule for 24 weeks. Objective responses were observed in 29 out of 51 patients (57%; CR 16%, PR 41%). Liver metastases responded in eight out of 12 evaluable patients (67%). Average response duration was 12.4 months and median overall survival was 23 months (range 1–90+). Toxicity was negligible.

The combination of weekly epirubicin and lonidamine is feasible and active in advanced breast cancer patients.

Introduction

Breast cancer is the most frequent neoplasm in women in European countries, with an estimated 135,000 new cases per year (24% of all cancer cases) and 58,000 recorded deaths per year (18% of all cancer deaths) [1].

Despite the improvements achieved in the overall outcome of breast cancer patients, metastatic spread is still frequent. In fact, up to 60% of the patients will ultimately develop distant metastases. The treatment of advanced breast cancer is still complex and, in part, controversial, as there is still no universally accepted therapy. However, conventional treatments have no curative impact on advanced disease, with a median survival of about two years after evidence of metastases [2].

Although several new active drugs such as the taxanes (paclitaxel and docetaxel) and vinorelbine have become available in the recent years, anthracyclines (doxorubicin and epirubicin) still play a major role in the treatment of advanced breast cancer, with objective response rates ranging from 30% to 50% when administered as single agents [3]. Anthracycline-containing polychemotherapy regimens achieve slightly better response rates, but a significant improvement in terms of survival has not been clearly demonstrated, in spite of greater toxicity [4]. Recent data indicate that weekly administration schedules may increase total drug exposure while decreasing its peak plasma levels, therefore reducing toxicity, with particular regard to cardiotoxicity, while retaining cytotoxic activity [5].

Lonidamine, a carboxylic indazol derivative, acts by inhibiting cellular energy metabolism and by modifying cellular membrane permeability [6–8]. This drug appears to potentiate the cytotoxic activity of various chemotherapeutic agents, such as anthracyclines and cisplatin, both *in vitro* and *in vivo* [9–12]. Lonidamine as a single agent achieves an objective response rate of about 14% in advanced breast cancer patients, with negligible toxicity, primarily consisting of myalgias and asthenia [13].

This phase-II trial was therefore conducted to study the activity and toxicity of the combination of weekly epirubicin plus lonidamine.

Patients and methods

Between October 1990 and October 1992, 51 consecutive patients with advanced breast cancer were enrolled in the study. All patients provided informed consent.

Eligibility criteria included: histologic diagnosis of breast carcinoma, metastatic lesions measurable and/or evaluable by physical examination, radiological tests, ultrasonography and/or computed tomography (CT) scan, age between 18 and 75 years, ECOG performance status ≤ 3, life expectancy of more than three months, adequate bone marrow (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin ≥ 9.0 g/dl), liver and renal functions within normal limits except in the presence of liver localizations of disease (ASAT/ALAT $\leq 1.5\times$ upper normal limit (UNL), serum bilirubin $\leq 1.5\times$ UNL, serum creatinine ≤ 1.5 mg/dl), normal left ventricular ejection fraction (LVEF). Prior non anthracycline-containing chemotherapy was allowed, either in adjuvant or first-line metastatic setting, completed at least four weeks before study entry. Prior hormone therapy was allowed, as well as prior radiotherapy, provided that at least four weeks had elapsed since the last treatment and no more than 20% of the bone marrow reserve had been irradiated. Irradiated lesions were not used for response assessment, unless clearly progressive.

Patients with brain metastases were considered not eligible. Other exclusion criteria included pregnant or lactating women, or women of childbearing potential not using adequate contraception; presence of active infections or cardiac disease.

Patient baseline evaluation consisted of complete medical history, physical examination, and PS assessment. All the patients were submitted to baseline chest radiograms, bone scan, and abdomen ultrasonography, as well as to other appropriate imaging studies to document the extent of disease.

Laboratory studies at presentation included determination of complete blood cell and platelet counts, biochemical profile, serum tumor markers (CEA, CA 15-3) and urine analysis. Cardiac function evaluation included ECG and LVEF measurement by echocardiography.

Complete blood cell and platelet counts were repeated once weekly during treatment. The patients underwent complete physical examination and biochemical profile every four weeks. ECG was repeated every four weeks, and echocardiography with LVEF determination after 12 and 24 weeks.

The treatment scheme was the following: epirubicin, 25 mg/m^2 IV once weekly for 24 weeks, in the absence of disease progression or unacceptable toxicity. The administration scheme of lonidamine was the following: from day 1 to 3, 150 mg p.o./day; from day 4 to 6, 300 mg p.o./day; from day 7 on, 450 mg p.o./day in three divided doses for the entire duration of the treatment. Retreatment with epirubicin was allowed in patients with Hgb values ≥ 8 g/dl, leukocyte counts $\geq 2.5 \times 10^9$/l, platelet counts $\geq 90 \times 10^9$/l. The antiemetic therapy consisted of ondansetron (8 mg IV) plus dexamethasone (4 mg IV) before the administration of epirubicin.

Toxicity and responses were defined according to WHO criteria [14]. A complete response (CR) was defined as complete disappearance of all detectable disease for at least four weeks. A partial response (PR) was defined as a 50% reduction in the sum of the diameters of all measurable and/or evaluable lesions for at least four weeks and no increase of already existing lesions or the appearance of a new lesion. Stable disease (SD) was considered no appearance of new lesions for six months, with no pre-existing lesions increasing by more than 25%. Progressive disease (PD) was defined as an increase of more than 25% in the sum of the products of the diameters of any evaluable lesions or the appearance of a new lesion. The objective response was evaluated at three and six months.

Patients with bone metastases were evaluated according to the following parameters: bone scan with radiograms aimed at the uptaking areas, CEA, CA 15-3, and alkaline phosphatase levels. The bone pain referred by the patients was measured by means of the visual analogue scale of Scott and Huskisson [15] at the beginning of the treatment and repeated every four weeks. Patients with bone metastases as the only site of disease were considered responders in the presence of radiologic evidence of decrease in size or recalcification of lytic lesions combined with the reduction in bone scan uptake or in the painful symptomatology, with a reduction in circulating tumor markers or in alkaline phosphatase levels.

Patients who received at least four weeks of therapy were considered evaluable.

Results

Patient characteristics are presented in Table 1. All patients were evaluable for toxicity. All but two patients could be evaluated in terms of response to treatment (one patient died for treatment- and disease-unrelated

Table 1. Patient characteristics

No. of patients entered	51
Age	
Median	54
Range	36–75
Performance status (ECOG)	
0–1	43
2–3	8
Menopausal status	
Pre-	12
Post-	39
Estrogen receptor status	
Positive	20
Negative	10
Unknown	21
Previous chemotherapy	
Adjuvant only (CMF 18 pts, anthracyclines 1 pt)	19
Advanced only	9
Adjuvant + advanced	1
Previous hormone therapy	
Adjuvant	15
Advanced	8
Dominant metastatic sites	
Bone	17
Soft tissue	20
Viscera	14
Disease free-interval	
Adjuvant CHT ($n = 20$)	
$\leq$ 12 months	2
12–24 months	7
24 months	11
No adjuvant CHT ($n = 31$)	
$\leq$ 12 months	6
12–24 months	7
24 months	18

causes and one was lost to follow-up after two treatment administrations). These two patients were considered progressive at the time of last follow-up for any further analysis.

Median number of treatment weeks was 24 (range 1–24), with 31 patients (60.7%) completing the planned treatment. The main reason for discontinuation was progressive disease (17 patients, 33%). No further treatment was given after week 24, even in patients with continuing response, and no hormonal maintenance therapy was administered. Median delivered dose-intensity (DI) was 23.5 mg/m^2/week (94% of the planned DI).

Objective responses were observed in 29 out of 51 patients (57%), eight of which were complete (16%) and 21 partial (41%). Five patients had SD (10%) and 17 had PD (33%). Liver disease responded in 8/12 evaluable patients (67%). The average duration of the response was 12.4 months. Median time to progression for the entire group of patients was 34 weeks. The median survival was 23 months (range 1–90+).

Treatment was generally well tolerated (Table 2) and no dose reductions were required. WHO grade 3 neutropenia was observed in only two patients (4%). There were no episodes of anemia or thrombocytopenia.

Gastroenteric tolerance was excellent, only one patient (2%) experienced grade 3 vomiting despite antiemetic therapy. No patients presented alterations of hepatic and/or renal function that could be attributed to the treatment. One patient (2%) had grade 3 cardiac toxicity with rhythm alterations and symptomatic dysfunction after the 4th administration of epirubicin (cumulative dose 100 mg/m^2). Grades 2 and 3 alopecia were observed in 10 patients (20%). Four patients developed a mycosis of the ungual bed. Twenty-two patients (43%) developed grades 1 and 2 myalgias which, however, did not require specific treatment.

Discussion

We first report herein the activity and toxicity of the combination of epirubicin, administered according to a weekly schedule, with lonidamine. The dose of lonidamine of 450 mg/day in three divided doses was chosen for the present study based on both pharmacokinetics and clinical considerations. Continuous administration of 360 mg/day, in two to three daily doses for at least four weeks, has been indeed shown to produce maximum serum concentrations of about 15 μg/ml within 2 h and 3μg/ml after 12 h; higher doses (430–520 mg/m^2/day by mouth) have produced almost identical concentrations. Moreover, peculiar non-hematological side effects (such as myalgias, asthenia, and epigastric pain) are known to be dose-dependent, while clinical efficacy is schedule-rather than dose-dependent [10, 16–17].

A high response rate of 57% (16% CR) was achieved in the present study, with negligible toxicity. Moreover, this combination regimen has proven

Table 2. Toxicity (evaluable patients: 51)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	49 (96%)	–	1 (2%)	2 (4%)	–
Thrombocytopenia	51 (100%)	–	–	–	–
Anemia	51 (100%)	–	–	–	–
Alopecia	17 (33%)	25 (49%)	9 (18%)	–	–
Nausea/vomiting	30 (59%)	17 (33%)	3 (6%)	1 (2%)	–
Mucositis	51 (100%)	–	–	–	–
Cardiac	49 (96%)	1 (2%)	–	1 (2%)	–
Myalgias	29 (57%)	21 (41%)	1 (2%)	–	–

highly active in patients with dominant visceral site of disease, with an objective response rate of 67% on liver metastases. Interestingly, no significant differences in response rate were observed whether patients were treated as first- or second-line strategy (56% and 70%, respectively). These results favourably compare with those obtained with single agent epirubicin administered on a three-weekly schedule, in which objective response rate ranges from 25% to 49% [18–20], as well as with those obtained with weekly epirubicin alone (25–50% [21, 22]. However, average duration of the response and median survival (12.4 and 23 months, respectively), evaluated after a median follow-up of more than five years, are not different from those reported in the literature in advanced breast cancer [2].

Our results also favourably compare with those reported by Moraglio et al. with the combination of lonidamine and epirubicin administered at the dose of 75 mg/m^2 on a three-weekly schedule (objective response rate 40%) [23]. On the other hand, Gardini et al. have recently reported on the high activity of epirubicin and cyclophosphamide plus lonidamine combination on liver metastases from breast cancer [24]. In a recent randomized study, the addition of lonidamine to epirubicin administered on a three-weekly schedule has yielded a significantly higher objective response rate as compared to epirubicin alone (59.4% vs. 40.2%, respectively), even in patients with liver metastases (63.3% vs. 35.3%, respectively) [25]. Similarly, Calabresi et al. have demonstrated in a randomized study [26] a significantly higher response rate for the addition of lonidamine to the FAC regimen as compared with FAC alone (66.3% vs 42.3%, respectively), even in patients with dominant visceral site of disease (60% vs. 34%, respectively). A statistically significant increase in the response rate on liver metastases has also been observed in metastatic breast cancer patients treated with doxorubicin plus lonidamine as compared with doxorubicin alone (68% vs. 33%, $p = 0.03$), in a recent randomized study [27].

In conclusion, the combination of lonidamine plus weekly epirubicin proves highly effective in advanced breast cancer, in spite of a toxicity which is not different from that observed with weekly epirubicin alone, except for myalgias which occurred in 43% of patients as a results of lonidamine administration. This allowed the delivery of a dose-dense treatment, without the need of dose-reduction or discontinuation. A schedule-dependent potentiation of anthracycline antitumor activity by lonidamine has been described both *in vitro* and *in vivo* [9–12]. Moreover, lonidamine has also recently proven effective in the recovery of clinical response to anthracycline-containing regimens [28]. In the present study, the use of a continuous weekly schedule might have further favoured the synergism between epirubicin and lonidamine. Although speculative, this hypothesis is supported by the observation that using a lower, and potentially less toxic, dose of epirubicin administered according to a weekly schedule (planned epirubicin DI: 25 mg/m^2/week) we obtained a response rate similar to that reported by Dogliotti et al. [25] with an epirubicin dose of 120 mg/m^2 every three weeks (planned epirubicin DI: 40 mg/m^2/week). Indeed, as recently suggested by Norton [29], the continuous exposure of tumor cells to an agent which alters membrane permeability, such as lonidamine, in combination with a DNA-damaging drug, such as epirubicin, may permanently impair tumor cell growth, possibly translating into a greater clinical efficacy. Although this hypothesis awaits definitive confirmation, the association of lonidamine with weekly schedules of epirubicin warrants further exploration.

References

1. Jensen OM, Esteve J, Moller H, Renard H: Cancer in the European Community and its member states. Eur J Cancer 26: 1167–1256, 1993
2. Clark GM, Sledge GW Jr, Osborne CK, McGuire WL: Survival from first recurrences: relative importance of prognostic factors in 1,015 breast cancer patients. J Clin. Oncol 1: 55–61, 1987
3. Hortobagyi GN: Treatment of breast cancer. N EngI J Med 339: 974–984, 1998
4. Harris JR, Morrow M, Norton L: Malignant tumors of the breast. In: De Vita VT Jr, Helman S, Rosenberg SA (eds) Cancer: Principles and Practice of Oncology. JB Lippincott, Philadelphia, 1997, pp 1557–1616
5. Twelves CJ, Dobbs NA, Aldhous M, Harper PG, Rubens D, Richards MA: Comparative pharmacokinetics of doxorubicin given by three different schedules with equal dose intensity in patients with breast cancer. Cancer Chemother Pharmacol 28: 302–307, 1991
6. Floridi A, Paggi MG, Marcante ML, Sivestrini B, Caputo A, De Martino C: Lonidamine, a selective inhibitor of aerobic glycolysis of murine tumor cell. J Natl Cancer Inst 66: 497–499, 1981
7. Floridi A, Paggi MG, D'Atri 5, De Martino C, Marcante ML, Silvestrini B, Caputo A: Effect of lonidamine on the energy metabolism of Erlich ascites tumor cells. Cancer Res 41: 4661–4666, 1981
8. De Martino C, Malorni W, Accinni L, Rosati F, Nista A, Formisano G, Silvestrini B, Arancia G: Cell membrane changes induced by lonidamine in human erythrocytes and T-lymphocytes and Erlich ascites tumor cells. Exp Mol Path 46: 15–30, 1987
9. Citro G, Cucco C, Verdina A, Zupi G: Reversal of adriamycin resistance by lonidamine in human breast cancer subline. Br J Cancer 64: 534–536, 1991
10. Savini S, Zoli W, Nanni O, Volpi A, Frassinetti GL, Magni E, Flamigni A, Amadori A, Amadori D: *In vitro* potentiation by lonidamine of the cytotoxic effect of adriamycin on primary and established breast cancer cell lines. Br Cancer Res Treat 24: 27–34, 1992
11. Silvestrini R, Zaffaroni N, Villa R, Orlandi R, Costa A: Enhancement of Cisplatin activity by lonidamine in human ovarian cancer cells. Int J Cancer 52: 813–817, 1992
12. Del Bufalo D, Zupi G: *In vitro* potentiation of epirubicin activity by lonidamine in a human breast cancer cell line. Int J Oncol 4: 737–740, 1994
13. Pronzato P, Amoroso D, Bertelli G, Conte PF, Cusimano MP, Ciottoli GB, Gulisano M, Lionetto R, Rosso R: Phase II study of lonidamine in metastatic breast cancer. Br J Cancer 59: 251–253, 1989
14. Scott J, Huskisson EC: Graphic representation of pain. Pain 2:175–184, 1976
15. Miller AB, Hoogstraten B, Staquet M, Winkler A: Reporting results of cancer treatment. Cancer 47: 207–214, 1981
16. Robustelli della Cuna G, Pedrazzoli P: Toxicity and clinical tolerance of lonidamine. Semin Oncol 18(Suppl 4): 18–22, 1991
17. Calabresi F: Drug resistance: lonidamine. Principles and Practice of Oncology Updates 8: 1–15, 1994
18. Perez DJ, Harvey VJ, Robinson BA, Atkinson CH, Dady PJ, Kirk AR, Evans BD, Chapman PJ: A randomized comparison of single-agent doxorubicin and epirubicin as first-line cytotoxic therapy in advanced breast cancer. J Clin Oncol 9: 2148–2152, 1991
19. Jain KK, Casper ES, Geller NL, Hakes TB, Kaufman RJ, Curie V, Schwartz W, Cassidy C, Petroni GR, Young CW: A prospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. J Clin Oncol 3: 818–826, 1985
20. Hortobagyi GN, Yap HY, Kau SW, Fraschini G, Ewer MS, Chawla SP, Benjamin RS: A comparative study of doxorubicin and epirubicin in patients with metastatic breast cancer. Am J Clin Oncol 12: 57–62, 1989
21. Beretta G, Locatelli C, Tabiadon D, Labianca R, Fraschini P, Luporini G: Epirubicin treatment of advanced breast carcinoma with the weekly low-dose regimen. Oncology 44: 6–12, 1987
22. Barni S, Archili C, Lissoni P, Paolorossi F, Crispino S, Tancini G: A weekly schedule of Epirubicin in pretreated advanced breast cancer. Tumori 79: 45–48, 1993
23. Moraglio L, Brema F, Pastorino G, Martini MC, Vallauri M: Combination of epirubicin and lonidamine for treatment of advanced breast cancer. Tumori 81: 107–111, 1995
24. Gardin G, Barone C, Nascimben O, lanniello G, Sturba F, Contu A, Pronzato P, Rosso R: Lonidamine plus epirubicin and cyclophosphamide in advanced breast cancer. A phase II study. Eur J Cancer 32A: 176–177, 1996
25. Dogliotti L, Berruti A, Buniva T, Zola P, Baù MG, Farris A, Sarobba MG, Bottini A, Alquati P, Deltetto F, Gosso P, Monzeglio C, Moro G, Sussio M and Perroni D. Lonidamine significantly increases the activity of epirubicin in patients with advanced breast cancer: results from a multicenter prospective randomized trial. J Clin Oncol 14: 1165–1172, 1996
26. Calabresi F, Di Lauro L, Marolla P, Gallocurcio C, Paoletti G, Calabrò A, Giannarelli D, Ballatore P, Foggi CM, Di Palma M, Stolfi R, Cortesi E: Fluorouracil, doxorubicin and cyclophosphamide versus fluorouracil, doxorubicin and cyclophosphamide plus lonidamine for the treatment of advanced breast cancer: a multicentric randomized clinical study. Semin Oncol 2(Suppl 4): 66–72, 1991
27. Amadori D, Frassineti GL, De Matteis A, Mustacchi G, Santoro A, Cariello S, Ferrari M, Nascimben O, Nanni O, Lombardi A, Scarpi E, Zoli W: Modulating effect of lonidamine on response to doxorubicin in metastatic breast cancer patients: results from a multicenter prospective randomized trial. Breast Cancer Res Treat 49: 209–217, 1998
28. Tomirotti M, Bernardo G, Epifani C, Biasioli R, Franchi R, Mensi F, Carnaghi P, Schieppati G, Scanni A: Recovery of response to adriamycin and cyclophosphamide by lonidamine in previously treated metastatic breast cancer patients. Int J Oncol 3: 213–217, 1993
29. Norton L: Evolving concepts in the systemic drug therapy of breast cancer. Semin Oncol 24(4 Suppl l0): 3–l0, 1997

Address for offprints and correspondence: Cecilia Nisticò, Service of Complementary Medical Oncology, Regina Elena Cancer Institute, viale Regina Elena 291, 00161 Rome, Italy; *Tel./Fax:* 39-6-49852237