Alternating intravenous and oral vinorelbine plus epirubicin with pegfilgrastim as neoadjuvant treatment of locally advanced breast cancer

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In order to downstage locally advanced breast cancer, neoadjuvant chemotherapy consisting of intravenous vinorelbine 25 mg/m^2 plus epirubicin 75 mg/m^2 given on day 1 and oral vinorelbine 60 mg/m^2 on day 8 was administered every 3 weeks for four courses. On day 2, all patients received a single subcutaneous injection of pegfilgrastim (6 mg). From March 2004 to June 2005, 22 patients were enrolled. Patients characteristics were: median age, 53 years (range: 39–70 years); postmenopausal, 7/22; clinical TNM stage, T2 ($n=14$), T3 ($n=8$), N0 ($n=17$) and N1 ($n=5$). The median number of courses was four (range: two to six courses) with full dose intensity. National Cancer Institute grade 3 haematological toxicities observed were neutropenia in 9% of patients, anaemia in 13% of patients and thrombocytopenia in 9% of patients; no toxicity grade 4 occurred. Two patients (9%) registered grade 2 polyneuropathy; no cardiac failure was observed. Conservative surgery was performed in 14 patients (63%). All patients were evaluable for response: complete pathological response was documented in three patients (13.6%); three patients (13.6%) obtained more than 75% of tumour size reduction; 11 other patients (50%) had 50% of tumour size reduction; stable disease was observed in five patients (22.7%). The present findings indicate that vinorelbine in combination with epirubicin is an effective and safe treatment in locally advanced breast cancer: this regimen obtained more than 50% of tumour size reduction in 77% of patients; the use of pegfilgrastim allowed full dose intensity. Oral vinorelbine on day 8 offers greater convenience to the patient by reducing the need for intravenous injection and the time spent in hospital.
***Anti-Cancer Drugs* 17:1081–1085 © 2006 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2006, **17**:1081–1085

Keywords: breast cancer, neoadjuvant treatment, oral chemotherapy

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Received 8 May 2006 **Accepted** 19 June 2006

Introduction

Neoadjuvant or primary chemotherapy turns out particularly suitable in the management of early breast cancer [1–3]. The different theoretical arguments that concur with the rationale for the use of neoadjuvant chemotherapy in this tumour type include: (1) the possibility to eradicate since the very beginning not detectable micrometastases, thus allowing one to achieve long-lasting disease-free intervals possibly resulting in a prolongation of patient's survival; (2) the chance that a significant shrinking of the primary tumour could enable more patients to become amenable to breast conservative surgery; and (3) the testing of the response of primary tumour to a given chemotherapy regimen that provides the opportunity for a shifting to alternative options in case of proof of clinical resistance and, consequently, the tailoring of treatment to the individual patient [4–6]. Over the past years, several cytotoxic drugs, chiefly anthracyclines and taxanes used either as single agent or in combination and/or sequentially with other antineoplastic drugs, have been tested in this setting, producing encouraging, even though not entirely satisfactory, results [7–9]. In fact, while this approach significantly increased the rate of breast preservation, so far no advantages in terms of survival as compared with adjuvant treatment have been observed.

More recently, injectable vinorelbine, a semi-synthetic vinca alkaloid, which has shown to be very active and well tolerated in the treatment of advanced breast cancer either alone or in combination [10–12], has also been evaluated in the neoadjuvant setting as, on account of its very good safety profile characterized by low incidence of alopecia and nausea/vomiting as compared with other antineoplastic agents, it was deemed particularly worthy of being utilized in this situation. Results of two phase II trials and one phase III randomized trial in combination with epirubicin appeared very interesting, with response rates of 70, 79 and 74%, and pathological complete response rates of 9.7, 15 and 12%, respectively [13–15].

The recently introduced oral formulation of vinorelbine seems to offer new and further opportunities for

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more flexible and suitable treatments. Reliable dose equivalence with the intravenous formulation has been demonstrated [16,17] with a bioavailability of about 40%. In two multicentre phase II studies in the first-line treatment of metastatic breast cancer the efficacy and safety profiles of oral vinorelbine were comparable to those previously reported for intravenous vinorelbine [18,19]. Recently, a study was designed to evaluate vinorelbine, alternating intravenous on day 1 and oral on day 8, in combination with epirubicin in first-line treatment of patients with metastatic breast cancer: the results showed that this regimen is effective and safe [20].

The present study aimed to evaluate a new regimen of neoadjuvant chemotherapy consisting of the alternate administration of intravenous on day 1 and oral vinorelbine on day 8 plus epirubicin on day 1 and pegfilgrastim in patients with locally advanced breast cancer.

Patients and methods

From March 2004 to June 2005, *22* women with proven locally advanced breast cancer, after having given written informed consent to their participation, entered the study.

Baseline eligibility criteria included diagnosis of locally advanced breast cancer (T2–T3, N0–N2, M0) measuring not less than 3 cm and no more than 7 cm, histologically or cytologically confirmed by a core or fine-needle or incisional biopsy for histopathologic diagnosis, mammography and ultrasonography (the latter in case of inconclusive mammography); performance status (Eastern Cooperative Oncology Group) 0–2; age ≤ 65 years; adequate bone marrow function (white blood cell count $\geq 4000/mm^3$, platelet count $\geq 100\,000/mm^3$, haemoglobin $\geq 10\,\mu l$); normal liver function (bilirubin and Serum Glutamic Oxaloacetic Transaminase within limits of normality); normal renal function with creatinine clearance values ≤ 60 ml/min; and normal cardiac function with left ventricular ejection fraction $\geq 50\%$.

Patients with prior history of breast cancer within the previous 2 years, prior anthracycline chemotherapy or prior high-dose chemotherapy with stem cell transplant as well as patients with uncontrolled infection, untreated central nervous system disease, active cardiovascular or pulmonary disease, history of myocardial infarction or unstable angina, diabetes, prior malignancy not treated with curative intent, or peripheral neuropathy of any aetiology were considered not eligible for the study.

Treatment consisted of epidoxorubicin $75\,mg/m^2$ by intravenous bolus followed by vinorelbine $25\,mg/m^2$ by intravenous infusion, both administered on day 1, and oral vinorelbine $60\,mg/m^2$ administered on day 8. On day 2, all patients received a single subcutaneous injection of pegfilgrastim (6 mg). Cycles were repeated every 21 days for at least two cycles and up to a number based on the investigator's decision or compatible with the patient's tolerability. Treatment had to be discontinued in the presence of unacceptable toxicity or disease progression.

Assessments of responses were performed according to World Health Organization criteria [21] every two cycles by repeating the clinical evaluations and imaging procedures used to define the extent of disease at baseline. Complete clinical remission was defined as the complete disappearance of the lesions on two separate measurements at least 4 weeks apart, a partial response was defined as at least 50% reduction of each lesion, stable disease was defined as a decrease of less than 50% or an increase of less than 25% of the preexisting lesions with no appearance of new lesions and progression of disease was defined as an increase greater than 25% or the appearance of new lesions. Pathological complete remission was defined as no histological evidence of residual invasive cancer.

Breast-conserving surgery or mastectomy along with axillary node resection were performed according to the clinical response, to the degree of tumour downstaging and to the surgeon's evaluation. Radiotherapy was routinely offered to all patients who underwent conservative surgery.

Toxicity evaluation was carried out according to National Cancer Institute Common Toxicity Criteria.

Results

Table 1 illustrates the baseline characteristics of the *22* patients enrolled. Their median age was 53 years (range, 39–70 years); 15 of them were premenopausal and seven were postmenopausal. According to American Joint Committee on Cancer classification, seven patients showed stage IIa disease, 11 stage IIb, three stage IIIa and six stage IIIb. Clinically positive lymph nodes were

Table 1 Patient characteristics

Age (years)	
median	53
range	39–70
Menopausal status	
premenopausal	15
postmenopausal	7
Histology	
ductal	12
ductal + lobular	2
lobular	7
cribriform	1
Clinical axillary nodal status	
positive	5
negative	17
Clinical stage	
IIA	7
IIB	11
IIIA	3
IIIB	1

Table 2 Response to treatment in 22 patients

Response	No. of patients (%)
Complete	4 (18)
Partial	13 (59)
Objective	17 (77)
Stable disease	5 (23)

Table 3 Haematological toxicity (per patient)

Grades	Anaemia	Neutropenia	Thrombocytopenia	Total patients
1	8	0	1	9
2	1	3	0	4
3	3	2	2	7
4	0	0	0	0
Total patients	12	5	3	20

observed in five out of 22 patients. All patients were initially not amenable to conservative surgery.

Ten (45%) patients received six cycles of primary chemotherapy, seven (32%) received four cycles and five (23%) only two cycles as no sign of tumour reduction was observed at the first evaluation carried out after the second chemotherapy cycle.

Clinical response was assessed by physical evaluation of the breast and nodes. Following induction chemotherapy, the overall objective clinical response rate was 77% (17 patients out of 22), with complete disappearance of the tumour (complete clinical remission) in four cases, 10 partial responses (two patients obtained more than 75% reduction of tumour size and eight achieved more than 50% reduction) and three minor responses. Stable disease was observed in five patients (23%). No progression was observed during treatment (Table 2). In the four patients who achieved clinical complete response (one of them with negative axillary nodes), the pathological complete response (pathological complete remission) was also ascertained.

All patients eventually underwent surgery and the overall lumpectomy rate was 14 out of 22 (63%).

Data concerning the toxicity of the treatment are showed in Table 3: the most common grade 1–2 side-effects consisted of fatigue, nausea/vomiting, diarrhoea and stomatitis. Two (9%) patients had grade 2 polyneuropathy. As far as haematological toxicity is concerned, grade 3 neutropenia appeared in two (9%) patients, anaemia in three (13.6%) patients and thrombocytopenia in two (9%) patients. No patient displayed febrile neutropenia or neutropenic sepsis. No toxic deaths or grade 4 haematological or nonhaematological side-effects were found. No patients experienced any cardiac symptom.

Discussion

Following the identification of the theoretical advantages deriving from neoadjuvant chemotherapy in the management of operable breast cancer, a series of clinical trials using different chemotherapy regimens have been carried out in order to confirm all the devised hypotheses. With these regimens, however, most of them anthracycline-based, which allowed one to achieve substantial clinical response rates ranging from a minimum of 60% to a maximum of 90% (the latter figure occasionally observed in smaller phase II studies) [1,22–23], the only certainty that has emerged is that this approach dramatically reduces the need for mastectomy [1–3]. On the contrary, no evidence so far exists demonstrating a gain in terms of survival for patients who undergo neoadjuvant chemotherapy as compared with adjuvant treatment. Six fundamental randomized studies, comparing different preoperative and postoperative chemotherapy regimens in patients with operable breast cancer, failed to demonstrate any significant survival advantage in patients treated with neoadjuvant chemotherapy. The study National Surgical Adjuvant Breast and Bowel Project B-18, likely the largest and the most important one, showed that at the median follow-up time of 9 years the disease-free survival and overall survival in both experimental groups were superimposable [24]. An important observation derived from the majority of studies, however, is that the achievement of complete pathological response (pathological complete remission) seems to be related to a significant improvement of disease-free survival [1,25].

In this regard, the results of the present study appear to fulfil the above-mentioned claims because the combination of intravenous and oral vinorelbine with epirubicin was able to induce 77% of tumour regression, thus supplying further support to the argument that large breast primary tumours (above 3 cm) can be downstaged to such an extent that it was possible to avoid radical mastectomy in 63% of patients. The most important remark, however, is that this regimen induced 18% of pathological complete remission: this figure is similar or even superior to the rates reported by other authors using anthracycline or nonanthracycline-containing regimens, so that it could potentially represent a promising perspective for an improvement of disease-free survival for patients with locally advanced breast cancer initially not amenable to conservative surgery. Worth noting is also the fact that these results have been reached without any particular problem for the patients, as demonstrated by the evidence that all of them received the projected doses of drugs, with only moderate and low incidence of haematological side-effects that positively reflected on patients' quality of life.

This is surely due to the support of growth factors that have improved the tolerability of this treatment regimen as compared with the conventional one based on the sole administration of injectable vinorelbine without the

support of growth factors. In this regard, worth mentioning are the experiences of Blomqvist *et al.* [26] who reported 75% of grade 3–4 neutropenia and two cases of severe febrile neutropenia; of the Scandinavian Breast Group Trial [12] in which the most important adverse event were represented by severe leucopenia in 50% of patients, associated with fever in 20% of patients or severe infection in 11%; and of Serin *et al.* [20] who in a multicentre phase II study reported grade 3 and 4 neutropenia in 16 and 49% of patients, respectively.

In our study, the incidence of severe haematological toxicity was low and no cases of febrile neutropenia and sepsis have been reported. The concurrent use of pegfilgrastim was important to maintain the frequency of drug administrations and to avert severe haematological toxicity, thus improving patient health-related quality of life, reducing total treatment costs in breast cancer [27,28] and, probably the most noteworthy remark, allowing patients to face surgery in the best health conditions.

Oral chemotherapy offers significant advantages over intravenous administration because of its greater convenience for the patient, its ease of administration and reduction of need for hospitalization. Patients with cancer showed a clear preference for oral chemotherapy [29,30] provided that its efficacy is similar to the intravenous alternative. Physicians have been reluctant, however, to use oral cytotoxic drugs, in the past, because of important interpatient variations in drug disposition.

With the new generation of oral cytotoxic drugs, including oral fluoropyrimidines [31] and oral vinorelbine [17], reliable blood exposure has been achieved. Therefore, these new drugs are now progressively replacing their intravenous counterpart.

Conclusion

This exploratory study demonstrates that the alternating intravenous and oral vinorelbine plus epirubicin schedule with pegfilgrastim as neoadjuvant treatment of locally advanced breast cancer is a very effective and safe approach, which, of course, deserves to be confirmed in randomized trials.

References

1 Hortobagyi GN, Buzdar AU, Montague E, Romsdahl M. Neoadjuvant chemotherapy for primary breast cancer. In: Jacquillat C, Weil M, Khayat D, editors. *Neo-adjuvant chemotherapy*. Paris: Colloque INSERM/John Libbey Eurotext; 1986. pp. 186–196.

2 Bonadonna G, Veronesi U, Brambilla C, Ferrari L, Luini A, Greco M, *et al.* Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. *J Natl Cancer Inst* 1990; **82**:1539–1545.

3 Sapunar F, Smith IE. Neoadjuvant chemotherapy for breast cancer. *Ann Med* 2000; **32**:43–50.

4 Schwartz GF, Birchansky CA, Komarnicky LT, Mansfield CM, Cantor RI, Biermann WA, *et al.* Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. *Cancer* 1994; **73**:362–369.

5 Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, *et al.* Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998; **16**:2672–2685.

6 Buchholz TA, Hunt KK, Whitman GJ, Sahin AA, Hortobagyi GN. Neoadjuvant chemotherapy for breast carcinoma: multidisciplinary considerations of benefits and risks. *Cancer* 2003; **98**:1150–1160.

7 Mauriac L, Durand M, Avril A, Dilhuydy JM. Effects of primary chemotherapy in conservative treatment of breast cancer patients with operable tumors larger than 3 cm: results of a randomised trial in a single centre. *Ann Oncol* 1991; **2**:347–354.

8 Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, *et al.* Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997; **15**: 2483–2493.

9 Scholl SM, Fourquet A, Asselain B, Pierga JY, Vilcoq JR, Durand JC, *et al.* Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumours considered too large for breast conserving surgery. Preliminary results of a randomised trial. *Eur J Cancer* 1994; **30A**:645–652.

10 Romero A, Rabinovich MG, Vallejo CT, Perez JE, Rodriguez R, Cuevas MA, *et al.* Vinorelbine as first-line chemotherapy for metastatic breast carcinoma. *J Clin Oncol* 1994; **12**:336–341.

11 Vici P, Colucci G, Gebbia V, Amodio A, Giotta F, Belli F, *et al.* First-line treatment with epirubicin and vinorelbine in metastatic breast cancer. *J Clin Oncol* 2002; **20**:2689–2694.

12 Ejlertsen B, Mouridsen HT, Langkjer ST, Andersen J, Sjostrom J, Kjaer M; Scandinavian Breast Group Trial (SBG9403). Phase III study of intravenous vinorelbine in combination with epirubicin versus epirubicin alone in patients with advanced breast cancer: a Scandinavian Breast Group Trial (SBG9403). *J Clin Oncol* 2004; **22**:2313–2320.

13 Ferrero JM, Namer M, Romaioli A. Neoadjuvant chemotherapy with a combination of vinorelbine and epirubicin in locally advanced breast cancer. Preliminary results of a phase II study [abstract] (preliminary results of a phase II study). *Proc Am Soc Clin Oncol* 1997; **16**.

14 Chen C, Shen K, Lu J. The combination of vinorelbine and epirubicin as neoadjuvant chemotherapy regimen in the treatment of local advanced breast cancer [abstract]. *Proc Am Soc Clin Oncol* 2003; **22**:57.

15 Chua S, Smith IE, A'Hern RP, Coombes GA, Hickish TF, Robinson AC, *et al.* Neoadjuvant vinorelbine/epirubicin (VE) versus standard adriamycin/cyclophosphamide (AC) in operable breast cancer: analysis of response and tolerability in a randomised phase III trial (TOPIC 2). *Ann Oncol* 2005; **16**:1435–1441.

16 Marty M, Fumoleau P, Adenis A, Rousseau Y, Merrouche Y, Robinet G, *et al.* Oral vinorelbine phase I pharmacokinetics and absolute bioavailability study in patients with solid tumours. *Ann Oncol* 2001; **12**:1643–1649.

17 Variol P, Nguyen L, Tranchand B, Puozzo C. A simultaneous oral/intravenous population pharmacokinetics model for vinorelbine. *Eur J Clin Pharmacol* 2002; **58**:467–476.

18 Amadori D, Koralewski P, Tekiela A. Efficacy and safety of Navelbine oral (NVBo) in first line metastatic breast cancer (MBC). *Eur J Cancer* 2001; **37**:S195 (abstr 713).

19 Freyer G, Delozier T, Lichinister M, Gedouin D, Bougnoux P, His P, *et al.* Phase II study of oral vinorelbine in first line advanced breast cancer chemotherapy. *J Clin Oncol* 2003; **21**:35–40.

20 Serin D, Verrill M, Jones A, Delozier T, Coleman R, Kreuser ED, *et al.* Vinorelbine alternating oral and intravenous plus epirubicin in first-line therapy of metastatic breast cancer: results of a multicentre phase II study. *Br J Cancer* 2005; **92**:1989–1996.

21 WHO. *WHO handbook for reporting results of cancer treatment*. Geneva: WHO; 1979.

22 Van der Hage JA, Van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer Trial 10902. *J Clin Oncol* 2001; **19**:4224–4237.

23 Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. *Cancer* 2002; **95**:681–695.

24 Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr* 2001; **30**:96–102.

25 Shannon C, Smith I. Is there still a role for neoadjuvant therapy in breast cancer? *Crit Rev Oncol Hematol* 2003; **45**:77–90.

26 Blomqvist C, Hietanen P, Teerenhovi L, Rissanen P. Vinorelbine and epirubicin in metastatic breast cancer. A dose finding study. *Eur J Cancer* 1995; **31A**:2406–2408; 903909.
27 Frampton JE, Keating GM. Spotlight on pegfilgrastim in chemotherapy-induced neutropenia. *BioDrugs* 2005; **19**:405–407.
28 Lyman GH. Pegfilgrastim: a granulocyte colony-stimulating factor with sustained duration of action. *Expert Opin Biol Ther* 2005; **12**:1635–1646.
29 Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997; **15**:110–115.
30 Borner MM, Schoffski P, de Wit R, Caponigro F, Comella G, Sulkes A, *et al.* Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. *Eur J Cancer* 2002; **38**:349–358.
31 DeMario M, Ratain M. Oral chemotherapy: rationale and future directions. *J Clin Oncol* 1998; **16**:2557–2567.