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Research paper

Oral idarubicin and cyclophosphamide for metastatic breast cancer in elderly patients

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The authors treated 39 heavily pretreated breast cancer patients, median age 72, with a combined oral regimen featuring idarubicin and cyclophosphamide, administered without hospitalization in cycles repeated every 4 weeks for a total not to exceed idarubicin 400 mg/m². Treatment was remarkably well tolerated, with generally mild hematological toxicity and only one discontinuation caused by severe neutropenia; non-hematologic toxicity consisted mainly of moderate nausea and vomiting in fewer than half the cycles, and hair loss of various severity in the majority of patients. Therapeutic results were graded as partial responses (13 cases), no change (NC; 11 cases) or progressive disease (11 cases) for a response rate of 37.2% (95% CI: 21.1–53.1%). The authors single out the NC issue as being of special interest, its mere occurrence being rewarding in the circumstance and its duration in excess of 5 months (seen in six cases) almost equivalent to therapeutic success. [© 1998 Lippincott-Raven Publishers.]

Key words: Anthracyclines, breast cancer, cyclophosphamide, elderly patients, idarubicin.

Introduction

Drug treatment of breast cancer offers a number of choices dictated by such factors as stage of malignancy, lymph node involvement, hormone dependence, patient's age and performance status. Among several regimens that have been tried, those featuring anthracyclines compounds like doxorubicin and epirubicin have proved highly effective in inducing and maintaining response.[1,2] Conversely the use of these drugs, specifically doxorubicin, has been limited by toxic reactions in the form of bone marrow suppression, hair loss, mucositis and congestive heart failure; plus local tissue necrosis in case of extravasation. All this invites the idea that aggressive drug therapy should be forgone when the risk/benefit ratio is unfavorable.

Idarubicin, a daunorubicin analog, proved active when administered orally.[3,4] The acute and chronic toxic effects of the drug were of the same description as those of the parent compound but definitely milder, implying a markedly better therapeutic index. Pharmacokinetic studies[5] show that idarubicin availability after oral dosing is about 30–40% of the administered dose. In addition, plasma levels of the active metabolite idarubicinol are both higher and longer lasting than those of the unchanged drug. Several studies[6–11] have shown that oral idarubicin as sole medication is active against advanced breast cancer with response rates between 13 and 36% depending on dosages and patient characteristics. Higher response rates of 41–49% were obtained when oral cyclophosphamide was added to oral idarubicin:[12–14] the combination is readily tolerated and seems suitable for the palliative treatment of elderly patients for whom disease control at a moderate toxicity price seems preferable to more aggressive although therapeutically more ambitious treatment.

Materials and methods

Thirty-nine outpatients were selected for age over 65; histologically confirmed advanced breast cancer, documented failure of previous radio-, hormono- and chemotherapy; presence of measurable or assessable disease; Karnofsky performance status > 50; life expectancy >2 months; WBC count > 4000/mm³ with platelet count > 100 000/mm³; and normal liver and renal function. Patients with myocardiopathy, brain

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metastasis, osteoblastic lesions as sole evidence of disease, or a record of mediastinal irradiation or adjuvant anthracycline chemotherapy were not included. Treatment consisted of idarubicin (hard gelatin capsules of 5-10 and 25 mg) 35 mg/m^2 on day 1 and cyclophosphamide 200 mg/m^2 on days 3-6. Both drugs were given orally in cycles repeated every 4 weeks to a maximum idarubicin cumulative dose of 400 mg/m^2. Dose reductions or treatment delays were applied on the basis of hematological and/or gastrointestinal toxicity as assessed by the WHO scoring system for cancer treatment[15] before each cycle. In case of bone marrow depression, drug dosages were reduced or treatment was momentarily stopped as follows: with neutrophils counts > 2000 and platelets > 100 000: no dose reduction; with neutrophils between 1900 and 1000 and platelets between 100 000 and 75 000: dosage down 75%; and with neutrophils < 1000 and platelets < 75 000: treatment suspended to restoration of normal values. Clinical, serological and X-ray examinations were done to assess treatment responses by conventional WHO criteria.[15] Blood picture and liver and renal function were retested before each course of treatment; chest X-ray, bone scintigrams and liver echograms were obtained routinely at intake, after the third cycle of chemotherapy and then every two cycles. Bone roentgenograms were obtained when scintigrams showed anything abnormal; abdominal echography, CT scans and neurological examinations were done only when indicated. Cardiac function was monitored by ECG in connection with each cycle; LVEF values were determined at intake and termination. All adverse events reported by patients or detected by investigators were recorded and classified by the WHO scoring system.[15] Toxicity scores for blood counts, nausea and vomiting, stomatitis, and mucositis were recorded both as worst occurrences per patient during treatment and as a frequency of adverse events per cycle. Alopecia was recorded only per number of cases. A 12 week treatment (three cycles) was the least required to make a patient amenable to an assessment of activity; if early progression occurred during that period, the patient was assessed only for toxicity. Patients showing stabilized disease (NC) after three cycles were given an additional three cycles and then, if continuing NC, were assigned to the investigator's preferred treatment. Patients making a partial response (PR) continued treatment to disease progression or important toxicity; never, at any rate, to exceed the allotted cumulative dose of idarubicin 400 mg/m^2. Time to progression and survival rates were evaluated by the actuarial method of Kaplan and Meier.[16]

Results

Thirty-nine postmenopausal women were recruited between September 1993 and September 1995 (Table 1). Median age was 72 years (range 65-84); median Karnofsky performance status was 80 (range 60-100). Histological diagnosis was ductal carcinoma in 27 cases (69.2%), lobular carcinoma in four cases (10.3%) and a mixed form in the remaining eight (20.5%). Fifteen patients (38.5%) were relapsing after adjuvant therapy; 16 (41.0%) after adjuvant plus advanced disease therapy and two (5.1%) after advanced disease therapy only; the remaining six

Table 1. Patient characteristics

Patients recruited	39
Median age (years)(range)	72 (65–84)
Median Karnofsky PS (range)	80 (60–100)
Histological diagnosis	
ductal carcinoma	27 (69.2%)
lobular carcinoma	4 (10.3%)
other	8 (20.5%)
Previous treatments	
adjuvant	15 (38.5%)
adjuvant+advanced disease	16 (41.0%)
advanced disease	2 (5.1%)
none	6 (15.4%)
Type of previous treatment	
chemotherapy ± hormone therapy	14 (35.9%)
hormone therapy	18 (46.1%)
radiotherapy	1 (2.6%)
none	6 (15.4%)
Main sites of disease	
skin/lymph nodes	17 (43.6%)
viscera	16 (41.0%)
bone	6 (15.4%)

Table 2. Number of patients and cycles

Total number of cycles administered					175				
mean number/patient					5 (range 1–9)				
No. of patients treated/cycle:									
cycle	1	2	3	4	5	6	7	8	9
patients	39	37	35	21	18	14	5	4	2

(15.4%) were treatment-naive. Previous treatments consisted of chemotherapy either alone or combined with hormonotherapy (14 cases), hormonotherapy alone (18 cases) and radiotherapy (one case). The main sites of metastasis were the skin and lymph nodes in 17 patients (43.6%), the viscera in 16 (41.0%), and bone in six (15.4%). A total of 175 cycles of oral idarubicin plus oral cyclophosphamide were administered, for a mean of five cycles per patient (range 1-9); however, only 12.8% of the patients continued treatment beyond the sixth cycle (Table 2). Thirty-five patients were assessable for activity; of the remaining four, one was excluded for severe leukopenia, one for cardiac disorders, one for protocol violation and one for drop out after the first cycle. Treatment responses were graded as PR in 13 cases (37.2%; 95% CI: 21.1-53.1%), NC in 11 cases (31.4%) and PD in 11 cases (31.4%). Partial responses per dominant metastasis sites were seen in five of 16 patients with skin and lymph node lesions (43.7%) and in five of 15 with visceral lesions (33.3%); no responses were seen in patients with bone lesions (Table 3). Median time to progression was 198 days; median survival time was 514 days (Figure 1).

Table 3. Response rate of 35 assessable patients

	Type of response		
	PR	NC	PD
N	13	11	11
%	37.2	31.4	31.4

Response (PR) according to the dominant site of metastasis: skin/lymph nodes, 7/16 (43.7%); viscera, 5/15 (33.3%); bones, 0/4 (–).

Toxicity data relative to 175 cycles are shown in Table 4. Hematological toxicity assessed at repeat cycle time was very low with only six episodes of leukopenia (one grade 1, three grade 3 and two grade 4); still, severe neutropenia (<0.5 ANC) required treatment discontinuation in one case. Anemia was seen in five cycles (three grade 1 and two grade 2); thrombocytopenia occurred in four cycles (three grade 1 and one grade 4). Non-hematological toxicity consisted of nausea and vomiting in 72 cycles (43 grade 1, 24 grade 2 and five grade 3), and mucositis in eight cycles (five grade 1, one grade 2 and two grade 3). Fever occurred in nine cycles, diarrhea in five, asthenia in four, conjunctivitis in two and gastric pain in four. Hair loss was seen in 34 patients (grade 1 in seven, grade 2 in 16 and grade 3 in 11). No patients developed clinical congestive heart failure or an LVEF drop below 15% of basal values; treatment was discontinued for an atrial flutter in only one case.

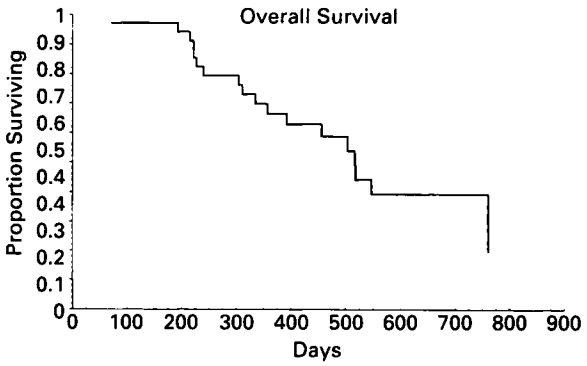

Figure 1.

Table 4. Toxicities

Type of toxicity	Grade					Total
	0	1	2	3	4	
Hematological						
leukopenia	171	1	–	3	2[a]	6
anemia	170	3	2	–	–	5
thrombocytopenia	171	3	–	–	1	4
Non-hematological						
nausea/vomiting	103	43	24	5	–	72
mucositis	167	5	1	2	–	8
fever	166	9	–	–	–	9
diarrhea	170	5	–	–	–	5
asthenia	171	3	1	–	–	4
conjunctivitis	173	2	–	–	–	2
gastric pain	171	–	4	–	–	4
atrial flutter	174	–	1	–	–	1

[a]Neutropenia

Discussion

It is generally recognized that metastatic cancer of the breast cannot be cured by currently available drugs. Whereas newly developed multidrug chemotherapy schemes have produced higher overall response rates, survival rates have not changed appreciably over the years and the outcome of disease remains dismal. This makes it mandatory for the investigator to make a painstaking choice of treatments taking into account a wide array of factors, among which the advanced age of patients is prominent. Indeed, we even lack a clear-cut definition of 'elderly oncological patient' and find all too few published studies dealing with breast cancer patients over age 65. Thus, oncology of the aged paradoxically amounts to a 'new' field of research, a curious mixture of hesitation, good common sense, fear and insufficient knowledge of 'old' patients.

The results of this study confirm earlier evidence that a combination of oral idarubicin plus oral cyclophosphamide is effective in breast cancer patients no longer responsive to endocrine therapy or classical chemotherapy. Idarubicin, in particular, offers the distinctive advantage of being suitable for oral administration thanks to its highly lipophilic nature and consequent gastrointestinal absorbability.[17] This permits complete treatment at home with no need for more aggressive parenteral procedures: patients are spared the discomfort of trips to the day hospital and the distress of i.v. infusions often made into poor, fragile veins. Systemically, too, the oral idarubicin plus cyclophosphamide combination is readily tolerated in terms of hematological and other toxicity (Table 4). In detail, we had only six episodes of leukopenia in 171 cycles administered, and nothing more than bouts of nausea and vomiting responsive to antiemetics. Home treatment, incidentally, involves markedly lower medical and nursing expenditure, with major savings in terms of hospitalization costs and of using expensive collateral products, especially the growth factors—an advantage of no mean order. Our data for treatment effectiveness (37% partial responses) is somewhat less impressive than those of Kolaric[12] and Lopez,[13] showing 41 and 49% and including a quota of complete responses. The difference may be attributed confidently to such variables as patient selection and evaluation criteria. In the two studies just quoted, the median age of patients was about 60 as opposed to 75 in our own series; also, all patients in Kolaric's group were not given any previous chemotherapy and therefore were more likely to respond than our heavily pretreated subjects.

Another aspect of our study that commands attention is the 31% incidence of NC. We definitely agree with Howell,[18] that an NC grading of better than 5 months duration should be regarded as a successful outcome; in fact, particularly in aged patients, the mere absence of progression is a success. We find it rewarding that fully six of our 11 NC responses (better than 50%) lasted longer than 5 months, i.e. 13, 5.5, 7, 7, 23+ and 10 months in those instances. Therefore, to summarize, we can say that a combined regimen of idarubicin and cyclophosphamide, both drugs being administered by the oral route, proved remarkably effective in a series of 39 elderly patients with metastatic breast carcinoma, treated at their home, yielding a fair 37.2% PR, a substantial 31.4% NC and an acceptable 31.4% disease progression. As discussed above, we were especially impressed with the important quota of NC cases that lasted more than 5 months, this being regarded as a successful outcome in the circumstances. Of course we must bear in mind that these results were obtained in an outpatient setting with oral doses exclusively, with obvious advantages in terms of patient comfort, systemic tolerability and taxpayer money savings.

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