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Original article

High incidence of central nervous system involvement in patients with metastatic or locally advanced breast cancer treated with epirubicin and docetaxel

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Summary

Background: Clinically overt central nervous system (CNS) involvement occurs in 10%–15% of patients with advanced breast cancer.

Patients and methods: The International Breast Cancer Study Group (IBCSG) conducted a dose-finding phase I trial of epirubicin (E) and docetaxel (D) as first-line therapy in advanced breast cancer patients. The study was expanded into a phase II at the recommended doses of E 90 mg/m^2 and D 75 mg/m^2 every three weeks. From July 1996 to May 1998, a total of 92 patients (median age 50 years) entered the two studies.

Results: Twenty-eight out of ninety-two patients treated with the combination of E and D (30%) developed CNS metastases (95% confidence limits, 26%-35%), which were cerebral in twenty-five patients, leptomeningeal in two, and both in one. Of these 28 patients, 19 (68%) had an objective response. Median time for the development of CNS metastases from the start of chemotherapy was 15 months (range 5–42), if excluding the 6 patients presenting CNS progression within 3 months from start of treatment. It is notable that 11 patients (39%) had progression in the CNS only. Median survival from appearance of brain metastases in the whole group was only three months (range 1–22). C-erbB-2 overexpression was found in 14 out of 16 patients (87%) in whom the assay was performed (3+ in 10, 2+ in 1 and 1+ in 3 cases).

Conclusions: As anthracycline- and taxane-containing regimens are increasingly used both in the metastatic and in the adjuvant setting, a careful monitoring of any neurological symptom is advisable. Our preliminary observation on the possible increase of incidence of CNS involvement in patients with advanced breast cancer receiving this effective drug combination requires further evaluation.

Key words: breast cancer, central nervous system involvement, Taxotere

Introduction

Central nervous system (CNS) metastases from breast cancer are becoming increasingly evident as patients live longer, because of better adjuvant and palliative treatments, and possibly because better diagnostic procedures (CT scan, MRI) are now available. Although breast cancer is the second most common cause of brain metastases, clinically overt manifestations occur in approximately 10%–15% of patients only [1]. On the other hand, an autopsy study in 1177 cases revealed a 23.6% incidence [2] in the very terminal phase of the disease.

So far, no follow-up program includes routine brain CT scan, unless symptoms are present, because of the overall low incidence of this kind of metastatic spread compared with other more common sites of relapse such as bone, soft tissues, or viscera.

Although the role of chemotherapy in cerebral metastases is still controversial, recent data indicate a similar response rate of systemic disease and cerebral disease to chemotherapy in patients with metastatic breast cancer [3, 4], thus refuting the common belief that diagnostic procedures should be undertaken only in case of a suggestive clinical picture.

Anthracyclines and taxanes are the most active drugs against breast cancer, achieving in combination an overall response rate ranging from 52% to 76% [5–7] with sustained activity at all disease sites. In 1996, the International Breast Cancer Study Group (IBCSG) conducted a dose-finding phase I trial of epirubicin (E) and docetaxel (D) as first-line therapy in metastatic or locally advanced breast cancer (LABC) [8]. The study was expanded, after the determination of the maximum tolerated doses of the combination, into a phase II study

using the recommended doses of E 90 mg/m^2 and D 75 mg/m^2 every three weeks without granulocyte colony-stimulating factor (G-CSF) support [9].

We report a high incidence of CNS relapse in the whole group of patients treated with this drug combination, even in those achieving an initial response to the treatment, with a significant incidence of CNS involvement as unique site of disease progression.

Patients and methods

Ninety-two patients with metastatic or locally advanced breast cancer were enrolled in two studies. The main eligibility criteria for the phase I study have been published elsewhere [8] and included: histologically or cytologically proven metastatic or locally advanced breast cancer, no prior chemotherapy for metastatic disease, possible prior hormonal therapy for advanced disease, adjuvant or neoadjuvant hormonal therapy or chemotherapy completed at least six months prior to study entry and not containing anthracyclines, adequate haematological, renal, hepatic and cardiac function, measurable or evaluable disease. A written informed consent was obtained.

Patients received a maximum of four cycles of the combination of E and D. Four additional cycles of D as a single agent at the same dose level were administered to responding patients. Response was defined according to the WHO criteria [10]. E and D were administered at escalating doses starting from E 75 mg/m^2 and D 75 mg/m^2 to E 120 mg/m^2 and D 85 mg/m^2; E was administered as a 15-minute infusion followed, after a one-hour interval, by D given as a 1-hour infusion. Treatment was repeated every three weeks provided a complete haematological recovery had occurred. A three-day prophylactic medication with oral dexamethasone (8 mg) 13 hours, 7 hours and 1 hour before D and then twice daily on days 1 and 2 was routinely given in combination with oral cimetidine (300 mg) once daily. No G-CSF support was routinely recommended unless febrile neutropenia or grade 4 prolonged haematological toxicity was encountered.

In the phase II study, previous treatment with anthracyclines was allowed, with doxorubicin or E not exceeding 240 mg/m^2 and 430 mg/m^2 in the adjuvant setting, respectively. The treatment procedures were the same as in the phase I study except that E was delivered at the dose of 90 mg/m^2 and D at the dose of 75 mg/m^2. Responding patients could receive a maximum of eight cycles of the combination.

Results

From July 1996 to May 1998, 92 patients (median age 50 years) were accrued in 2 studies. Their characteristics are summarised in Table 1.

Twenty-three patients in the phase I study (55%) and twenty-seven (54%) in the phase II study had dominant visceral disease , whereas twenty-eight (66%) and thirty-three (66%) patients had at least two metastatic sites. Oestrogen receptor status was negative in 14 (33%) and 14 (28%) patients, respectively.

Twenty-eight patients (30%) (95% confidence limits: 26%–35%) had CNS relapse: this was cerebral in twenty-five patients, leptomeningeal in two (cytologically confirmed) and both in one (Table 1). Median age was 54 years (range 39–66). Oestrogen receptor status was negative in 10 patients (38%), positive in 12 (43%) and unknown in 6. Six patients had LABC only and eight were metastatic at first diagnosis (3 had lung, 2 nodal, 2 bone and 1 liver disease). Median disease-free interval for the remaining 14 patients (50%) was 28 months (range 13–204); 11 of them (73%) had received adjuvant chemotherapy (CMF in 10 patients and LMF in 1 patient). Seventeen patients (61%) had visceral dominant disease at baseline, eleven patients presenting with lung metastases, five with liver metastases, and one with both disease sites.

Table 1. Patient characteristics.

	Phase I	Phase II	CNS relapse
Number of patients	42	50	28
Age (years)			
Median	51.5	46	54
Range	32–68	22–66	39–66
Dominant disease site at study entry			
Viscera (liver)	23 (12)	27 (18)	17 (6)
Locoregional	8	10	6
Bone	7	10	4
Soft tissue	4	3	1
ER status			
Positive	18	27	12
Negative	14	14	10
Unknown	10	9	6
Adjuvant CT	29	22	11
Response to E and D	25	34	19
CNS progression only (%)	4 (16)	7 (20)	11 (39)
Median progression-free interval (months)	5	5	15

Of the 28 patients with CNS relapse, 1 patient was treated at the lowest dose level (E 75/D 75 mg/m^2), 1 at E 120/D 75 mg/m^2 and 2 patients at the highest dose level (E 120/D 85 mg/m^2) in the phase I study, the remaining 24 patients were treated at the recommended dose level of E 90/D 75 mg/m^2.

Nineteen patients (68%) had an objective response, three had a stable disease and six had disease progression.

Only 5 out of the 16 patients (31%) who received either whole brain radiotherapy (15 patients) or intrathecal chemotherapy (1 patient) survived more than 6 months from diagnosis (range 6–22), whereas median survival from brain involvement was only 3 months (range 1–22) in the whole group of patients. Among the 11 patients with CNS progression of disease only, seven received radiotherapy, three did not and one was treated with intrathecal chemotherapy. Median survival in this group of patients was six months (range 1–22).

Median time to the development of CNS metastases from start of chemotherapy was 15 months (range 5–42), excluding the 6 patients presenting CNS progression within 3 months from study entry. In four of these six cases, CNS progression was associated with concomitant progressive disease in all metastatic sites of prior bulky disease. All 28 patients presented with symptoms of intracranial hypertension requiring further assessment (CT scan and/or MRI). It is worth noting that 11 patients (39%) had CNS progression only, without evidence of new distant metastases.

We retrospectively assessed c-erbB-2 expression on

histological specimens by immunohistochemistry (Dako test): 16 cases were studied and 14 (87%) were positive (10 cases were 3+, 1 was 2+ and 3 cases 1+), 1 was negative and 1 was not evaluable.

Considering the overall group of patients who had either a complete response or a partial response and who subsequently experienced relapse, 11 out of 58 (19%) had isolated CNS progression while maintaining a systemic response.

Discussion

CNS relapse is not a common clinical finding during treatment and follow-up of patients affected by breast cancer. No clear-cut prognostic factors for the occurrence of CNS metastases have been identified even if it is common experience that brain relapse seems to develop more frequently in younger patients with larger or aggressive tumours (especially inflammatory breast cancer) [11].

The incidence of CNS involvement in our group of patients appears to be higher than expected, especially considering that the protocol was designed either as a first-line treatment in the metastatic setting or as neo-adjuvant treatment in patients with locally advanced breast cancer only; moreover, the regimen was effective and safe [8].

It is difficult to attribute our observation exclusively to 'chance'. Almost half of the patients certainly had a biologically aggressive disease as demonstrated by the presence of two patients with inflammatory breast cancer, oestrogen receptor negative tumours (38% of patients) and by the presence of visceral disease at baseline (61% of patients), but the median disease-free interval from initial diagnosis and the overall CNS progression-free interval were quite long (28 and 15 months, respectively). In a similar poor prognosis population of metastatic breast cancer patients only 3 out of 70 patients (14%) had brain relapse as their only site of recurrence [12].

There are at least two other reports in the literature suggesting that breast cancer patients treated with adjuvant chemotherapy have an increased incidence of brain metastases as the first site of recurrence, in comparison with control patients who did not receive any kind of treatment [13, 14]. This observation could easily be explained with the sanctuary site 'hypothesis', as a consequence of an intact blood–brain barrier. On the other hand, experimental studies in mice have shown that the blood–brain barrier is intact inside and around brain metastases smaller than 0.2 mm^2 but not in larger lesions, thus implying that the barrier should not be a major obstacle for chemotherapy of brain metastases [15], at least in the advanced phase of the disease. Patients treated with adjuvant chemotherapy have longer systemic disease-free intervals than untreated patients, eventually allowing for the uncontrolled growth of cancer cells already present in the CNS at diagnosis.

As there is emerging evidence in the literature that brain metastases respond to systemic chemotherapy [3, 4] including drugs not considered to penetrate the blood–brain barrier, such as taxanes [16], our findings become even more intriguing. In fact, most patients (68%) responded to treatment, with a median time to disease progression of 8.5 months, and 39% of patients with CNS relapse did not show systemic progression. Even if we consider CNS as a sanctuary site, there appears to be quite a particular disease aggressiveness in our series of patients, who otherwise obtained an overall good response to therapy, which prompted us to report the data of an active and safe regimen [8].

The observation of a particular outcome prompted us to review c-erbB-2 expression as a possible negative predictive and prognostic marker. The information was obtained in 16 patients and over-expression was retrospectively demonstrated in 14 patients (87%). However, it is difficult to establish whether c-erbB-2 over-expression was associated with CNS involvement, because no evaluation was carried out in patients without CNS metastases due to the multi-institutional accrual of patients.

Freilich et al. [17] reported the CNS progression rate in a series of 152 consecutive patients treated with paclitaxel in 5 phase II trials at MSKCC. Seventy-eight patients (51%) treated in the different protocols obtained a partial (53 patients) or minor response (25 patients); fifty-two of them had subsequent disease progression and six of these (12%) had isolated CNS involvement while maintaining a systemic response. As in our experience, all patients developed neurologic symptoms that yielded a neurologic and diagnostic assessment.

Several hypotheses could explain why patients with untreated metastatic breast cancer who presumably no longer have an intact blood–brain barrier and who usually respond to systemic chemotherapy had such a peculiar disease behaviour: possible local pharmacological interactions between anthracyclines and taxanes or detrimental effects of prophylactic corticosteroids are worth considering. While it is well established that patients undergoing chronic steroid therapy for organ transplantation are at increased risk of developing tumours, and in particular human herpes virus associated Kaposi's sarcoma [18], no historical data on breast cancer incidence are available so far.

Our study focuses on two important clinical issues: first, it is extremely important to carefully evaluate the development of any neurologic symptom in patients treated with taxanes in order to differentiate between a drug-induced peripheral neuropathy, which can cause distal sensory or motor symptoms, and a true CNS recurrence. Secondly, our observations raise the provocative issue of prophylactic cerebral treatment, at least in patients achieving a systemic complete remission that can often translate into a long-lasting disease-free survival. Although this attitude does not represent standard practice, it should be investigated in a clinical trial. This is particularly important if we consider the dire short-term prognosis in our group of patients after CNS progression (3 months overall median survival).

Further data are warranted and urgently needed to better investigate this particular aspect of an otherwise powerful drug combination widely used both in the metastatic and in the adjuvant setting, especially in high-risk patients who are also at higher risk of CNS micrometastatic involvement. Another question relates to breast cancer natural history: are we going to face, in the near future, more patients with isolated brain involvement as a consequence of prolonged survival induced by adjuvant chemotherapy? If so, should we plan new therapies and follow-up attitudes? If our data with E and D, as well as those of MSKCC with anthracyclines and paclitaxel [17] are confirmed by other groups, a thorough investigation by pharmacologists will be of great interest.

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