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Short communication

Carboplatin activity in untreated metastatic breast cancer patients – results of a phase II study

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Summary. Due to the favourable results previously obtained with cisplatin in breast cancer (54% response rate), we studied a second-generation platinum analogue, carboplatin, in patients with previously untreated breast cancer. A total of 20 patients were entered in the study and all were evaluable. The median age was 57 years and all patients were in menopause. Karnofsky scores of 80–100 and 40–70 were registered in 14 and 6 cases, respectively. The predominant metastatic site was soft tissue in 12 subjects, visceral organs in 5 and bone in 3; 14 patients had >2 metastatic sites. Carboplatin was given i.v. at a dose of 400 mg/m^2 on day 1, with a 3-week rest period. In 13 patients who did not respond or whose disease recurred after carboplatin treatment, the CMFVP, CAP or FAC regimen was given as second line treatment. Carboplatin activity was observed in 4 patients [2 complete remissions (CRs) and 2 partial responses (PRs)], for a response rate of 20% (4/20); the 2 PRs were observed in soft tissue and bone and the 2 CRs, in lung, liver and bone. Remission lasted 2–10 months ($\bar{X}$, 4 months). CMFVP given as second-line chemotherapy to 13 patients produced 7 PRs (7/13, 54%). Toxicity was moderate, producing no drug-related deaths. Anemia (grade I–II) was recorded in seven patients; grade I–II leukopenia, in six; and grade III–IV leukopenia in two (median leukocyte nadir, 1,600/mm^3). Thrombocytopenia was observed in three cases (grades I, II and III; median platelet nadir, 47,800/mm^3). Unpleasant nausea/vomiting was pronounced (12 cases of grade III–IV) in 19 subjects. There were no cases of neuro- or nephrotoxicity. Due to permanent myelosuppression, no more than five cycles could be given. Our study showed that, unlike cisplatin, carboplatin given at a dose of 400 mg/m^2 has low antitumorigenic activity in breast cancer patients and produces pronounced myelotoxicity. Additional first-line chemotherapy studies using carboplatin are needed to define the antitumorigenic activity of this platinum analogue.

Introduction

Carboplatin is a second-generation platinum analogue, which in preclinical and clinical phase I/II studies has shown gastrointestinal and auditory toxicity lower than those observed for cisplatin, as well as minimal renal toxicity, even when given without hydration [3, 7]. Our previous experience and the reports on the pronounced antitumorigenic activity of cisplatin in breast cancer (response rate, 54%), also confirmed by other investigators, have made cisplatin one of the most efficient cytostatic drugs for treatment of this tumor [4, 5, 6, 9–11]. Because of such results, we also decided to conduct a clinical study on the effectiveness of carboplatin in metastatic breast cancer. Knowledge on the antitumorigenic effect of carboplatin in breast cancer is based on very scant reports referring mainly to previously treated patients. In most cases the results obtained in preliminary studies, published in the form of abstracts, were not encouraging [1–3, 8, 12]. Because the accurate evaluation of the antitumorigenic effect of a cytostatic drug entails a clinical trial in previously untreated patients, we carried out the present trial in view of a limited number of published reports. Considering the positive results obtained with cisplatin in breast cancer, we assumed that the newer, less toxic analogue of this cytostatic drug might demonstrate similar, if not higher, antitumorigenic activity.

Patients and methods

From January until June 1988, 20 consecutive untreated patients with histologically proven metastatic breast cancer were entered in the study. The eligibility criteria included an age of <70 years (pre- and postmenopausal) and a Karnofsky performance status of >40. Patients who had undergone prior irradiation and hormone therapy were not excluded if the interval between their latest treatment and the beginning of the present study was at least 4 weeks. Normal bone marrow, liver and

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Abbreviations: CMFVP, cyclophosphamide, methotrexate, fluorouracil, vincrisine, prednisolone; CAP, cyclophosphamide, Adriamycin, platinum; FAC, fluorouracil, Adriamycin, cyclophosphamide

Table 1. Patients' characteristics

	Patients (*n*)
Patients entered in the study	20
Evaluable patients (≥2 cycles)	20
Age (years)	49–64
Median age (years)	57
Premenopausal patients	0
Postmenopausal patients	20
Previous radiation	7
Previous hormone therapy	1
Performance status (Karnofsky scale):	
40–70	6
80–100	14
Steroid receptor-positive (ER, PgR)	15
Predominant metastatic site:	
Soft tissue	12
Visceral organs	5
Bones	3
Organ sites involved (*n*):	
1	7
2	9
3	2
4	1
5	1

ER, Estrogen receptor; PgR, progesterone receptor

Table 2. Response of patients with metastatic breast cancer to carboplatin

Predominant metastatic site	Patients (*n*)	Complete response	Partial response	No change	Progression	Objective response (CR + PR)
Soft tissue	12	–	1	2	9	1
Visceral organs	5	1	–	2	2	1
Bones	3	1	1	–	1	2
Totals	20	2	2	4	12	4/20(20%)

95% confidence interval, 8%–42%

Table 3. Toxic side effects of treatment with 400 mg/m² carboplatin

Toxicity	Patients (*n* = 20)
Anemia:	
Grade I	4
Grade II	3
Grade III–IV	–
Leukopenia:	
Grade I	2
Grade II	4
Grade III–IV	2
Thrombocytopenia:	
Grade I	1
Grade II	1
Grade III	1
Creatinine	–
Neurotoxicity	–
Ototoxicity	–
Nausea/vomitting	
Grade I	1
Grade II	6
Grade III–IV	12
Stomatitis	–
Alopecia	–

kidney function was required for the trial. All patients had to have either uni- or bidimensionally measurable disease, and only those with an expected survival of at least 6 weeks were included. The informed consent of patients was also obtained. Subjects with brain metastases were excluded from the study.

Prior to therapy, all patients underwent a complete staging workup to document the extent of disease, which included a clinical examination, blood count, serum biochemistry, chest and skeletal X-ray, liver and bone scan, liver ultrasound, and computerized axial tomographic (CAT) scan when necessary. A total of 20 patients meeting the foregoing criteria were entered in the trial; their characteristics are shown in Table 1. All 20 subjects were evaluable and received ≥2 cycles of carboplatin. Their age was 49–68 years ($\bar{X}$, 57 years), and all were in menopause. Seven patients had previously received radiotherapy and one had undergone hormone therapy. The majority of the patients (14) had an excellent performance status (Karnofsky score 80–100). Soft-tissue metastases were predominantly recorded in 12 cases; visceral organ metastases, in 5; and bone metastases, in 3. In 13 subjects, ≥2 involved organ sites were observed. The majority of patients were in a good-risk group (high performance score, predominantly soft-tissue metastases, grade I/II pathohistology, positive steroid receptors in 15 cases).

Carboplatin was given i. v. at a daily dose of 400 mg/m² on day 1 as a brief (30-min) infusion without hyperhydration. Therapy was carried out every 3–4 weeks until the development of disease progression or dose-limiting toxicity. For patients achieving a complete remission (cR) the plan envisioned six chemotherapy cycles, after which treatment would be stopped and the patients would be followed up. Partial responders (PRs) and no-change cases were treated until a relapse occurred. If bone marrow toxicity or nephrotoxicity was observed, the next cycle was postponed (not more than 2 weeks) until blood count and serum creatinine levels, respectively, returned to normal; thus, no dose adjustments were made. All patients were monitored regularly, particularly their blood count and serum creatinine levels, and were checked for ototoxicity and neurotoxicity as well. Leukocytes and thrombocytes were controlled once a week between cycles. In cases of primary resistance or relapse in spite of treatment, a second-line chemotherapy regimen was given [CMFVP, CAP or FAC].

Response and toxicity criteria recommended by the International Union Against Cancer (UICC)/WHO committee were used [13]. The duration of response was measured from the start of treatment until the occurrence of relapse, and survival was determined from the start of treatment until the time of death.

Results

All patients entered in the present study were evaluable for response and toxicity. In all, 12 patients received 2 chemotherapy cycles, 2 subjects completed 3 courses, 3 patients were given 4 cycles, and 3 subjects received 5 courses ($\bar{X}$, 3). The administration of carboplatin produced 4 responses among 20 patients (20% overall response; 95% confidence interval, 8%–42%): 2 CRs (lung + liver and bone) and 2 PRs (soft tissue and bone; Table 2). Surprisingly, the complete restitution of an osteolytic lesion on the sixth right rib was documented by chest X-ray after three chemotherapy cycles. The remissions lasted 2–10 months ($\bar{X}$, 4 months). The patient who achieved a CR in the liver and lung was in remission for 10 months after receiving 5 cy-

cles of carboplatin chemotherapy. All other subjects who responded to treatment also experienced recurrence of their disease. A total of 16 patients who either did not initially respond to carboplatin or experienced a relapse were treated with second-line chemotherapy: 13, with CMFVP; 1, with CAP; and 2, with FAC. Altogether, 8 of 16 patients responded to treatment (50%); 7 of 13 showed a PR to CMFVP treatment, and 1 responded partially to CAP. No response was observed in two patients who were treated with the FAC regimen. These data show that the CMFVP regimen is not cross-resistant to previous carboplatin administration. The duration of survival, including primary and second-line therapy, ranged from 8 to 18+ months ($\bar{X}$, 13 months).

The toxic side effects observed in the present study are shown in Table 3. Anemia, which is usually induced by cisplatin, was also evident during carboplatin treatment (4 cases, grade I; 3 cases, grade II; 35%). Leukopenia (grade I, 2 cases; grade II, 4 cases; grade III/IV, 2 cases) was observed in 40% of our patients (median leukocyte nadir, 1,600/mm^3). Thrombocytopenia was recorded in 3 subjects (grades I, II and III), and the median thrombocyte nadir was 47,000/mm^3 without hemorrhage. Thus, myelosuppression was recorded in 60% of our patients (12/20). The most unpleasant side effect was nausea and vomiting, which occurred in 19 of 20 subjects (12 cases, grade III/IV) in spite of antiemetic administration (high-dose metoclopramide and corticosteroids). Because of permanent myelosuppression, no more than five cycles of carboplatin could be given; thus, only three patients could complete five cycles. All three subjects spontaneously recovered from myelosuppression 1–2 months after the discontinuation of treatment. No case of neurotoxicity, nephrotoxicity or ototoxicity was recorded.

Discussion

Due to the favourable results previously obtained with cisplatin, our phase II trial of carboplatin, a newer less toxic platinum analogue, was focused on patients with untreated metastatic breast cancer. However, at a dose of 400 mg/m^2, carboplatin elicited an objective response in only 20% of patients (4/20), showing lower antitumorigenic activity than cisplatin. Nevertheless, CRs were recorded in the lung, liver and bone, which is unusual for single-agent antitumorigenic activity. When they occurred, remissions developed very rapidly, usually after two cycles. The therapeutic results appeared to be independent of prior radiation therapy and steroid receptor status. In comparing carboplatin activity in breast cancer with the response to cisplatin, it should be mentioned, that the high response to cisplatin by patients with breast cancer (54%) was obtained using a dose of 120 mg/m^2, which is not conventionally used in phase II platinum studies.

One dose-limiting side effect was bone marrow toxicity; myelosuppression was recorded in 60% of our patients (anemia, leukopenia and thrombocytopenia) and was also a dose-limiting factor. Due to permanent myelosuppression induced by carboplatin, our patients could not receive more than five cycles of the drug. Furthermore, pronounced nausea and vomiting were recorded in nearly all patients, which is contrary to previous reports on the gastrointestinal toxicity of carboplatin. However, no case of nephro-, oto- or neurotoxicity was recorded. In our opinion, an advantage of carboplatin is its easy administration without prolonged hyperhydration, which is also uncomfortable for the patients.

Thus far, few reports have been published on carboplatin activity in breast cancer. Moreover, the numbers of involved patients were inadequate, and subjects had usually been heavily pretreated. However, the results of the present study correlate well with two recently reported studies in previously untreated patients. In 1989, Carmo-Pereira et al. [2] reported on the administration of the same dose of carboplatin (400 mg/m^2) in 15 patients with untreated metastatic breast cancer. These authors observed a low response rate (2 partial responses; 13%). Toxicity involved mild leukopenia and pronounced nausea and vomiting (60% of patients). In 1990 Martin et al. [8] reported a response (400 mg/m^2 carboplatin) in 29% (6/21) of patients with untreated breast cancer, observing moderate toxicity. Considering the range of responses (13%, 20%, 29%) mentioned in these studies, the question arises as to whether the present dose of 400 mg/m^2 carboplatin was too low to produce a response equivalent to that obtained using 120 mg/m^2 cisplatin. As 400 mg/m^2 carboplatin is equivalent to 100 mg/m^2 cisplatin, the carboplatin dose to be actually given may be as high as 600–700 mg/m^2, particularly in patients with good renal function (glomerular filtration rate).

All other phase II studies were performed in previously treated patients, with poor results. Thus, Martin et al. [8] reported no response in 14 patients, observing marked myelotoxicity and nausea/vomiting. Similarly, in a randomized phase II trial (iproplatin vs carboplatin), Vermorken et al. [12] observed no response in 11 patients. Booth et al. [1] and Franks et al. [3] could not register a response in 14 and 31 patients, respectively; in both of these studies, myelosuppression was the dose-limiting factor.

In summary, unlike cisplatin carboplatin given at a dose of 400 mg/m^2 has low antitumorigenic activity in patients with untreated breast cancer patients, in whom it produces pronounced myelotoxicity and gastrointestinal disturbances. However, since only a few studies in untreated patients have thus far been reported, additional first-line chemotherapy trials of carboplatin in breast cancer, perhaps testing a higher dose and comparing the results with those obtained using cisplatin (randomized phase II trials), are needed to define the antitumorigenic activity of this second-generation platinum analogue.

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