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Original Article

Platinum-based Chemotherapy in Metastatic Breast Cancer: The Leicester (UK) Experience

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ABSTRACT:
Aims: After failure of anthracycline- and taxane-based chemotherapy in metastatic breast cancer, treatment options until recently were limited. Until the introduction of capecitabine and vinorelbine, no standard regimen was available. We conducted a retrospective study to determine the efficacy and toxicity of platinum-based chemotherapy in metastatic breast cancer.
Materials and methods: Forty-two women with metastatic breast cancer previously treated with anthracyclines (93%) and/or taxanes (36%) received mitomycin–vinblastine–cisplatin (MVP) ($n = 23$), or cisplatin–etoposide (PE) ($n = 19$), as first-, second- and third-line treatment at a tertiary referral centre between 1997 and 2002. Chemotherapy was given every 3 weeks as follows: mitomycin-C (8 mg/m^2) (cycles 1, 2, 4, 6), vinblastine (6 mg/m^2), and cisplatin (50 mg/m^2) all on day 1; and cisplatin (75 mg/m^2) and etoposide (100 mg/m^2) on day 1 and (100 mg/m^2) orally twice a day on days 2–3.
Results: The response rate for 40 evaluable patients (MVP: $n = 23$; PE: $n = 17$) was 18% (95% confidence interval [CI]: 9–32%). The response rate to MVP was 13% (95% CI: 5–32%, one complete and two partial responses) and to PE 24% (10–47%, four partial responses). Disease stabilised in 43% (26–63%) and 47% (26–69%) of women treated with MVP and PE, respectively. After a median follow-up of 18 months, 37 women (MVP: $n = 19$; PE: $n = 18$) died from their disease. Median (range) progression-free survival and overall survival were 6 months (0.4–18.7) and 9.9 months (1.3–40.8), respectively. Median progression-free survival for the MVP and PE groups was 5.5 and 6.2 months (Log-rank, $P = 0.82$), and median overall survival was 10.2 and 9.4 months (Log-rank, $P = 0.46$), respectively. The main toxicity was myelosuppression. Grades 3–4 neutropenia was more common in women treated with PE than in women treated with MVP (74% vs 30%; $P = 0.012$), but the incidence of neutropenic sepsis, relative to the number of chemotherapy cycles, was low (7% overall). The toxicity-related hospitalisation rate was 1.2 admissions per six cycles of chemotherapy. No treatment-related deaths occurred. MVP and PE chemotherapy have modest activity and are safe in women with metastatic breast cancer. Decatris, M. P. *et al*. (2005). *Clinical Oncology* **17,** 249–257

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Introduction

Breast cancer is the most common female cancer worldwide [1], and the second most common cause of death after lung cancer in women in Western Europe and North America. Despite adjuvant therapies, many women relapse with metastatic disease. A significant proportion of such women have hormone-resistant disease, which often requires palliative chemotherapy [2,3]. Anthracyclines and taxanes are two of the most active classes of drug frequently used in first- and second-line treatment of metastatic breast cancer [2,4,5]. Of the women in whom disease eventually relapse; 60–70% are suitable candidates for further palliative chemotherapy [5]. Routine use of taxanes outside a clinical trial after anthracycline failure was uncommon practice in our centre, until the UK's National Institute for Clinical Excellence approved them for use in this setting in 2000–2001 [6,7]. After taxane failure, treatment options for such patients were until recently limited. The National Institute for Clinical Excellence approved vinorelbine monotherapy as one option after anthracycline failure in December 2002 [8], and capecitabine as third-line therapy after anthracycline and taxane failure in May 2003 [9]. Before this, and in the absence of a standard regimen after anthracycline-failure, platinum-based chemotherapy was considered a reasonable alternative [5]. The synergistic effect of cisplatin in combination with trastuzumab (Herceptin®) in heavily pre-treated women with metastatic breast cancer [10], and the results of the herceptin–docetaxel–platinum salt combination [11], renewed interest in the use of platinum-based

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chemotherapy for metastatic breast cancer, and led us to review our experience in this disease using a retrospective analysis.

The platinum-based regimens we used included mitomycin–vinblastine–cisplatin (MVP), cisplatin–etoposide (PE) and cisplatin–vinorelbine. The results of the cisplatin–vinorelbine regimen, used in patients with abnormal liver function due to metastatic breast cancer, have been reported elsewhere [12]. The other two regimens were in routine use in our unit for the management of non-small-cell lung cancer and small-cell lung cancer, respectively, and the choice of either regimen in the women with metastatic breast cancer who were treated was arbitrary. Platinum-based combination chemotherapy was used as first-line therapy in women with metastatic breast cancer who received anthracycline in combination with or without taxane-based chemotherapy in the adjuvant or neoadjuvant setting. It was also used as second- or third-line treatment for women with metastatic breast cancer who progressed while on, or relapsed after, previous anthracycline combined with or without taxane-containing chemotherapy for metastatic disease, and, rarely, in the first-line treatment of women new to chemotherapy. Carboplatin was used to replace cisplatin for those women who developed significant cisplatin-induced nephrotoxicity or neurotoxicity. The objectives of the study were to determine the response rate, progression-free survival and overall survival, and to assess the toxicity for patients treated in this setting.

Patients and Methods

Eligibility Criteria

This analysis included women receiving MVP/carboplatin, (MVCarbo), or PE for first-, second- or third-line metastatic breast cancer. The electronic records of 229 consecutive women with advanced breast cancer referred to a single consultant from 1997 (when platinum-based chemotherapy started being used in our unit) until March 2002 were reviewed to identify women who fulfilled the inclusion criteria. These were subsequently applied retrospectively. The 42 women who were identified (18% of the database) were treated between June 1997 and September 2002. All women had histologically confirmed breast cancer, performance status 0–2 (World Health Organization criteria), and were at least 18 years old; there was no upper age limit. Women with brain metastases or inflammatory breast cancer were included. Previous adjuvant or neoadjuvant chemotherapy, and previous endocrine therapy or palliative radiotherapy for metastatic disease, was acceptable. The chemotherapy regimens were either MVP, mitomycin (8 mg/m^2) (cycles 1, 2, 4, 6 only), vinblastine (6 mg/m^2) (maximum dose 10 mg), cisplatin (50 mg/m^2), all given intravenously on day 1, or PE, cisplatin (75 mg/m^2) on day 1, etoposide (100 mg/m^2 iv) on day 1 and (100 mg/m^2) twice a day orally on days 2–3. Both MVP and PE were given every 3 weeks. Patients who developed cisplatin-induced neurotoxicity were changed to MVCarbo, where we replaced cisplatin with carboplatin area under the curve 5-6 and calculated the creatinine clearance by the Cockroft and Gault formula [13].

Evaluation of Response and Toxicity

Evaluation included history and physical examination before each cycle of chemotherapy. Metastatic disease was assessed clinically and radiologically. Patients with chest-wall metastases as the only site of disease had photographs taken with a Polaroid camera at baseline and after completion of chemotherapy. Radiological evaluations were made by a computed tomography at baseline and after completing platinum-based chemotherapy. In patients with lung metastases or pleural effusion, if definite evidence of progression was seen on a plain chest radiograph, a computed tomography was not carried out. Documented radiological responses (complete/partial) were recorded from the computed tomography reports after completing chemotherapy. The World Health Organization criteria [14] were used for the definitions of complete and partial response, stable and progressive disease. Chemotherapy was discontinued if progressive disease was documented, if patients experienced no symptomatic benefit or if significant toxicity was seen.

Patients had full blood count and serum biochemistry before each treatment. The number and duration of hospital admissions and numbers of day-case admissions related to the treatment were also recorded. Although the evaluation of toxicities is inherently difficult in a retrospective analysis, careful examination of all patients' medical records was made in order to identify toxicities experienced by each patient. Particular attention was paid during the study period for acute toxicity from the date of the first cycle of platinum-chemotherapy up until 1 month after the last cycle. Haematology and biochemistry results covering the above period were accessed, and grades 3–4 haematological/non-haematological toxicities were recorded. The common toxicity criteria (CTC version 2.0) were used.

Survival Analysis

Follow-up data were collected from patients' records, and survival curves were plotted using the Kaplan–Meier method [15]. The date the first cycle of platinum-based chemotherapy was given and the last outpatient appointment attended by each patient (or date of death) were used to calculate the overall survival. For progression-free survival, the date the first cycle of platinum-based chemotherapy was given and the date of the first clinical/radiological examination, which confirmed progression, or the last follow-up evaluation was used. Events were censored on 1 August 2003. Survival curves were plotted using the statistics software package SPSS (version 11.0, SPSS Inc., Chicago, USA). Fisher's exact and Mann–Whitney U tests, for the significance of differences between the two groups, were carried out using SPSS, and 95% confidence intervals (CI) for response rates were calculated using the Vassar on-line calculator [16].