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A Phase II Study of Etoposide, Cisplatin plus Methotrexate in Patients with Advanced Refractory Breast Cancer

M. Jouve, T. Dorval, V. Mosseri, T. Palangie, P. Beuzeboc, E. Garcia-Giralt, A. Livartowski, S. Scholl and P. Pouillart

THE PROGNOSIS of patients with advanced breast cancer (ABC) refractory to standard chemotherapy is dismal; the overall response rate to salvage chemotherapy for patients previously exposed to doxorubicin is 21% with a median survival of 4–6 months [1]. Recent reports suggest a possible activity of the combination of etoposide (E) and cisplatin (C) in heavily pretreated patients [2–4]. We thus initiated a phase II trial in patients with ABC refractory to the FAC combination (doxorubicin–cyclophosphamide–5-fluorouracil). Methotrexate (M) was chosen as an additional drug because of its known activity against breast cancer [6] and at least partial non-cross resistance with the FAC combination.

Patients with ABC refractory to the FAC combination, a Karnofsky index above 60% and a life expectancy of more than 12 weeks were eligible. Patients aged over 70 were not eligible. The doses and schedule of the combination were E 60 mg/m^2 intravenously (i.v.) days 1, 2, 3 and 4 ; P 30 mg/m^2 i.v. days 1, 2, 3 and 4 ; M 200 mg/m^2 day 1 given as a 24-h continuous infusion followed by leucovorin rescue. Tumour measurement was repeated monthly; if a response or stable disease was reached, E, C and M were offered in a 4-weekly schedule until disease progression, major intolerance or to a total of six cycles. Responses were evaluated according to the WHO criteria [9].

From February 1992 until November 1992, 18 patients entered the study. All patients had progressive disease while on FAC therapy. Patient characteristics are listed in Table 1.

Patients had between one and six courses (mean of four) of EPM and a total of 75 courses was administered. Among the first 11 patients, we observed one partial response. According to Gehan's model, 7 additional patients were entered. No further response was observed. Toxicity was tolerable. 7 patients (29 courses) had no side-effects other than alopecia. In all other patients, nausea and vomiting grade 2 or 3 were common ; six episodes of bone marrow toxicity of WHO grade 2 were scored with two reversible infectious complications. Peripheral neurotoxicity (WHO grade 2) was observed in 4 patients. No renal toxicity was detected.

Table 1. Patients' characteristics

Number of patients	18
Mean age (years)	48 (range 26–70)
Mean performance status	80 % (range 60–100)
Number of metastatic sites	
1	11 patients
2	4 patients
⩾3	3 patients
Prominent metastatic site	
Lung	10 patients
Liver	4 patients
Soft tissue	4 patients

All patients progressed while on therapy.

C and E have been considered inactive in ABC when tested in phase II trials [7–9] ; however, recent data suggest that the combination has at least additive activity in pretreated metastatic breast cancer and provocative results have been reported with first-line E and P in untreated patients [5]. M is an active drug in breast cancer without apparent cross resistance with first-line treatment protocols.

With one response among 18 patients, our trial does not confirm the results reported by others. An analysis of the dose intensity does not show any significant difference between this protocol and those described in other trials. The characteristics of the patients (resistance to an anthracyclin-based chemotherapy) could partly explain the poor results of this trial.

In conclusion, this combination cannot be recommended to ABC patients who progress while on an anthracyclin-based chemotherapy.

Correspondence to M. Jouve.
M. Jouve, T. Dorval, T. Palangie, P. Beuzeboc, E. Garcia-Giralt, A. Livartowski, S. Scholl and P. Pouillart are at the Service de Médecine Oncologique; and V. Mosseri is at the Unité de biostatistique, Institut Curie, 26 rue d'Ulm, 75231 Paris, Cedex 05, France.
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1. Henderson JC. Chemotherapy for advanced disease. In Harris JR, Hellman S, Henderson JC, *et al.* eds. *Breast Diseases*. Philadelphia, PA, Lippincott, 1987, 428–479.
2. Cocconi G, Tonato M, Di Costanzo F, *et al.* Platinum and etoposide in chemotherapy refractory metastatic breast cancer. A phase II trial of the Italian Oncology Group for Clinical Research (G.O.I.R.C.). *Eur J Cancer Clin Oncol* 1986, **22**, 761–764.
3. Krook JE, Loprinzi CL, Schaid DJ, *et al.* Evaluation of the continuous infusion of etoposide plus cisplatin in metastatic breast cancer: a collaborative North Central Cancer Treatment Group/ Mayo Clinic phase II study. *Cancer* 1990, **65**, 418–421.
4. Cox EB, Burton GV, Olsen GA, *et al.* Cisplatin and etoposide : an effective treatment for refractory breast carcinoma. *Am J Clin Oncol* 1989, **12**, 53–56.
5. Cocconi G, Bisagni G, Bacchi M, *et al.* Cisplatin and etoposide as first-line chemotherapy for metastatic breast cancer : a prospective randomized trial of the Italian Oncology Group for Clinical Research. *J Clin Oncol* 1991, **9**, 664–669.
6. Vogler WR, Furtado VP, Huguley CM Jr. Methotrexate for advanced cancer of the breast. *Cancer* 1968, **21**, 26–30.
7. Miller AR, Hoogstraten B, Staquet M, *et al.* Reporting results in cancer treatment. *Cancer* 1981, **47**, 207–214.
8. Forastiere AA, Hakes TB, Wittes JT, *et al.* Cisplatin in the treatment of metastatic carcinoma. A prospective randomized trial of two dosage schedules. *Am J Clin Oncol* 1982, **5**, 243–247.
9. Hwee-Yong Y, Salem P, Hortobagyi GN, *et al.* Phase II study of *cis*-dichlorodiaminoplatinum (II) in advanced breast cancer. *Cancer Treat Rep* 1978, **62**, 405–408.
10. Sledge GW, Etoposide in the management of metastatic breast cancer. *Cancer* 1991, **67**, 266–270.