Cancer Chemother Pharmacol (1990) 25: 463–464

Cancer Chemotherapy and Pharmacology

Short communication

Phase II study of teniposide in advanced breast cancer

Janne Boas[1], Dorte Rasmussen[1], Ole Paaske Hansen[2], Svend Aage Engelholm[3], and Per Dombernowsky[1]

[1] Department of Oncology, Herlev Hospital, University of Copenhagen, Denmark
[2] Department of Internal Medicine C, Bispebjerg Hospital, Copenhagen, Denmark
[3] Department of Oncology ONK, The Finsen Institute, Copenhagen, Denmark

Summary. In a phase II study, 19 patients with previously treated, advanced breast cancer received 50 mg/m^2 teniposide (VM-26) i.v. on days 1–5 every 3 weeks. One partial response (PR) (5%) was observed. Toxicity consisting of leukopenia and thrombocytopenia was frequent and severe. VM-26 has minimal therapeutic activity when given at this dose and on this schedule to patients with heavily pretreated metastatic breast cancer.

Introduction

The podophyllotoxin derivate teniposide (VM-26) has high activity in malignant lymphomas, leukemia, small-cell lung cancer, and testicular cancer [1, 4]. In most other solid tumors, its activity is either low or the drug has not been tested properly. We report a phase II study of VM-26 in pretreated patients with advanced breast cancer.

Patients and methods

Included in the study were women aged <70 years with histologically proven, progressive breast cancer not amenable to surgery or radiotherapy. Other inclusion criteria included: prior chemotherapy, including alkylating agents and anthracyclines for metastatic disease; measurable or evaluable lesions; a performance status (PS) of ≤ 2; a WBC count of $\geq 3.0 \times 10^9$/l; and a platelet count of $\geq 100 \times 10^9$/l, unless bone marrow involvement was documented. Normal kidney and liver function was also mandatory. Patients with CNS metastases, secondary malignancies, radiotherapy to indicator lesions, and hormonal therapy or chemotherapy in the previous 4 weeks were not eligible. Patients' informed consent was mandatory, and the study was approved by the regional scientific ethical committee.

VM-26 was dissolved in 500 ml saline and given i.v. over 30 min at a dose of 50 mg/m^2 on days 1–5 every 3 weeks. Subsequent cycles of VM-26 were postponed by 1 week if toxicity persisted until the day of scheduled retreatment. If WBC counts on the day of retreatment were between 2.5 and 3.0×10^9/l and/or platelet counts were between 75 and 100×10^9/l, the dose was reduced to 75%. If WBC counts were $\leq 2.5 \times 10^9$/l and/or platelet counts were $\leq 75 \times 10^9$/l, treatment was postponed. If the nadir WBC counts were $< 1.0 \times 10^9$/l or nadir platelet counts were $< 50 \times 10^9$/l, the next dose was reduced to 67%. Reductions were made in the daily dose and not in the number of treatment days. The dose was escalated by 25% if nadir WBC counts were $> 2.0 \times 10^9$/l and platelet counts were $> 100 \times 10^9$/l in the previous course.

A minimum of two courses were required for being fully evaluable, unless rapid progression or unacceptable toxicity occurred. Patients showing a response or disease stabilization remained on study until progressive disease was observed. Assessments of response and toxic side effects were carried out according to WHO criteria [7].

Results

A total of 20 patients entered the study. One patient was ineligible, as her disease was not evaluable. The evaluable patients had a median age of 55 years (range, 42–67 years). In all, 15 patients had a PS of 0 or 1, and 4 had a PS of 2. All patients had previously received chemotherapy including alkylating agents and anthracyclines (median number of previous cytostatic agents, 4; range, 2–6). A total of 11 patients had also received endocrine therapy, and 9 had undergone prior radiotherapy. The median number of treatment courses with VM-26 was 3 (range, 2–25). Dose escalation and reduction were undertaken in 9 and 5 cases, respectively. Of the 19 patients, 3 died early (after 11, 21, and 21 days) due to progressive disease.

One partial response (PR) (5.3%; 95% confidence limits, 0.1%–26.0%) was observed. This response was seen in a patient with complete disappearance of a supraclavicular lymph node and a PR in osteolytic bone metastases; the duration of response was 25 months. Three patients were registered as showing no change (NC), with durations of 4, 5, and 6 months.

Toxicity consisting of leukopenia and thrombocytopenia was dominant. The median WBC and platelet nadirs were 2.4×10^9/l (range, 0.1–5.4 $\times 10^9$/l) and 153×10^9/l (range, 1–362 $\times 10^9$/l), respectively. WBC counts below 3.0, 2.0, and 1.0×10^9/l were observed in 75%, 38%, and 19%, respectively and platelet counts below 100, 50, and 25×10^9/l were determined in 38%, 38%, and 25% of the patients, respectively.

Offprint requests to: Dorte Rasmussen, Department of Oncology, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

Table 1. Single agent activity of VM-26 in advanced breast cancer

Author and reference	Dose and schedule	No. of patients	Response No. of patients
Spremulli [5]	100 mg/m^2 weekly	20	5
Tirelli [6]	100 mg/m^2 weekly	20	1
Cox [2]	60 mg/m^2 day 1–5 q. 3 weeks	11	1
EORTC [3]	30 mg/m^2 day 1–5 q. 3 weeks	22	2
Boas (present study)	50 mg/m^2 day 1–5 q. 3 weeks	19	1

Severe thrombocytopenia was observed in four patients with nadir values of 1, 16, 23, and 24×10^9/l, respectively. Clinical bleeding occurred in three of these, and one patient died of bleeding on day 57. Three of the four patients also experienced severe but non-fatal leukopenia (WBC counts of 0.1, 0.1, and 0.5×10^9/l). Two of the patients with severe myelosuppression had histologically documented bone marrow metastases prior to treatment. Only one o the patients whose dose was escalated experienced thrombocytopenia (platelet nadir, 24×10^9/l). Alopecia was observed in all patients; none suffered from severe nausea or vomiting (WHO grade 3–4).

Discussion

In this phase II study of VM-26 in heavily pretreated patients with advanced breast cancer, 1 PR (5%) was observed in 19 patients. Table 1 shows other studies using VM-26 in advanced breast cancer. In the previous studies using daily or weekly schedules, some activity was observed [5, 6]; in more recent studies, including our own, in which the drug was given on days 1–5 every 3 weeks, the activity was very modest, with only 4 PRs being reported in 52 patients. This low activity was observed at dose levels creating moderate to severe dose-limiting, hematologic toxicity.

Based on these studies, there is no place for VM-26 in the treatment of patients with heavily pretreated breast cancer. However, the activity of VM-26 in patients with less extensive pretreatment is at present unknown.

References

1. Bork E, Hansen M, Dombernowsky P, Hansen SW, Pedersen AG, Hansen HH (1986) Teniposide (VM-26), an overlooked highly active agent in small cell lung cancer. Results of a phase II trial in untreated patients. J Clin Oncol 4: 524–527
2. Cox EB, Vogel CL, Carpenter JT Jr, Raney M (1988) Phase II evaluation of teniposide (VM-26) in metastatic breast carcinoma. A Southeastern Cancer Study Group trial. Invest New Drugs 6: 37–40
3. European Organization for Research on the Treatment of Cancer, Cooperative Group for Leukemias and Hematosarcomas (1972) Clinical screening of epipodophyllotoxin VM-26 in malignant lymphomas and solid tumors. Br Med J 2: 744–748
4. O'Dwyer P, Alonso MT, Leyland-Jones B, Marsoni S (1984) Teniposide: a review of 12 years of experience. Cancer Treat Rep 68: 1455–1466
5. Spremulli E, Schultz JJ, Speckhart VJ, Wampler GL (1980) Phase II study of VM-26 in adult malignancies. Cancer Treat Rep 64: 147–149
6. Tirelli U, Frenchin G, Crivellari D, Veronesi A, Galligioni E, Trovó MG, Talamini R, Tumolo S, Grigoletto E (1984) Phase II study of VM-26 in extensively pretreated breast cancer. Am J Clin Oncol 7: 451–452
7. WHO Handbook for Reporting Results of Cancer Treatment (1979) WHO, Geneva

Received 19 May 1989/Accepted 14 September 1989