Cancer Chemother Pharmacol (1982) 7: 223–225

Cancer Chemotherapy and Pharmacology

Phase II Study of VP16-213 (Etoposide) in Refractory Metastatic Breast Carcinoma*

F. C. Schell[1], H. Y. Yap[1], G. N. Hortobagyi[1], B. Issell[2], and L. Esparza[1]

[1] Medical Breast Service, Department of Medicine, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, Texas 77030
[2] Bristol Laboratories, P. O. Box 657, Syracuse, New York 13201, USA

Summary. *VP16-213 is a semi-synthetic derivative of podophyllotoxin. Preclinical trials have indicated a marked schedule dependency in the L1210 system suggestive of an advantage to short-cycle times and divided dose regimens. Seventy-seven patients with advanced breast carcinoma were studied. All patients had failed conventional combination chemotherapy (median prior chemotherapy: 23 months). All had prior Adriamycin and more than half had prior exposure to vinca alkaloids. The patients were randomly allocated to either: 1) intermittent bolus – 50–70 mg/m²/day over 1 h daily for 5 days (39 patients), or 2) infusion – 50–70 mg/m²/day as a continuous infusion for 5 days (38 patients). In the intermittent group, three patients were inevaluable (early death) and one was lost to follow-up. In the infusion group, four patients were inevaluable (early death), two were lost to follow-up and one refused further treatment. In the intermittent group of 35 evaluable patients, five (14%) achieved partial remission, three (9%) had responses less than partial, six (17%) had stable disease, and 21 (60%) had progressive disease. In the infusion group of 31 evaluable patients, one (3%) achieved complete remission, three (10%) achieved partial remission, three (10%) had responses less than partial, five (16%) had stable disease and 19 (61%) had progressive disease. Principle toxicity observed was myelosuppression, which was severe (granulocytes < 1,000) in approximately 50% with nadirs occuring at about day 12. Recovery was rarely prolonged beyond day 20. Nausea and vomiting were moderate with the intermittent schedule and almost absent with the infusion schedule. One patient in the intermittent group developed an anaphylactoid reaction requiring discontinuation of the drug. Congestive heart failure was precipitated by the fluid load in five patients on the infusion schedule. VP16-213 has significant antitumor activity in refractory breast carcinoma and merits further evaluation. The infusion schedule showed no advantage over the intermittent schedule of this study.*

Introduction

Combination chemotherapy has become the most effective modality of treatment for metastatic carcinoma of the breast [1, 5]. Various drug combinations including Cyclophosphamide, Methotrexate and 5-fluorouracil have been reported to produce objective remissions in the range of 50% of treated patients [4, 6]. When Adriamycin is added to these combinations, the response rate is reported to be as high as 70% of treated patients [3, 7, 9]. The median duration of these remissions ranges between 6–15 months with survival between 12–24 months. Our own experience reveals that less than 10% of patients treated with combination chemotherapy remain in complete remission beyond 2 years.

It is evident, therefore, that new drugs or different combinations are necessary to improve the remission rate and the survival duration. Several chemotherapeutic agents, either alone or in combination have been studied in an attempt to reinduce remissions in patients failing on first line chemotherapy [2, 11, 12]. The response rates on these regimens have been substantially lower and survival times shorter than those obtained with front line chemotherapy.

VP16-213 is a semi-synthetic derivative of podophyllotoxin, which is extracted from plants of the genus podophyllum. It's chemical formula is: 4′demethyl-epipodophyllotoxin-β-D-ethylidene glucoside. It has shown activity in preclinical studies

Send offprint requests to F. C. Schell at the above address

* Presented in part at the American Society of Clinical Oncology Meeting, Washington, D.C., May 3, 1981

0344-5704/82/0007/0223/$01.00

against the Walker carcinosarcoma in the rat, the Ehrlich ascites sarcoma 37 and 180 and in the L1210 leukemia; marked schedule dependence has also been demonstrated in the L1210 system [10].

In early clinical trials, the cumulative response rate to VP16-213 as a single agent was reported at 5% [8]. In view of our own experience with continuous infusion vinca alkaloids [12], we elected to do a phase II trial comparing VP16-213 as an intermittent 5-day bolus randomized against a continuous 5-day infusion.

Patients and Methods

Seventy-seven patients with advanced breast carcinoma who had failed primary combination chemotherapy including standard agents (Adriamycin, 5-fluorouracil, Cyclophosphamide and Methotrexate) and often prior phase II agents were entered on this study. Patient characteristics are outlined in Table 1.

The median prior chemotherapy was 23 months. All patients had prior exposure to Adriamycin combinations, and more than half had previously been exposed to vinca alkaloids. Patient eligibility was restricted to patients with a performance status of 3 or better on the UICC scale and who had clearly measurable lesions. Patients also had to be free of evidence of central nervous system involvement. The patients designated as good risk candidates (serum bilirubin less than 2 mg% and adequate bone marrow reserve) were treated with 70 mg/m^2/day either as a continuous infusion over 120 h or as an intermittent daily bolus dose over 1 h daily. Poor risk patients (serum bilirubin greater than 2 mg% but less than 5 mg% or who were considered to have a poor bone marrow reserve) received VP16 according to the same schedule at a dose of 60 mg/m^2/day. Treatment cycles were 21 days providing adequate recovery from toxic symptoms was accomplished by that time. Dosage was de-escalated or escalated in 20% incriments providing toxic effects were judged excessive or sufficiently mild to warrant dose change. In view of the previously reported episodes of anaphylaxis, epinepherin, antihistamines and corticosteroids were kept on hand while patients were treated, particularly when the bolus treatment was to be used.

Table 1. Patient characteristics

	Intermittent	Infusion
Age: median (range)	52 (30–74)	53 (39–68)
UICC Performance Status: median (range)	2 (0–3)	3 (0–3)
Metastasis sites patient: median (range)	3 (1–5)	3 (1–5)
Involved sites:		
Liver	5 (14%)	7 (23%)
Lung/Pleura	22 (63%)	16 (52%)
Soft tissue	21 (60%)	19 (61%)
Bone	19 (54%)	15 (48%)
CNS	6 (17%)	9 (29%)
Bone only	2 (6%)	2 (6%)
Soft tissue only	5 (14%)	4 (13%)
Prior chemotherapy:		
No. of prior regimens: Median (range)	3 (1–4)	3 (1–4)
Total months of prior chemo: median (range)	25 (7–65)	22 (6–44)
Prior vinca alkaloids	30 (86%)	24 (77%)

Table 2. Response rate

	Intermittent	Infusion	Total
CR	–	1 (3%)	1 (2%)
PR	5 (14%)	3 (10%)	8 (12%)
< PR	3 (9%)	3 (10%)	6 (9%)
SD	6 (17%)	5 (16%)	11 (17%)
PD	21 (60%)	19 (61%)	40 (60%)

Response duration

	Intermittent	Infusion	Total
Time to progression: Months (range)	4 (3–10)	5 (2–12+)	5 (2–12+)

Results

Of the 77 patients treated on this study, 39 were randomized to the intermittent bolus therapy and 38 were randomized to the continuous infusion. In the intermittent group, three patients were inevaluable due to early death and 1 was lost to follow-up. In the infusion group, four patients were inevaluable due to early death, two were lost to follow-up, and one refused further therapy. In the intermittent group of 35 evaluable patients, five (14%) achieved partial remission, three (9%) had responses less than partial, six (17%) had stable disease, and 21 (60%) had progressive disease. In the infusion group of 31 evaluable patients, one (3%) achieved complete remission, three (10%) had responses less than partial, five (16%) had stable disease and 19 (60%) had progressive disease. These results are outlined in Table 2. The principle toxicity observed was myelosuppression, which was severe (granulocytes less than 1,000) in approximately 50% with nadirs occuring at about day 12. Recovery was rarely prolonged beyond day 20. Thrombocytopenia followed a similar pattern, but was less severe. Nausea and vomiting were moderate with the intermittent schedule, but were essentially absent when the patients were treated with a continuous infusion. One patient in the intermittent treatment group developed an anaphylactoid reaction requiring discontinuation of the drug. The patient rapidly responded to the usual therapy with antihis-

Table 3. Toxicity

	Intermittent (%)	Infusion (%)
Total No. of patients	35	31
Alopecia	(29)	(23)
Nausea/Vomiting (moderate to severe)	(29)	(3)
Anorexia	(29)	(19)
Diarrhea	(11)	(13)
Anaphylactoid reaction	(3)	(0)
Congestive heart failure (Reversible: secondary to saline)	(3)	(16)
Thrombocytopenia ($< 100{,}000/mm^3$)	(35)	(40)
Hemorrhage (life-threatening)	(0)	(0)
Granulocytopenia ($< 1{,}000/mm^3$	(60)	(50)
Infections	(11)	(19)

tamines, epinepherin and steroids. Five patients on the continuous infusion developed congestive heart failure. No patients had serious sequelae from this complication, and all responded rapidly to diuretic therapy. Alopecia was noted in only about one-fourth of the patients. Other GI toxicities including anorexia and diarrhea were seen in from 10–30% of the patients. Infections were observed during myelosuppression in less than 20% of patients and no episodes of life-threatening hemorrhage or infection were seen in this study. Toxicity data are outlined in Table 3.

Discussion

VP16-213 demonstrated activity against refractory breast cancer in approximately 23% of patients treated, with slightly less than 15% achieving partial remission or better. We feel that since this was a highly pretreated population with a median of approximately 2 years of prior chemotherapy and a median UICC performance status between 2 and 3, that this activity is real. We did not observe the expected advantage to the continuous infusion treatment. We speculated that this might be secondary to the fact that the group randomized to infusion therapy tended to have a somewhat poorer performance status and a somewhat higher tumor burden. The congestive heart failure which was observed was felt to be secondary to the large saline load which was administered during this therapy since the drug was stable for only 6 h in solution and required significant doses of sodium chloride during administration. Alopecia was reported less frequently than in other studies with this drug; however, we feel this may represent a falsely low figure since many patients already had alopecia secondary to prior treatment on chemotherapy. It is our conclusion from this study that VP16-213 has demonstrated encouraging activity and warrants investigation in chemotherapy combinations early in the course of breast cancer patients. It would appear from this study that it demonstrates an activity similar to that which would be expected from the standard agents which presently are used in front line therapy for metastatic carcinoma of the breast.

References

1. Broder LE, Tormey DC (1974) Combination chemotherapy of carcinoma of the breast. Cancer Treat Rev 1: 183–203
2. Buzdar AU, Tashima CK, Blumenschein GR (1978) Mitomycin-C and metestrol acetate in treatment of breast cancer refractory to hormonal and combination chemotherapy. Cancer 41: 392–396
3. Cardenas JO, Blumenschein GR, Gutterman JU (1975) Sequential combination chemoimmunotherapy for advanced metastatic breast carcinoma. Am Soc Clin Oncol 16: 231 (Abstract no. 1041)
4. Cannellos GP, DeVita VT, Gold GL (1976) Combination chemotherapy for advanced breast cancer: response and effect on survival. Ann Int Med 84: 389–392
5. Carter SK (1974) The chemical therapy of breast cancer. Semin Oncology 1: 131–144
6. De Lena M, Branbilla C, Morabito A, Bonadonna G (1975) Adriamycin plus Vincristine compared to and combined with Cyclophosphamide, Methotrexate and 5-fluorouracil for advanced breast cancer. Cancer 35: 1108–1115
7. Hortobagyi GN, Gutterman JU, Blumenschein GR (1977) Chemoimmunotherapy of advanced breast cancer with BCG. In: Mathe G, (ed) Recent Results in Cancer Res, vol 62. Springer, Berlin Heidelberg New York, pp 143–150
8. Issell BF, Crooke ST (1979) Etoposide (VP16-213). Cancer Treat Rev 6: 107–124
9. Jones SE, Durie BGN, Salmon SE (1975) Combination chemotherapy with Adriamycin and Cyclophosphamide for advanced breast cancer. Cancer 36: 90–97
10. Stahelin H (1973) Activity of a new alycosidic lignan derivative (VP16-213) related podophyllotoxins in experimental tumors. Eur J Cancer 9: 215–221
11. Yap HY, Benjamin RS, Blumenschein GR (1979) Sequential L-asparaginase (ASP) and high dose methotrexate (MTX) in refractory stave IV breast cancer. Cancer Treat Rep 63: 77–83
12. Yap HY, Blumenschein GR, Keating MJ, Hortobagyi GN, Tashima CK and Loo TL (1980) Vinblastine given as a continuous 5-day infusion in the treatment of refractory advanced breast cancer. Cancer Treat Rep 64: 279–283

Accepted July, 1981