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Phase II Study of Oral VP-16-213 in Hepatocellular Carcinoma*†

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Abstract—*In a disease-oriented phase II study, 26 patients with hepatocellular carcinoma were treated with oral VP-16-213 at 120 mg/m²/day for 5 consecutive days, repeated every 3 weeks. Of 24 evaluable patients, 3 achieved partial remission (PR) for 12, 16 and 35 weeks respectively. Minor regression or stabilization of the disease (NC) was achieved in 8 patients for a median duration of 15 weeks. Patients with PR and NC experienced similar median survival (22 weeks), whereas non-responders had a median survival of less than 8 weeks. Results of this trial indicate that VP-16-213 has limited but definite anti-tumor activity in hepatocellular carcinoma.*

INTRODUCTION

PRIMARY hepatocellular carcinoma is most commonly associated with a dismal prognosis. Prolonged survival is occasionally seen after partial hepatectomy. However, this surgical procedure may be successfully undertaken in a minority of patients only [1].

Standard fraction radiation therapy alone is rarely effective [2], but promising results have been recently reported with whole-liver irradiation combined with intrahepatic arterial chemotherapy [3]. Systemic chemotherapy has yielded little progress in the therapy of this disease [4]. The fluoropyrimidines and, more recently, adriamycin and neocarzinostatin have been found to induce tumor regression in one-third of the patients at the most [5–8]. Results of the various chemotherapy series are fairly inconsistent, which may be at least partially ascribed to geographical factors and other prognostic variables of poorly understood significance.

The single agent activity of VP-16-213 in hepatocellular carcinoma has been investigated in a single small series [9]. Encouraging findings in this study prompted the Early-Clinical Trials Group of the EORTC to initiate a confirmatory disease-oriented phase II study with VP-16-213 in hepatocellular carcinoma. The oral formulation of the drug was selected for the trial in view of the previously reported biological activity with this method of drug administration [10].

MATERIALS AND METHODS

Patients

Twenty-six patients entered the study between September 1978 and May 1980. All had histologically confirmed, measurable hepatocellular carcinoma. Hepatomegaly was considered as a measurable lesion, if a clearly palpable liver edge extended at least 5 cm below the xiphoid process of the costal margin on quiet respiration.

The drug was given in drinking ampules at a dosage of 120 mg/m² daily for 5 consecutive days. Courses were repeated once every 3 weeks. Dilution of the ampules in orange juice was recommended to improve the taste of the preparation. Standard antiemetics were prescribed as indicated.

The protocol called for a treatment of at least 6 weeks unless life-threatening progression of the disease occurred earlier. Patients achieving partial remission or stabilization of

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the disease were continued on the same treatment until progression. The full dosage of VP-16-213 was given if WBC were >4000/mm^3 and platelets >100,000/mm^3. The dosage was reduced by 1/3 if WBC were 3000–4000/mm^3 and/or platelets 75,000–100,000/mm^3 at scheduled re-treatment. VP-16-213 was withheld until recovery from myelosuppression if WBC were <3000/mm^3 and/or platelets <75,000/mm^3.

Partial remission (PR) was defined as a 30% or more reduction in the sum of liver measurements below each costal margin at the midclavicular line and xiphoid process, with simultaneous improvement of all pre-treatment abnormalities of the liver function, concurrent improvement of the performance status of at least 10 points in the Karnofsky scale and no significant loss of weight. Conventional criteria (WHO) for defining PR ($\geq$50% reduction) in extrahepatic lesions were used. Tumor regression which was insufficient to qualify for a PR according to these definitions was reported as stabilized disease (NC).

RESULTS

Of 26 patients entered in the trial, two were considered not evaluable for anti-tumor activity: one died 5 days after the beginning of the treatment, the other patient was lost to follow-up before the second course of treatment. Pre-treatment characteristics of the 24 evaluable patients are detailed in Table 1. Among these patients, 3 achieved partial remission (response rate, 12.5%; 90% confidence limits, 1–24%). Objective tumor regression was detected within 3 weeks after starting therapy in 2 patients, whereas more than 12 weeks of treatment were needed to meet the criteria of PR in the third patient.

All responding patients showed good performance status (Table 2). All had measurable hepatomegaly. Only one was slightly jaundiced and exhibited a mild liver function impairment. None had ascites. One patient also had one solitary lung metastasis, and another responding patient had one cytologically proven osteolytic lesion in the left clavicula which was not considered to be measurable. In one PR the AFP was unknown; in the two others it was markedly elevated prior to entering the trial and significantly decreased with VP-16-213. One of the responding patients had failed to respond to prior chemotherapy with a conventional dose schedule of methotrexate.

The duration of the PRs was 12, 16 and 35 weeks respectively. The patient with the shortest remission duration (12 weeks) died, while still responding, following a dramatic episode of pulmonary embolism. This complication was reported as the cause of death in at least 6 patients in this trial. Three patients, who underwent post-mortem examination, were found to have extensive tumor growth into the lumen of the inferior vena cava.

Eight patients showed minor regression or stabilization of the tumor with VP-16-213 for a median of 15 weeks (range, 6–28 weeks). It is noteworthy that in two of these the AFP levels decreased significantly during the treatment period. None of these 8 patients showed ascites; two were jaundiced with serum bilirubin levels of 1.5–3.0 mg%.

The survival time from initiation of therapy was similar in PRs and NCs, with median figures of 22 weeks in either group (range, 10–59 weeks). In contrast, non-responders had a much shorter median survival of less than 8 weeks. Among the 13 non-responders, 8 had serum bilirubin levels >1.5 mg% and 5 had ascites.

Leukopenia was the most important toxic effect encountered in this trial. The median WBC nadir was 2300/mm^3 (1200–5400) and its median occurrence was on day 15. Throm-

Table 1. Pre-treatment patient characteristics

No. of evaluable pts.	24
Age in yrs	61 (32–81)
Performance status (Karnofsky)	70 (40–90)
Prior chemotherapy	6
Response to prior chemotherapy	0
Prior radiotherapy	0
Measurable disease:	
hepatomegaly only	18
hepatomegaly and/or	
subcutaneous metastases	1
lung metastases	3
bony metastases	2
Alpha-fetoprotein (AFP):	
unknown	6
positive	13
negative	5
HB_s Ag:	
unknown	17
positive	3
negative	4
Ascites:	
yes	5
no	19
Bilirubin serum level:	
≤1.5 mg%	13
1.5–3.0 mg%	6
3–10 mg%	3
>10 mg%	2

bocytopenia was of lesser importance: the median nadir of the platelet counts was 130,000/mm^3. Myelosuppression did not correlate with the degree of liver impairment. About 2/3 of the patients complained of non-hematologic side-effects of the treatment: nausea and vomiting (12 patients), anorexia (10 patients), stomatitis (6 patients).

DISCUSSION

VP-16-213 is a semi-synthetic epipodophyllotoxin derivative which acts *in vitro* by preventing cells from entering mitosis or by destroying them in the pre-mitotic phase [11, 12]. Possibly, it also inhibits DNA-synthesis [13]. The compound has anti-tumor activity in acute non-lymphoblastic leukemia, Hodgkin's and non-Hodgkin's lymphomas and some solid tumors, notably small-cell carcinoma of the lung [12, 14–16].

VP-16-213 was reported by one of us to be highly effective for the treatment of hepatocellular carcinoma, with 4 responses out of 7 patients [9]. The results of the present study (3 PRs out of 24 evaluable cases) failed to fully confirm these favorable preliminary data. It should, however, be stressed that owing to the limited number of patients in both series, the range of response rate (90% confidence limits) of both studies is overlapping.

Less encouraging findings are frequently reported in co-operative trials as compared to pilot institutional studies. An analysis of the response rate by pre-treatment characteristics would suggest that patients with good performance status and without pronounced impairment of the liver function are more likely to respond (Tables 1, 2). Accordingly, a poorer selection of patients might account, at least in part, for the rather disappointing results in this subsequent trial. In fact, even the difference in survival between responders and non-responders may be primarly related to a different distribution of the only partially known prognostic factors. However, a much larger population of patients would have been needed in order to ascertain these suggestions.

The high proportion of NCs in this and other trials ([19]; G. Falkson: personal communication) is worthy of note. This finding could be biased by too short observation times, or might reflect a particular kinetic behaviour in a subset of patients. On the other hand, pre-treatment characteristics and survival time were similar in PRs and NCs. Moreover, substantial decrease in the serum AFP levels suggestive of significant tumor shrinkage was noted in two NCs [17, 18]. It is thus conceivable that our criteria of response were inappropriate to properly assess the anti-tumor effect of chemotherapy in hepatocellular carcinoma.

Our data are consistent with a limited, but definite, anti-tumor activity of oral VP-16-213 as a single agent in the treatment of this tumor. Of note, the median survival time of PR and NC in our study was similar to that reported for patients responding to adriamycin and neocarzinostatin [7, 8]. The efficacy of VP-16-213 relative to these latter drugs cannot be ascertained without randomized trials.

At present, however, we feel that data on the single agent activity of VP-16-213 given intraveneously should be urgently procured for hepatocellular carcinoma. Although it is known that approximately 50% of the oral dose of VP-16-213 is absorbed [9], new data have lately shown that this absorption is more erratic than previously thought and clearly impaired patients with a poor intestinal function (D'Incalci, unpublished observations). That may, in fact, lead to an underestimation of the single agent activity of VP-16-213 in gastro-intestinal malignancies, particularly in hepatocellular carcinoma, when the drug is given orally. Accordingly, this fact might also account for the somewhat inconsistent results in our two subsequent trials.

Table 2. Characteristics of responding patients

Age	Performance status (Karnofsky)	A.F.P.	HB_s	Ascites	Liver function tests bilirubin	alk.ph.	Evaluable lesion	Day of response	Duration in wks
64	70	+	X	no	N	N	hepatomegaly	14	12*
61	80	X	X	no	N	N	hepatomegaly lung mets.	21	16
32†	80	+	–	no	3	315	hepatomegaly	84	35

*Patient died in remission because of pulmonary embolism.
†Patient had prior chemotherapy with methotrexate (no response).
X Unknown.

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