Chronic Oral Etoposide and Tamoxifen in the Treatment of Far-Advanced Hepatocellular Carcinoma

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BACKGROUND Hepatocellular carcinoma (HCC) is a chemoresistant tumor that frequently expresses a high level of p 170 glycoprotein of the multidrug-resistance (MDR) gene. Preliminary data suggested that VP-16 showed modest activity in HCC. Recently, schedule-dependent cytotoxicity of VP-16 has been demonstrated. In this study, we tested the therapeutic efficacy of chronic oral VP-16 plus tamoxifen, a potential MDR-reversing agent, in patients with far-advanced HCC.

METHODS. A prospective single-arm study was conducted in the National Taiwan University Hospital. To be eligible, patients must have had unresectable and non-embolizable HCC, objectively measurable tumors, adequate hemogram with absolute granulocyte count greater than or equal to 2,000/mm^3, and platelet count greater than or equal to 1×10^5/mm^3, total serum bilirubin less than or equal to 3.0mg/dl, age less than or equal to 75 years, and a Karnofsky performance status of greater than or equal to 50%. The treatment included VP-16 (Bristol-Myers-Squibb, Princeton, NJ), 50 mg/m^2/day, orally, Days 1 to 21, and tamoxifen (Pharmachemie B.V., Haarlem, Netherlands), 40 mg/day, orally, Days 1 to 21; repeated every 5 weeks.

RESULTS Between December 1990 and December 1993, a total of 33 patients were enrolled in the study. There were 28 men and 5 women, with a median age of 51 years. They received an average of 3.2 (range: 1–10) courses of chemotherapy. ECOG (Eastern Cooperative Oncology Group) Grade 3 and Grade 4 leucopenia developed in 6 patients (18.2%) and 4 (12.1%) patients, respectively. Grade 3 and 4 thrombocytopenia developed in 2 patients (6.1%). Treatment-related death occurred in one patient due to sepsis. Mild gastrointestinal toxicities were common with Grade 1 and 2 nausea, Grade 1 and 2 vomiting, Grade 1 and 2 diarrhea, and Grade 1 and 2 stomatitis, developed in 13 (39.4%), 7 (21.2%), 12 (36.4%), and 16 (48.5%) patients, respectively. Grade 3 and 4 gastrointestinal toxicities were rare. Deep vein thrombosis occurred in one patient (3.0%). Eight patients (24.2%, 95% confidence interval 11%–42%) had achieved a partial remission, with a median time-to-progression of 6 months (2–11). Median survivals of the responders and non-responders were 8.0 and 3.0 months, respectively ($P < 0.05$). The median Karnofsky performance status of the responders improved from 70% to 80%.

CONCLUSIONS. Chronic oral VP-16 and tamoxifen has modest activity and acceptable toxicity in far-advanced HCC, and is a useful palliative treatment in about a quarter of such patients. ***Cancer* 1996; 77:872–7.** © *1996 American Cancer Society.*

KEYWORDS: hepatocellular carcinoma, VP-16, tamoxifen.

Combatting hepatocellular carcinoma (HCC) with systemic chemotherapy has been a frustrating experience for physicians of modern medicine. The activity of single agents is limited, with only a few drugs showing a response rate greater than 10%.[1,2] Moreover, combination chemotherapy has proven equally disappointing because it rarely demonstrates meaningful clinical efficacy.[1,2]

The drug-refractory nature of most HCC is probably related to its high incidence of multidrug-resistance (MDR) gene expression.[3] We have demonstrated that in HCC cell lines such as Hep3B, the p 170 glycoprotein is functionally active, and its drug exporting ability can be partly reversed by a known MDR-reversing agent such as tamoxifen.[4,5]

VP-16 is a relatively new drug in clinical oncology and its efficacy over HCC has not been extensively studied. Preliminary data suggested that VP-16 shows real although modest activity against HCC, with a single-agent response rate of 10% to 15%.[6,7] Recently, the cytotoxic effect of VP-16 has been shown to be highly schedule-dependent. With more protracted administration, VP-16 appeared to have a greater activity, and it produced clinical remission in patients who had been refractory.[8,9] It is therefore reasonable to test if prolonged administration of oral VP-16 might produce a respectable response in patients with HCC.

Tamoxifen, an anti-estrogenic triphenylethylene, was found to be an MDR-reversing agent in cancer cell lines including HCC.[10-12] Recently, tamoxifen revealed many other biologic activities that may have therapeutic implications in cancers. Among these are protein kinase C (PKC) inhibition,[13,14] calmodulin inhibition,[15] insulin growth factor inhibition,[16] transforming growth factor-α inhibition,[17] transforming growth factor-β1 induction,[18] and immune reaction modulation.[19] It is suspected that some of these activities may be responsible for the sporadic therapeutic effect of tamoxifen on various cancers.[20,21] Recently, tamoxifen has been shown to be effective in prolonging overall survival in some HCC patients.[22,23] The putative mechanism is hormonal regulation of the cancer cell growth of HCC. The latter has long been suspected to be closely associated with sex hormones.[24,25]

There is currently no data confirming that tamoxifen is a clinically useful MDR-reversing agent.[26-28] Also, the dose required to induce an in vivo MDR-reversing effect is unknown.[26-28] Although serum concentration of as much as 3 μM to 4 μM of tamoxifen can be safely achieved with high-dose protocols,[28,29] results of animal studies have indicated that the concentration of tamoxifen can be much greater in tumor tissues than it is in sera, and hence, these results contradict the need for high-dose protocols.[30] In this study, we adopted a 40 mg daily dose of tamoxifen in conjunction with chronic oral VP-16 to form an experimental protocol which can be easily given on an outpatient basis.

METHODS

Patients

Eligibility criteria for patients in this study included the following: (1) histologically confirmed HCC, or α-fetoprotein greater than or equal to 400 ng/ml with a hepatic tumor highly suggestive of HCC by imaging studies and by necessary clinical examinations that excluded other possible diagnoses; (2) unresectable and nonembolizable tumors, carefully assessed by the individual experts; (3) objectively measurable diseases by CT scan and chest X-rays; (4) adequate hemogram with absolute granulocyte count (AGC) greater than or equal to 2,000 mm^3, and platelet count greater than or equal to 1×10^5 mm^3; (5) adequate renal function with serum creatinine less than or equal to 2.0 mg/dl, and adequate hepatic function with serum total bilirubin less than or equal to 3.0 mg/dl; (6) adequate performance status with Karnofsky status greater than or equal to 50%; (7) age less than or equal to 75 years; (8) no recent active treatments including surgery, radiotherapy, chemotherapy, transarterial embolization, or other regional treatment within one month; and (9) signed informed consent.

Treatments

VP-16 (Bristol-Myers-Squibb, Princeton, NJ) 50 mg/m^2/day, orally, Days 1 to 21, and tamoxifen (Pharmachemie B.V., Haarlem, Netherlands) 40 mg/day, orally, Days 1 to 21, were administered every 5 weeks. If AGC was 1500 to 2000/mm^3 or platelet count was 7.5 to 10.0×10^4/mm^3 on Day 36, a subsequent course was started with a 25% reduction of VP-16 dose. Premature discontinuation of VP-16 and tamoxifen was carried out if AGC was less than or equal to 1000/mm^3, or platelet count reached less than or equal to 7.5×10^4/mm^3 before Day 21. For patients with any Grade 3 or greater Eastern Cooperative Oncology Group (ECOG) treatment-related toxicity, a 25% dose reduction of VP-16 was carried out in subsequent courses. Since gastrointestinal absorption of VP-16 is relatively heterogeneous,[31] a schedule for dose-escalation was also adopted. For patients with nadir AGC greater than or equal to 2000/mm^3 and nadir platelet count greater than or equal to 1.0×10^5/mm^3, and no other Grade 2 or greater (ECOG) treatment-related toxicity, the dose of VP-16 was escalated 25% for the next course. Readjustment of the VP-16 dose was carried out for subsequent courses according to the results of toxicity evaluation of the latest course given.

Patients who achieved complete remission (CR) or partial remission (PR) were continued on protocol treatment until disease progression or unacceptable treatment-related toxicity developed. Patients who achieved stable disease (SD) received two courses of treatment.

Survival was calculated from the date of chemotherapy to the date of death or last follow-up. For the responders, time to progression was defined as the date of chemotherapy to the date that evidence of tumor progression emerged.

TABLE 1
Clinicopathological Features of Patients

	All patients	Responders	Non-responders	P
No. of patients	33	8	25	NS
Male/Female	28/5	7/1	21/4	NS
Median age (yr)	51	51	51	NS
KPS				
≥ 80%	12 (36%)	4 (50%)	8 (32%)	NS
70–79%	7 (21%)	1 (12%)	6 (24%)	NS
60–69%	11 (33%)	3 (13.8%)	8 (32%)	NS
50–59%	3 (9%)	0	3 (12%)	NS
Child classification				
A	30 (91%)	8 (100%)	22 (88%)	NS
B	3 (9%)	0 (0%)	3 (12%)	NS
Extrahepatic metastasis	8 (24%)	3 (38%)	5 (20%)	NS
Tumor characteristics				
Diameter > 10 cm	17 (52%)	2 (25%)	15 (60%)	NS
Diffuse infiltration	14 (42%)	3 (38%)	11 (44%)	NS
Cirrhosis[a]	17/27 (63%)	3/7 (43%)	14/20 (70%)	NS
HBsAg (+)	21 (64%)	4 (50%)	17 (68%)	NS
α-FP < 400 ng/ml	10 (30%)	3 (38%)	7 (28%)	NS
Previous treatment				
None	21 (64%)	5 (63%)	16 (64%)	NS
Operation	5 (15%)	2 (25%)	3 (12%)	NS
TAE	9 (27%)	1 (13%)	8 (32%)	NS

[a] Histological diagnosis was available in 27 patients.
KPS: Karnofsky performance status scale; HBsAg: hepatitis B virus surface antigen; α-FP: α-fetoprotein; TAE: transarterial embolization.

Evaluation

Patients were carefully followed up for evaluation of toxicities and response. Hemogram was examined weekly during systemic chemotherapy. Blood chemistry, serum α-fetoprotein, and imaging studies were examined after each course of treatment.

CR was defined as the disappearance of all clinically detectable tumors for at least four weeks. PR was defined as at least a greater than or equal to 50% reduction in the sum of the products of all measurable tumors, without appearance of any new lesions for at least four weeks. SD was defined as a reduction of less than 50% or an increase of less than 25% of all measurable tumors with no appearance of new lesions for at least 4 weeks.

Statistics

Patients' survival data were analyzed by the estimation method proposed by Kaplan and Meier.[32] Differences between survival curves were evaluated by the log rank test.[33] Comparisons of the frequencies of other clinical parameters were evaluated by X^2 analysis and Fisher's exact test.

RESULTS

Clinicopathologic Features of the Patients

Twenty-seven patients had histologic diagnosis for tumor and nontumor parts of the liver. Among these, 4 patients were diagnosed by specimens from previous operations and 23 patients were diagnosed by needle biopsies from tumor and nontumor parts of the liver. Six patients were diagnosed by a marked elevated serum α-fetoprotein level (greater than 400 ng/ml) accompanied by a clinical picture and imaging studies indicating advanced HCC.

Pertinent clinicopathologic features of the patients are tabulated in Table 1. Five and 9 patients had recurred from previous surgical treatment or transarterial embolization treatment, respectively. At the time of entry, 17 patients had huge hepatic tumor (> 10 cm in diameter) and 14 had diffuse, infiltrative hepatic lesions. There was no patient with fibrolamellar HCC or evidence of tumor encapsulation.

Evaluation of Toxicities

Thirty-three patients had received a total of 108 courses of chemotherapy, an average of 3.2 courses per patient (range: 1–10). Dose reduction or escalation according to the protocol was administered in 8 patients (24.2%) and 3 patients (9.1%), respectively. Hematologic and nonhematologic toxicities are shown in Table 2.

A skin lesion, which is rarely reported as a complication of etoposide, characterized by itching, brownish pigmentation, and maculopapular eruptions, developed in eight patients.[34] These lesions, predominantly distributed

TABLE 2
Toxicity of Oral VP-16 and Tamoxifen

	No. of patients (%)	
Hematologic	Grade III	Grade IV
Leucopenia	6 (18.2%)	4 (12.1%)
Thrombocytopenia	1 (3.0%)	1 (3.0%)
Infection	2 (6.1%)	2 (6.1%)
Non-hematologic	Grade I/II	Grade III
Nausea	13 (39.4%)	2 (6.1%)
Vomiting	7 (21.2%)	0
Diarrhea	12 (36.4%)	2 (6.1%)
Stomatitis	16 (48.5%)	1 (3.0%)
Alopecia	31 (93.9%)	0
Dermatitis	8 (24.2%)	0

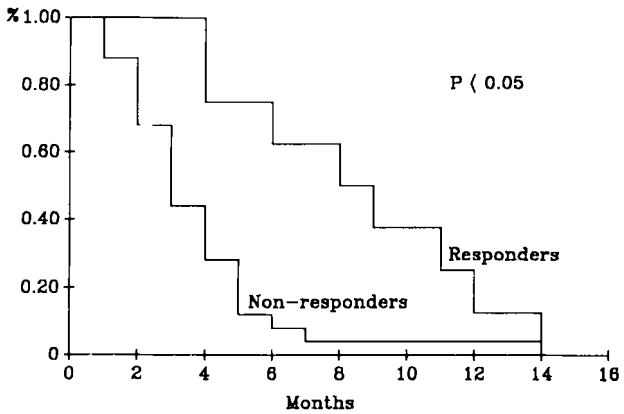

FIGURE 1. Responders had a significantly better survival curve than that of nonresponders.

on the low abdominal wall, buttocks, and thighs, could be alleviated by topical corticosteroid treatment.

Evaluation of Response

There were no patients who experienced CR. Eight patients (24.2%, 95% confidence interval 11% to 42%) achieved PR, with time to progression of 3, 4, 4, 5, 7, 7, 10, and 12 months, respectively.

Comparison of the responders and nonresponders revealed no remarkable differences regarding sex, age, performance status, Child's classification, extrahepatic metastasis, tumor characteristics, cirrhosis, status of HBsAg, serum α-fetoprotein level, and previous treatments (Table 1).

Although comparison of survival between responders and nonresponders is not a valid way of establishing therapeutic efficacy, the survival of the responders was significantly better than that of the nonresponders in this study (Fig. 1). The median survival of responders and nonresponders was eight and three months, respectively.

The performance status of the responders improved from a pretreatment median value of 70% to a post-treatment value of 80%. The improvement was mostly on alleviation of abdominal pain and fullness (five patients), increased appetite (four patients), increased body weight (four patients), and increased activity (five patients).

Of the 23 patients with initial elevated serum α-fetoprotein, eight experienced a significant (34.8%) decrease in their values (greater than 25% reduction) after chemotherapy. Five of the eight patients with objective tumor response experienced an elevated serum α-fetoprotein level before starting chemotherapy. All of these five patients had a decrease in their serum α-fetoprotein level after chemotherapy; degree of declinement was proportional to the degree of tumor response.

DISCUSSION

HCC occurs less frequently in Western countries. In areas of Africa and Asia, however, it is one of the most common malignant tumors.[2] In Taiwan, it is currently the number one cause of cancer death. To date, surgery continues to be the only hope for a cure for HCC patients, but the overwhelming majority of patients are not candidates for radical resection at the time of diagnosis. For suitable patients, regional therapy such as transarterial embolization or chemoembolization are commonly used as temporary measures to control the tumors.[2] However, within a short period of time, most HCC patients enter a Phase with far-advanced disease, for which effective treatment is not available.

Progress in treating HCC patients with systemic chemotherapy has been slow. Doxorubicin remains the most active drug, with a single-agent tumor response rate of about 10% to 20%.[1,2] Results from clinical trials using multiagent chemotherapy for HCC patients failed to show any beneficial effect beyond single agents.[1,2] New drugs have continuously been tested for their activity against HCC, without encouraging results. For example, 0 out of 14 HCC patients responded to taxol in a recent Phase II study conducted in Taipei, Taiwan (Whang-Peng J, personal communication). Therefore, before any new drug can be invented for the purpose of fighting HCC, it may be worthwhile to look into those old drugs, the therapeutic efficacy of which can be improved either by biochemical modulation or by modification of the drug administration schedule. VP-16 appears to be one of the drugs worth addressing for this purpose.

Preliminary results have indicated that VP-16 shows modest activity against HCC. In a Phase II study by Cavalli et al., oral VP-16 administered in increments of 120 mg/m^2/day for 5 consecutive days, repeated every 3 weeks, resulted in a remission rate of 12.5%.[5] In another pilot study, Melia et al. administered parenteral VP-16 in increments of 180 mg/m^2/day for 3 consecutive days for 2

weekly intervals, and observed a remission rate of 18%.[7] Recently, the schedule-dependent cytotoxicity of VP-16 has been advocated.[8,9] With prolonged oral administration, VP-16 has been more effective but not more toxic.[8,9] This can be partly explained by the mechanism of action in VP-16.[35,36] VP-16 damages DNA by interacting with topoisomerase II. This enzyme normally catalyzes DNA topoform interconversions by introducing a transient enzyme-bridged, double-strand break in one of the two crossing DNA segments. By stabilizing the DNA-topoisomerase II complex, VP-16 prevents the DNA strands from rejoining, with subsequent double-strand breaks. Topoisomerase II is most active during the G2 Phase of the cell cycle, thus accounting for the cycle-specific activity of VP-16 and the need for prolonged administer. Furthermore, it appears that the interaction of VP-16 with topoisomerase II is reversible once the VP-16 concentration falls below a critical level. It would follow that prolonged exposure to a critical VP-16 concentration, i.e., greater than 1 μg/ml, would enhance the antineoplastic activity of the drug by prolonging its interaction with topoisomerase II. Pharmacokinetic study of VP-16 has demonstrated that, following an oral dose of 160 mg/m^2, mean peak plasma concentrations of 9 μg/ml occurred between 1 and 4 hours, and remained above 1 μg/ml for more than 12 hours.[37] The bioavailability of oral VP-16 is even greater when the dose is less.[31] Following an oral dose of 100 mg, the serum level has been shown to be more than 1 μg/ml for a prolonged period of time.[31]

Further enhancement of the therapeutic efficacy of VP-16 against HCC is possible. The chemoresistant nature of HCC is believed to be, at least in part, related to its high incidence of MDR-1-gene-encoded p 170 glycoprotein expression.[3] We have demonstrated that the p 170 glycoprotein of Hep3B, a human HCC cell line, is a functionally active exporter of anticancer drugs, and this function can be blocked by MDR-reversing agents such as cyclosporin-A and tamoxifen.[4,5] Since VP-16 is one of the anticancer drugs which are exported by p 170 glycoprotein,[38] it is reasonable to incorporate tamoxifen into the VP-16 regimen, in the hope that it might further enhance the cytotoxicity of VP-16 against HCC. Currently, the dose of tamoxifen required for an MDR-reversing effect is still unknown. In the test tubes, the concentrations required for an enhancement of drug retension ranged from 1 to 10 μm, depending on different experimental systems.[4,10-12] Although serum levels of tamoxifen equilibrates at about 0.5 μm to 1.5 μm following a 10 mg/m^2 twice daily dose in clinical trials,[39] animal studies have demonstrated that the concentration of tamoxifen in tumor tissues is usually more than 10 times the concentration in sera.[30] In our study, a relatively low dose of tamoxifen (40 mg/day) was adopted. The magnitude of tamoxifen's contribution to the therapeutic efficacy of our regimen cannot be determined by this study design. A higher response rate needs to be obtained before a randomized Phase III study comparing the effect of tamoxifen can be justified. It should also be mentioned that an antagonistic effect from tamoxifen on the cytotoxicity of VP-16 may exist in some hormonally-regulated tumors.[40] Recent evidence has suggested that HCC may be closely related to sex hormones.[22-28]

In this single-arm Phase II study of patients with far-advanced HCC, chronic oral VP-16 and tamoxifen caused PR in about a quarter of the patients. Since treatment-related toxicity has been acceptable, and the regimen can be easily given on outpatient service, it may worth a therapeutic trial in selected patients. In our hands, the responders usually experienced good palliative results of their symptoms.

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