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ORIGINAL ARTICLE

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Combination chemotherapy involving orally administered etoposide and JM-216 in murine tumor models

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Abstract *Purpose*: Orally administered VP-16 (etoposide) was evaluated in combination with an orally administered platinum analog, JM-216 [ammine/cyclohexylamine diacetatodichloride Pt(IV)], in mice bearing murine tumors, for therapeutic synergy. *Methods*: The treatment schedules used involved two courses of therapy, each course consisting of administration every day for 5 days beginning on either day 4 or day 5 posttumor implantation, and again on day 11 or day 12 postimplantation. *Result*: The amounts of each drug tolerated in the combination treatment setting were much less than their individual maximum tolerated doses (MTDs). Thus, to be used safely, each drug's dose had to be greatly reduced from the amount tolerated when the drugs were given individually. Multiple experiments using a staged P388 leukemia model implanted intravenously yielded confirmatory data supporting the existence of a therapeutic synergy for the drug combination. Identical regimens applied in the staged M5076 sarcoma model implanted subcutaneously, however, were not considered to have yielded data indicative of therapeutic synergy. *Conclusions*: A clinical phase I study using this combination chemotherapy can be recommended on the basis of the results obtained in the leukemia model.

Key words Etoposide · VP-16 · JM-216 · Therapeutic synergy

Introduction

Ammine/cyclohexylamine diacetatodichloride Pt(IV) (JM-216) is a platinum coordination complex currently undergoing clinical trials as an orally administered antitumor agent [9–11]. The preclinical oral antitumor activity of JM-216 has been described by Rose et al. [12] and Kelland et al. [6]. Subsequent to these initial demonstrations of oral activity, McKeage et al. [8] described the therapeutic advantage of a consolidated schedule comprising five daily treatments for JM-216 in two different tumor models, as opposed to a single bolus or chronic daily administrations.

The clinical efficacy of parenterally administered etoposide (VP-16) is well established in several neoplastic disease settings [5], and its efficacy when orally administered is currently being investigated. The activity of orally administered VP-16 in tumor-bearing animals was initially reported by Stahelin [17]. He found that mice implanted subcutaneously (s.c.) or intraperitoneally (i.p.) with L1210 leukemia achieve a significant increase in lifespan following the oral administration of VP-16, and that VP-16 is also active orally in rats bearing intramuscular (i.m.) or s.c. Walker carcinoma.

The clinical evaluation of JM-216 will also include an assessment of its efficacy when used in combination with other orally administered anticancer agents, including VP-16. The basis for comtemplating such an evaluation is found in the clinical success of combination chemotherapy involving parenterally administered cisplatin (or carboplatin) and VP-16 [5] and the preclinical data which indicate a likely therapeutic synergy [1,7,14].

The purpose of the present studies was to determine whether a preclinical therapeutic synergy exists in a tumor model between orally administered JM-216 and VP-16 given in combination.

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Materials and methods

Mice

Female DBA/2, C57BL/6, (BALB/c × DBA/2)F_1 (CDF_1) hybrid and (C57BL/6 × DBA/2)F_1 (BDF_1) hybrid mice, 16–20 g, were purchased from Harlan Sprague-Dawley Co. (Indianapolis, Ind.). They were provided with food and water *ad libitum*. All studies

involving these animals were conducted in accordance with Bristol-Myers Squibb Company (BMS) animal care and use committee guidelines.

Tumors

The murine P388 leukemia was passaged i.p. as ascites once weekly in syngeneic DBA/2 mice. The murine M5076 sarcoma was passaged s.c. biweekly in syngeneic C57BL/6 mice. For experiments, P388 cells were implanted i.v. into BDF_1 mice and M5076 tumor fragments were implanted s.c. into BDF_1 mice.

Drugs

VP-16 was added to water with sufficient Tween 80 (approximately 1% by volume) to effect suspension. JM-216 was suspended in peanut oil. Bulk VP-16 was provided by BMS and bulk JM-216 was provided by the Johnson-Matthey Co.

The administration schedule used for both VP-16 and JM-216 was the same in all experiments, i.e. oral administration once daily for 5 days, repeated twice with 3 days rest between cycles. The only exception was in the final P388 experiment where a dose of 800 mg/kg of VP-16 had to be administered each day in two doses of 400 mg/kg, administered 1 h apart. Treatment was initiated on day 4 or day 5 postimplantation in the P388 leukemia studies, and on day 5 in the M5076 sarcoma studies. In combination treatment groups, VP-16 was always given first, followed 1–2 h later by JM-216. This sequence, of minimal separation as it may have been, was instituted for the practical reason of not wanting to administer too great a volume of suspended compounds at one time to the mice, and assuming that gastric emptying of the aqueous vehicle-based drug (VP-16) would be more readily accomplished.

Assessment of biological activities

Therapeutic results are presented in terms of: (a) increases in lifespan reflected by the relative median survival time (MST) of drug-treated (T) and control (C) groups of mice (i.e. %T/C values), and cures (overtly free of tumor at time of necropsy); and (b) primary tumor growth inhibition in the M5076 experiments determined by calculating the relative median times for T and C mice to grow tumors of 1 g and expressed as T−C values (in days). Tumor growth was measured twice weekly with a caliper and weights calculated assuming a density of 1, using the formula for an ellipsoid of: $wt(mg) = a \times b^2/2$, where a is the length and b is the width of the tumor. Statistical comparisons were made using a modified Wilcoxon test [4]. All tumor experiments were terminated 75 days postimplantation and any surviving animals were necropsied.

The dose of a compound which yielded the maximum therapeutic effect in an experiment was termed the optimal dose. The activity criterion for increased lifespan was a %T/C of $\geq$125%. The activity criterion for tumor inhibition was a delay in primary M5076 tumor growth of $>$13 days (which was consistent with 1 $\log_{10}$ cell kill based upon a 4-day tumor volume doubling time). There were six mice per group in the toxicity experiments, six or eight mice per group in the P388 leukemia experiments and eight mice per group in the M5076 experiments. Treated mice dying prior to their tumors reaching 1 g, or before any deaths in the parallel untreated control group, were considered to have died from drug toxicity. Treated groups of mice experiencing more than an average 5 g of body weight loss following completion of therapy were recorded as having probably undergone excessively toxic treatment even in the absence of obvious drug-related deaths. Groups of mice with more than one death attributable to drug toxicity were considered to have had excessively toxic treatments and their data were not used in the evaluation of a drug's or drug combination's antitumor efficacy. The highest dose of a drug, or combination of drugs, not causing excessive toxicity (as defined above) was referred to as the maximum tolerated dose (MTD). The combination toxicity index (CTI) was estimated from informal inspection of the data [15].

A two-drug combination yielding a therapeutic outcome greater than can be obtained using either drug alone under identical conditions of treatment, and at equitoxic levels, is termed therapeutic synergy [3,13,18].

Results

Toxicity studies

Dose range-finding studies in nontumor-bearing CDF_1 mice were used to help define the MTDs for VP-16, JM-216, and the two drugs in combination (Table 1). The treatment schedules used were identical to the schedule described for use in the therapy experiments.

The MTD for JM-216 was 40 mg/kg per dose; 80 mg/kg per dose caused the death of all six treated mice. Subsequent therapeutic studies using the M5076 tumor model confirmed these toxicity data (see below). With regard to VP-16, 400 mg/kg per dose was evaluated in two experiments and tolerated both times. Greater doses of VP-16 were not assessed in these preliminary toxicity experiments.

A few selected dose combinations involving VP-16 and JM-216 were evaluated in nontumor-bearing mice. All mice receiving 400 mg/kg per dose of VP-16 with $\geq$ 20 mg/kg per dose of JM-216 were killed by the treatments. Lower titrated doses of both compounds caused at least half the treated mice to die until a tolerated combination dose level was found: 100 mg/kg per dose of VP-16 plus 10 mg/kg per dose of JM-216. Assuming single agent MTDs of 400 mg/kg per dose for VP-16 and 40 mg/kg per dose for JM-216, the tolerated doses of the drugs used in combination represented only 25% of each drug's respective individual MTD, consistent with a CTI of 0.5. No overt manifestations of drug toxicities were observed using the combination treatments (in this or subsequent studies) that were distinct from those seen with either drug alone.

Table 1 Effect of VP-16, JM-216, and combinations of the two, in non-tumor-bearing CDF_1 mice. Treatments were given orally daily for 5 days on a day 1 and 8 schedule

Treatment (mg/kg per dose)		Median survival time (days)	No. alive/total [a]
VP-16	JM-216		
–	80	15.0	0/6
–	40	> 40	6/6
–	20	> 40	6/6
400 [b]	–	> 40	6/6
200	–	> 40	6/6
400	80	9.5	0/6
400	40	11.0	0/6
400	20	12.5	0/6
200	20	14.0	0.6
200	10	15.5	2/6
100	20	≥ 28	3/6
100	10	> 40	6/6

[a] Assessed approximately 4 weeks following the end of treatment(s)
[b] Evaluated twice yielding identical results

M5076 studies

An initial experiment involving this tumor model resulted in nearly all the treatment groups showing excessive toxicity (data not shown). Only one drug treatment, 40 mg/kg per dose of JM-216, yielded a usable result: a %T/C of 163% and a T−C value of 23.5 days. Greater dose levels of JM-216, e.g. 80 mg/kg per dose, were too toxic, confirming the results observed in the toxicity experiments. In this same initial experiment, a regimen of 400 mg/kg per dose of VP-16 was also judged too toxic since half the treated mice died prior to any of the control mice. None of the combination regimens yielded interpretable data as a result of excessive toxicity.

Lower doses of individual drugs and especially drug combinations were used in a second M5076 experiment (Table 2). Treatment with 400 mg/kg per dose of VP-16 was tolerated in this study and yielded a %T/C of 126% accompanied by a T−C value of 13.8 days. The more effective drug in this tumor model, JM-216, achieved a maximum %T/C of 153% at 20 mg/kg per dose accompanied by a T−C value of 17.5 days, but a greater delay in tumor growth (24.5 days) was produced following treatment at 40 mg/kg per dose. This higher dose of JM-216 resulted in a %T/C of 134% and one early death attributable to drug toxicity. In comparison, several JM-216 plus VP-16 combination regimens produced delays in tumor growth of between approximately 21 and 25 days, accompanied by %T/C values of 138–148%. Some of these treatments were also associated with early deaths from drug toxicity. The therapeutic results attributable to combination chemotherapy were judged to be comparable to the best effects obtained with solo treatment with JM-216.

It will be noted that there was a reasonable, but imperfect, correlation between lifespan increases and tumor growth delays. This is often explained by the fact that the most effective regimens with regard to primary tumor inhibition are at the limit of tolerability and may cause delayed lethality, which in a tumor-bearing animal cannot be readily dissociated from tumor-induced death (typically as a consequence of metastatic disease). Hence, slightly less than optimal tumor (primary) inhibitory drug doses are observed to yield slightly greater increases in lifespan. In evaluating the M5076 data for therapeutic synergy, both lifespan and tumor growth delay endpoints were considered equally.

P388 studies

In the first of two P388 leukemia experiments described (expt. A, Table 3), JM-216 achieved a maximum %T/C of 206% at its MTD of 40 mg/kg per dose. Solo treatment with VP-16 resulted in a maximum %T/C of 282% at 400 mg/kg per dose, but essentially comparable increases in lifespan were produced by doses of 200 and 600 mg/kg per dose. Although there was no indication in this experiment, in which BDF_1 mice were used, that 600 mg/kg per dose was not tolerated, in a pilot study (data not shown) using CDF_1 mice (as had been used in the toxicity experiments) this dose had caused nearly 6 g of body weight loss, but no obvious drug-associated deaths. Additionally, unlike the toxicity data compiled with CDF_1 mice (Table 1), combinations of 200 mg/kg per dose of VP-16 plus 10 and 20 mg/kg per dose of JM-216 were tolerated by BDF_1 mice bearing P388 leukemia. The similar therapeutic outcomes achieved with the aforementioned combination drug regimens were pooled (lifespan data were combined as if from one large group) and compared graphically with the best effects obtained with each drug alone (Fig. 1). In comparison with the increases in lifespan caused by the optimal solo drug therapies, these best combination regimens produced %T/C values in excess of 400%, including one cured mouse. An attempt was made to confirm and extend the indication of therapeutic synergy observed.

In the second P388 experiment (expt. B, Table 3), treatment was initiated on day 5 post implantation and treatment group sizes were increased to eight mice each; otherwise, the format of the experiment was the same

Table 2 Effects of combination chemotherapy using VP-16 and JM-216 on staged s.c. M5076 murine sarcoma. All treatments were administered orally daily for 5 days in two cycles initiated on days 5 and 12 post-implantation. VP-16 preceded JM-216 by 1–2 h when both drugs were given (*TOX* toxicity)

Treatment (mg/kg/dose)		Med. S.T. (%T/C)	T−C (days)	No. mice alive/total (day 30)[a]
VP-16	JM-216			
400	–	126	13.8	8/8
200	–	125	12.0	8/8
–	80	*TOX*	*TOX*	1/8
–	40	134	24.5	7/8
	20	153	17.5	8/8
400	10	*TOX*	*TOX*	6/8
400	5	148	21.5	7/8
200	20	141	24.5	7/8
200	10	138	24.3	8/8
200	5	139	18.5	7/8
100	40	*TOX*	*TOX*	2/8
100	20	145	25.3	8/8
100	10	127	16.0	8/8

[a]There were no tumor-free mice alive on day 75 postimplantation. No control mice died prior to day 30 postimplantation

Table 3 Effect of combination chemotherapy using VP-16 and JM-216 on staged i.v. P388 murine leukemia. All treatments were administered orally daily for 5 days in two cycles initiated on days 4 (or day 5, expt. B) and 11 (or day 12, expt. B) postimplantation. VP-16 preceded JM-216 by 1–2 h when both drugs were given. There were six mice in each treatment group in expt. A and eight in expt. B, and always eight mice in the control groups (*ND* not determined, *TOX* toxicity)

Treatment (mg/kg/dose)		Expt. A %T/C	Cures/total[a]	Expt. B %T/C	Cures/total[a]
VP-16	JM-216				
800	–	*ND*		300	
600		276		272	
400	–	282		306	
200	–	276		256	–
–	80	188		183	
	60	*ND*		178	–
–	40	206		156	–
–	20	153		144	
400	10	400[b]	2/6	*ND*	
400	5	359		456*	2/8
200	20	471*	1/6	450[b]	
200	10	400*		389*	1/8
200	5	335		361	1/8
100	40	*TOX*		267[b]	
100	20	388*		378*	
100	10	347		311	

*$P < 0.05$ compared with the best solo drug therapy
[a]Cures were determined on day 75 postimplantation
[b]More than 5 g of body weight loss

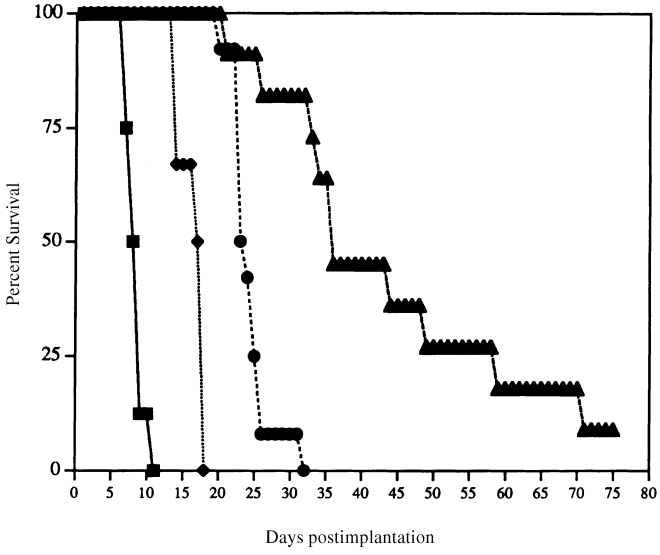

Fig. 1 Combination chemotherapy of staged P388 leukemia implanted i.v. using orally administered JM-216 and VP-16. All treatments were oral daily for 5 days, beginning on day 4 postimplantation, and repeated beginning on day 11 postimplantation. The data shown are derived from Table 3. Control (■), JM-216 40 mg/kg (◆), VP-16 400 and 600 mg/kg (●), VP-16 200 mg/kg plus JM-216 10 and 20 mg/kg (▲)

as in the initial study. A maximum solo regimen of 800 mg/kg per day of VP-16 was made possible by splitting the amount delivered per administration in half, i.e. 400 mg/kg per administration, and delivering both within 1 h of each other. This treatment caused nearly 4 g of weight loss and a %T/C of 300%, but it was not superior to the %T/C of 306% associated with administering half the amount of VP-16. JM-216, at 80 mg/kg per dose, which caused 4 g of body weight loss but no obvious drug-related deaths, produced a maximum %T/C of 183%. The greatest increases in lifespan were produced by combination chemotherapy regimens. One of these regimens, 200 mg/kg per dose of VP-16 plus 20 mg/kg per dose of JM-216, produced a %T/C of 450%. This treatment, however, caused 5 g of weight loss, and one death on day 11, and may be considered to have been at the very limit of tolerability. Equally effective was the combination of 400 mg/kg per dose of VP-16 plus only 5 mg/kg per dose of JM-216, which produced a %T/C of 456% and two cures in eight mice without any early deaths. Other combination chemotherapy regimens resulted in %T/C values of $\geq$ 361%, and were considered to have been tolerated. These data confirmed the results of the initial P388 experiment.

Discussion

The evaluation of orally administered VP-16 and JM-216 in nontumor-bearing BDF_1 mice permitted an assessment of lethality uncomplicated by tumor-associated deaths. Using data from these toxicity studies, a CTI for the drugs was found to be about 0.5, i.e. only 25% of each drug's individual MTD could be used safely in combination. In the therapy experiments, greater doses of each compound were safely administered in combination (than in the toxicity experiments), but the MTDs associated with the individual drugs were also greater. It is more difficult to judge the MTD of each drug and drug combination in a tumor setting, but from the data available a CTI of between 0.5 and 1.0 seems probable.

The term therapeutic synergy used to describe the outcome of the experiments reported here has been defined as a therapeutic response to a drug combination which is superior at equitoxic doses (typically an MTD) to the maximum response obtainable by either drug alone [3,13,18]. No other definition or mathematical configuration of dose effects is implied.

Schabel et al. [14] described the therapeutic synergy of cisplatin plus VP-16 against staged P388 leukemia

implanted i.p. In their studies, treatment initiation was withheld to day 5 postimplantation, at a time when tumor body burden was estimated to be on the order of 10^8 cells. Neither drug alone was particularly effective against the advanced P388 disease, but the two drugs in combination showed very marked synergism and prompted the investigators to comment that the magnitude of the synergy had not, in their extensive experience, been seen with any drug combination against any other experimental system.

Several other investigators have likewise described a therapeutic synergy associated with the combination of parenterally administered cisplatin plus VP-16. Burchenal et al. [1] have found that the combination results in a therapeutic improvement in mice bearing P388 leukemia, compared to the effect of each drug individually. Mabel [7] has evaluated cisplatin in combination with 12 other antitumor agents against murine tumors and obtained the best results with VP-16. This combination was more effective than MTDs of either drug alone against both advanced i.p. P388 leukemia as well as B16 melanoma.

On the basis of the aforementioned preclinical data, and the often established clinical confirmation of the utility of cisplatin plus VP-16 combination chemotherapy, we sought to investigate the therapeutic potential of orally administered JM-216 and VP-16. The tumor models we chose to use were those we knew to be responsive to both drugs, although the models differed in their susceptibility to the two drugs. With regard to the schedules of therapy to be applied, we chose to keep this constant in both models and decided upon two repeated courses of five daily treatments based on published reports (see below).

McKeage et al. [8] have conducted a schedule-dependency study of orally administered JM-216 in mice bearing either the murine ADJ/PC6 plasmacytoma or the human ovarian PXN109 T/C carcinoma model. They found, for example, that in the latter model, tumor growth delays and maximal tumor regressions were greatest using repeated cycles of five daily drug administrations than with either single bolus doses or chronic daily drug administrations. These investigators also found that the MTD for five daily doses of JM-216 given orally, repeated at 3- or 4-week intervals, was 60 mg/kg per day. This dose level is within the range of MTD values described in our studies. Nicolson et al. [11] have recently reported the results of a treatment regimen comprising five daily administrations during a phase I clinical evaluation of JM-216. They found a good correlation between myelosuppression and total platinum Cmax on the last day of therapy.

The utility of consecutive daily treatment schedules has been established clinically in small-cell lung carcinoma patients receiving VP-16 [2,16]. Thus, for both VP-16 and JM-216, there were preclinical and/or clinical data to support the use of a schedule comprising five daily treatments as a regimen worthy of evaluation in our attempts to demonstrate a synergistic effect of these drugs.

In summary, the combination of two anticancer drugs, VP-16 and JM-216, was evaluated orally in two murine tumor models, staged i.v. P388 leukemia and s.c. M5076 sarcoma. The amounts of each drug tolerated in the combination chemotherapy setting were much less than their individual MTD levels (a CTI of < 1). Demonstration of therapeutic synergy was confirmed in the leukemia model, but identical regimens applied in the sarcoma model were not considered to be therapeutically synergistic. Additional preclinical studies aimed at exploring different intervals between drug administrations, the opposite sequence of drug administrations to that evaluated in these studies, and the effects of the combination in other tumor models would provide potentially useful information.

Considering the conflicting results in the two tumor models used, which model might have greater relevance or predictability for the clinical setting? Since there is a poor histological correlation between preclinical and clinical drug responsiveness of tumors, there is no reason to presume the solid tumor model would be the more predictive. A drug's activity in a murine leukemia model does not preclude its utility in nonhematological clinical malignancies. The potential relevance of the current P388 data is supported by the aforementioned dramatic therapeutic synergy between parenterally administered cisplatin and VP-16 [1,14] against P388 leukemia and the utility of this combination clinically against solid tumors. The preclinical data presented were considered to be sufficiently encouraging to provide a rationale for the judicious evaluation of oral VP-16 and JM-216 in a clinical setting. Accordingly, a phase I clinical trial has been initiated under the auspices of the Canadian National Cancer Institute.

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