Cancer Chemother Pharmacol (1990) 27: 85–88

Cancer Chemotherapy and Pharmacology

Combination salvage chemotherapy using cisplatin and teniposide for patients with refractory germinal testicular tumors

Toshihiko Kotake and Tsuneharu Miki

Department of Urology, The Center for Adult Diseases, 1-3-3, Nakamichi, Higashinari-ku, Osaka, Japan

Received 5 June 1990/Accepted 26 July 1990

Summary. Ten patients with refractory germ-cell tumors were treated with a chemotherapy regimen consisting of teniposide and cisplatin (VM-26 and CDDP; P-VM therapy). Three patients (30%) achieved a complete remission (CR) after chemotherapy alone, and another three subjects (30%) attained a CR following chemotherapy and radiation therapy. Three of the six complete responders relapsed but were rendered disease-free by re-salvage therapy. Among the responders, six patients (60%) are alive and remain disease-free after follow-up periods ranging from 18 to 84 months (median, 48 months). However, the toxicity of P-VM therapy was high, with severe myelosuppression being observed in nine patients; nevertheless, all side effects were reversible. We concluded that the P-VM regimen seems to be effective in the treatment of refractory testicular cancers.

Introduction

The treatment of patients with germinal cell tumors has dramatically improved with the introduction of CDDP-containing chemotherapeutic regimens [3]. A complete remission (CR) rate of about 70% can now be achieved using these regimens. However, even with such highly effective treatments, 30% of the patients achieve only a partial remission (PR) and 10% of complete responders are known to experience recurrences [15]. Discovering how to use salvage therapy successfully in such refractory cases is our major goal in the treatment of advanced testicular tumors.

Chemotherapy is the mainstay of salvage therapy, but the appropriate choice of anticancer agents has always been a problem. Most candidates have developed resistance to the PVB regimen (cisplatin, vinblastine, and bleomycin), and standard antineoplastics are ineffective in many of these cases [15]. However, in 1980 Williams et al. [15] demonstrated that etoposide (VP-16), a semisynthetic derivative of podophyllotoxin, is not cross-resistant with other available antineoplastic drugs and that when given in combination with cisplatin (CDDP), it is effective against refractory testicular tumors [13].

Recognizing the reported activity of VP-16, in the present study we investigated a two-drug regimen consisting of CDDP and VM-26 (teniposide, another semisynthetic podophyllotoxin derivative that is similar to VP-16) in ten patients with refractory testicular cancer. The details of this study are reported herein.

Patients and methods

From February 1981 to October 1988, ten patients with refractory testicular tumors who had failed to respond to conventional initial treatment were treated with VM-26-containing salvage chemotherapy. The clinical characteristics of each patient are presented in Table 1. The mean age of our patients was 29 years (range 24–51 years). The pathology of the removed primary testicular tumors included pure seminoma in two subjects and non-seminomatous tumors in eight cases. At initial diagnosis, the clinical tumor stage according to the classification system of the Japanese Urological Association [8] was stage II in three patients and stage III in seven. Two subjects had non-bulky disease and eight had bulky disease.

All patients had previously been treated with first-line chemotherapy consisting of cisplatin, vinblastine, and bleomycin, the so-called PVB therapy, with additional retroperitoneal lymph node dissection (RPLND) having been carried out in four cases and radiotherapy, in one case. Of the ten patients entered in this study, six responded only partially to first-line chemotherapy with or without adjuvant surgery and four relapsed after having achieved a CR while on the initial treatment. Residual or recurrent metastatic lesions were seen in the lung in only three patients, in the retroperitoneum in only four subjects, and in multiple sites in three cases.

The salvage chemotherapy regimen in this study consisted of 20 mg/m^2 CDDP given daily on days 1–5 and 50 mg/m^2 VM-26 given weekly on days 1 and 4 by intravenous push injection; in all, three to four cycles were given (Table 2). At the time of CDDP administration, sufficient hydration and diuresis were given to ensure adequate diuresis. To prevent hypotension during the administration of VM-26 (supplied by Bristol Arzneimittel), the drug was dissolved in 200 ml normal saline and then infused slowly over 30 min.

Offprint requests to: T. Kotake, Osaka, Japan

Table 1. Clinical characteristics of 10 patients who received VM-26-containing salvage chemotherapy

Patient numbers	Age (years)	Histology	Stage	Prior therapy	Response to prior therapy	Metastatic site at salvage chemotherapy
1	25	E+C	IIIB	PVB	CR→Relap	Lung
2	29	S+C	IIIC	PVB+RPLND	CR→Relap	RL
3	27	E+C	IIIB	PVB	PR	Lung
4	24	E+T	IIA	PVB+RT	CR→Relap	Lung
5	51	E+S	IIIB	PVB+RPLND	PR	RL
6	29	S+E+T	IIIB	PVB	PR	Lung+brain
7	45	S	IIB	PVB+VP-16	PR	RL
8	33	E+T+C	IIIB	PVB	PR	Lung+RL
9	27	E+C	IIIB	PVB+RPLND	PR	RL
10	48	S	IIB	PVB+RPLND	CR→Relap	RL, liver, VI

RPLND, Retroperitoneal lymph node dissection; RT, radiation therapy; Relap, relapse; RL, retroperitoneum; VI, supraclavicular metastasis; S, seminoma; E, embryonal carcinoma; T, teratoma; C, choriocarcinoma

Table 2. Salvage P-VM chemotherapy regimen

Compound	Dose schedule
CDDP	20 mg/m^2 × daily 5 for 3 weeks (3–4 courses)
VM-26	50 mg/m^2 twice weekly ×6 weeks

The response to treatment was defined as follows: a CR consisted of complete disappearance of all radiographically documented disease and normalization of the tumor markers; a PR, a decrease of ⩾50% in the sum of the products of two diameters of all lesions; and no response (NR), an increase or a decrease of <50% in the initial tumor size. The durations of response and survival were calculated from the start of the treatment.

Results

The results of the present salvage therapy in our ten patients are shown in Table 3. Patients 1, 2, and 5 achieved a CR after receiving P-VM therapy alone; subject 5 relapsed but showed no evidence of disease (NED) after subsequent combined treatment with P-VP (CDDP+VP-16) and radiation therapy (RT). Patients 3, 4, and 6 achieved a CR after combined P-VM and RT; although cases 4 and 6 relapsed, they achieved NED after retreatment with third-line chemotherapy such as the P-VP regimen. Patients who failed to achieve a CR did poorly. All 4 patients (cases 7–10) who showed only a PR to salvage therapy have since died of progressive disease. The overall results of salvage chemotherapy were as follows: 6 subjects (60%) achieved a CR and 4 (40%) showed a PR. Of those achieving a CR, 3 relapsed; however, further salvage therapy resulted in NED in all of these cases. As the final outcome, 6 subjects (60%) achieved NED and 4 (40%) died. The survival from the start of salvage chemotherapy ranged from 48 to 89 months, with a median of 83 months (Table 3). Of the 7 patients who received only the P-VM regimen (cases 1, 2, 5, and 7–10), 3 (43%) achieved a CR and 4 (57%), a PR. Eventually, 3 (43%) showed NED (43%), whereas 4 (57%) died (Table 3).

Nine patients had received prior chemotherapy, whereby severe myelosuppression was observed. Although 90% of these subjects had severe leukopenia (WBC, <1,000/m^3), there was no death due to infection. Anemia and thrombocytopenia were observed in almost all cases. In addition, gastrointestinal toxicity affected all

Table 3. Response to salvage therapy

Patient number	Salvage therapy	Response to salvage therapy	Additional salvage therapy	Present status	Response duration (months)	Survival (months)
1	P-VM	CR		NED	83	83
2	P-VM	CR		NED	84	84
3	P-VM+RT	CR		NED	89	89
4	P-VM+RT	CR-Relap	R-VP+RT	NED	3	84
5	P-VM	CR-Relap	R-VP+RT	NED	3	66
6	P-VM+RT	CR-Relap	P-VP+L-X	NED	20	48
7	P-VM	PR	RPLND+RT	Dead	1	8
8	P-VM	PR	P-VP+RT+B-X	Dead	3	10
9	P-VM	PR		Dead	6	6
10	P-VM	PR		Dead	3	6

RT, Radiation therapy; Relap, relapse; RPLND, retroperitoneal lymph node dissection; B-X, resection of brain metastasis; L-X, resection of lung metastasis; NED, no evidence of disease

Table 4. Results of salvage chemotherapy in refractory testicular cancer

Authors	Regimen	Patients (*n*)	Number of CR (%)	Number of CR with surgery (%)	Disease-free (%)
Williams and Einhorn [13]	VP-16+CDDP ADM BLM	45	11(24)	24(53)	18(40)
Hainsworth et al. [5]	VP-16+CDDP ADM BLM	44	8(19)	19(43)	10(23)
Pizzocaro et al. [10]	VP-16+CDDP BLM	32	12(38)	21(66)	15(47)
Hansen et al. [6]	VP-16 CDDP BLM	26	6(23)	11(42)	7(27)
Einhorn [1]	VP-16+CDDP+ifosfamide	39	9(23)	14(36)	14(36)
Present study	VM-26 or VP-16+CDDP	10	6(60)	6(60)	6(60)

patients, peripheral neuropathy was observed in 70% of cases, and renal toxicity and hair loss were seen in 30% and 90% of the patients, respectively. Although none of these adverse reactions was severe, one patient refused further CDDP treatment for fear of vomiting. Transient hypotension occurred in 10% of cases at the time of VM-26 administration; this problem was solved by increasing the infusion volume to 1 l and giving the drug by slow infusion.

Discussion

The success rate in the treatment of advanced testicular cancer has improved dramatically due to CDDP-containing chemotherapy such as PVB [3] and VAB-6 therapy [11], which result in a CR rate of approximately 70%. However, 30% of patients achieve only a PR, and 10%–15% of subjects experience disease recurrence [2, 13].

In patients who are resistant to first-line chemotherapy (refractory testicular tumors), the results of salvage therapy remain far from satisfactory. Therefore, the improved success of salvage therapy may be said to be our present major goal in the treatment of testicular cancer. A majority of refractory testicular tumors are resistant to first-line chemotherapy such as PVB therapy, among other regimens. It is impossible to achieve an effective cure by repeating the same regimen [2, 15], and refractory cases have been considered to be practically hopeless [4, 9, 14].

In 1980, Williams et al. [15] reported that salvage chemotherapy combining VP-16 and CDDP [with the occasional addition of bleomycin (BLM) and Adriamycin (ADM)] resulted in a CR in 14 of 33 patients with refractory testicular cancer. These results were drastically superior to those described in previous reports. Subsequently, many institutions published reports on salvage chemotherapy using VP-16. The results are compiled in Table 4, showing reported CR rates of 19%–38% and NED rates of 23%–47%.

As shown in Table 4, CDDP and VP-16 were given in all of the regimens and ADM and BLM were included in some. According to Hainsworth et al. [5], the addition of ADM and BLM only enhances the toxicity without improving the response rates. We feel likewise and think that this should be taken into consideration in the future use of salvage chemotherapy.

At Indiana University, the cyclophosphamide analogue ifosfamide (IFX) has been shown to be effective in refractory testicular cancer [12]. Using a combination of VP-16, CDDP, and IFX as salvage therapy, Einhorn [1] has achieved a CR rate of 23%. In any case, due to this improvement in salvage therapy response, the overall response of advanced testicular cancer has improved by approximately 20%, with a final cure rate approaching 80% [2].

Taking the results of Williams et al. [15] into consideration, in 1981 we started a regimen using VM-26 in combination with CDDP (P-VM therapy). In 7 patients treated with only the P-VM regimen, a CR was achieved in 3 cases (43%) and NED, in 3 (43%). If the 3 cases in which radiation therapy was given concurrently with the P-VM regimen are included, 6 of the 10 patients (60%) achieved a CR, with NED finally resulting in these cases (60%, Table 3). Although the number of cases is small, the results are noteworthy (Table 4). We therefore feel that VM-26, like VP-16, is also effective in salvage chemotherapy of testicular cancer. If VM-26 continues to be available, we should investigate its potential use as one of the major antineoplastic agents in salvage chemotherapy.

In patients 4–6, we achieved NED by using P-VP therapy as third-line salvage chemotherapy (radiotherapy was concurrently given in two cases) following relapse after P-VM.

From these cases, it appears that even in patients resistant to P-VM, resalvage using P-VP may be possible. This issue warrants further investigation and may offer a possible choice for third-line salvage chemotherapy.

There are reports that radiotherapy is not very effective in the salvage therapy of non-seminomatous tumors [7]. However, in our study it played an active role in the treatment of refractory disease. Patients 3, 4, and 6 (Table 3), who had refractory metastatic lesions in the lung and brain, were given radiotherapy concurrently with the P-VM regimen. As third-line therapy, we also gave radiotherapy concurrently with P-VP to patients 4 and 5. It was felt that these patients would not be able to achieve CR with 1–3 courses of P-VM or P-VP; therefore, during the final 2–3 three courses they were given radiotherapy (25–40 Gy) concurrently with chemotherapy and CR was achieved. We must note, however, that all of these subjects had only one or, at most, three lesions and that each was no more than 3 cm in diameter. These four cases involved non-seminomatous tumors. Based on our experience, we would like to suggest that when given in combination with chemotherapy, radiotherapy may be effective even against non-seminomatous tumors that are said to be radio-resistant. Spot radiation is particularly effective against small pulmonary and brain metastases. In other words, salvage

radiotherapy can play an important role in the salvage therapy of testicular cancer.

Since our patients had undergone prior therapy with PVB, adverse reactions such as myelosuppression, gastrointestinal toxicity, renal toxicity, and peripheral neuropathy were observed. However, there were no chemotherapy-related deaths. In conclusion, our investigation of the efficacy of salvage therapy in testicular cancer shows that although the advent of VM-26 and VP-16 has improved the response to treatment, the NED rate remains far from satisfactory. Additional investigations should be conducted to develop more effective third-line salvage therapy.

Conclusions

We conducted salvage chemotherapy using VM-26 or VP-16 in combination with CDDP in ten patients with refractory testicular cancer that was resistant to the standard PVB regimen. Our results were as follows:

1. Of 7 patients receiving only P-VM, the initial response was a CR in 3 cases (43%) and a PR in 4 (57%); the final outcome was NED in 3 cases (43%).

2. Among the 7 subjects receiving only P-VM and the 3 patients given concurrent radiotherapy, a CR was achieved in 6 cases (60%) and a PR, in 4 (40%); a final outcome of NED was achieved in 6 cases (60%).

Although salvage chemotherapy with the P-VM and P-VP regimens is very effective, the CR rate remains only 40%. In the future, we must work toward developing even better third-line chemotherapy.

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