Complete Remission of Metastatic Teratoma from Malignant Testicular Tumor Using Salvage Chemotherapy with VP-16 (Etoposide), CDDP, and ACNU

—Case Report—

Hideyuki SUWA, Junya HANAKITA, Shogo NISHI, Kiyoshi NISHIHARA, Fumito OHTA, Hiroshi SAKAIDA and Kouji IIHARA

Department of Neurosurgery, Shizuoka Prefectural General Hospital, Shizuoka

Abstract

A 26-year-old male with an intracranial teratoma, metastasizing from a testicular yolk sac tumor refractory to cis-diamminedichloroplatinum (CDDP), vinblastin, and bleomycin (PVB) therapy, was successfully treated with a combination of etoposide (VP-16), CDDP, and ACNU (salvage chemotherapy). Emergency surgery for subcortical hemorrhage discovered the metastasis, diagnosed as a yolk sac tumor. CDDP chemotherapy failed to prevent recurrence, and total removal was impossible due to subdural invasion. He underwent radiation therapy and salvage chemotherapy. A third operation found only scar tissue. Maintenance salvage chemotherapy was continued. He was doing well 30 months after the first operation.

Key words: metastatic brain neoplasms, malignant teratoma, chemotherapy, VP-16 (etoposide)

Introduction

Since the introduction of combined chemotherapy using cis-diamminedichloroplatinum (CDDP), vinblastin, and bleomycin (PVB therapy) for testicular tumors, long-term survival has been achieved in cases of intracranial malignant teratomas as well as gonadal germ cell tumors. However, not all cases achieved complete or partial remission and some relapses soon after treatment have occurred.

Here we discuss the complete remission of metastatic yolk sac tumor in the brain treated with etoposide (VP-16), CDDP, and ACNU, the so-called salvage chemotherapy.

Case Report

A 26-year-old male had been treated for advanced testicular tumor in another hospital in January 1987. Radiological examination identified right testicular tumor, multiple coin lesions in the lung (Fig. 1A), and lymphadenopathy in the para-aortic region. Serum alpha-fetoprotein was as high as 600 ng/ml. An orchiectomy was performed on January 6, 1987. The testicular tumor weighed 175 gm, and was diagnosed as yolk sac tumor (Fig. 2). Postoperatively, he underwent PVB therapy 3 times followed by CDDP,

Fig. 1 Radiological findings on initial admission. A: Chest x-ray film showing multiple coin lesions. B: Postcontrast CT scan revealing no intracranial metastasis.
This chemotherapy was thought to have achieved complete remission based on the disappearance of all metastatic tumors on the chest x-ray film and normalization of the serum alpha-fetoprotein level. A postcontrast computed tomographic (CT) scan showed no abnormal findings (Fig. 1B) and the neurological findings were normal.

He suddenly developed left hemiparesis and became comatose on August 5, 1987, and was admitted to our hospital the next day. His consciousness level was III-200 on the Japan Coma Scale and totally 7 on the Glasgow Coma Scale with left hemiplegia. A precontrast CT scan revealed subcortical hemorrhage in the right frontal lobe (Fig. 4A). Cerebral angiography showed no feeding arteries or tumor stain. A chest x-ray film demonstrated no abnormal findings.

An emergency operation was performed for subcortical hematoma removal and external decompression. The gross appearance was a mixture of glassy gray tissue within the hematoma. Histological examination revealed evidence of yolk sac tumor (Fig. 5). A postoperative CT scan revealed no evidence of residual tumor (Fig. 4B). The consciousness level and left hemiparesis improved in the 2 weeks post-

![Fig. 2 Photomicrograph of the primary testicular tumor showing the features of yolk sac tumor. HE stain, × 100.](image)

![Fig. 3 Clinical course. Leukocytopenia is always followed by thrombocytopenia 1 or 2 days after administration of VP-16 but recovers within a week. PVB: combination chemotherapy of cis-diaminedichloroplatinum (CDDP), vinblastine, and bleomycin, PVE: combination chemotherapy of CDDP, vinblastine, and cyclophosphamide (Endoxan). •: white blood cell (WBC), ○: platelet (Plts), *: alpha-fetoprotein (AFP).](image)
operatively. CDDP (50 mg) was given intravenously on September 9.

In October, however, a CT scan showed tumor recurrence (Fig. 6A), despite the normal serum alpha-fetoprotein level. A second operation was performed on October 22, 1987. A glassy gray tumor involved the ependyma of the lateral ventricle and invaded into the subdural space, which prevented gross total removal. A postcontrast CT scan after second operation showed an abnormal enhanced area (Fig. 6B). Postoperative chemotherapy using arterial administration of 175 mg ACNU and 100 mg CDDP was started on October 30, 1987. He underwent whole brain (30 Gy) and local (20 Gy) irradiation between November 2 and December 14, 1987. Intravenous administration of VP-16 (180 mg/day) was given for 5 consecutive days from December 14. The abnormal enhanced area persisted on a follow-up CT scan (Fig. 6C), but could not distinguish between tumor recurrence and scar formation. A second course of VP-16 was administered from May 12, 1988.

On September 28, 1988, gallium scintigrams and a CT scan indicated tumor recurrence (Figs. 7 and 8A), so the third operation was performed. However, histological examination revealed only scar tissue. A third course of VP-16 was given from November 2, 1988, followed by intra-arterial administration of ACNU (176 mg) and CDDP (119 mg) on November 7, 1988. Further ACNU (125 mg) and CDDP (100 mg) were administered on May 9, 1989, and a fourth

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**Fig. 4** A: Precontrast CT scan obtained 7 months after the operation for primary testicular tumor, showing massive subcortical hemorrhage in the right frontal lobe. B: Precontrast CT scan after the hematoma removal, demonstrating no residual hematoma or tumor.

**Fig. 5** Photomicrograph of the metastatic brain tumor showing similar findings to primary lesion. HE stain, x 200.

**Fig. 6** A: Postcontrast CT scan after CDDP treatment, demonstrating an abnormal enhancement indicating tumor regrowth. B: Postcontrast CT scan taken after second craniotomy, showing minimal mass effect but abnormal enhancement is still shown. C: Postcontrast CT scan after treatment with VP-16, CDDP, and ACNU. The abnormal enhanced area persists but can not distinguish between recurrent tumor and scar formation.
A follow-up CT scan demonstrated no evidence of tumor recurrence (Fig. 8B).

He was doing well with no signs of tumor recurrence 30 months after the first operation.

**Discussion**

Approximately 15% of malignant testicular tumors are thought to metastasize to the brain. Some tumors are refractory to PVB therapy or recur and cannot again be treated with the same chemotherapy. Therefore, a new therapeutic method is required for such refractory cases.

VP-16 was investigated many times in the late 1970s, and the results of phase II study using VP-16 for malignant testicular tumor were reported in 1985. These reports investigated recurrent cases previously treated with other chemotherapeutic drugs and since VP-16 was effective, it became an important drug in urology for refractory advanced testicular tumors as the so-called salvage chemotherapy. The mechanism of action of VP-16 in tumor cells is thought to be prevention of deoxyribonucleic acid (DNA) synthesis in the S and G2 phases by means of single-strand breaks in DNA, which is cytotoxic to tumor cells. It is administered over 3-5 consecutive days in a total dose of 300-600 mg/m², repeated every 3 or 4 weeks. As VP-16 is cell cycle specific and the half life is 3-7 hours, 3-5 fractions are more effective than a single dose. Maximum levels of the drug in the cerebrospinal fluid (CSF) are below 15% of the plasma level, showing the very poor water solubility of VP-16 limits the CSF presence.

Side effects with intravenous administration include alopecia in almost all cases and mild gastrointestinal toxicity. Laboratory analysis reveals myelosuppression in the majority of cases. Leukopenia and thrombocytopenia are more serious than anemia, with the former found in 70% of cases, and the latter in 30%. Leukocyte nadirs usually appear between the 11th and 19th days and thrombocyte nadirs between the 11th and 17th days from the beginning of intravenous drug administration. Recovery occurs by the 21st day. No serious complications occurred in some cases with triple the usual dosage (1500 mg) and no cumulative toxicity with repeated administration, but in others serious myelosuppression occurred with the usual dosage.

Simultaneous use of both CDDP and VP-16 is effective against malignant tumor. Use of VP-16 only may be effective for advanced testicular tumor refractory to initial chemotherapy containing CDDP, but may not achieve complete remission. However, salvage chemotherapy combining VP-16 and CDDP achieved 41% complete remission and 30% long-term survival in 80 cases. Pizzocaro et al. treated 40 advanced testicular tumors with CDDP, VP-16, and bleomycin and surgical removal of residual tumors. This strategy achieved 82.5% complete remission with a mean survival of 24 months (13-40 months). They suggested the addition of VP-16 to the initial chemotherapy.

Gotoh et al. reported that salvage chemotherapy of CDDP and VP-16 given to four cases of advanced testicular tumor refractory to PVB therapy succeeded in complete remission in high dosage using 100 mg/m² CDDP and 500 mg/m² VP-16 in 5 doses, while low-dose therapy with 100 mg/m² CDDP and 50 mg/m² VP-16 failed to salvage in two cases. They advocated that high-dose salvage chemotherapy should be given immediately to patients with far advanced testicular tumor.
There are very few reports of VP-16 treatment of primary intracranial malignant germ cell tumor. Kobayashi et al.\(^1\) reported four cases treated with CDDP and VP-16, observing tumor regression in all cases (three complete and one partial), a 100% response rate. Therefore, primary intracranial germ cell tumors may be effectively treated with low doses of VP-16 because of the synergic reaction of VP-16 and CDDP. However, as only a small amount of VP-16 enters the CSF, high-dose therapy will have a more complete effect on primary germ cell tumors.

We treated the present metastasis from the malignant testicular tumor by a combination of intrarterial administration of 100 mg/m\(^2\) ACNU and 80 mg/m\(^2\) CDDP and intravenous administration of 500 mg/m\(^2\) VP-16. After the previous PVB therapy, the patient suffered sudden intracerebral hemorrhage containing malignant testicular tumor cells. Following the first craniotomy, the metastatic lesion grew despite administration of CDDP (50 mg). The residual tumor, not totally removed at the second operation, disappeared after VP-16 therapy and was replaced by scar tissue found by the third operation. There was no tumor recurrence. These findings suggest that salvage chemotherapy combining VP-16, CDDP, and ACNU has a remarkable effect on malignant testicular tumor. In this case leukocytopenia was a significant side effect, but the leukocyte nadirs occurred 1 week after VP-16 administration, and recovered within a week every time. We could therefore be prepared to deal with this side effect by thrombocyte transfusion for the thrombocytopenia and the oral administration of antibiotics, antifungal drugs, and saline ultranebrizer containing antifungal drug for the leukocytopenia.

VP-16 has no cumulative toxicity and the clinical side effects can be dealt with adequately, so it can be given periodically and repeatedly for primary and metastatic malignant teratomas.

**Addendum**

The patient was still enjoying life without any signs of tumor recurrence in May, 1991.

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*Address reprint requests to: H. Suwa, M.D., Department of Neurosurgery, Shizuoka Prefectural General Hospital, 4-27-1 Kita-ando, Shizuoka 420, Japan.*