Evaluation of Treatment for Childhood Medulloblastoma, with Special Reference to Combination Therapy with Interferon and Radiation

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Abstract

Thirteen children, aged 6 months to 14 years, underwent surgery for medulloblastoma at Chiba University Hospital from 1971 to 1985. The nine patients treated prior to 1980 received postoperative irradiation therapy with or without chemotherapy. Since 1980, four patients have been treated postoperatively with interferon (IFN) plus radiation therapy. The IFN was administered intramuscularly once or twice a week throughout the period of radiation therapy.

Six of the nine patients not treated with IFN died within 1 year. In this group, the 3- and 5-year survival rates were 33% and 22%, respectively. One of the four patients treated with IFN died within 10 months of surgery, and another is disabled. The remaining two patients are in good condition. The 3- and 5-year survival rates in the IFN group were both 75% as of the last follow-up in January of 1986.

Key words: medulloblastoma, interferon, radiation therapy, combination therapy

Introduction

Medulloblastoma accounts for 20–30% of all intracranial tumors in children.^{1,4)} It is considered a highly malignant tumor because of its early recurrence and intraspinal metastasis. Many authors believe that radiation therapy is, at the present time, the most reliable treatment for this tumor, but the poor prognosis even with irradiation demands more effective therapy.²²⁾ Clinical trials of interferon (IFN) for malignant intracranial tumors have increased in number, but so far its effectiveness as a single therapy is reportedly only 20–30%,^{19,20)} which is about the same as that of other chemotherapies. Since 1980, the authors have treated medulloblastoma with a postoperative combination of IFN and irradiation, and our results have been encouraging.

Patients and Methods

We treated 13 children with medulloblastoma, aged 6

months to 14 years, at Chiba University Hospital from 1971 to 1985. All underwent tumor resection through suboccipital craniectomy. The diagnosis of cerebellar medulloblastoma was confirmed in all cases by histological examination of surgical specimens. Our principle of treatment was to remove as much of the tumor as possible and then to irradiate the whole neuroaxis, with at least 4500 rads applied to the posterior fossa. Before 1980 nine patients received radiation therapy with or without chemotherapy; since 1980 four patients have been given IFN and irradiation. The patients' characteristics and their treatments are summarized in Table 1.

We used human leukocyte IFN, type α , induced by HVJ (Sendai virus), which produces high titers of crude IFN. The crude IFN was purified by a modification of Cantell's method.^{2,18)} The specific activity of the IFN was 6×10^6 to 6×10^7 units/mg protein. The IFN, 250×10^4 to 500×10^4 units per day, was administered intramuscularly once or twice at the end of each week throughout the period of radiation therapy (Table 2). These treatments were started 1 week after operation. The last follow-up was conducted in January of 1986.

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Table 1 Cases of cerebellar medulloblastoma in children

Case No.	Age	Sex	Type of operation	Radiation			Survival time	Outcome
				Whole brain	Posterior fossa	Whole spine		
1	3 yrs	M	partial				1 mo	dead
2	2 yrs	F	partial	2800	3800		9 mos	dead
3	1 yr	F	biopsy	1000	4500	2500	7 mos	dead
4	6 mos	M	subtotal		5060		9 mos	dead
5	1 yr	F	subtotal	3000	5000		11 yrs 3 mos	alive
6	8 yrs	M	partial	5060		2970	3 yrs 4 mos	dead
7	14 yrs	F	partial	3840	5280	3050	6 mos	dead
8	5 yrs	F	subtotal	4120		2520	5 mos	dead
9	8 yrs	M	subtotal	4540		2560	6 yrs 11 mos	alive
10*	5 yrs	F	subtotal	2990	4490	2400	4 yrs 11 mos	alive
11*	4 yrs	M	partial	3140	5240	2500	4 yrs 9 mos	alive
12*	12 yrs	M	subtotal	4540	5940	5000	3 yrs 6 mos	alive
13*	5 yrs	M	partial	3000	4600	5000	10 mos	dead

*Treated with IFN.

Table 2 Summary of patients treated with IFN

Case No.	IFN- α dose (IU)		Performance status (%) [*]
	Weekly	Total	
10	$5 \times 10^6 \times 2$	1.75×10^8	90
11	$5 \times 10^6 \times 2$	1.30×10^8	100
12	$5 \times 10^6 \times 2$	1.55×10^8	30
13	$2.5 \times 10^6 \times 1$	3.75×10^7	—

*Karnofsky *et al.*¹⁰⁾

Results

As shown in Tables 1 and 2, Cases from 1 to 9 were treated up to 1979 without IFN, and Cases from 10 to 13 were treated with IFN since 1980.

The postoperative courses of the nine patients treated without IFN are shown in Fig. 1. Six died within 1 year. There are only two survivors: 11 years, 3 months and 6 years, 11 months. These patients are free of disease and enjoy a useful life. The longest follow-up period was 11 years, 3 months. The 3- and 5-year survival rates were 33% and 22%, respectively (Fig. 2).

One of the four patients treated with combined IFN and radiation therapy died 10 months after craniectomy (Fig. 3). The remaining three are alive at 3.5 to almost 5 years postoperatively. Two are in good condition and one is bedridden. The tumor metastasized to the left frontal tip in one survivor and to the frontal base in another. The 3- and 5-year survival rates are both 75%, according to the criteria of Culter *et al.*³⁾ (Fig. 2).

Fig. 1 Postoperative courses of medulloblastoma in children treated before 1980 with surgery and radiation therapy, with or without chemotherapy. R: radiation, C: chemotherapy, L: local recurrence, S: spinal cord metastasis, E: extracranial metastasis, D: dead, A: alive.

Case Reports

Case 10: A 5-year-old female underwent subtotal removal of a medulloblastoma, followed by irradiation and IFN therapy. The IFN was injected intramuscularly in a total dose of 1.75×10^8 units. Remission persisted for 2 years, 7 months, when a recurrence was detected on the left frontal tip. The metastatic tumor was removed and radiation therapy was administered postoperatively. At 4 years, 11 months after her initial surgery, she is healthy and is attending school.

Fig. 2 Survival rate of medulloblastoma in children. ○: treated with surgery plus radiation therapy, with or without chemotherapy (1971 to 1979). ●: treated with IFN in combination with surgery and radiation therapy (1980 to 1985). △: National Survey conducted in Japan in 1982.

Fig. 3 Postoperative courses of medulloblastoma in children treated since 1980 with surgery followed by IFN in combination with radiation therapy. *Frontal lobectomy.

Case 11: Radiation therapy and IFN, in a total dose of 1.30×10^8 units, were given to a 4-year-old male following partial removal of a medulloblastoma. Four years, 9 months later, he is free of tumor and doing well.

Case 12: A 12-year-old male already had two metastatic lesions in a cerebellar hemisphere at the time of surgery for the original tumor. Postoperatively he received irradiation to the whole brain (4540 rads), followed by local irradiation. A spinal metastasis was also found at the Th₁₂-L₂ level; it was decompressed by laminectomy and irradiated with 5000 rads. IFN was administered 31 times in a total dose of 1.55×10^8 units. The patient was in remission for 16 months, until a recurrence was detected. The new tumor was treated with irradiation and IFN. A

few months later, a frontal base metastasis was found (Fig. 4), and this was also treated with irradiation and IFN. During the most recent follow-up period, he was hospitalized to treat another local regrowth.

Case 13: A metastatic lesion in the spinal cord was noticed at the time of diagnosis of cerebellar medulloblastoma in a 5-year-old male. Postoperatively, a total of 3.75×10^7 units of IFN was given in conjunction with irradiation to the whole neuroaxis. After a 9-month remission, a new metastasis was observed in the sacral region. This patient died 1 month after the recurrence despite retreatment with irradiation.

Discussion

Medulloblastoma is regarded as highly malignant because of its early recurrence and high frequency of spinal metastasis. Although irradiation is believed to be the most effective therapy for this tumor, 6 years ago we found, on reviewing the medulloblastoma cases managed in our hospital, that the outcome of such treatment is very poor. For that reason, in 1980 we introduced IFN therapy. In this report we compare the results of therapy for medulloblastoma before and after IFN was added to our treatment regimen.

There have been several reports of brain tumors treated with IFN alone.^{7,19,20} Although the experimental work can be seen in the literature,^{11,17} as far as we know, only our group has reported on combination therapy with IFN and irradiation in clinical cases of medulloblastoma.^{15,16}

Six of the nine patients not treated with IFN died within 1 year of initial surgery. The 3- and 5-year survival rates were 33% and 22%, respectively. These

Fig. 4 Case 12. *left:* A linac-graphy. Note that the cribriform plate was covered with an eye shield. *right:* CT scan showing metastasis to the frontal base.

results are about the same as those of the 1982 National Survey in Japan. Odake *et al.*²²⁾ reviewed 13 cases of medulloblastoma and concluded that the poor outcomes were partly due to inadequate radiation therapy, which did not adhere to the general principle that the whole neuroaxis must be irradiated and in which doses were not high enough. We found that a total irradiation dose of 4500 to 5000 rads to the posterior fossa was not administered in some of our cases. In other cases, the spinal cord was not irradiated. We attribute the differences in treatment partly to differences in the patients' physical condition and age and partly to differences of opinion among the surgeons.

Of the four patients to whom we administered IFN along with irradiation, only one died within 1 year of treatment. Of the remaining three survivors, two had metastases. We have speculated the reason for metastasis as follows; some areas had not been irradiated although we believed that the whole neuroaxis had been irradiated. One patient had a metastasis to the cribriform plate, which was concave at the midline and had been blocked by an eye shield during irradiation (Fig. 4). Another had a metastasis to the frontal tip, which apparently had shifted out of the irradiation field because of the strict localization of the field. These sites are easily missed if special attention is not paid to them during irradiation. This pitfall, which has been noted by others^{9,12)} as well, was not recognized until computerized tomographic scanning (CT scan) became available. Therefore, the irradiation should be applied to the entire central nervous system; no area should be missed.

Some authors^{6,21,25)} believe that only extensive removal of the tumor yields a good prognosis, while others^{12,13)} contend that surgery does not improve the prognosis. Our own results were equivocal. Among the patients treated before 1980, two of the four who underwent subtotal (macroscopic) tumor removal are still alive and functioning well. Both of the children subjected to subtotal removal after 1980 are alive, although only one is in good condition. Obviously, we cannot draw conclusions from these results, because the patient population was too small.

Treatment for malignant brain tumors with IFN- α ^{7,20)} and IFN- β ^{14,19,24)} alone has been reported. Hirakawa *et al.*⁷⁾ stated that partial remission (clinical or radiological improvement) was obtained in two of 10 malignant brain tumor cases with IFN- α . Nagai¹⁹⁾ reported that IFN- β was effective (more than 50% reduction of tumor size by CT scan) in 22.2% of their malignant brain tumor series. The results are almost the same with IFN- α and IFN- β . No significant differences in efficacy between system-

ic and local administration have been noted, although local injection has been known to cause meningitis.²⁰⁾ IFN does not appear to be a particularly promising agent for therapy of malignant brain tumors when used alone.⁷⁾ Hirakawa *et al.*⁷⁾ reported two cases of medulloblastoma among their brain tumor series. Although one experienced a partial response to IFN, the other showed no improvement, and both patients died. Nagai¹⁹⁾ reported that among the seven cases of medulloblastoma in his series of 54 malignant brain tumors, a complete response (tumor disappearance by CT scan) was obtained in two with IFN monotherapy.

A precise clinical regimen for combination therapy with IFN and irradiation has not yet been established, primarily because it is not clear whether IFN confers a cytoprotective effect or augments the efficacy of irradiation. Our laboratory studies¹⁷⁾ clearly indicated that the suppression of growth by irradiation was not enhanced when sarcoma 180 cells were pretreated with IFN. Pretreatment with IFN apparently reduced the effect of irradiation on these cells, or showed radioprotective activity. The growth suppression was significantly enhanced when IFN was treated after irradiation. Ito⁸⁾ observed similar effects with IFN. Talas *et al.*²⁶⁾ reported that the survival of mice was prolonged when radiation was administered after an IFN inducer was given, when the serum IFN level was at its highest. These investigators also found radioprotective activity by IFN in endogenous spleen colony formation tests. IFN is thought to inhibit cell proliferation by preventing the cells from entering the G₁-S phase,^{5,23)} which prevents DNA synthesis and thereby provides a radioprotective effect. On the other hand, when IFN was administered after irradiation, the cells damaged by irradiation, especially those cells on the verge of death, are apt to receive inhibition of DNA synthesis by IFN, by which suppression of cell growth is enhanced. If IFN likewise alters the cell cycle *in vivo*, it is reasonable to irradiate prior to IFN administration. Accordingly, we administered IFN at the end of each week. However, the method of administration of IFN needs to be studied in further detail. The necessary amount of IFN dosage and irradiation are also required to be investigated.

In conclusion, our findings suggest that in the treatment of medulloblastoma, combination therapy with IFN and irradiation may be superior to treatment without IFN. Further study is needed to determine the most effective treatment regimen.

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