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ADDITION OF IFN-α TO TREATMENT OF MALIGNANT BRAIN TUMORS

BERTA JEREB, GABRIJELA PETRIČ-GRABNAR, BORIS KLUN, JANEZ LAMOVEC, MIHA ŠKRBEC and EVGEN ŠOOŠ

Despite many attempts to improve the survival after surgery of patients with malignant astrocytoma the prognosis is poor. We have used natural IFN-α in 16 patients with malignant astrocytoma treated between 1987 and 1990; 6 for recurrent tumors. Radiation therapy was given in 2 Gy fractions daily to a total dose of 50 Gy in the tumor area, 5 fractions per week and IFN twice per week, cisplatinum 60 mg/m^2 i.v. every second week and vincristine 2 mg every week in 12-h i.v. infusions. Eight patients were reoperated when clinical deterioration suggested recurrent tumor; histological examination showed no residual tumor in 7 of them. Of these 8 patients 3 are alive and well, 2 of them after more than 5 years. The study suggests that malignant astrocytoma can be successfully eradicated with surgery, irradiation, IFN-α and chemotherapy. The treatment had, however, unacceptably high neurotoxicity. Earlier removal of the tumor necrosis, before clinical deterioration, could possibly diminish the high complication rate and consequently improve survival.

Despite many attempts to improve the survival of patients with malignant gliomas after surgery, including different radiation techniques and/or chemotherapy (1–5), little progress has been made and the prognosis of these patients remains extremely poor. The introduction of IFNs, applied systemically or locally, has not changed this situation (6–10).

We have used IFN-α, a product of the Immunological Institute of Zagreb, Croatia, and have reported earlier on 17 patients who have received IFN-α through an Ommaya reservoir in combination with postoperative irradiation: 9 of these patients also received chemotherapy. Despite the favorable local treatment effect the survival was poor, and in most of these patients the death was probably due to delayed toxicity of the combined treatment (11).

Some reports on large series of patients show lower early survival rates in patients treated more aggressively as compared with those who had radiotherapy alone (12); the different regimens did, however, result in comparable 5-year survival rates (about 25%). This could indicate higher toxicity and lower tolerance to the more aggressive therapy.

We now report our observations on 16 patients treated more recently with surgery, chemotherapy, radiotherapy and IFN-α, 8 of whom had surgical removal of the tumor area after treatment when clinical deterioration occurred. The treatment protocol was approved by the ethical committee and informed consent was signed by the patients.

Material and Methods

Sixteen patients with malignant brain tumors, 9 malignant astrocytoma and 7 with glioblastoma classified according to Kernohan (13) were treated between February 1987 and July 1990 with surgery, radiation therapy (RT), chemotherapy (ChT) and IFN-α through an Ommaya reservoir, 6 of them for recurrent tumors and 8 as their first treatment (Tables 1 and 2). Some of the patients have been included in a preliminary report (11). All patients underwent surgery with total or partial tumor removal except one who had only biopsy. The catheter was placed in the tumor cavity and the Ommaya reservoir subcutaneously on the scalp. Postoperative treatment consisted of RT, ChT and IFN-α as described earlier (11), with some modifications: All patients with glioblastoma except one

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From the Institute of Oncology (B. Jereb, G. Petrič-Grabnar, J. Lamovec), Clinic of Neurosurgery, (B. Klun) and Insitute of Radiology (M. Škrbec), Clinical Center, Ljubljana, Slovenia and Institute of Immunology (E. Šooš), Zagreb, Croatia
Correspondence to: Dr Berta Jereb, Institute of Oncology, Zaloska 2, 61105 Ljubljana, Slovenia.
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Table 1

Seven patients with glioblastoma (one recurrent)

Case No. (consecutive)	Sex	Age (yrs)	Site	Sugery		RT (Gy)		IFN-α No. of applic.	Cispl pl (VCR)	Follow-up	Histology	
				Date month/year	Type	Max.	Fract.				Reop.	Autopsy
1	M	50	frontoparietal R	1/87	PR	45	3	15x	1x (3x)	dead 10 mo	—	no tumor (mening., abscess, infect)
4	M	53	frontoparietal L	4/87	biopsy	45	3	5x	2x (3x)	dead 2 mo at home	—	—
5	M	57	frontoparietal L	4/87	PR	9	3	3x	1x (1x)	dead 1 mo	—	no tumor (*bronchopneum.*)
6	M	66	parietooccipital L	10/87	TR	45	3	14x	2x (4x)	dead 6 mo	10/87 gliosis, no tumor	no tumor (pancreatitis)
8	M	48	parietal R	11/87	PR	45	3	8x	1x (2x)	dead 5 mo at home (probably abscess)	11/87 no tumor, necrosis	—
14	M	59	parietal R	10/89	PR	54	2	3x	3x (5x)	dead 3 mo	—	—
16 (C)	F	45	pariet. L	1/90	PR				20x			
				11/90	PR							
				3/92	PR	24	2	8x	3x (3x)	39 mo AWD > 1yr	residual tumor	—

Abbreviations: TR = total resection, PR = partial resection, (C) = recurrence after surgery, irradiation and chemotherapy, VCR = vincristine, Cispl = cisplatin

Table 2

Nine patients with malignant astrocytoma (5 recurrent)

Case No. (consecutive)	Sex	Age (yrs)	Site	Sugery		RT (Gy)		IFN-α No. of applic.	Cispl pl (VCR)	Follow-up	Histology	
				Date month/year	Type	Max.	Fract.				Reop.	Autopsy
2	M	22	parietal L	2/87	PR	45	3	18x	2x (4x)	NED 5 years	12/87 gliosis, necrosis, no tumor	—
3	M	53	frontoparietal L	4/87	PR	45	3	10x	2x (3x)	dead 3 mo at home	—	—
7 (A)	M	42	frontoparietal L	1/87	PR				2x	dead 24 mo	6/88 gliosis,	—
				7/87	PR	45	3	8x	(3x)	nursing home	necrosis, no	
				6/88	TR					(possibility tuberculosis)	tumor	
9 (B)	M	40	parietal L	5/87	PR				2x			
				8/87	PR	24	2	6x	(2x)			
				10/87	PR					NED > 5 yrs	10/87 gliosis, no tumor	—
10	M	63	parietal L	12/87	PR	50	2	7x	(5x)	dead 9 mo (bronchopneumonia)	—	—
11	M	54	frontotemporal R	9/88	PR	54	2	7x	(7x)	dead 35 (31 mo)	2/90 necrosis, gliosis	—
12 (B)	M	20	parietooccipital R	3/88	TR					dead 18	—	—
				2/89	PR	20	2	3x	(5x)	(7) mo		
13 (A)	M	61	occipital R	1/89	TR							
				4/89	PR	50	2	13x	3x (1x)	dead 15 (12) mo	9/89 gliosis, no tumor	no tumor
15 (B)	M	36	parietooccipital R	5/86	PR					dead 43	-	residual
				12/89	PR	26	2	3x	(1x)	(8) mo		tumor

Abbreviations: TR = total resection, PR = partial resection, (A) = recurrence after surgery alone, (B) = recurrence after surgery and irradiation, VCR = vincristine, Cispl = cisplatin

received irradiation of the whole brain and additional local boost. The boost was given to the tumor area, as it appeared on the CT before sugery, with a margin of 2 cm. Patients with malignant astrocytoma were treated with irradiation of the hemisphere (patient Nos. 10 and 11) with a boost to the tumor area. The dose in the patients, who had no previous radiation treatment, was 30 Gy in the whole brain or hemisphere and a boost of 15 Gy, given in 3 Gy daily fractions 5 times per week (TDF 92). After 1987 the daily fractions were 2 Gy and the maximal total dose 54 Gy or TDF 88. Patients, who were treated for recurrent tumor after previous irradiation received only 24 Gy (2 Gy daily fractions). Treatment was discontinued in one patient (No. 5) because of intercurrent broncho-pneumonia.

The chemotherapy consisted of cisplatinum 50 mg/m^2 i.v. every second week and vincristine 2 mg every week in 12-h i.v. infusion. Three patients (Nos. 11, 15, 16) were given vincristine only.

IFN-α 2×10^6 IU was diluted in 2–4 ml distilled water under sterile conditions immediately before the injection. The area of the skin above the reservoir was prepared with antiseptic solution. With sterile technique the reservoir was punctured with a 25 gauge needle, a syringe attached to the needle and fluid aspirated for cytology and culturing of bacteria. Then the syringe containing the IFN-α solution was attached and the solution slowly injected into the reservoir.

Malignant cells were not identified in any of the samples aspirated from the reservoir. The usual cytological finding was: neutrofilic leukocytes, lymphocytes, macrophages and cell detritus. Infection in the reservoir was proven in 9 patients; one of those had infection of the tumor (No. 1) and died later on in bacterial meningitis. All infected patients had their reservoir removed and received intensive treatment with antibiotics. Apart from this, no prophylactic antibiotic treatment was given. ChT was discontinued in some patients who therefore did not receive the planned dose (Tables 1 and 2).

When we became aware of the fact that local tumor control might be possible and that the majority of our patients died of treatment complications, we first tried to remove the Ommaya reservoir on clinical deterioration in order possibly to remove the cause of infection and thus the fatal complication. We also tried to have autopsy performed to confirm the preliminary impression of local tumor control.

Results

Eight patients were reoperated and 8 were not. None of the latter patients survived. No residual tumor was found in 4 of the 5 patients in whom autopsy was performed. In 2 patients who died of infection (Nos. 1 and 13) and in one who died of pancreatitis (No. 6) no tumor was found at autopsy. In 5 patients we had no histology after treatment and the cause of death was not known, although in one (No. 3) the probable cause was local abscess (CT finding, fever, leukocytosis). Patient No. 11 a 'long-term survivor', died without tumor, most likely from late neurotoxicity (leukoencephalopathy). In 7 of the 8 patients who were reoperated, histological examination showed no residual tumor whereas in one patient with glioblastoma (No. 16) residual tumor was found. Three of these patients are alive with minimal residual neurological deficits, 2 of them after more than 5 years, both these patients had malignant astrocytoma. The third patient had glioblastoma and is living with residual tumor.

Discussion

There have been several reports on brain toxicity after intrathecal or intramuscular (i.m.) application of IFN-α. In 9 patients who received IFN-α intraventricularly for leptomeningeal disease, progressive neurotoxic syndrome occurred during treatment and abated after its discontinuation (12). Ten patients who received IFN-α by i.m. injections experienced fatigue-astenia syndrome, as a manifestation of neurotoxicity, within the first week of treatment (14). In another series of 14 patients, neurotoxicity syndrom (lethargy, confusion) occurred in 8 patients 4–7 weeks after start of therapy, and disappeared when interferon was discontinued (15). It is interesting, however, that intratumoral administration of IFNs seems to be well tolerated (16); thus none of the 10 patients in this report (16) had evidence of encephalopathy; autopsy, however, was performed only in one patient. Chronic, progressive deterioration of the patients was in one report assumed to have been caused by infection which was a major problem of the IFN-α administration through the Ommaya reservoir (9). Intracerebral injection of IFN-α in mice caused an endomorphin-like opioid effect, which was preventable and reversible by the opiate antagonist naloxone (17).

Subacute neurologic deterioration without recurrent brain tumor developing a few months after radiation therapy alone, has also been observed. On basis of histological examinations it has been suggested that this is the result of demyelination secondary to a direct neurotoxic effect of radiation (18) and that this effect can be enhanced by chemotherapy. In these it appeared within one year after treatment. It may seem that IFN-α toxicity occurs during treatment, whereas delayed neurotoxicity is caused by irradiation and enhanced by chemotherapy.

The 2 patients who are long-term survivors without signs of recurrence both had malignant astrocytoma (one recurrent) while there were no cures among the 7 patients with glioblastoma. This observation does of course not allow any conclusion, due to the number of patients. However, it seems obvious that in all types of patients, whether treated primarily or for recurrence, the presented experimental treatment is beyond the limits of tolerance of the brain.

Surgery, postoperative radiation, and chemotherapy in combination with IFN-α can be locally effective in controlling malignant astrocytoma. However, toxicity of this combined treatment is still not acceptable (11, 19). The knowledge about pharmacokinetics (20) of IFN-α might help better to establish the tolerance to IFN-α of the brain; it is known, for instance, that the neurotoxicity after treatment with IFN-α alone can be reversible (21). The question whether earlier removal of the necrotic masses after completed treatment could stop this process which, in most of our cases, seemed to be progressive and irreversible, merits further investigation. It also seems reasonable to decrease the total as well as the daily radiation dose. The aim of a new prospective study would be to achieve a tolerable degree of toxicity but still effective local tumor control.

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