Intratumoral Adjuvant Chemotherapy With Doxorubicine In Glioblastoma Multiforme and Anaplastic Astrocytoma

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Abstract : Intratumoral local chemotherapy was applied as adjuvant treatment to 20 patient with recurrent types of anaplastic astrocytoma (AG3-4) and glioblastoma multiforme (GBM). A multiport catheter was implanted into the tumour and a portable Ommaya reservoir was placed under the scalp over the open craniotomy bone flap. Doxorubicine (Adriamycine) was given 0.5mg per day for ten days ,and a total of ten treatments were programmed monthly for each case. Pre-operative Karnofsky performance score was between 60 and 70%. Control CT scans of the patients showed the tumour to be progressive in 40 %, regressive in 30%, and stable in 30%. In two patients a local scalp infection and a cerebellar abscess due to Nocardia asteroides developed as complications of the treatment , but no other sistemic or local side effects were detected. Mean survival in the anaplastic astrocytoma and GBM groups was 98.9 and 46.1 weeks respectively. In conclusion, intratumoral doxorubicine treatment was found to be effective against systemic i.v. administration in the anaplastic astrocytoma group rather than the GBM group.

Key words: Chemotherapy, Intratumoral, Doxorubicine, Cerebellar abscess

INTRODUCTION

Several chemotherapeutic drugs have been used either as single agents or as combination chemotherapy in the treatment of malignant gliomas. The antineoplastic activity of doxorubicine (Adriamycine=ADM) (an antitumoral agent of antibiotic origin isolated from streptomyces peucetius var. caesius) has been clearly demonstrated (1). It has the ability to show specific immunosuppressive activity as an inhibitor of reverse transcriptase enzyme. ADM is not a phase-specific agent. Besides bone-marrow depression, stomatitis and hyperurichaemia have been reported as known side effects. Because of its poor penetration into blood-brain barrier and severe neurotoxicity, ADM is not considered suitable for systemic brain tumour chemotherapy (18). On the other hand, its effectiveness in the prevention of systemic metastases and in combination therapy as adjuvant chemotherapy has been reported (23,24).

Instilling drugs directly into the CSF or glioma tissue has been repeatedly shown to increase survival and improve quality of life by diminishing the disadvantages due to the blood-brain barrier (4,7,9). Previous attempes at intratumoral chemotherapy for brain tumours have been reported for a variety of drugs, including bleomycin (2), methotrexate (MTX) (7,10,24,28,29), cisplatin (3), interferon and nitrosoureas (17,32).

In this study, the antitumoral effect of doxorubicine (Adriamycine=ADM) as intratumoral local chemotherapy was investigated in twenty anaplastic astrocytoma and glioblastoma multiforme (GBM) patients.

MATERIALS AND METHODS

Twelve anaplastic astrocytoma and eight glioblastoma patients were included in the programme. They all had been irradiated and received CCNU chemotherapy with 110mg/m2 doses before recurrent tumour was diagnosed in control CT-scans. There were 11 women and 9 men with a mean age of 48 years and mean performance status of 64.4%

on the Karnofsky scale. Histopathological diagnosis was based on the WHO classification of 1990 with an malignant astrocytoma / GBM rate of 60%. Two patients had been operated four times, six three times, and ten patients twice.

Intratumoral chemotherapy was started on the second post-operative day after a control of CT-scan for the prompt site of the catheter. Microinjections of doxorubicine were administered per-operatively to each recurrent glioma case. Doxorubicine (Adriamycine, Farmitalia), was given post-operatively through the Ommaya reservoir (20) in doses of 0.5mg daily for 10 days and repeated monthly ten times. ECG, blood uric acid, creatinin, white blood cells and platelets were monitored routinely throughout the drug administration.

In addition, ADM 60-75mg/m was administered intravenously in ten recurrent anaplastic astrocytoma and ten GBM as a consequent comparison group. In these systemic ADM treated groups , Karnofsky performance scale mean score were 68.3% and 60%, respectively.

CT-scanning was performed bimonthly postoperatively with and without contrast enhancement to measure the size of the the tumour. Median survivals were calculated using the Kaplan-Meier method (12). For statistical analysis , student t , F and e tests were used for the significant differences.

RESULTS

CT-scans of a right-sided occipital anaplastic astrocytoma case before and after the intratumoral local chemotherapy treatment was shown in Figure 1 a, b. The maximal total dose of 50mg ADM was reached only twice in two anaplastic astrocytoma patients. The mean total dose was 22.5mg.

Mild side effects were headache in three patients, and slight hyperurichaemia in one . In one patient, local irritative infection due to leakage of ADM to the scalp was observed. In another patient, an aseptic meningitis occurred and was treated with corticosteroids. One patient developed a left sided cerebellar abscess which was removed by suboccipital craniectomy (Figure 2). Culture of the specimen revealed Nocardia astroides as a severe complication of the treatment. This complication developed other than the local site of the administered drug may be explained in terms of its immunosuppressive effect. All other side effects disappeared in the first 72 hours. Mean survival was 98.9 weeks in the anaplastic astrocytoma (AG3-4) group and 46.1 weeks in the the GBM group. Comparison of the survival rates of the patients receiving systemic (i.v.) and intratumoral ADM chemotherapy revealed a significant effectiveness of local as opposed to the systemic chemotherapy in the anaplastic astrocytoma group ($p<0.5$). No significant statistical difference was found in the GBM patient group ($p > 0.5$) (student t test) (Table I).

Median survivals were calculated as 67.5 weeks in locally treated and 60 weeks in intravenously treated malignant astrocytoma groups, and 44.5 and 45 weeks in the GBM groups, respectively (Figure 3). CT scans of the patients showed: tumours to be progressive 40%, regressive 30% and stable 30% .

Histopathological investigation of biopsy material after intratumoral ADM administration revealed some tissue necrosis and hyalinisation processes in the vessels, as shown in Figures 4a, b.

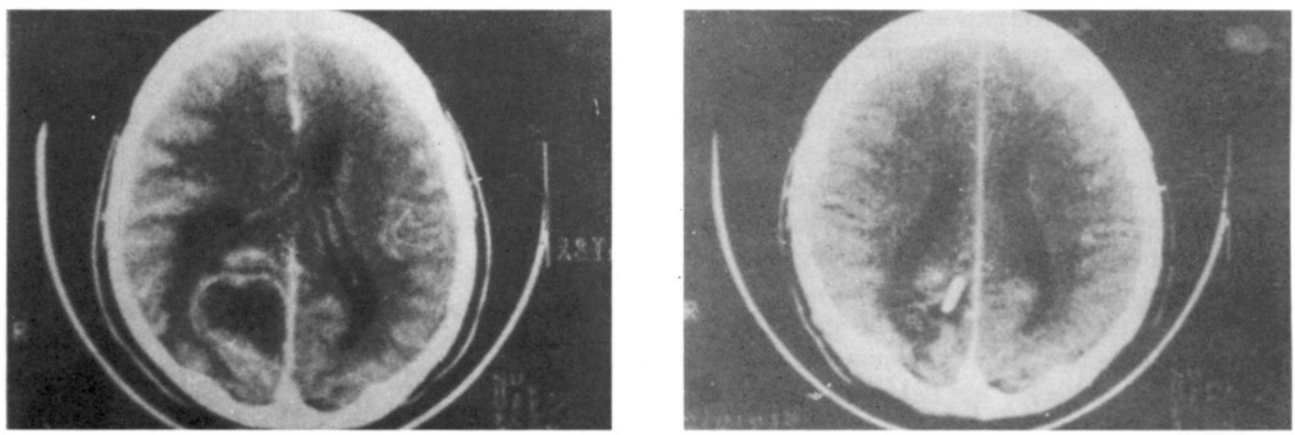

Fig. 1a, b : CT-scan showing decrease in the size of an anaplastic astrocytoma before (a) and six months after (b) intratumoral ADM treatment.

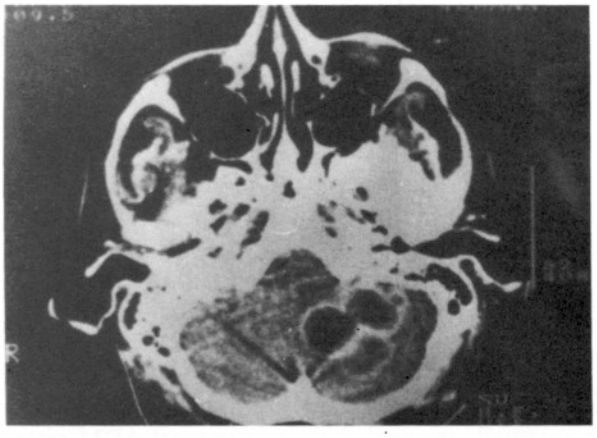

Fig. 2 : Ct scan of a patient showing a left sided cerebellar abscess during intratumoral ADM chemotherapy as a complication of the procedure.

Table I : Comparison of Mean and Median Survivals of Cases Treated With Adjuvant İntratumoral and Systemic ADM Chemotherapy

Tumours	Nof of patients (n)	Mean age	Mean Karnofsky Performance Score	Mean Survival (in weeks)	Median Survival in weeks)	p (Student t test)
Intratumoral ADM Chemotherapy						
Anaplastic astrocytoma	12	46.1	66%	**98.9*** weeks *two patients are still living	67.5 weeks	**p<0.5**
GSM	8	51.7	63.3%	**46.1** weeks	44.5 weeks	**p>0.5**
Systemic (i.v.) ADM Chemotherapy						
Anaplastic astrocytoma	10	47.4	68.3%	**62.0** weeks	60.0 weeks	**p<0.5**
GBM	10	52.3	60%	**42.9** weeks	45.0 weeks	**p>0.5**

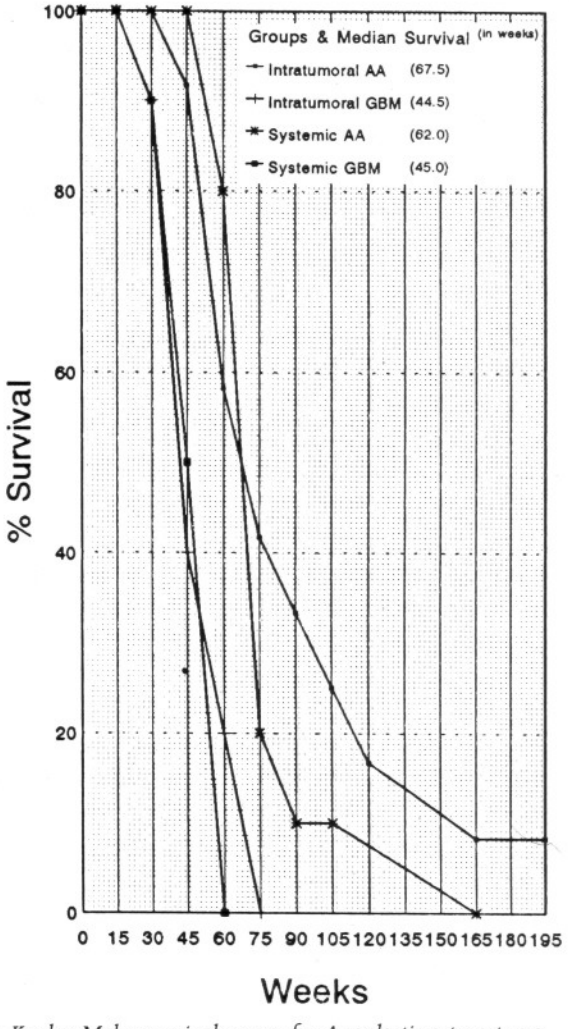

Fig. 3 : Kaplan-Meler survival curves for Anaplastic astrocytoma (AA) and GBM patients treated with intratumoral or systemic ADM chemotherapy

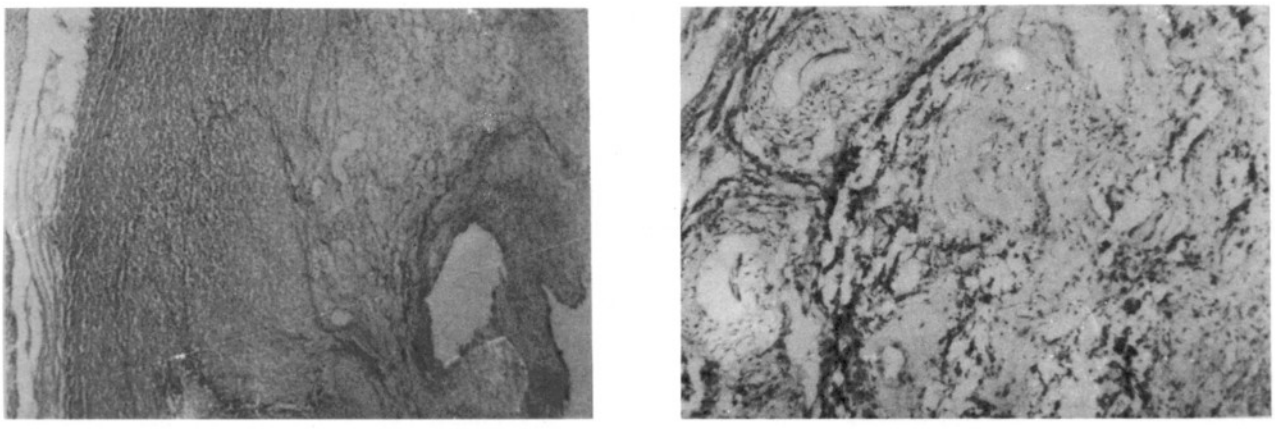

Fig. 4 a, b : Tissue necrosis (A) and hyalinisation processes in the vessels (B) after intratumoral ADM chemotherapy in biopsy material.

DISCUSSION

During the past decade there has been great interest in identifying the best drug for the chemotherapy of brain tumours. The basic principle of chemotherapy is that the drug must reach all parts of the tumour, and the side effects must be minimal. The blood-brain barrier prevents the delivery of chemotherapeutic agents into the brain tissue and CSF is not an adequate pathway to reach solid tumours within the brain (29). In 1968, Ommaya described his initial experience with the insertion of a CSF reservoir and a manual pump. In that early review, there was a complication rate of 28% in 60 patients, consisting largely of seizures and infection; in addition, pump failure occurred in 23% (23). The surgical technique was altered in subsequent years, showing more favourable complication rates in recently published articles (8,16). Direct delivery of drugs into a brain tumour through multiple implanted catheters by a stereotactic procedure has been tried (9), but a few biopsies have been performed after intratumoral chemotherapy (19). MTX, Bleomycin, Cisplatin, BCNU and other water-soluble nitrosoureas and ADM were the antineoplastic drugs used for this purpose (5,8,13,20,26,27,28,32,33).

We believe that 0.5mg ADM was not adequate as a single dose. In some studies,mainly carried out by the Japanese researchers (11,25,30,31), the total dose of ADM in intratumoral administration was reported as 5-10mg. Our total dose was much higher, ranging from 30 to 50mg (mean 22.5 mg). Throughout the study the postulated total dose of 50mg was not achieved and no seizures,cardiotoxicity or nephrotoxicity occurred in any of the cases. Yoshida reported a local chemotherapy study in 79 patients; 63 with ADM, 5 with a combination of ADM and bleomycin, 7 with bleomycin and 4 with MTX and reported 8 local infections and 4 meningitis cases as complications of this procedure (33). Mean survival was 806 days in the AG3 and 757 days in the AG4 group which was close to our findings (692 days in the anaplastic astrocytoma group).

Surgical implantation of biodegradable polymer containing chemotherapeutic drugs into the tumour may be considered as a therapeutic option (8). With this technique Kubo reported 91% of 18 months' survival in 91% of 20 anaplastic astrocytoma cases and 12 months in 47% of 23 GBM patients with intratumoral ADM treatment (14). Median survival of patients treated with surgery alone is approximately 20 weeks in GBM patients, and surgery plus radiation therapy, 45-50 weeks (6). With our method the median survival was 44.5 weeks in the GBM and 67.5 weeks in the anaplastic astrocytoma group.

Apart from unexpected complications, our study showed that the dose and side effects of the drug were minimal in intratumoral chemotherapy. Serial stereotactic biopsies may help to determine the dose of the drug in the tumour and pathological follow-up.

In conclusion, evaluation of the mean survival rate of the patients, though the sizes of the groups were small, showed that intratumoral ADM treatment was significantly more effective in the recurrent anaplastic astrocytoma group than the GBM group.

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