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Conventional radiotherapy combined with carbogen breathing and nicotinamide for malignant gliomas

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Received 4 August 1994; revision received 22 February 1995; accepted 28 February 1995

Abstract

High grade malignant gliomas are among the most radioresistant human tumors and total doses up to 80 Gy are inadequate to achieve long-term local control in most of the patients. Hypoxia has been demonstrated in primary brain tumors and may be one of the reasons for their radioresistance. In experimental models carbogen breathing and nicotinamide have been shown to act against hypoxia by different mechanisms and both modalities were tested in 16 patients with supratentorial malignant gliomas in combination with a conventional radiotherapy scheme (50 Gy in 25 daily fractions). The present study was performed to determine the feasibility and toxicity of conventional radiotherapy combined with carbogen breathing and nicotinamide. The unexpectedly high incidence of acute liver toxicity, the possible increase of subacute and late CNS toxicity, and the absence of a higher effectivity led us to reconsider this new treatment modality for patients with malignant gliomas.

Keywords: Malignant astrocytic neoplasms; Malignant gliomas; Glioblastoma multiforme; Carbogen breathing; Nicotinamide; Toxicity

1. Introduction

The disappointing results of current treatment modalities for patients with malignant gliomas necessitate the search for new treatment approaches. The standard therapy for high grade malignant gliomas consists of surgery and postoperative radiotherapy. Although radiotherapy significantly prolongs survival, the absolute survival benefit is only modest. Local recurrence is almost always the cause of failure and several factors such as intrinsic radiosensitivity, tumor cell kinetics, and hypoxia are thought to be the underlying reasons. A

relatively high intrinsic radioresistance of human brain tumors has been reported by Fertil and Malaise after determining α , the mean inactivation dose, and the surviving fraction after 2 Gy (SF₂) in vitro [3]. Others, however, have found a wide range of SF₂-values and postulate that not only the high intrinsic radioresistance of high grade malignant gliomas but also other factors determine their incurability by radiation therapy [19]. One of the other factors might be the high proliferative capacity of malignant gliomas [10]. Because of these tumor characteristics, in some radiotherapy schemes the tumor dose was increased and overall treatment time shortened. Hyperfractionation up to total doses of 80 Gy in 5.5 weeks (three fractions of ~1 Gy per day) [5]

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and accelerated fractionation to 60 Gy in 2 weeks (three fractions of 1.6 Gy per day) [13], however, have not led to improved survival. Extrinsic factors such as the presence of hypoxia may further compromise the radiosensitivity of the clonogenic tumor cell compartment. The presence of hypoxic cells in human malignant gliomas has been demonstrated in vivo [12,16]. There is some clinical evidence that these hypoxic tumor cells can be sensitized by metronidazole [20]; although subsequent studies with metronidazole and other hypoxic cell radiosensitizers showed no positive effect on survival when combined with standard dose radiotherapy. Of all clinical studies with the objective to reduce the hypoxic tumor cell compartment in malignant gliomas there is no evidence that the measures taken to reduce the hypoxia really had the desired effect.

This paper deals with the acute toxicity and treatment results of conventional radiotherapy combined with carbogen breathing and nicotinamide.

2. Patients and methods

Sixteen consecutive patients with histologically proven malignant supratentorial astrocytic neoplasms, who fulfilled the inclusion criteria (age between 18 and 70 years; WHO performance status of 0–3; no severe heart or lung disease; no severe liver or kidney function disturbances; written informed consent), were entered into the study over the period November 1992 to January 1994. The extent of neurosurgical intervention ranged from biopsy only to macroscopically total resection. Detailed information about each individual patient is summarized in Table 1. In this series there was only one patient (No. 2) with a macroscopically total resection.

After neurosurgery, but before the start of radiotherapy MRI-scans, with and without gadolinium-DTPA, were made to determine the result of the surgical procedure and the tumor extension at the start of radiotherapy. The target volume consisted of the contrast enhancing region with a 2-cm margin. Patients were treated with megavoltage equipment (4 or 6 MV) by weighted parallel opposing beams. In an overall treatment time of 5 weeks a total dose of 50 Gy was administered in 25 daily fractions of 2 Gy. There was no reduction of the target volume during the treatment period. Radiotherapy was combined with carbogen breathing by the method presented earlier [11]. Carbogen breathing started 5 min before irradiation and was continued during treatment. Six grams of nicotinamide dissolved in orange squash were ingested 1.5 h before each treatment. Actual plasma and tissue concentrations of nicotinamide were not measured, but others have shown that a mean peak level of 159.5 $\mu\text{g/ml}$ could be measured in healthy volunteers 45 min after ingestion of 6 g nicotinamide [9]. It is expected that the plasma level will stay above 100 $\mu\text{g/ml}$ for 1–2 h after reaching

Table 1
Patient characteristics

No.	Gender	Age	Hist.	EO	WHO
1	M	64	4	PR	1
2	F	55	4	TR	1
3	M	52	4	PR	1
4	M	45	3	BI	1
5	M	64	4	BI	3
6	M	48	4	PR	1
7	M	51	4	PR	1
8	M	48	4	PR	1
9	F	51	3	BI	1
10	M	55	4	BI	3
11	M	60	4	PR	3
12	M	59	4	PR	1
13	F	61	4	PR	2
14	M	63	4	PR	1
15	M	47	4	PR	1
16	F	46	4	PR	1

Patient number, gender, age at the time of diagnosis, histologic grade according to Daumas-Duport [2], extent of operation (EO) (TR, total resection; PR, partial resection; BI, biopsy), and performance status according to WHO at the start of radiotherapy.

its peak. Animal data suggest that such a level will be sufficient for substantial radiosensitization.

The effect of the treatment on tumor and normal CNS was evaluated with MRI scans at 1 and 3 months after completion of treatment and every 3 months thereafter. In one patient with claustrophobia evaluation was performed by CT-scans.

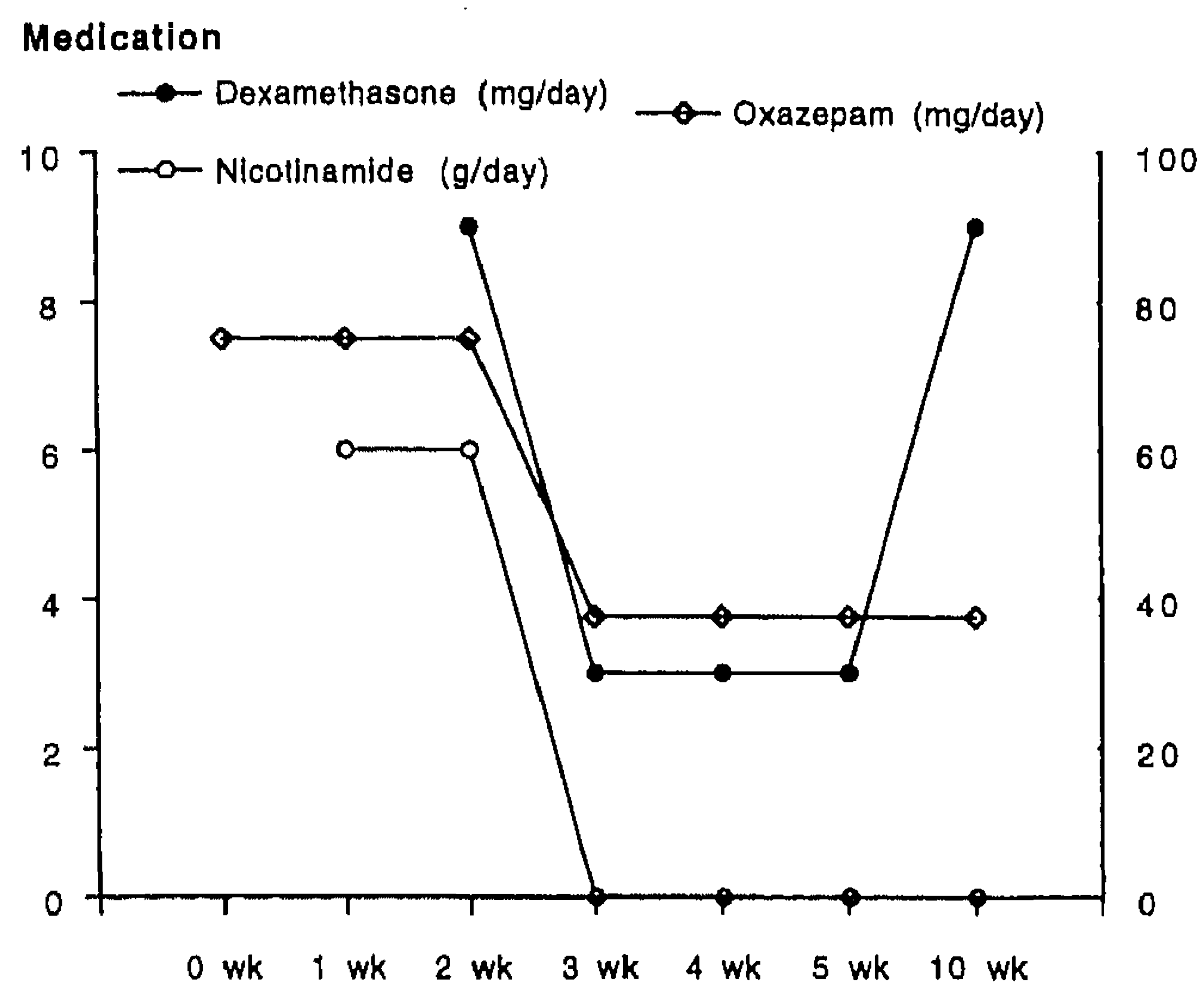
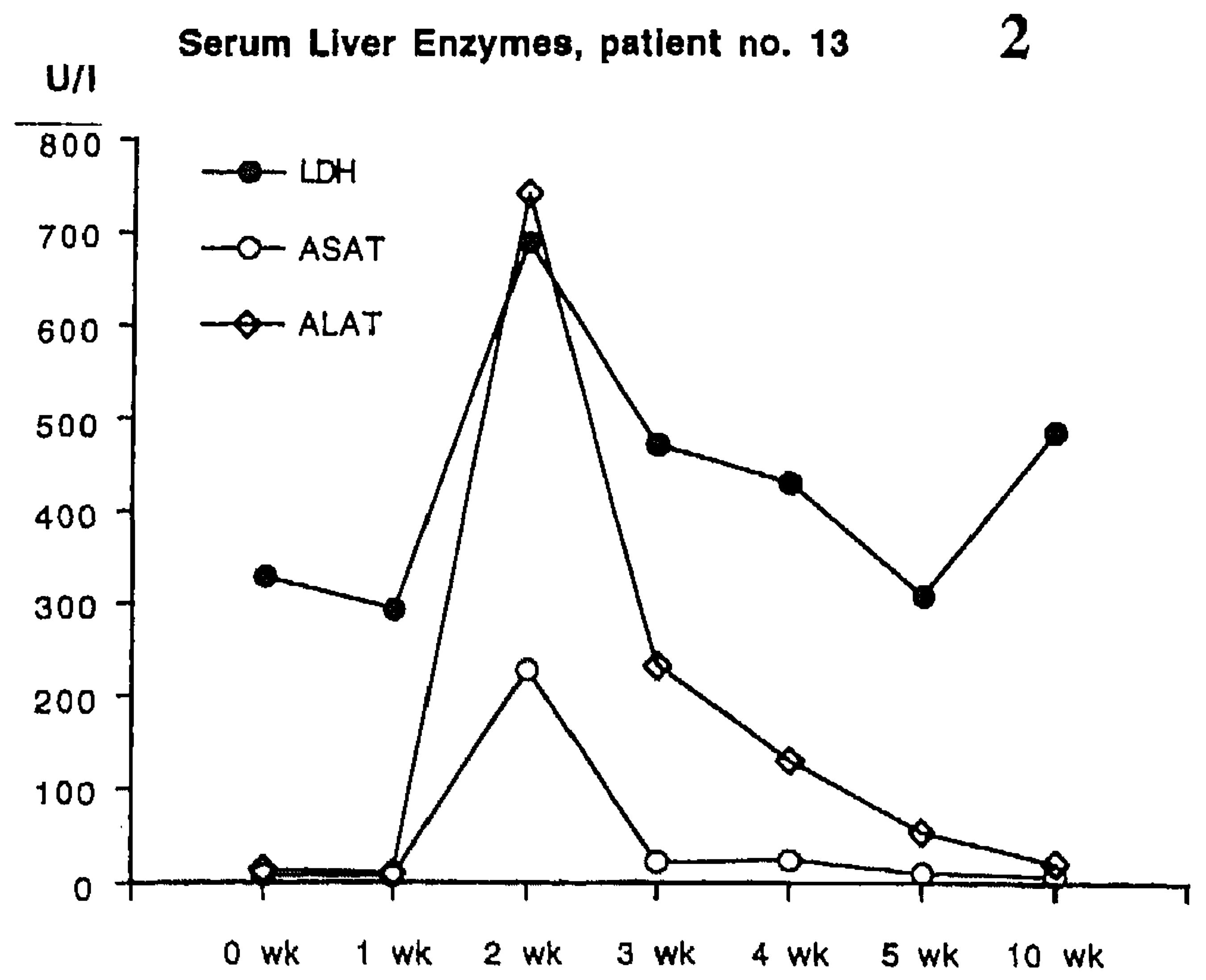
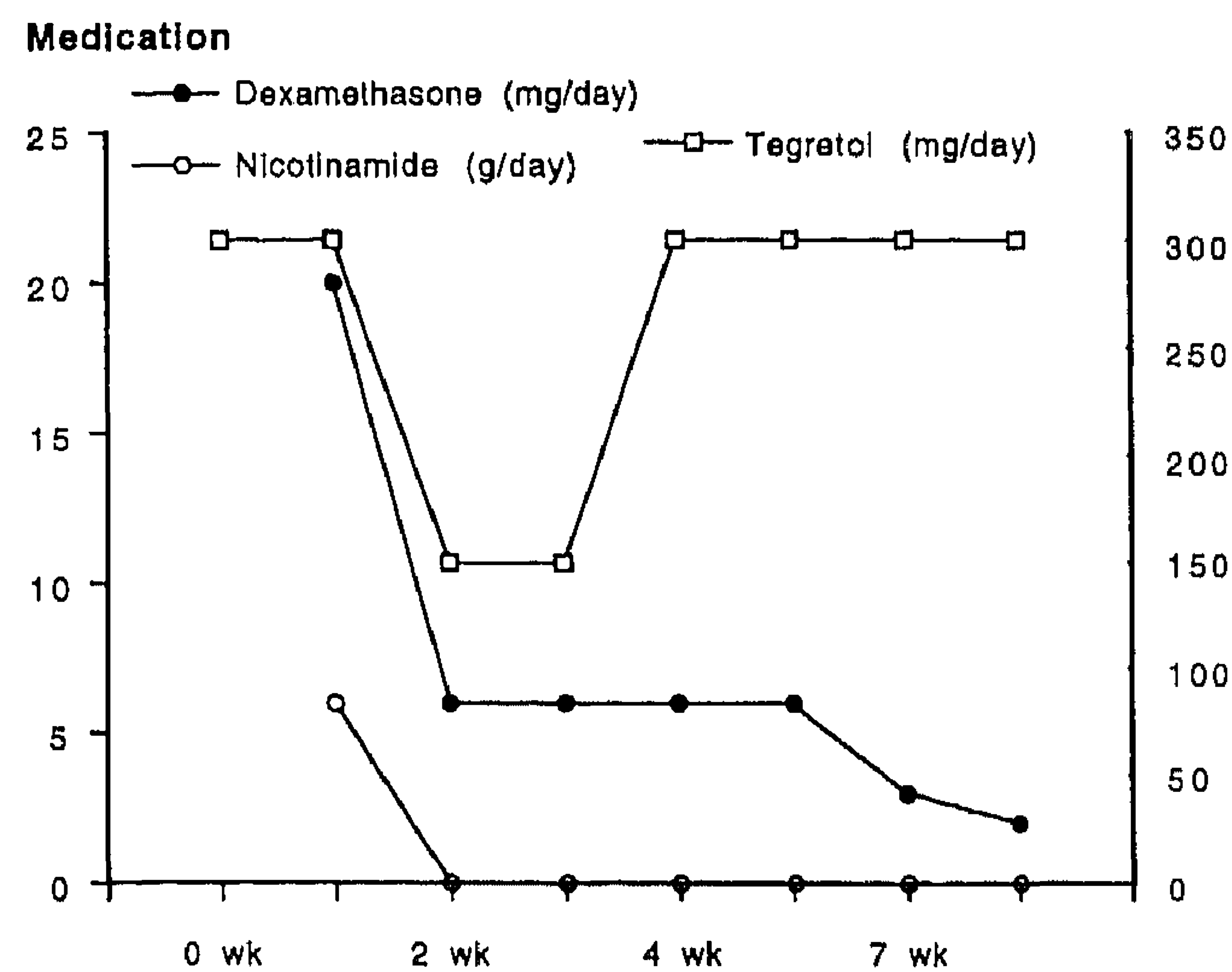
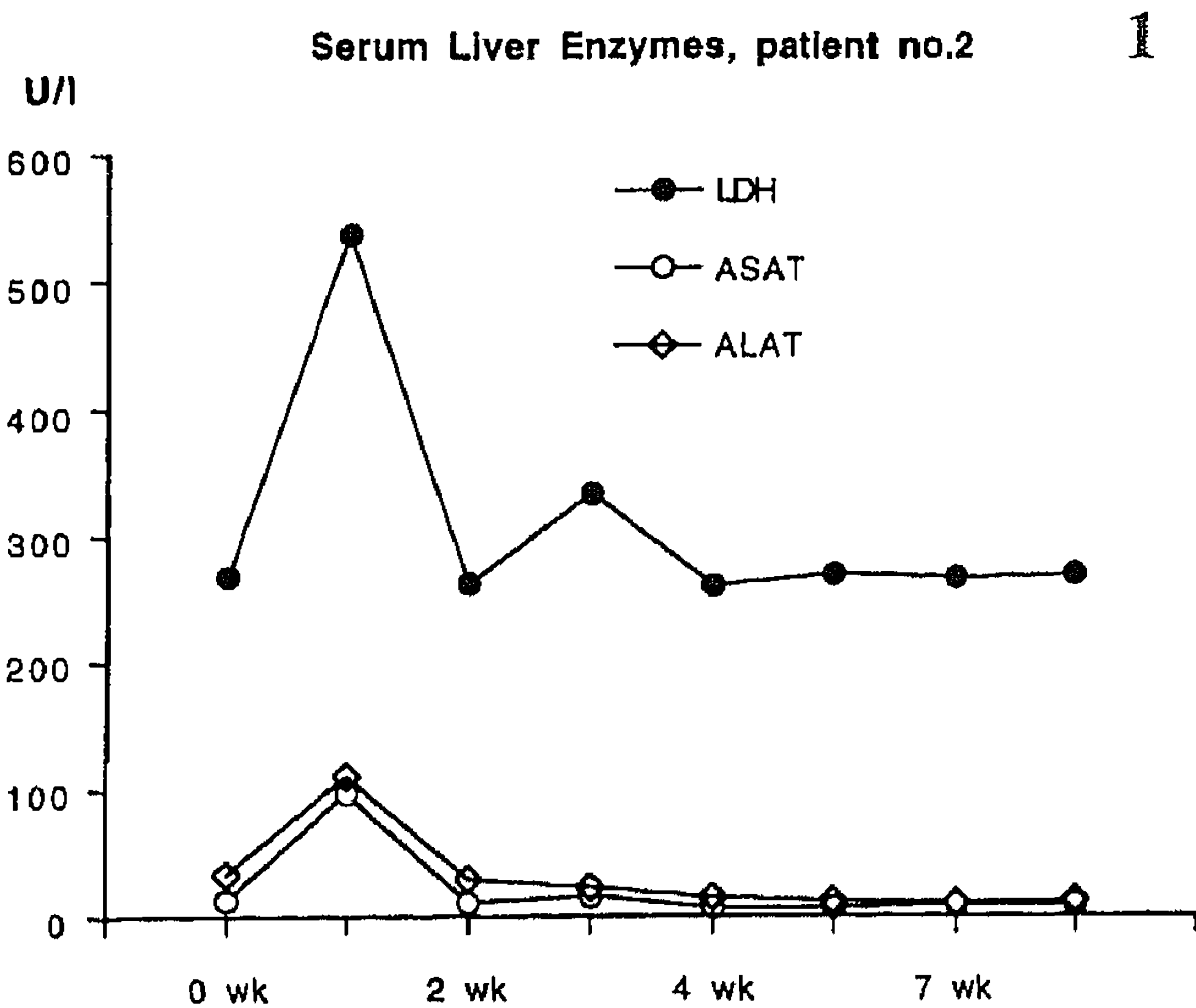
This clinical study has been approved by the local ethical committee and informed written consent was given by all patients before treatment.

3. Results

3.1. Acute effects

3.1.1. Liver toxicity

In four of the 16 patients (Nos. 2, 4, 5 and 13) there was a clear relationship between nicotinamide medication and serum liver enzyme disturbances. In two of these four patients (Nos. 2 and 13) nicotinamide led to severe nausea and vomiting which necessitated hospitalization in the first and second week of treatment, respectively. The clinical symptoms were accompanied by hepatic toxicity reflected in elevated liver serum enzymes (LDH, ASAT, ALAT) (Figs. 1, 2). The clinical symptoms and liver enzyme disturbances disappeared within a few days after stopping nicotinamide medication. Another patient (No. 5) started treatment with already some elevated liver serum enzymes which worsened after moderate doses (1.5 and 3 g) of nicotinamide. Neurological deterioration in the 4th week of treatment led to abolishing the intake of nicotinamide. In the fourth patient (No. 4) the nicotinamide-related liver enzyme dis-



Figs. 1, 2. Two patients with severe acute hepatic toxicity due to nicotinamide. The upper panels show the changes in serum liver enzymes in relation to medication (bottom panels). The first patient (No. 2) used Tegretol® (carbamazepine; 3 × 100 mg) in combination with nicotinamide. Three administrations of 6 g of nicotinamide caused severe clinical symptoms and liver toxicity. The second patient (No. 13) used Atrovent® (ipratropium-bromide; 2-4 × 250 µg) and Seresta® (oxazepam; 3 × 25 mg) together with nicotinamide. In the second week of treatment (after 8 × 6 g nicotinamide) toxicity became apparent.

turbances were only moderate and he was able to complete the planned treatment. The high frequency of liver enzyme disturbances may be due to concomitant medication with known liver toxicity such as corticosteroids (Nos. 4 and 5); benzodiazepines (Nos. 5 and 13) or anti-epileptics (Nos. 2 and 4).

3.1.2. Psychiatric disorders

Two of the 16 patients (Nos. 8 and 16) showed psychiatric symptoms during treatment. The first patient experienced paranoia and visual hallucinations after 4 weeks of therapy. These symptoms disappeared after the administration of anti-psychotic medication and the patient was able to complete the treatment. In the second patient paranoia and auditory hallucinations

occurred during the second week of treatment. Because of the severity of the symptoms and their unclear etiology it was decided to stop carbogen breathing and nicotinamide. Within 3 days the symptoms disappeared and radiation treatment was completed without further complications. In the week following treatment, however, the patient experienced a relapse into paranoia and hallucinations and needed anti-psychotic medication.

Whether nicotinamide and carbogen breathing induces or sensitizes patients with brain tumors to the development of psychotic symptoms remains unclear.

3.1.3. Carbogen breathing

Carbogen breathing according to the method described by Kaanders and Van der Maazen [11] is tolerated

well by most patients. The high content of carbondioxide causes an increased breathing rate after 2–3 min but most patients were able to continue carbogen breathing for 10–15 min. Carbogen breathing was stopped in two patients (Nos. 5 and 12) in the fifth week of treatment because of neurological deterioration and in one patient (No. 16) because of psychotic symptoms in the third week of treatment.

3.2. Subacute and late effects

Because long-term survival is rare for patients with malignant gliomas, only limited information is available on the subacute and late toxicity. Corticosteroid medication may be a measure for radiation-induced edema and the need for continued corticosteroid medication after completion of treatment may reflect toxicity, although tumor progression may also be the underlying reason. In this patient group only two patients were able to discontinue the corticosteroid medication. All other patients experienced an increase of neurological symptoms when steroids were decreased or stopped.

In three patients (Nos. 6, 9 and 12) evaluation of the treatment with MRI-scans showed an increase of edema without signs of tumor progression. Despite high doses of corticosteroids two of these patients (Nos. 6 and 12) died rapidly and no additional scans could be made. In the third patient (No. 9) a remarkable effect of corticosteroid medication was noticed. At 3 months after finishing therapy she experienced an epileptic attack and a deterioration of her neurological status. Until then she had not used corticosteroid medication. The MRI-scan showed severe edema with a shift of the midline structures. After corticosteroid therapy a considerable reduction of the midline shift was noted on the MRI-scan reflected in a great improvement of the clinical situation. Although the good response to corticosteroids might indicate that in this patient the neurological deterioration was related to treatment-induced toxicity, a contribution by tumor progression is difficult to rule out, especially since 6 months after the first signs of edema progressive tumor growth was evident.

3.3. Tumor responses and survival

MRI-scans were made at 1 and 3 months after completion of therapy and every 3 months thereafter. One patient (No. 13) was evaluated with CT-scans due to claustrophobia. In none of the 16 patients was a complete or partial response as defined by the criteria of Macdonald et al. [15] noticed.

At the time of the last evaluation (February 1995) 14 of the 16 patients have died. Two patients are alive at 17 and 27.5 months after surgery, but both have clinical and radiological evidence of tumor progression. The survival (with a median of 233 days and two patients surviving more than 1.4 years) estimated according to Kaplan-Meier is comparable with historical controls.

4. Discussion

Hypoxia and (accelerated) proliferation of tumor cells are factors that negatively influence the outcome of radiation therapy. There is a substantial amount of data that indicate that some tumors are better controlled when radiation therapy is combined with measures that counteract either hypoxia or proliferation of tumor cells. The best clinical examples are probably cervical cancers [8] and head and neck tumors [6,1,4]. Although several studies indicate that hypoxia and fast proliferation of tumor cells are also present in malignant gliomas [12,10], the contribution of these factors to the radioresistance of malignant gliomas is unclear. Until now, attempts to counteract either hypoxia or fast proliferation by hypoxic cell sensitizers, hyperbaric oxygen, hyperfractionation, or accelerated fractionation have not led to improvement of treatment results. A combination of both approaches as described by ARCON (accelerated radiotherapy combined with carbogen breathing and nicotinamide) might be more promising.

Acceleration of radiation therapy limits the time for extensive proliferation of tumor cells between fractions and should result in a higher cure rate in fast proliferating tumors. However, by reducing the overall treatment time acute and eventually late normal tissue reactions become limiting factors.

Laboratory studies have shown that carbogen breathing and nicotinamide leads to increased therapeutic ratios when applied in combination with fractionated radiotherapy. The higher effectiveness of this combined modality treatment is at least partly due to a reduction in the number of hypoxic cells. In experimental tumors enhancement ratios of 1.2 to 2.0 [14,17,18] have been obtained. Although increased radiation sensitivity of normal tissues was observed, enhancement ratios were far less pronounced (dose enhancement factors of 1.1 to 1.2) resulting in a selective sensitization of tumor cells. Of the normal tissues, the rat spinal cord seems the most affected by the ARCON treatment. A decrease in radiation tolerance of ~20% was observed when radiation was combined with carbogen breathing and nicotinamide [7].

Therefore, one may conclude that combination of accelerated radiotherapy with carbogen breathing and nicotinamide could lead to a substantial decrease in radiation tolerance of the normal CNS of up to ~40%. However, this loss of tolerance may be more than compensated for by the positive results in experimental tumors from combined treatment with carbogen breathing and nicotinamide, and allows clinical testing in malignant brain tumors. To reduce the risk of severe radiation-induced CNS toxicity, it was decided to combine carbogen breathing and nicotinamide with a conventional radiation scheme with a reduced total dose (50 Gy instead of 60 Gy). To test the feasibility and toxicity 16 patients were entered into the study.

An unexpectedly high incidence of acute toxicity was

encountered, most of it could be attributed to nicotinamide. Nicotinamide has been clinically applied in many different diseases and in high daily doses [21]. Although transient liver toxicity has been reported, the incidence was very low. Therefore, it was surprising that in this pilot study of only 16 patients two had severe hepatic toxicity. Another two developed psychiatric disorders. Whether this was due to the primary brain tumor or to the nicotinamide medication is unclear. Patients with primary brain tumors may be more susceptible to this possible side effect of nicotinamide. A permanent dependence on corticosteroids was noted in 14 of the 16 patients. This might reflect increased CNS toxicity but the poor overall survival due to tumor progression does not allow us to draw firm conclusions.

From this study it is also apparent that most of the patients were able to breath carbogen for 10–15 min. However, when neurological status deteriorates, carbogen breathing may become too great a burden. On the basis of these experiences it is advised that carbogen breathing should not be attempted in patients with a performance status worse than WHO level 2.

This pilot study in which patients with malignant supratentorial gliomas were treated with radiation (50 Gy in 2-Gy daily fractions) in combination with carbogen breathing and nicotinamide brings us to the conclusion that a higher than expected acute toxicity was seen from nicotinamide and that five of 16 patients were unable to complete the planned treatment. No benefit of survival was found when compared with historical control studies. The expected increase in late toxicity when carbogen breathing and nicotinamide are combined with higher doses or accelerated schemes of radiation will probably limit the clinical use of carbogen breathing and nicotinamide in patients with malignant gliomas. Some patients, however, might benefit from the proposed treatment modifications. Pre-treatment testing of changes in tumor oxygenation and tumor perfusion in vivo by means of MRS, SPECT, or PET could select patients for specific treatment modalities.

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