Cancer Chemother Pharmacol (1999) 43: 178–179

CLINICAL TRIAL REPORT

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Safety and potential effectiveness of daunorubicin-containing liposomes in patients with advanced recurrent malignant CNS tumors

Received: 9 March 1998 / Accepted: 27 July 1998

Despite significant advances in surgical and radiotherapeutic management, the prognosis for patients with glioblastoma multiforme (GBM) remains dismal. The results of chemotherapy are particularly disappointing, As most chemotherapeutic agents are incapable of crossing the partially intact blood-brain barrier present in these patients. We [7] and other investigators [6, 9] have shown that anthracycline derivatives are effective against malignant glioma cells in vitro. Subsequently we found that the anthracycline mitoxantrone had some activity against recurrent glioblastoma patients when injected locally via an Ommaya reservoir [2]. However, the effect of local chemotherapy is always hampered by limited drug diffusion into the tumor.

In attempts to overcome this targeting restriction, liposomes are being investigated as delivery agents for anticancer drugs. Antitumor agents entrapped in liposomes have the advantage of a long circulation time, reduced systemic toxicity, and increased uptake by the tumor. We report on our preliminary experience with daunorubicin encapsulated in distearoylphosphatidylcholine/cholesterol liposomes with a diameter of 60–80 nm.

The daunorubicin/liposome combination is stable in the bloodstream and targets solid tumors [8] In animal models the amount of daunorubicin taken up by tumor tissue is 10-fold greater after liposome-mediated delivery than after delivery of free drug [4, 5]. Furthermore, Albrecht et al. [1] have reported high concentrations of the drug in human malignant astrocytomas after intravenous administration of 2 mg/kg liposomes-encapsulated daunorubicin; our preliminary results also suggest a good penetration of the drug into tumor tissue (unpublished findings).

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We recently conducted a pilot study on 16 patients with recurrent brain tumors in computerized tomography (CT)-documented progression, who received daunorubicin-containing liposomes intravenously. Overall, 15 of our patients had recurrent GBM and 1 had disseminated medulloblastoma. Their mean age was 54 years, their Karnofsky performance status (KPS) was less than 60, and their life expectancy was no more than 2 months. When enrolled, the patients were receiving only steroids. All gave their informed consent. All had received surgery and radiotherapy as well as various chemotherapy protocols involving nitrosoureas, platinum compounds, etoposide, and procarbazine. Nine patients had undergone reoperation at disease recurrence.

The daunorubicin-containing liposomes were given in three dose regimes: four patients received 80 mg/m^2, five received 100 mg/m^2, and seven received 120 mg/m^2 every 3 weeks. Each patient received at least two cycles, with treatment being repeated until disease progression as documented by contrast-enhanced CT scan.

The KPS remained unchanged in all patients except one, a GBM patient whose KPS improved from 60 to 80 with concomitant disease stabilization (Fig. 1). Six patients (37%) achieved stable disease (SD) or a partial response (PR) according to McDonald's criteria (see Table 1). It is reasonable to assume that anthracycline derivatives would be at least partially effective against tumors previously treated with platinum or nitrosoureas, since the mechanism underlying the development of resistance to anthracyclines differs from that reported for nitrosoureas and platinum-based drugs [3]. Our results suggest that anthracycline encapsulated in liposomes can produce some antitumor response, with the benefit lasting from 2 to 5 months. No patient complained of nausea, vomiting, phlebitis, or stomatitis; furthermore, no hepatic, renal, or cardiac toxicity was encountered. Myelo-suppression is the most common adverse event encountered with anthracyclines, but no significant anemia occurred in our patients; the hemoglobin count was never less than 12 mg/dl; granulocy-

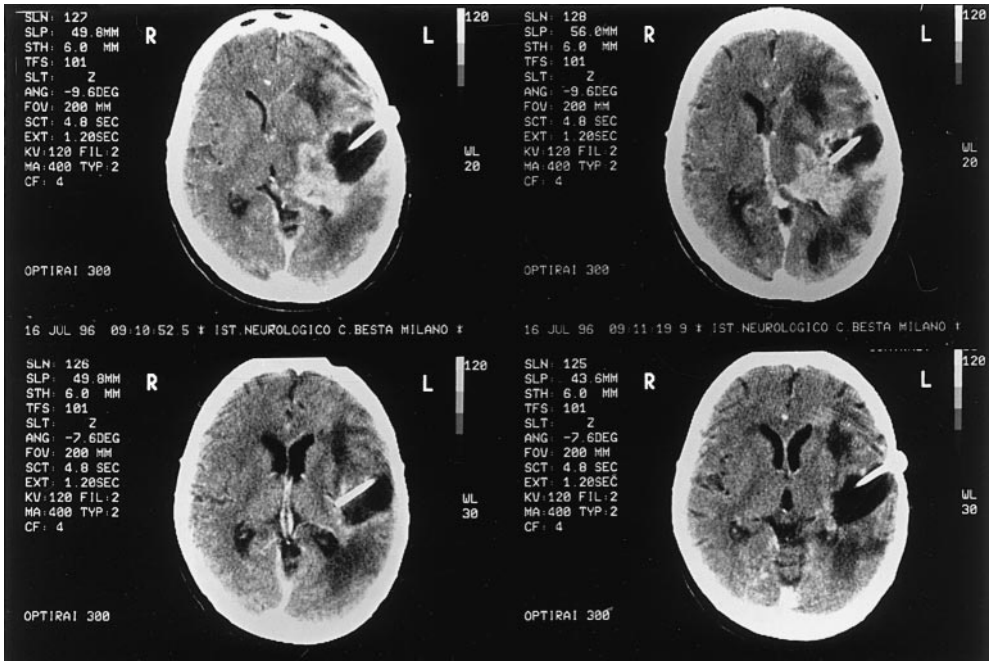

Fig. 1 CT scan of a partially responding patient with previously progressing GBM. An improvement in the KPS score concomitant with tumor shrinkage persisted for 5 months

Table 1 Tumor responses to daunorubicin-containing liposomes. Only patients who responded (PR or SD) to the treatment are listed

Histology	Dose mg/m^2	Cycles given (*n*)	PR	SD	Duration of response (weeks)
GBM (1/4)	80	2		1	8
GBM	100	3		1	18
GBM (2/5)	100	5	1		22
GBM	120	3		1	9
GBM (2/6)	120	3		1	12
Medulloblastoma (1)	120	3	1		18

Table 2 Myelosuppression encountered in the present study

Entry dose level (mg/m^2)	Nadir count ($\times 10^3/\mu l$)		
	WBC Median (range)	Granulocyte Median (range)	Platelet Median (range)
80	6.4 (3.3–10.4)	4.4 (2.6–6.5)	202 (181–312)
100	3.8 (3.0–9.0)	2.2 (1.8–5.8)	217 (148–289)
120	4.2 (0.8–5.4)	2.8 (2.0–3.2)	137 (58–233)[a]

[a] Thrombocytopenia lasted 2 weeks

topenia (nadir < 2000/μl) and thrombocytopenia (< 75,000/μl) occurred in two cases at the 120-gm/m^2 dose level (see Table 2). This limited trial suggests that 100 mg/m^2 liposome-entrapped daunorubicin might be the optimal dose for the achievement of responses without side effects. In conclusion, the lack of significant systemic toxicity observed in conjunction with some effectiveness in patients with documented progressive disease makes this approach worthy of further investigation.

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