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LETTER TO THE EDITOR

An overview of published results from randomized studies of nitrosoureas in primary high grade malignant glioma

Sir – The prognosis of patients with high-grade malignant glioma is poor. Despite improve results following radiotherapy after neurosurgery, the median survival time is about 9 months, and the proportion of 2-year survivors about 5–10%.

Studies involving the use of adjuvant chemotherapy have been conducted, but the results from individual studies have not yet established its role in the management of the disease.

As a preliminary exercise in designing a new MRC trial, we recently carried out an overview of published results from randomised studies of nitrosoureas in primary high-grade malignant glioma. Our intention was to assess the effect of a nitrosourea, given adjuvant to radiotherapy, on survival.

A literature search using 'Medline' and 'Cancerlit' identified over 200 references on therapy for brain tumours, since 1975. Of these, we isolated the randomised trials of high-grade gliomas with chemotherapy, in which the control group received surgery and radiotherapy, and the treatment group, chemotherapy adjuvant to surgery and radiotherapy. Thirteen such studies were found, and in 10 of these, the chemotherapy was a single agent nitrosourea. Six of these 10 studies reported survival times, two relapse-free intervals and two, both. We decided to use survival rates as our measure of treatment effect, and the 8 studies giving this information are listed in Table I. The dose of CCNU in the studies ranged between 100–130 mg m^{-2} per cycle, for BCNU the range was 200–240 mg m^{-2}, and for Methyl-CCNU, 150–220 mg m^{-2}. In each case, the cycle length was 6–8 weeks (Table I). The radiotherapy regimes employed in the various studies did not differ greatly, being generally between 5,000 and 6,000 cGy (Table II).

We looked at survival rates at 6, 12, 18 and 24 months in each treatment group, and calculated an overall difference weighted in a manner which takes into account the size of each trial. The results at 12 and 24 months are summarised in Table III. The overall differences at 12 and 24 months were statistically significant – approximately 9% better survival in the nitrosourea patients at 12 months ($P=0.002$) and 3.5% at 24 months ($P=0.046$).

There are some important limitations to these data – firstly, the problem of publication bias – positive results are more likely to be published than negative results – and we have used only published studies. However, the 4 largest – and carrying the most weight in the overview – were organised by the BTSG (2 studies, (Walker *et al.*, 1978; 1980), the Scandinavian Glioblastoma Study Group (SGSG, 1985), and one jointly by the RTOG and the ECOG (Chang *et al.*, 1983), and we have some reason to believe that these large cooperative groups publish their results regardless of

Table I Studies giving survival rates as a measure of treatment effect

Author	*Nitrosourea*	*Dose (mg m^{-2})*	*Number of patients*	
			Control	*Control+ nitrosourea*
Solero *et al.* (1979)	CCNU or BCNU	130 or 240	32	70
SGSG (1985)	CCNU	120	118	126
Walker *et al.* (1980)	BCNU or MeCCNU	240 or 220	94	183
Brisman *et al.* (1976)	CCNU or BCNU or MeCCNU	100 or 200 or 150	16	17
Walker *et al.* (1978)	BCNU	240	93	100
Chang *et al.* (1983)	BCNU	240	148	165
EORTC (1978)	CCNU	130	11	8
Garret *et al.* (1978)	CCNU	100	37	37

Table II Radiotherapy regimes

Author	*Radiotherapy*
Solero *et al.* (1979)	50 Gy/5 weeks
SGSG (1985)	40 Gy/5 weeks/10 fractions or 50 Gy/5 weeks/20 fractions
Walker *et al.* (1980)	60 Gy/6–7 weeks/20–35 fractions
Brisman *et al.* (1976)	30 Gy/3 weeks to brain +30 Gy/3 weeks to tumour
Walker *et al.* (1978)	50 Gy/5–6 weeks/25–30 fractions
Chang *et al.* (1983)	60 Gy/7 weeks/35 fractions
EORTC (1978)	55–60 Gy
Garret *et al.* (1978)	45 Gy/4 weeks

Table III Results at 12 and 24 months

Author	*12 month survival (%)*			*24 month survival (%)*		
	Control	*Control+ nitrosourea*	*Diff.*	*Control*	*Control+ nitrosourea*	*Diff.*
Solero (1979)	40	61	+21	17	17	0
SGSG (1985)	45	45	0	9	7	−2
Walker *et al.* (1980)	35	43	+8	10	14	+4
Brisman *et al.* (1976)	31	35	+4	25	5	−20
Walker *et al.* (1978)	24	32	+8	1	5	+4
Chang *et al.* (1983)	35	45	+10	15	21	+6
EORTC (1978)	6	49	+43	0	22	+22
Garret *et al.* (1978)	34	51	+17	16	42	+26
Overall difference			+8.8			+3.4
Standard error			2.8			1.7
Z (*P* value)		3.1 (0.002)			2.0 (0.046)	

outcome. Secondly, incomplete data meant we had to omit some trials, while several of those used gave survival information in graphical form, from which we had to read the survival rates. An assumption we had to make in calculating standard errors was that all patients had complete follow-up, which was inlikely to be uniformly true. Finally, we have no measure of the quality of life of these patients.

We would conclude that there is evidence, admittedly limited, that a course of nitrosourea only, given adjuvant to radiotherapy, does increase survival of high-grade glioma patients by a small amount. The challenge is to find a chemotherapy combination which will enhance this apparent improvement.

Yours, etc.,

S.P. Stenning, L.S. Freedman, N.M. Bleehen
MRC Cancer Trials Office and Clinical Oncology and Radiotherapeutics Unit,
MRC Centre, Hills Road, Cambridge, CB2 2QH, UK.

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