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Temozolomide in the treatment of recurrent malignant glioma in Chinese patients

替莫唑胺對惡性神經膠質瘤復發的華裔患者的治療情況

Objective. To determine the anti-tumour efficacy and safety profile of temozolomide in local Chinese patients with recurrent malignant glioma.
Design. Open-label trial.
Setting. University teaching hospital, Hong Kong.
Patients. Twenty-two patients had been enrolled in the study since 2001. Patients had to show unequivocal evidence of tumour recurrence or progression on gadolinium-enhanced magnetic resonance imaging after failing conventional radiotherapy and surgery for initial disease. Histology reviewed by a neuropathologist was required to show anaplastic glioma (anaplastic astrocytoma, anaplastic oligodendroglioma, or mixed anaplastic oligoastrocytoma) or glioblastoma multiforme.
Interventions. Patients were treated with temozolomide (200 mg/m^2 per day for the first 5 days of a 28-day cycle for four cycles) and monitored clinically every month and radiologically (gadolinium magnetic resonance imaging) at 6 months.
Main outcome measures. Six-month progression-free survival and objective response rate.
Results. Twenty-two patients with recurrent malignant glioma were recruited between January 2001 and July 2004. Progression-free survival at 6 months was 54.5%. The mean progression-free survival for all patients was 7.2 months. The objective response rate, determined by gadolinium magnetic resonance imaging, was 9% for patients demonstrating a complete or partial response and a further 45% for patients demonstrating stable disease. Temozolomide was well tolerated orally with minimal adverse events.
Conclusion. Preliminary results showed that temozolomide had an acceptable safety profile and anti-tumour activity in recurrent malignant glioma in local Chinese population. The results were comparable with those of western studies.

目的：確定替莫唑胺對惡性神經膠質瘤復發的本地華裔患者的抗腫瘤功效及安全使用狀況。
設計：開放試驗。
安排：大學教學醫院，香港。
患者：2001年起共22名患者參與研究。患者在接受傳統放射治療及針對初期疾病的外科手術證實無效後，由釓強化磁共振成像診斷為腫瘤復發或惡化，並由一位神經病理學家透過組織學診斷為退化神經膠質瘤（包括退化星細胞瘤、退化少突神經膠質細胞瘤或退化混合少突星細胞瘤）或多形成膠質細胞瘤。
療法：所有患者均接受4個週期的治療（每次週期為28天，首5天每天服用200 mg/m^{2}的替莫唑胺），並且每月前往覆診以監察進度；6個月後接受釓強化磁共振成像放射檢查。

Key words:
Astrocytoma;
Brain neoplasms;
Disease-free survival;
Glioblastoma;
Neoplasm recurrence

關鍵詞：
星細胞瘤；
腦癌；
無病存活；
成膠質細胞瘤；
癌復發

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主要結果測量：為期 6 個月的無惡化存活率及客觀反應率。
結果：2001 年 1 月至 2004 年 7 月期間，共 22 名惡性神經膠質瘤復發患者接受治療。6 個月後的無惡化存活率為 54.5%，而所有患者的無惡化存活期平均為7.2個月。對於腫瘤消失或腫瘤縮細超過一半的患者，由磁共振成像確定的客觀反應率為9%，而病況穩定的患者，客觀反應率為45%。患者對替莫唑胺口服劑耐受良好，只有輕微不良反應。
結論：初步結果顯示，以替莫唑胺治療本地華人惡性神經膠質瘤復發，是可接受的安全療法並有抗腫瘤功用，與西方研究結果接近。

Introduction

Malignant glioma is an incurable disease and the most malignant of primary brain tumours. The mainstay of treatment is surgical debulking and radiotherapy, although overall survival remains poor. The median survival is 9 months for glioblastoma multiforme (GBM) and 18 months for anaplastic glioma. Several chemotherapeutic agents, most notably the nitrosoureas, have been used with modest effect. Their use is nonetheless tempered by their side-effects. Opinions of physicians in Europe and the United States on the use of chemotherapy are divided.

Temozolomide is an alkylating agent that is orally active and has shown clinical efficacy in the treatment of recurrent malignant glioma. Oral dosing achieves excellent bioavailability and good penetration into the central nervous system. Phase I and phase II trials have shown that side-effects are well tolerated. The United States Food and Drug Administration approved temozolomide in 1999 for patients with anaplastic astrocytoma (AA).

This study commenced in Hong Kong in 2001 as a prospective, open-label, and compassionate-use study in patients with recurrent malignant glioma. The study objectives were to determine the 6-month progression-free survival (PFS), response rate, and safety profile of temozolomide in Chinese patients.

Methods

Patients with recurrent malignant glioma treated at the Prince of Wales Hospital, the Chinese University of Hong Kong were recruited into the study between January 2001 and July 2004.

Patient eligibility

Patients were eligible for study if they had unequivocal evidence of tumour recurrence or progression as shown by gadolinium (Gd)-enhanced magnetic resonance imaging (MRI) after failing conventional radiotherapy and surgery for initial disease. Inclusion criteria included supratentorial malignant glioma (histological types included AA, GBM, anaplastic oligodendroglioma, and mixed anaplastic glioma), a Karnofsky performance status of 70 or above, and aged below 70 years. Patients were also required to have adequate haematological, renal, and liver functions as shown in the Box. Patients prescribed steroid therapy for neurological stability were recruited only if the dose was stable or reducing. Patients who were pregnant, considered a poor medical risk, or with a life expectancy of less than 12 weeks were excluded (Box).

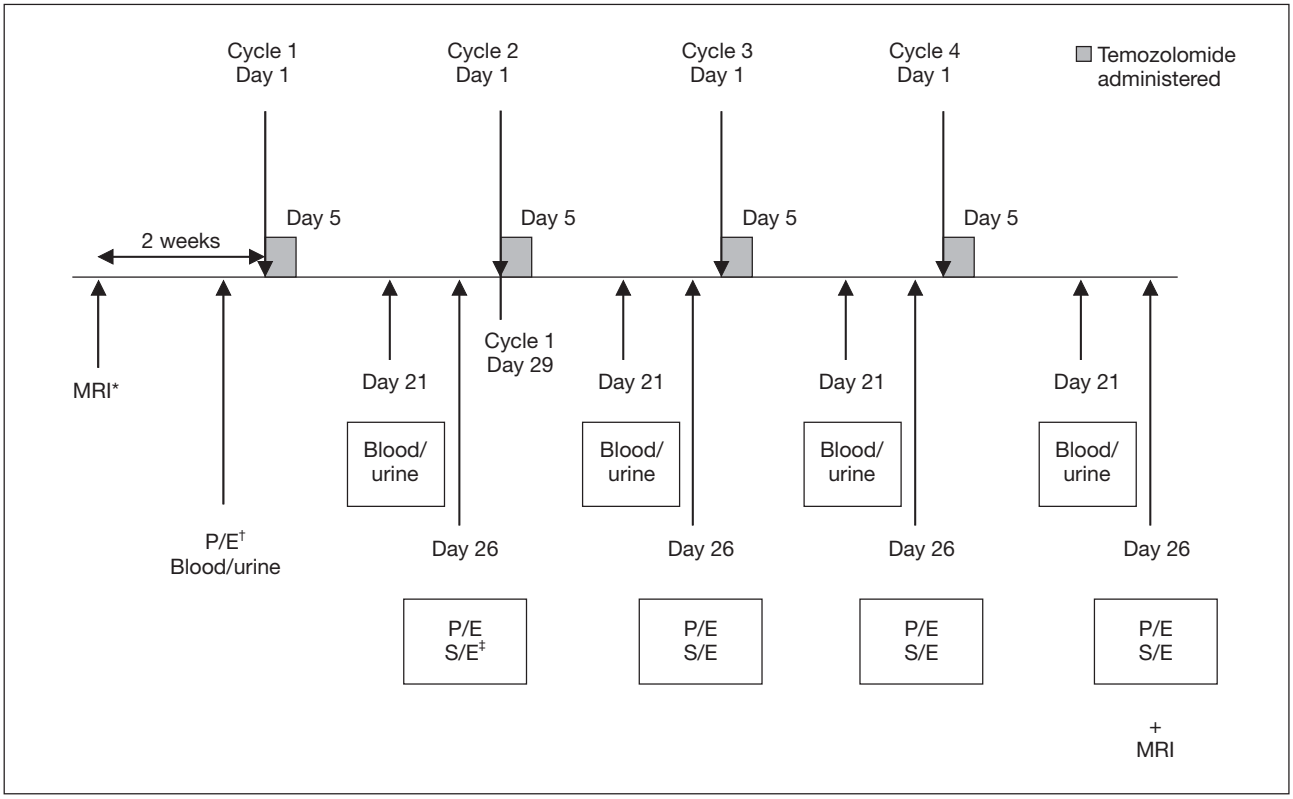
Inclusion and exclusion criteria

Inclusion criteria
- Histologically proven supratentorial malignant (high-grade) glioma reviewed by a neuropathologist
- Radiologically (gadolinium magnetic resonance imaging) proven disease progression or clinical progress (Karnofsky performance status/cognitive deterioration)
- Karnofsky performance score of ≥70
- Age <70 years
- Adequate haematological, renal, and liver functions:
  i. Absolute neutrophil count ≥1500 /mm^3
  ii. Platelet ≥100 000 /mm^3
  iii. Haemoglobin ≥90 g/L
  iv. Creatinine <1.5 times of upper limit
  v. Bilirubin <1.5 times of upper limit
  vi. Aspartate aminotransferase <2 times of upper limit
  vii. Alkaline phosphatase <2 times of upper limit

Exclusion criteria
- Increasing dose of steroid for at least 1 week prior to administration of temozolomide
- Neurological unstable and poor medical risk patients
- Life expectancy of <12 weeks
- Pregnant or breast-feeding women

Treatment regimen

Temozolomide was administered once per day for the first 5 consecutive days in a 28-day cycle. The drug was given orally at a dose of 200 mg/m^2 (body surface area) as a morning fasting dose. Anti-emetics were given during the 5 days. Toxicity was reviewed and a neurological clinical examination performed between days 21 and 26. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (CTC). The subsequent dose was reduced to a minimum of 100 mg/m^2 in the presence of haematological grade 3 or 4 toxicity and non-haematological grade 4 toxicity. No dose escalation was allowed. Patients completed four cycles of chemotherapy and were then subjected to image evaluation (Fig 1).



* MRI magnetic resonance imaging
† P/E physical examination and clinical assessment
‡ S/E side-effects

Fig 1. Temozolomide schedule

Evaluation of response

Response was assessed by neurological clinical examination and neuroimaging. Baseline neurological clinical examination and MRI were performed within 2 weeks of commencing therapy. Neurological clinical examination was performed between days 21 and 26 of every cycle. General condition, mental status, performance status, and neurological examination were reported at each visit. Any deterioration, excluding reversible causes (seizure, electrolyte disturbance, or infection), was considered clinical deterioration. Patients with clinical deterioration were treated as non-responders and chemotherapy stopped. Those who remained clinically stable underwent neuroimaging evaluation (Gd-enhanced MRI). A complete response (CR) was defined as disappearance of the enhanced tumour. Partial response (PR) referred to a more than 50% reduction in lesion size using bi-dimensional measurements (product of largest perpendicular diameters). Progressive disease referred to a 25% or more increase in lesion size. Stable disease included all other conditions (Table 1). Chemotherapy was discontinued for the following reasons: unacceptable toxicity, dose reduction falling below 100 mg/m^2 per day, patient refusal to continue the drug for any reason, evidence of disease progression (clinical or radiological progression), and non-compliance with evaluation protocol.

Table 1. Neuroimaging evaluation

Response	Evaluation
Complete response	Complete disappearance of enhanced tumour
Partial response	Reduction of >50% in lesion size using bi-dimensional measurements (product of largest perpendicular diameters)
Progressive disease	Increase in lesion size by ≥25% using bi-dimensional measurements
Stable disease	All other conditions

Results

From January 2001 to July 2004, 22 (10 male, 12 female) patients with recurrent malignant glioma were recruited. All had unequivocal radiological recurrence of the tumour. The mean age was 41.4 years (standard deviation, 14.1 years). There were nine

Table 2. Patient characteristics and results

Characteristic	Result, n=22
Sex (male:female)	10:12
Mean age (years) [SD, range]	41.4 (14.1, 16-64)
Total cycles of chemotherapy	114
Histology	
Glioblastoma multiforme	13
Anaplastic glioma	9
Anaplastic astrocytoma	3
Oligodendroglioma	3
Oligoastrocytoma	3
6-month progression-free survival (95% CI) [%]	54.5 (33.7-75.4)
Response rate (No. of patients)	
Objective responses (complete and partial responses)	2 (9%)
Progressive disease	10 (45%)
Stable disease	10 (45%)
Progression-free survival (SE*, 95% CI) [months]	7.2 (1.1, 4.9-9.4)
Overall survival (SE, 95% CI) [months]	15.0 (2.2, 10.6-19.4)
Haematological grade 1 or 2 toxicity (No. of cycles)	11 (9.6%)
Non-haematological grade 1 or 2 toxicity (No. of cycles)	9 (41%)

* SE standard error

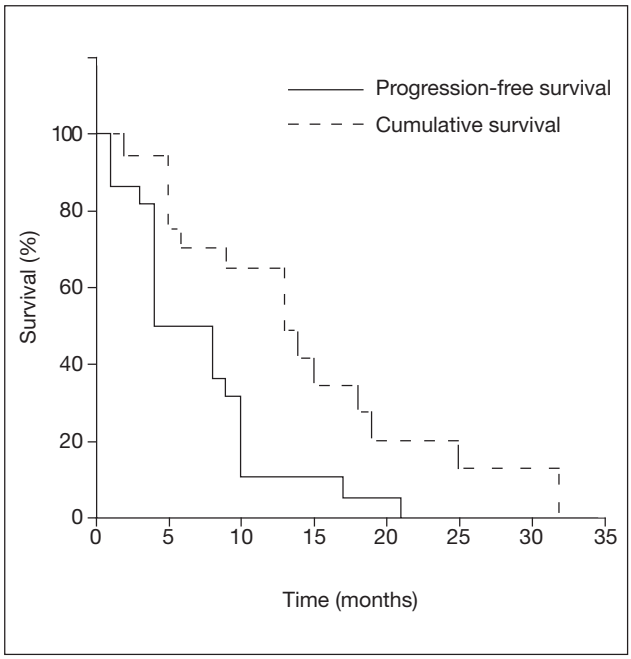


Fig 2. Kaplan-Meier estimate of 6-month progression-free survival and cumulative survival

Table 3. Tumour location and pre-chemotherapy status

Patient No.	Sex/age (years)	Location	Primary treatment	Debulking before chemotherapy	Pre-chemotherapy tumour volume (mm^3)
1	M/16	Right/temporal	Surgery/radiotherapy	Yes	37 331
2	M/38	Left/frontal	Surgery/radiotherapy	No	34 955
3	F/60	Right/frontal	Surgery/radiotherapy	Yes	12 370
4	M/18	Left/frontal	Surgery/radiotherapy	Yes	25 380
5	M/26	Left/temporal	Surgery/radiotherapy/immunotherapy	Yes	13 770
6	M/53	Right/frontal	Surgery/radiotherapy	No	22 862
7	M/49	Left/frontal	Surgery/radiotherapy	No	14 800
8	F/44	Right/frontal	Surgery/radiotherapy	No	550
9	F/50	Left/thalamus	Surgery/radiotherapy	No	27 370
10	F/61	Right/temporal	Surgery/radiotherapy	No	8060
11	F/56	Left/frontal	Surgery/radiotherapy	Yes	1450
12	M/39	Right/frontal	Surgery/radiotherapy	Yes	18 070
13	F/37	Left/frontal	Surgery/radiotherapy	Yes	3750
14	M/22	Right/frontal	Surgery/radiotherapy	No	5890
15	F/21	Left/thalamus	Surgery/radiotherapy	No	2250
16	F/32	Right/frontal	Surgery/radiotherapy	No	10 400
17	F/53	Left/temporal	Surgery/radiotherapy	Yes	57 600
18	M/46	Right/frontal	Surgery/radiotherapy	No	21 645
19	F/46	Right/frontal	Surgery/radiotherapy	No	63 960
20	M/48	Left/frontal	Surgery/radiotherapy	No	37 791
21	F/64	Left/temporal	Surgery/radiotherapy	Yes	80
22	F/49	Left/parietal	Surgery/radiotherapy	No	2541

anaplastic glioma of which three were anaplastic oligodendroglioma and three were anaplastic oligoastrocytoma, and 13 GBM (Table 2).

All patients had undergone surgery (excision or biopsy) and radiotherapy as primary treatment and none had received chemotherapy prior to the study. One patient received a course of immunotherapy (adoptive cellular immunotherapy) as adjuvant therapy after radiotherapy in another medical

centre. Recurrence occurred 10 months later and he was recruited to this study for chemotherapy.

Debulking surgery was performed for decompression of recurrent disease in nine patients prior to commencement of temozolomide. The pre-chemotherapy mean tumour volume was 19 222 mm^3 (Table 3).

The 6-month PFS was 54.5% (95% confidence interval [CI], 33.7-75.4%). The objective response rate was 9% (1 with CR and 1 with PR). A further 45% of patients achieved disease stability as their best response. The mean PFS was 7.2 months (standard error [SE], 1.1 months; 95% CI, 4.9-9.4 months). The mean cumulative survival from the time of recurrence was 15.0 months (SE, 2.2 months; 95% CI, 10.6-19.4 months) [Fig 2].

Twenty-two patients underwent 114 cycles of chemotherapy. Haematological grade 1 or 2 toxicity occurred in 11 (9.6%) cycles of five patients. No patient required dose reduction or had a life-threatening event. Non-haematological grade 1 or 2 toxicity, mostly nausea and vomiting that was effectively managed with anti-emetics, occurred in 41% (9/22) of patients.

Discussion

Malignant glioma is an incurable disease. The prognosis remains poor with few breakthroughs in management over the past few decades. Surgery serves two purposes: it provides tissue for histological proof, and removal of the tumour (in whole or in part) allows decompression. There is also increasing evidence that survival and quality of life improve with maximal surgical resection.[1,2] Radical surgery nonetheless does not offer a cure. During the search for a chemotherapeutic agent, radiotherapy was shown to confer definite but modest survival benefit in malignant glioma.[3,4] A quarter of a century later no further advances have been made, despite the intensive research and enthusiasm to develop effective chemotherapy. Recurrent malignant glioma presents an even worse dilemma for which there is no standard treatment.

Temozolomide is a prodrug and an alkylating agent. It is orally active with high bioavailability and readily crosses the blood brain barrier. It spontaneously hydrolyses to 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) which degrades to a highly reactive cation that methylates guanines in DNA at the O^6 position, causing base pair mismatch. Unsuccessful cycles of the mismatch repair eventually lead to breaks and permanent nicks in the daughter strand preventing mitotic division and the cell undergoes apoptosis. In a randomised, multicentre study of patients with glioblastoma, temozolomide produced a better 6-month PFS than procarbazine (21% vs 8%).[5]

Our study of Chinese patients showed that 6-month PFS and response rate were comparable with those of a Caucasian population. The 6-month PFS for GBM and AA were 21% and 46%, respectively.[6] The 6-month PFS showed a more favourable result in our patients (>50%). This could be due to the higher proportion of anaplastic glioma in the group (9/22; 41%).

Temozolomide was well tolerated by Chinese patients. There was a moderate emetogenic effect: up to 40% of patients had nausea and vomiting during the days of drug ingestion (days 1-5). In most cases it was considered mild to moderate (CTC grade 1-2) and was relieved by anti-emetics (ondansetron). The drug had predictable and reversible myelosuppression. Nadir platelet and neutrophil counts typically occur 21 to 26 days after beginning a cycle. Of the 114 cycles of chemotherapy, 11 (9.6%) cycles resulted in grade 1 or 2 haematological toxicity (mostly mild neutropenia). No grade 3 or 4 toxicity was recorded. None of the patients had complications related to the transient myelosuppression. Temozolomide has demonstrated a very safe drug profile in Chinese population.

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