# Feasibility and safety of extended adjuvant temozolomide beyond six cycles for patients with glioblastoma

**Sonia YP Hsieh, Danny TM Chan *, Michael KM Kam, Herbert HF Loong, WK Tsang, Darren MC Poon, Stephanie CP Ng, WS Poon**

A B S T R A C T

**Introduction:** Temozolomide is the first chemotherapeutic agent proven effective for patients with newly diagnosed glioblastoma. The drug is well tolerated for its low toxicity. The current standard practice is concomitant chemoradiotherapy for 6 weeks followed by 6 cycles of adjuvant temozolomide. Some Caucasian studies have suggested that patients might benefit from extended adjuvant cycles of temozolomide (>6 cycles) to lengthen both progression-free survival and overall survival. In the present study, we compared differences in survival and toxicity profile between patients who received conventional 6-cycle temozolomide and those who received more than 6 cycles of temozolomide.

**Methods:** Patients with newly diagnosed glioblastoma without progressive disease and completed concomitant chemoradiotherapy during a 4-year period were studied. Progression-free survival was compared using Kaplan-Meier survival curves. T-test, U-test, and correlation were chosen accordingly to examine the impact of age, extent of resection, MGMT promoter methylation status and adjuvant cycles on progression-free survival. For factors with a P value of <0.05 in univariate analyses, Cox regression hazard model was adopted to determine the strongest factors related to progression-free survival.

**Results:** The median progression-free survival was 17.0 months for patients who received 6 cycles of temozolomide (n=7) and 43.4 months for those who received more than 6 cycles (n=7) [P=0.007, log-rank test]. Two patients in the former group and one in the latter group encountered grade 1 toxicity and recovered following dose adjustment. Cycles of adjuvant temozolomide were correlated with progression-free survival (P=0.016, hazard ratio=0.68).

**Conclusion:** Extended cycles of temozolomide are safe and feasible for Chinese patients with disease responsive to temozolomide.

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**SYP Hsieh,** MB, BS, MSc
**DTM Chan *,** FRCS, FHKAM (Surgery)
**MKM Kam,** FRCR, FHKAM (Radiology)
**HHF Loong,** MB,BS, MRCP (UK)
**WK Tsang,** FRCR, FHKAM (Radiology)
**DMC Poon,** FRCR, FHKAM (Radiology)
**SCP Ng,** PhD
**WS Poon,** FRCS, FHKAM (Surgery)

*CUHK Otto Wong Brain Tumour Centre, The Sir Yue-kong Pao Centre for Cancer, Prince of Wales Hospital, Shatin, Hong Kong*

* Corresponding author: tmdanny@surgery.cuhk.edu.hk

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**New knowledge added by this study**

- Extended adjuvant temozolomide beyond 6 cycles is safe and feasible. The approach has improved progression-free survival.

**Implications for clinical practice or policy**

- For glioblastoma patients with disease that is responsive to temozolomide, extended adjuvant cycles can be suggested.

## Introduction

Glioblastoma multiforme (GBM) has been a conundrum for all clinicians. The standard approach includes maximal safe resection, irradiation with concurrent temozolomide (TMZ), and 6 cycles of adjuvant TMZ.[1] Addition of chemotherapy to radiotherapy can prolong survival among GBM patients, with a median increase in survival of 2.5 months.[1] Since then, no further breakthrough treatment has emerged.

Of note, there is still insufficient evidence to support 6 cycles as the optimal adjuvant amount of TMZ for GBM. Only few studies have suggested that extended use of TMZ is safe and beneficial for prolonged survival.[2] The main concern of extended use of TMZ is haematological toxicity. It is attributed to the depletion of $O^6$-methylguanine-DNA methyltransferase (MGMT) protein activity in both GBM cells and haematopoietic stem cells.[3] Nonetheless, compared with other alkylating agents,

  

## 延長替莫唑胺輔助化療至超過6個週期以治療膠質母細胞瘤的可行性和安全性

謝宜蘋、陳達明、甘冠明、龍浩鋒、曾偉光、潘明駿、吳志萍、潘偉生

**引言：**替莫唑胺（TMZ）是首個被證實對膠質母細胞瘤（GBM）新診斷患者有效的化療藥物。由於毒性低，TMZ治療的耐受性有良好表現。現行的治療方法是同步進行放射治療及化學治療6個星期，緊接着6個週期的TMZ輔助化療。根據一些針對白種人的研究，延長TMZ輔助化療（即超過6個週期）可能可以改善GBM患者的疾病無惡化存活期和總存活期。本研究把接受常規6週期和超過6個週期TMZ輔助化療的兩組患者，比較他們的存活期和毒性差異。

**方法：**研究對象為4年期間新診斷GBM和沒有惡化跡象，並已完成放化療的患者。使用Kaplan-Meier存活曲線比較疾病無惡化存活期。使用T檢驗、U檢驗和相關性試驗檢測年齡、腫瘤切除範圍和MGMT啟動子甲基化狀態和佐劑週期對疾病無惡化存活期的影響。把單變量分析中P值<0.05的因素，採用Cox迴歸危險模型來找出與疾病無惡化存活期最相關的因素。

**結果：**接受常規6週期和超過6個週期TMZ輔助化療的兩組患者各有7例，其疾病無惡化存活期分別為17.0個月和43.4個月（P=0.007，log-rank檢驗）；一級毒性反應亦分別有2例和1例，受影響的患者在調整劑量後均回復正常。TMZ輔助化療與疾病無惡化存活期相關（P=0.016，風險比=0.68）。

**結論：**延長輔助化療週期對於對TMZ有反應的華藉患者是安全和可行的。


the low toxicity profile of TMZ has motivated clinicians to try its extended use after balancing the benefits and side-effects for each patient.[4]

Our institution offers the option for GBM patients with at least stable disease to step up to adjuvant cycles of TMZ. In this study, we report the experience of extended use of TMZ and its impact on newly diagnosed GBM patients.

# Methods

## Study design

We retrospectively reviewed the brain tumour registry of the Chinese University of Hong Kong Otto Wong Brain Tumour Centre, and identified patients with primary GBM during January 2010 to December 2013. Those patients who received surgical intervention and standard concomitant chemoradiotherapy after surgery (60-Gy irradiation with concomitant TMZ for 6 weeks, then followed by at least 6 cycles of adjuvant TMZ) were chosen as candidates for the study.

## Surgical intervention

An experienced neuroradiologist was responsible for determining the extent of resection (EOR) by reading the postoperative day-1 magnetic resonance imaging (MRI) scans. A total resection indicated that the entire preoperative contrast-enhanced lesion seen on T1-weighted images was excised. If there was residual enhancement on T1-weighted images as well as T1-subtraction sequence, the case would be labelled as subtotal resection.

## Irradiation and temozolomide protocol

As a standard practice, a postoperative irradiation of 60 Gy was given to all patients within 4 weeks of surgery. Temozolomide was prescribed concurrently during radiotherapy at 75 mg/d/m$^2$ for 6 weeks, followed by 6 or more cycles of adjuvant TMZ at a dosage of 150-200 mg/d/m$^2$ for 5 consecutive days every 28 days. After completion of standard 6-cycle TMZ, all patients with at least stable disease were offered the chance of extended TMZ, regardless of individual prognostic factors. Whether or not they proceeded to extended TMZ was a decision made principally by patients and their relatives and also with neurosurgeons and clinical oncologists, on the basis of a detailed assessment of the patient's clinical performance (neurological status and toxicity profile) and tumour response to TMZ. Anti-emetics were given during the 5 days. To achieve early detection of TMZ toxicity, haematological profile including complete blood picture with differential count, and liver and renal functions were assessed monthly on about day 21 to day 25. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.[5]

## Follow-up schedule

All patients were followed up regularly with both clinical and radiological assessments of disease status. They were seen by a neuro-oncologist every 2 weeks after surgery, daily during irradiation, and monthly when being given adjuvant TMZ. For radiological assessment, patients were subjected to a scanning protocol with contrast-enhanced MRI of the brain at postoperative day 1, 2 weeks after completion of radiation, and every 3 months thereafter. These standardised protocols ensured that disease progression of all patients could be monitored in a timely manner. Disease progression was determined according to Macdonald's criteria. In short, deteriorating neurological status, increasing tumour size, and appearance of new enhancement were suggestive of disease progression.[6]

## Statistical analysis

Progression-free survival (PFS) was calculated from the date of surgical intervention to the date of progression. As the aim of this study was to compare the therapeutic effect of standard 6-cycle TMZ with that of more than 6 cycles of TMZ, only

 

patients with neither neurological deterioration nor radiological signs suggesting progression for more than 28 days upon completion of the sixth cycle of adjuvant TMZ were eligible. The MGMT promoter status and EOR were regarded as categorical factors while age and cycles of adjuvant TMZ were assigned as the continuous variables for which correlation was chosen as the tool for analysis. T-test, U-test, and correlation were chosen accordingly to examine the impact on PFS of each factor. For those factors with a P value of <0.05 in univariate analyses, a Cox regression hazard model was adopted to determine those strongly related to PFS. All statistical analyses were done using the SPSS (Windows version 22.0; IBM Corp, Armonk [NY], US).

This audit review was conducted in accordance with the principles outlined in the Declaration of Helsinki.

TABLE 1. Demographics and basic characteristics of patients

| Demographics / characteristic | Temozolomide | |
|---|---|---|
| | 6 Cycles (n=7) | >6 Cycles (n=7) |
| Mean (range) age (years) | 50 (25-67) | 53 (34-71) |
| Sex (M:F) | 5:2 | 5:2 |
| EOR | | |
| Total resection | 5 (71.4%) | 2 (28.6%) |
| Debulking | 2 (28.6%) | 5 (71.4%) |
| MGMT promoter status | | |
| Methylated | 6 (85.7%) | 6 (85.7%) |
| Unmethylated | 1 (14.3%) | 1 (14.3%) |
| Median (range) No. of cycles | 6 | 13 (8-26) |

Abbreviations: EOR = extent of resection; MGMT = $O^6$-methylguanine-DNA methyltransferase

# Results

## Basic demographics

From January 2010 to December 2013, there were 14 patients who fulfilled the inclusion criteria. Their mean age at presentation was 52 (range, 25-71) years with a male preponderance: 10 male versus 4 female patients. Total resection was achieved in seven patients. For the remaining seven, six underwent subtotal resection and one could only have tumour biopsy. The MGMT promoter status was available in all cases and was methylated in 12 cases and unmethylated in the remaining two. After completion of standard concomitant chemoradiotherapy in all cases, extended adjuvant TMZ was initiated in seven cases (Table 1).

In total, 134 cycles of adjuvant TMZ were given, with 92 cycles given to the seven patients who proceeded to extended maintenance TMZ treatment. The median number of cycles given was 13 (range, 8-26) in the latter group. With regard to TMZ-related toxicity, two patients in the 6-cycle group had grade 1 haematological toxicity (thrombocytopaenia and neutropaenia) and one patient in the >6-cycle group developed mildly deranged alanine aminotransferase (ALT; grade 1, defined as "more than upper limit of normal and less than three times the upper limit of normal by CTCAE"[5]) during the fifth cycle of adjuvant TMZ that subsequently subsided.

## Survival and associated prognostic factor

Progression-free survival differed significantly between the two groups: 17.0 (95% confidence interval [CI], 14.4-19.6) months for 6-cycle versus 43.4 (95% CI, 17.8-69.0) months for the >6-cycle group (P=0.007, log-rank test; Fig).

Progression-free survival at 12 months was 85.7% for both groups, and that at 18 months declined to only 28.6% for the 6-cycle group compared with

TABLE 2. Progression-free survival and overall survival in the two groups of patients

| Survival | 6 Cycles | >6 Cycles |
|---|---|---|
| PFS (95% CI) [months] | 17.0 (14.4-19.6) | 43.4 (17.8-69.0) |
| PFS | | |
| At 12 months | 85.7% | 85.7% |
| At 18 months | 28.6% | 71.4% |
| OS (95% CI) [months] | 30.9 (22.4-39.4) | 48.4 (24.3-72.4) |

Abbreviations: CI = confidence interval; OS = overall survival; PFS = progression-free survival

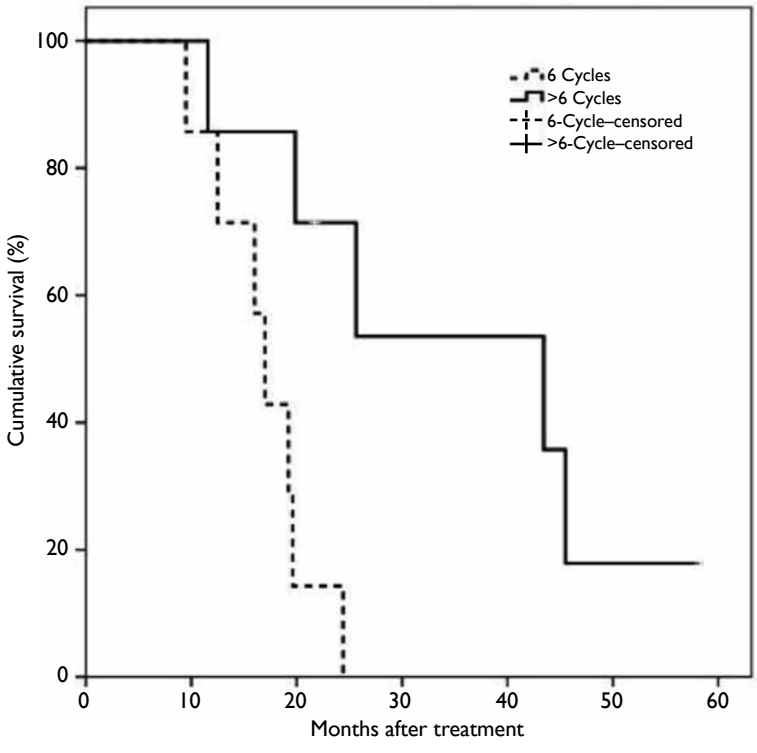


FIG. Kaplan-Meier progression-free survival curves of patients with different treatments

  

71.4% for the >6-cycle group (Table 2; Fig).

Three out of seven patients in the >6-cycle group were still alive at their last follow-up. Their median overall survival was 48.4 (95% CI, 24.3-72.4) months. In the 6-cycle group, the median overall survival was 30.9 (95% CI, 22.4-39.4) months. No statistical significance was observed by the end of the study (P=0.07, log-rank).

All factors including age, gender, and MGMT status were well balanced, except for the EOR. Despite the higher proportion of patients with subtotal resection who elected to receive extended TMZ, EOR was not predictive of longer PFS (P=0.482, Mann-Whitney *U* test). When subgrouping the cohort with MGMT promoter status, there was no evidence to suggest that methylated MGMT promoter status favoured patients with better PFS (P=0.882, Mann-Whitney *U* test). Age was also not correlated with PFS (P=0.09, Pearson correlation). Cox-regression hazard model suggested that increased cycles of TMZ were associated with prolonged PFS (P=0.016; hazard ratio=0.68 per cycle; 95% CI, 0.48-0.94) [Table 3].

## Discussion

Despite recent advances in its therapy, GBM is still an incurable disease, characterised by rapid and inevitable recurrence even with intensive treatment. Ample clinical research has been carried out with the intention of defeating the disease, but the prognosis of GBM remains dismal. Temozolomide is the first chemotherapeutic agent proven to be effective. The standard treatment after maximum safe resection has two components, irradiation with concomitant TMZ and adjuvant TMZ at a higher dosage for 6 cycles. Under this regimen, survival is favourably improved.[1] Since then, no other encouraging milestones have been achieved.

### Comparison of progression-free survival and toxicity with other studies

Our audit review showed a significant correlation between the number of cycles of TMZ and PFS. One patient in the >6-cycle group showed a continuous yet prominent shrinkage of the non-operable GBM (bilateral corpus callosum) after initiation of the seventh cycle of TMZ and finally achieved complete response after 12 cycles. The patient had only mildly deranged ALT during the fifth cycle of adjuvant TMZ and this subsided on its own.

Temozolomide was well-tolerated by most patients. One of our previous studies also demonstrated its satisfying anti-tumoural activity as well as its safety profile among ethnic Chinese population.[7] Extended usage of TMZ upon completion of standard 6-cycle adjuvant courses has become common practice in many institutions.[4,8,9]

A literature search revealed only a few reports with similar settings and conclusions. Three non-randomised retrospective studies with decent sample sizes demonstrated an indispensable impact of extended adjuvant TMZ. The reported PFS ranged from 13 to 24.6 months; the overall survival was also improved.[2,8,10] One very recent pooled analysis of four randomised clinical trials, however, showed a slightly different result—PFS was the only outcome that increased with the cumulative prescription of TMZ.[11] Blumenthal et al[11] reported that treatment with extended maintenance TMZ was significantly associated with better PFS with a hazard ratio of 0.77 (6 cycles vs >6 cycles). To conclude, the positive impact of long-term use of TMZ on PFS is supported by much evidence. Its influence on overall survival, however, needs further clarification.

TABLE 3. Univariate analyses for progression-free survival

| Variable | P value |
|---|---|
| Age | 0.09 |
| EOR | 0.482 |
| MGMT promoter status | 0.882 |
| Increased cycles of TMZ | 0.016 |

Abbreviations: EOR = extent of resection; MGMT = $O^6$-methylguanine-DNA methyltransferase; TMZ = temozolomide

### Toxicity after long-term usage of temozolomide

By sacrificing its only alkyl component to the TMZ-induced lethal depletion of alkyl products on tumoural DNA, MGMT serves as a suicidal DNA repair enzyme. Theoretically, this irreversible depletion of the MGMT protein could be exploited by increasing tumoural exposure to TMZ. The effect might be even more prominent when MGMT promoter is hypermethylated, although the impact of MGMT promoter methylation could not be demonstrated in the present study. Nonetheless this mechanism also accounts for myelosuppression, the main concern of long-term use of TMZ, since MGMT protein in normal cells can also be depleted by TMZ. It is more common in haematopoietic stem cells contributing to toxicity for patients using this alkylating agent.[3] In a cohort that comprised 114 patients, 39 (34%) were observed to have CTCAE grade 3 haematological toxicity during administration of TMZ. The study included all patients who received 1 to 57 cycles of TMZ.[8] The French SV3 Study also evaluated the effect of prolonged TMZ and suggested that 39.6% of cases developed haematological toxicity beyond the second cycle.[10] Toxicity to a certain degree discourages both clinicians and patients from increasing the dosage

 

of TMZ during adjuvant therapy, and for extending use of TMZ beyond 6 cycles. In the current study, only 21.4% (3/14) of our patients encountered mild side-effects. Neuro-oncologists, however, remain reluctant to persuade patients to receive long-term TMZ. It is generally accepted by clinicians that long-term use of alkylating agents is unwise since they are likely to be the eventual cause of myelosuppression and secondary cancers.

### Clinical and financial situation in Hong Kong

In our institute, all patients with at least stable disease for more than 28 days after completion of the sixth cycle of adjuvant TMZ will be offered the option of continuing TMZ beyond 6 cycles, after being given detailed information about possible future side-effects. Of note, TMZ is funded in Hong Kong only for the first six adjuvant cycles; patients need to pay thereafter, making the inherent socio-economic bias unavoidable.

This study had several limitations. The sample size was relatively small. The analyses presented may provide only limited and preliminary evidence. Moreover, due to the nature of this study, only patients with disease responsive to TMZ yet with no or mild TMZ-related toxicity were qualified for the study.

## Conclusion

Extended treatment with TMZ is safe and effective in Chinese patients with disease that is responsive to it. Careful assessment and consideration of continuing adjuvant TMZ is feasible for this group of patients.

## Declaration

All authors have disclosed no conflicts of interest.

**References**


1. Stupp R, Mason WP, Van Den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
2. Barbagallo GM, Paratore S, Caltabiano R, et al. Long-term therapy with temozolomide is a feasible option for newly diagnosed glioblastoma: a single-institution experience with as many as 101 temozolomide cycles. Neurosurg Focus 2014;37:E4.
3. Wick W, Platten M, Weller M. New (alternative) temozolomide regimens for the treatment of glioma. Neuro Oncol 2009;11:69-79.
4. Mason WP, Maestro RD, Eisenstat D, et al. Canadian recommendations for the treatment of glioblastoma multiforme. Curr Oncol 2007;14:110-7.
5. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed 31 Mar 2016.
6. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990;8:1277-80.
7. Chan DT, Poon WS, Chan YL, Ng HK. Temozolomide in the treatment of recurrent malignant glioma in Chinese patients. Hong Kong Med J 2005;11:452-6.
8. Seiz M, Krafft U, Freyschlag CF, et al. Long-term adjuvant administration of temozolomide in patients with glioblastoma multiforme: experience of a single institution. J Cancer Res Clin Oncol 2010;136:1691-5.
9. Hau P, Koch D, Hundsberger T, et al. Safety and feasibility of long-term temozolomide treatment in patients with high-grade glioma. Neurology 2007;68:688-90.
10. Rivoirard R, Falk AT, Chargari C, et al. Long-term results of a survey of prolonged adjuvant treatment with temozolomide in patients with glioblastoma (SV3 Study). Clin Oncol (R Coll Radiol) 2015;27:486-7.
11. Blumenthal DT, Stupp R, Zhang P, et al. ATCT-08. The impact of extended adjuvant temozolomide in newly-diagnosed glioblastoma: A secondary analysis of EORTC and NRG Oncology/RTOG. Neuro Oncol 2015;17(Suppl 5):v2.


  