Original Article

# Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of High-Grade Glioma

The Singapore Cancer Network (SCAN) Neuro-Oncology Workgroup

## Abstract

**Introduction: The SCAN Neuro-Oncology workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for systemic therapy for high-grade glioma in Singapore. Materials and Methods: The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. Results: Six international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2013), the European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma (2014), the European Society of Medical Oncology (2014), the Canadian GBM Recommendations Committee (2007) and the Australian Cancer Network (2009). Recommendations on the systemic therapy of high-grade glioma were produced. Conclusion: These adapted guidelines form the SCAN Guidelines 2015 for systemic therapy of high-grade glioma.**

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**Key words: Anaplastic glioma, Chemotherapy, Glioblastoma**

## Introduction

Malignant gliomas are the most common primary malignant brain tumours, with an annual incidence of about 5 per 100,000.[1] It is associated with a dismal prognosis, poor quality of life and cognitive dysfunction.

Surgical resection and radiation therapy (RT) have been the mainstays of treatment. There is increasing evidence to support the addition of systemic therapies.[2,3] In fact, for patients with glioblastoma, chemoradiation with temozolomide has become standard of care, and has raised average life expectancy from 12 to 14 months. Bevacizumab, an anti-angiogenic agent, is an emerging treatment alternative in the recurrent glioblastoma.[4]

Recently, attention is being drawn to molecular markers that may predict responsiveness to systemic therapies. Specifically, chromosomes 1p19q co-deletion in oligodendroglial tumours has been shown to be associated with improved outcome after treatment with procarbazine, lomustine and vincristine (PCV) and RT.[5]

Despite improvement in multi-modality treatment, malignant gliomas eventually recur or progress. These guidelines summarise current evidence in systemic therapy of high-grade glioma.

## The SCAN Guidelines for the Systemic Therapy of High-Grade Glioma

The SCAN Guidelines are clinical practice guidelines for the systemic treatment of high-grade glioma. It includes adults with anaplastic astrocytomas, anaplastic oligodendroglioma and anaplastic mixed oligoastrocytoma (World Health Organization (WHO) grade III), and glioblastoma (WHO grade IV).

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of high-grade glioma. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

## Target Users of the Guidelines

The guidelines will be of interest to oncologists, neurologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients with high-grade glioma.

Address for Correspondence: Dr Tham Chee Kian, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
Email: Tham.C.K@nccs.com.sg

## Guideline Recommendations/Development

The SCAN neuro-oncology workgroup comprises a panel of 3 medical oncologists and 1 neurologist from Singapore with special interests in the management of brain tumours. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework[6] was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 3 main management issues which were selected for this topic (Table 1):

1. Front-line Systemic Therapy for Anaplastic Glioma
2. Front-line Systemic Therapy for Glioblastoma
3. Systemic Therapy for Recurrent High-Grade Glioma

Five international guidelines were selected for review (Supplementary Table 1):

- "NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Central Nervous System Cancers" (version 2.2013) by the National Cancer Comprehensive Network (NCCN, USA)[7]
- "EANO Guideline for the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastoma" by the European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma – 2014[8]
- "High-Grade Malignant Glioma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up" by the European Society of Medical Oncology (ESMO) – 2014[9]
- "Canadian Recommendation for the Treatment of Glioblastoma Multiforme" by the Canadian GBM Recommendations Committee – 2007[10]
- "Clinical Practice Guidelines for the Management of Adult Gliomas: Astrocytomas and Oligodendrogliomas" by the Australian Cancer Network – 2009[11]

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of high-grade glioma, it will be reviewed earlier.

## 1. Front-line Systemic Therapy for Anaplastic Glioma

There is emerging evidence to support use of systemic therapy in treatment of newly diagnosed anaplastic glioma. Specifically, fractionated external beam RT with adjuvant or neoadjuvant chemotherapy is now a standard of care for patients with 1p19q co-deleted anaplastic oligodendroglioma and oligoastrocytoma.

### *Procarbazine, Lomustine and Vincristine (PCV)*

The largest trial conducted in patients with malignant glioma showed that adjuvant PCV given at 6-week intervals derived no benefit over RT alone.[12] A subsequent meta-analysis of 12 randomised controlled trials of 3004 patients demonstrated a significant increase in survival with use of chemotherapy (HR = 0.85; 95% CI, 0.78 to 0.91; $P$ <0.0001), with an absolute increase in 1-year survival of 6% from 40% to 46%.[13] This finding was consistent with previous meta-analysis, which showed an increase in 1-year and 2-year survival for patients treated with adjuvant chemotherapy compared to RT alone.[14]

RTOG 9402, a phase III trial of adjuvant PCV in anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma patients with Karnofsky performance score (KPS) ≥60, initially failed to demonstrate improved overall survival (OS) in patients receiving adjuvant PCV (PCV followed by RT) compared to RT alone at 3 years.[15] In addition, 65% of patients in treatment arm experienced grade III or IV toxicity and 1 patient died. Subsequently, a long-term follow-up (median follow-up 11.3 years) reported there remained no difference in median survival by treatment for the entire patient cohort (4.6 years for PCV plus RT

Table 1. Singapore Cancer Network (SCAN) Guidelines for the Systemic Therapy of High-Grade Glioma

| | Guideline Recommendations |
|---|---|
| Recommendations for Front-line Systemic Therapy for Anaplastic Glioma | NCCN Guidelines:<br>- 1p/19q deletion should be tested on all anaplastic oligodendroglioma or oligoastrocytoma.<br>- For patients with good PS, and anaplastic astrocytoma, anaplastic oligodendroglioma or oligoastrocytoma without 1p19q co-deletion, fractionated external beam radiation therapy (EBRT) remains the standard after surgical intervention. Temozolomide or PCV with deferred RT is a reasonable choice. Fractionated RT concurrent with temozolomide is another reasonable option but has not been shown to be beneficial in a small local retrospective study.<br>- For patients with good PS, and anaplastic oligoastrocytoma or anaplastic oligodendroglioma harbouring 1p19q co-deletion, we recommend RT with adjuvant PCV after surgical intervention. Fractionated RT concurrent with temozolomide is a reasonable option after discussion with patients regarding current limited phase III clinical data.<br>- For patients with poor PS, hypofractionated RT, temozolomide or best supportive care alone is reasonable. |
| Recommendations for Front-line Systemic Therapy for Glioblastoma | NCCN Guidelines:<br>- Fractionated RT concurrent with temozolomide followed by adjuvant temozolomide is the standard of care for glioblastoma patients age ≤70 years with good PS, defined by WHO PS ≤2 (Category I). Dose-dense therapy is not recommended.<br>- For glioblastoma patients age >70 years with good PS, options of treatment include hypofractionated RT, temozolomide with deferred RT or RT with concurrent temozolomide followed by adjuvant temozolomide. We suggest checking MGMT promoter methylation status in this group, and recommend temozolomide therapy if positive.<br>- The routine addition of bevacizumab as upfront therapy is not recommended.<br>- The role of nimotuzumab as front-line therapy was debated. One of the workgroup members felt that the randomised phase II Cuban trial provided sufficient evidence to recommend nimotuzumab, in addition to RT, as front-line therapy in rare situations where myelosuppression of temozolomide cannot be tolerated. The rest of the workgroup members argued that the trial was conducted with small patient numbers with results not reproduced in other trials, had also not been supported by other national guidelines committees and that given its additional cost and lack of confirmatory trial data, nimotuzumab cannot be recommended as standard front-line therapy.<br>- Given the lack of data on front-line therapy in patients with poor PS, combination therapy with PCV, temozolomide monotherapy, RT alone or best supportive care is reasonable. |
| Recommendations for Systemic Therapy for Recurrent Malignant Gliomas | NCCN and ESMO Guidelines:<br>- For patients with good PS, reasonable chemotherapy options include temozolomide, lomustine, combination PCV, cyclophosphamide, platinum-based agents and irinotecan.<br>- Bevacizumab, as monotherapy or in combination with other chemotherapy, may also be considered in recurrent glioblastoma.<br>- For patients with poor PS, best supportive care is reasonable. |

ESMO: European Society for Medical Oncology; MGMT: 0-6-methylguanine-DNA methyltransferase; NCCN: National Cancer Comprehensive Network; PCV: Procarbazine, lomustine and vincristine; PS: Performance status; RT: Radiation therapy; WHO: World Health Organization

vs 4.7 years for RT; HR = 0.79; 95% CI, 0.60 to 1.04; $P$ = 0.1).[16] Patients with 1p19q co-deleted tumours, however, survived longer than those with non-co-deleted tumours (PCV plus RT: 14.7 vs 2.6 years, HR = 0.36; 95% CI, 0.23 to 0.57; $P$ = 0.001; RT: 7.3 vs 2.7 years, HR = 0.40; 95% CI, 0.27 to 0.60; $P$ = 0.01). Also, the median survival of those with co-deleted tumours treated with adjuvant PCV was twice that of patients receiving RT (14.7 vs 7.3 years; HR = 0.59; 95% CI, 0.37 to 0.95; $P$ = 0.03). For those with non-co-deleted tumours, there was no difference in median survival by treatment arm (2.6 vs 2.7 years; HR = 0.85; 95% CI, 0.58 to 1.23; $P$ = 0.39).

In the same period, the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor Group conducted a prospective phase III study of adjuvant PCV (RT followed by PCV) in age ≤70 years and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, and demonstrated significant improved 5-year progression free survival (PFS) (1.9 vs 1.1 years) but not OS when compared to RT alone.[16] With 12 years follow-up, median OS was significantly prolonged in the adjuvant PCV arm when compared to RT arm (42.3 vs 30.6 months).[5] Similar to findings from RTOG 9402, subgroup analysis of a cohort of 76 patients with 1p19q co-deletion from

EORTC 26951 trial, showed that treatment with adjuvant PCV resulted in significantly improved median OS compared to RT alone (not reached vs 112 months).[5] In contrast, the patients without co-deletion showed no difference in survival. It is worth noting that 38% of patients in the chemoradiation arm discontinued adjuvant PCV due to toxicity.[17]

*Temozolomide*

Temozolomide is an alkylating agent. Newly diagnosed anaplastic oligodendroglioma has shown response to temozolomide monotherapy.[18,19] In addition, benefits of combined chemoradiation with temozolomide in grade III glioma have been extrapolated from phase III trials conducted in glioblastoma patients.[2,3] A local retrospective study of 62 patients however failed to show significant difference between patients who received chemoradiation with temozolomide and RT only (PFS: 14.8 vs 16.7 months; OS: 34.1 vs 27.4 months).[20] Results from 2 ongoing phase III trials, CODEL (ClinicalTrials.gove NCT00887146) and CATNON (NCT00626990) will answer the question of whether chemoradiation with temozolomide is beneficial in patients with newly diagnosed 1p19q-co-deleted and non-1p19q deleted anaplastic gliomas respectively.

*Sequence of Chemoradiation*

NOA-04 phase III trial randomised 318 patients with anaplastic glioma to receive RT (arm A), PCV (arm B1) or temozolomide (arm B2) at diagnosis.[21] At unacceptable toxicity or disease progression, arm A was randomised to receive PCV or temozolomide, whereas arm B1 or B2 received RT. The study examined a total of 274 patients with anaplastic glioma (144 anaplastic astrocytoma, 91 anaplastic oligoastrocytoma, 39 anaplastic oligodendroglioma) using a modified intention-to-treat analysis, and demonstrated no significant difference in time-to-treatment failure (TTF), PFS and OS among the 3 treatment arms. Hence, PCV or temozolomide can be an upfront treatment option to defer RT treatment in a selected group of patients with anaplastic glioma.

*Cost-effectiveness*

To the best of our knowledge, there are no cost-effectiveness analyses available for systemic therapy in anaplastic glioma.

**Recommendations for Front-line Systemic Therapy for Anaplastic Glioma**

All members of the workgroup supported the adoption of NCCN guidelines. 1p/19q deletion should be tested on all anaplastic oligodendroglioma or oligoastrocytoma.

For patients with good PS, and anaplastic astrocytoma, anaplastic oligodendroglioma or oligoastrocytoma without 1p19q co-deletion, fractionated external beam radiation therapy (EBRT) remains the standard after surgical intervention. Temozolomide or PCV with deferred RT is a reasonable choice. Fractionated RT concurrent with temozolomide is another reasonable option but has not been shown to be beneficial in a small local retrospective study.

For patients with good PS, and anaplastic oligoastrocytoma or anaplastic oligodendroglioma harbouring 1p19q co-deletion, we recommend RT with adjuvant PCV after surgical intervention. Fractionated RT concurrent with temozolomide is a reasonable option after discussion with patients regarding current limited phase III clinical data.

For patients with poor PS, hypofractionated RT, temozolomide or best supportive care alone is reasonable.

**2. Front-line Systemic Therapy for Glioblastoma**

Combined chemoradiation is currently standard of care for glioblastoma patients age ≤70 years with good PS.

*Temozolomide*

Benefits of combined chemoradiation with temozolomide were demonstrated in a large phase III, randomised trial. Stupp et al assessed temozolomide in 573 glioblastoma patients age ≤70 years with a WHO PS ≤2, and showed that RT with concurrent and adjuvant temozolomide improved median (14.6 vs 12.1 months), 2-year (26.5% vs 10.4%) and 5-year (10% vs 2%) survivals when compared with RT alone.[2,3] Significant improvement in survival outcome did not adversely affect health-related quality of life (HRQOL).[22]

Temozolomide is administered at 75 mg/m$^2$ daily concurrent with RT, followed by 150 to 200 mg/m$^2$ for 5 days every 28 days for 6 cycles post-RT.[2,3] Alternate dose-dense regime showed no improvement in survival outcomes.[23]

A local cohort study of 50 adult patients with glioblastoma treated with adjuvant temozolomide demonstrated similar median (13.6 months) and 2-year (24.4%) survival rates as the large European Multicentre Study.[24] It supports the use of temozolomide in our local population. Of note, there were no grade IV haematological or gastrointestinal toxicity in the patient cohort. Nevertheless, we recommend monitoring of blood count during chemoradiation therapy. Prophylaxis against *Pneumocystis jiroveci* pneumonia is advised when temozolomide is administered concurrent with RT due to risk of lymphopenia and subsequent opportunistic infection.

*Special Population—Elderly Patients (Age >65 Years)*

The first randomised trial examining the effectiveness of an abbreviated RT course (40 Gy in 15 fractions over 3

weeks) in older patients (age ≥60 years) with glioblastoma showed no significant difference in OS compared to those who received standard RT (60 Gy in 30 fractions over 6 weeks).[25] Patients in the abbreviated RT arm also had similar KPS and reduced increment in corticosteroid requirements.

The Nordic randomised phase III trial assessed treatment in 342 glioblastoma patients age >60 years with WHO PS ≤2.[26] After 4 years of recruitment, in light of positive results from the EORTC 26981 trial, age cutoff was raised to >65 years. Better median survival was demonstrated in patients >70 years who received temozolomide (200 mg/m$^2$ on days 1 to 5 of every 28 days for up to 6 cycles) or hypofractionated RT (34.0 Gy administered in 3.4 Gy fractions over 2 weeks) than those who received standard RT (60.0 Gy administered in 2.0 Gy fractions over 6 weeks) (9.0 vs 7.0 vs 5.2 months). Survival did not differ between treatments for patients aged 60 to 70 years.

The NOA-08 randomised phase III trial assessed treatment in 373 high-grade glioma (malignant astrocytoma or glioblastoma) patients age >65 years with KPS ≥60,[27] and demonstrated that dose-dense temozolomide (100 mg/m$^2$ on days 1 to 7 of every 14 days) alone was non-inferior to RT (60.0 Gy administered in 1.8-2.0 Gy fractions over 6 to 7 weeks) (median OS 8.6 vs 9.6 months). There was no significant difference in HRQOL between the 2 treatment groups. Event-free survival (EFS) was longer in patients with MGMT promoter methylation (see below) who received temozolomide than in those who underwent RT (8.4 [95% CI, 5.5 to 11.7] vs 4.6 months [95% CI, 4.2 to 5.0]), whereas for patients with no methylation of the MGMT promoter, EFS was longer for those who received RT (3.3 [95% CI, 3.0 to 3.5] vs 4.6 months [95% CI, 3.7 to 6.3]).

A meta-analysis of 5 studies, including the Nordic and NOA-08 trials, showed a marginally significant reduction in mortality in elderly GBM patients receiving temozolomide monotherapy compared to RT.[28] This borderline significance was lost after sensitivity analysis. The role of early RT and temozolomide will be better defined with results from the ongoing EORTC and National Cancer Institute of Canada (NCIC) Clinical Trial Group elderly trial (NCT00482677).

*O-6-methylguanine-DNA Methyltransferase (MGMT)*

MGMT is a DNA repair enzyme that can adversely affect tumour response to DNA-alkylating agents. Methylation of MGMT gene promoter results in gene-silencing and has been shown to improve median OS in glioblastoma patients age ≤70 years with a WHO PS ≤2 (18.2 vs 12.2 months).[29] Among high-grade glioma patients age >65 years, those with MGMT promoter methylation also demonstrated longer median OS compared to those without methylation (11.9 vs 8.2 months; HR = 0.62; 95% CI, 0.42 to 0.91; $P$ = 0.014).[27] Its predictive role in treatment response to temozolomide alone was suggested in the NOA-08 trial as discussed above. Similarly, the Nordic trial demonstrated a non-significant improvement in median OS in glioblastoma patients with MGMT promoter methylation compared to those without methylation (9.7 vs 6.8 months; HR = 0.97; $P$ = 0.81).[26] This improvement in survival was not seen in patients treated with RT only. Overall, MGMT methylation status remains at best a prognostic marker. Its predictive role in response to therapy requires validation in future prospective studies.

*Bevacizumab*

Bevacizumab was thought to be able to improve outcomes in patients with newly diagnosed glioblastoma by potentiating the therapeutic effects of both RT and chemotherapy. This was supported by 2 phase II studies that showed favourable OS and PFS compared to historical controls respectively.[30,31] However, 2 subsequent randomised, placebo-controlled phase III trials of standard chemoradiation (concurrent temozolomide and RT followed by adjuvant temozolomide) with or without bevacizumab in newly diagnosed glioblastoma patients failed to demonstrate any survival benefits in patients treated with bevacizumab compared to placebo.[32,33] Although both trials showed similar adverse effects of bevacizumab, AVAglio[32] demonstrated maintenance of HRQOL, while RTOG 0825[33] reported increased symptom burden, worse HRQOL and decline in neurocognitive function.

*Nimotuzumab*

Nimotuzumab is a humanised monoclonal antibody that binds to epidermal growth factor receptor (EGFR) and alters cell division. A randomised, double-blind phase II trial conducted in patients with high-grade glioma and KPS ≥60 demonstrated improved median OS when treated with nimotuzumab and RT compared to RT alone (17.8 vs 12.6 months; HR = 0.64; $P$ = 0.032).[34] Of note, majority of the patients in this trial have anaplastic astrocytoma (41 anaplastic astrocytoma and 29 glioblastoma multiforme), hence results from this study cannot be generalised to patients with glioblastoma. A German phase III trial also showed no significant PFS or OS difference in glioblastoma patients treated with standard chemoradiation (temozolomide and RT) with or without nimotuzumab; EGFR amplification status did not predict treatment response.[35] In both studies, there was a trend towards improved efficacy in MGMT non-methylated glioblastoma patients. This efficacy stratified by MGMT methylation status remains to be validated.

*Cost-effectiveness*

Alongside the landmark trial by Stupp et al,[2] economic data were collected prospectively for a subgroup of 219 (38%) patients, and analysed from the perspective of the public healthcare system in the Netherlands, Switzerland and Canada.[36] The incremental cost-effectiveness ratio (ICER) was estimated at USD $40,716 per life-year gained, comparable to accepted first-line chemotherapy in cancer patients. In England, an economic evaluation of treatment with temozolomide in the adjuvant and concomitant phase revealed an additional cost of around USD $11,971 for an additional 0.217 quality-adjusted life year (QALY) per patient, translating to a base-case ICER of USD $55,254/QALY.[37] Similarly, in China, the addition of temozolomide increased the cost and QALY relative to RT alone by USD $25,328 and 0.29 respectively, giving rise to an ICER of USD $87,940/QALY.[38] Authors in both of these latter studies concluded that temozolomide is not a cost-effective option for glioblastoma patients but suggested an improved cost-effectiveness with selection and treatment of patients with more favourable prognostic factors. There is currently no local cost-effectiveness study available.

## Recommendations for Front-line Systemic Therapy for Glioblastoma

All members of the workgroup supported the adoption of NCCN guidelines.

There is unanimous agreement that fractionated RT concurrent with temozolomide followed by adjuvant temozolomide is the standard of care for glioblastoma patients age ≤70 years with good PS, defined by WHO PS ≤2 (Category I). Similar efficacy to European Multicentre Phase III trial has been demonstrated in a local study.[24] Dose-dense therapy is not recommended.

For glioblastoma patients age >70 years with good PS, options of treatment include hypofractionated RT, temozolomide with deferred RT or RT with concurrent temozolomide followed by adjuvant temozolomide. We suggest checking MGMT promoter methylation status in this group, and recommend temozolomide therapy, if positive.

The routine addition of bevacizumab as upfront therapy is not recommended.

The role of nimotuzumab as front-line therapy was debated. One of the workgroup members felt that the randomised phase II Cuban trial provided sufficient evidence to recommend nimotuzumab, in addition to RT, as front-line therapy in rare situations where myelosuppression of temozolomide cannot be tolerated. The rest of the workgroup members argued that the trial was conducted with small patient numbers with results not reproduced in other trials, had also not been supported by other national guidelines committees and that given its additional cost and lack of confirmatory trial data, nimotuzumab cannot be recommended as standard front-line therapy.

Given the lack of data on front-line therapy in patients with poor PS, combination therapy with PCV, temozolomide monotherapy, RT alone or best supportive care is reasonable.

## 3. Systemic Therapy for Recurrent High-Grade Glioma

Current available chemotherapy is not curative and recurrence or progression of malignant glioma will eventually occur. There is currently no established standard systemic therapy for patients who have experienced treatment failure.

### *Chemotherapy*

Continuous temozolomide (50 mg/m$^2$) is a treatment option in patients with recurrent or progressive malignant glioma. The RESCUE study, a phase II study, demonstrated good 6-month PFS rates of 23.9% and 35.7% in glioblastoma and anaplastic astrocytoma patients respectively.[39] Other possible regimes include temozolomide at 200 mg/m$^2$/day for 5 days in 28-day cycles for chemotherapy-naïve patients and 150 to 200 mg/m$^2$/day for 5 days in 28-day cycles for patients previously treated with chemotherapy.[40-42]

The role of PCV in recurrent oligodendroglioma was examined retrospectively in a cohort of patients treated with first-line temozolomide within the EORTC study 26971, and demonstrated a modest response rate of 17% and 6-month PFS of 50%.[43] Brada et al conducted the first randomised trial of temozolomide versus PCV in chemotherapy-naïve patients with recurrent high-grade glioma, and demonstrated no clear significant survival benefits of temozolomide over PCV.[40] This study also compared 2 temozolomide treatment schedules and showed that the 5-day schedule (200 mg/m$^2$/day for 5 days in 28-day cycle) improved overall PFS, OS and global quality of life when compared to the 21-day schedule (100 mg/m$^2$/day for 21 days in 28-day cycle).

Lomustine, another treatment option, was used as a comparator in the first phase III trial conducted in patients with recurrent glioblastoma.[44] The trial was terminated early as study drug, enzasturin, failed to demonstrate superior PFS to lomustine (6-month PFS 11.1% vs 19.0%; $P = 0.13$). A subsequent phase III trial also failed to demonstrate significant PFS improvement with cediranib, an oral pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor, as monotherapy (HR = 1.05; 95% CI, 0.74 to 1.50; $P = 0.90$) or in combination with lomustine (HR = 0.76; 95% CI, 0.53 to 1.08; $P = 0.16$), versus lomustine alone in patients with recurrent glioblastoma.[45]

Two phase II studies of cyclophosphamide conducted in patients with recurrent, temozolomide-refractory glioblastoma and anaplastic astrocytoma showed 6-month

PFS of 20% and 30% respectively.[46,47]

For recurrent or progressive oligodendroglioma patients treated with surgery, RT, PCV and temozolomide, carboplatin and teniposide are also treatment options. Use of carboplatin and teniposide as third-line chemotherapy is supported by a phase II study demonstrating a 6-months PFS of 34.8%.[48]

Other treatment options include etoposide (VP16) in patients with recurrent supratentorial malignant glioma previously treated with RT and nitrosurea,[49] and CPT-11 (irinotecan) in patients with recurrent temozolomide-refractory anaplastic astrocytoma[50] and anaplastic oligodendroglioma.[51] In a pooled analysis of 596 patients enrolled in The North American Brain Tumor Consortium (NABTC) phase II studies conducted from 1998 to 2002, 6-month PFS was 28% and 16%, and median OS was 39 weeks and 30 weeks, for patients with recurrent grade III and grade IV tumours respectively.[52] The data serves as historical controls.

*Bevacizumab*

Bevacizumab is a humanised monoclonal antibody against VEGF and inhibits angiogenesis. Its role in recurrent glioblastoma has been defined by 2 phase II studies. Friedman et al evaluated the efficacy of bevacizumab, alone and in combination with irinocetan, in patients with recurrent glioblastoma, and demonstrated MRI-defined objective response rates (ORR) of 28.2% and 37.8% as well as 6-month PFS rates of 42.6% and 50.3% respectively.[4] The PFS demonstrated was similar to a previous trial.[53] In the other pivotal phase II study by Kreisl et al, bevacizumab monotherapy yielded ORR of 71% and 35% based on Levin and MacDonald criteria respectively, 6-month PFS of 29% (95% CI, 18% to 48%), and median OS of 31 weeks (95% CI, 21 to 54 weeks).[54] Treatment with bevacizumab was associated with a reduction of corticosteroids requirement in both trials.

In patients with recurrent anaplastic gliomas, treatment with single-agent bevacizumab demonstrated median OS of 12 months (95% CI, 6.08 to 22.8), median PFS of 2.93 months (2.01 to 4.93) and 6-month PFS of 20.9% (10.3 to 42.5).[55] A pooled analysis of 96 patients with recurrent grade III malignant glioma enrolled in 3 consecutive phase II bevacizumab salvage trials demonstrated 6-month PFS and median OS of 39.1% and 9.2 months respectively among patients who continued bevacizumab therapy after study progression, compared to 23.1% and 10.3 months in patients who initiated non-bevacizumab containing therapy, suggesting that salvage therapies following bevacizumab failure have modest activity independent of further use of bevacizumab.[56] Reported serious adverse events associated with bevacizumab include hypertension, spontaneous colon perforation, poor wound healing and thromboembolic events.[57]

Combination therapies with bevacizumab have also been studied in prospective trials. In a phase II trial, treatment with bevacizumab and irinotecan in patients with recurrent grade III glioma demonstrated 6-month PFS of 55% and 6-month OS of 79%.[58] In a more recent open-label, multicentre phase II study of lomustine, bevacizumab or combination treatment with lomustine and bevacizumab in patients with first recurrence of glioblastoma, only the combination therapy arm met prespecified criteria for further assessment in phase III studies (9-month OS: lomustine 43% (95% CI, 29 to 57); bevacizumab 38% (25 to 52); lomustine 90 mg/$m^2$ + bevacizumab 59% (43 to 73)).[59]

*Cost-effectiveness*

Due to the lack of statistically significant extension of median survival time and quality of life data, estimation of cost per QALY is difficult. For glioblastoma, the incremental cost per progression-free week for temozolomide was estimated at USD $1534 when compared to procarbazine, and USD $613 when compared to placebo (assuming placebo would give no cost and no effect).[60] For anaplastic astrocytoma, cost per progression-free week for temozolomide against placebo was USD $629. There is no local study on cost-effectiveness.

## Recommendations for Systemic Therapy for Recurrent Malignant Gliomas

All members of the workgroup support the adoption of NCCN and ESMO guidelines.

There is currently no established systemic therapy for recurrent malignant glioma. For patients with good PS, reasonable chemotherapy options include temozolomide, lomustine, combination PCV, cyclophosphamide, platinum-based agents and irinotecan.

Bevacizumab, as monotherapy or in combination with other chemotherapy, may also be considered in recurrent glioblastoma. For patients with poor PS, best supportive care is reasonable. The SCAN workgroup acknowledges that there is no local data on systemic therapy in recurrent high-grade glioma.

***Conflicts of Interest***

*Dr Chan reports receiving honoraria from Eli Lilly, MSD and Bayer; Dr Tham, receiving honoraria from Merck Sonoro; Dr Lin and Dr Ong have nothing to disclose.*

***Workgroup Members***

*The Members of the SCAN Neuro-Oncology Workgroup are Section Lead and Workgroup Chairperson: Chee Kian Tham, MBBS, MMed (Int Med), MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Xuling Lin, MBBS, MMed (Int Med), MRCP (UK), Department of Neurology, National Neuroscience Institute Singapore, Singapore; Sin Jen Ong, MBBS (London), MMed (Int Med), MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Daniel BY Chan, MBBS (Hons), MRCP (UK), FAMS (Med Onc), SOC@KWGE Oncology Centre, Gleneagles Medical Centre Singapore, Singapore.*

***Reviewers***

*Invited reviewers were Thomas Kaley, MD, Department of Neurology, Memorial Sloan Kettering Cancer Center, USA; Sith Sathornsumetee, MD, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand.*

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Supplementary Table 1. International Guidelines for the Systemic Therapy of High-Grade Glioma

| Guideline Title | | NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Central Nervous System Cancers v.2.2013 | EANO Guidelines for the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastomas | High-Grade Malignant Glioma: ESMO Clinical Practice Guidelines | Canadian Recommendations for the Treatment of Glioblastoma Multiforme | Clinical Practice Guidelines for the Management of Adult Gliomas: Astrocytomas and Oligdendrogliomas |
|---|---|---|---|---|---|---|
| Year Released | | 2013 | 2014 | 2014 | 2007 | 2009 |
| Guideline Developer | | National Comprehensive Cancer Network (NCCN) | European Association for Neuro-Oncology (EANO) | European Society for Medical Oncology (ESMO) | Canadian GBM Recommendations Committee | Australian Cancer Network |
| Frontline Systemic Therapy for Anaplastic Glioma | | | | | | |
| AO/ AOA | KPS ≥70; 1p19q co-deleted | Fractionated external beam RT + PCV [cat I] or Fractionated external beam RT + TMZ or PCV or TMZ [cat IIB] | CT with alkylating agent with or without RT [II, B] | RT + PCV [I,B]; stated no difference in efficacy was apparent between PCV and TMZ [III,B] | Not applicable | No specific recommendations |
| | KPS ≥70; 1p19q uni- or non-deleted | Fractionated external beam RT [cat I] or Fractionated external beam RT + TMZ or PCV or TMZ | | | Not applicable | No specific recommendations |
| AA | KPS ≥70 | Fractionated external beam RT [cat I] or Fractionated external beam RT + TMZ or PCV or TMZ | Involved-field RT [I, A] or TMZ [II, B] or PCV [II, B] | | Not applicable | Adjuvant CT and RT [II] |
| AG | KPS <70 | Fractionated external beam RT or PCV or TMZ or BSC | Not specified | | Not applicable | No specific recommendations |
| Member Votes | | 4 of 4 votes | | | | |
| Frontline Systemic Therapy for Glioblastoma | | | | | | |
| GBM | Good PFS (KPS ≥70 or ECOG ≤2) | Age ≤70 : Fractionated external beam RT + concurrent and adjuvant TMZ [cat I]; Age >70: Fractionated external beam RT [cat I] + concurrent and adjuvant TMZ or Fractionated external beam RT (hypofractionated) [cat I] or TMZ (if MGMT positive) | Age <65 – 70 yr: Involved-field RT + concomitant and adjuvant (six cycles) TMZ [I,A]<br>Age ≥65 – 70 yr: RT + TMZ or hypofractionated RT [I,A] or TMZ [I,A] based on MGMT promoter methylation status | No recommendations | Concomitant (75 mg/m$^2$ x typically 42 days) + adjuvant (5/28-day schedule; start 150 mg/m$^2$ then increase to 200 mg/m$^2$ at cycle 2) TMZ | Age ≤70: concomitant and adjuvant TMZ; age >70: consider adjuvant TMZ only [III] |
| | Poor PFS (KPS <70 or ECOG >2) | Fractionated external beam RT (hypofractionated or standard) or PCV or TMZ or BSC | | Concomitant and adjuvant (5 days every 4 weeks x 6 cycles) TMZ [I,A] | No recommendations | No recommendations |
| Member Votes | | 4 of 4 votes | | | | |

AG: Anaplastic glioma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; BSC: Best supportive care; cat: Category; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; GBM: Glioblastoma multiforme; KPS: Karnofsky performance score; MGMT: O-6-methylguanine-DNA methyltransferase; PCV: Procarbazine, lomustine and vincristine; PFS: Performance status; RMG: Recurrent malignant glioma; RT: Radiation therapy; TMZ: Temozolomide; yr: Year(s); [ ]: Recommendation

Supplementary Table 1. International Guidelines for the Systemic Therapy of High-Grade Glioma (Con't)

| Guideline Title | | NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Central Nervous System Cancers v.2.2013 | EANO Guidelines for the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastomas | High-Grade Malignant Glioma: ESMO Clinical Practice Guidelines | Canadian Recommendations for the Treatment of Glioblastoma Multiforme | Clinical Practice Guidelines for the Management of Adult Gliomas: Astrocytomas and Oligdendrogliomas |
|---|---|---|---|---|---|---|
| Systemic Therapy for Recurrent Malignant Gliomas | | | | | | |
| RMG | Diffuse/ multiple | BSC (if performance status) or systemic CT or surgery for symptomatic, large lesion or alternating electric field tx [GBM - cat IIB] | AG: TMZ<br>GBM: nitrosurea regimens or TMZ rechallenge or bevacizumab or recruitment into clinical trials [II,B] | No established CT regimen; single agent nitrosurea in some patients; Erlotinib/imatinib failed to show antitumour efficacy [II,C]; Bevacizumab +/- irinotecan effect on life expectancy unknown [III,C]; re-operation [IV,C]; CT-impregnated polymers with repeat radical op show marginal survival benefits [II,B] | Consider repeat resection; no established optimal CT strategy | CT has modest activity in recurrent high-grade astrocytoma |
| | Local resectable | Resection +/- carmustine wafer; and BSC (if poor performance status) or systemic CT or reirradiation [cat IIB] or alternating electric field therapy [GBM - cat IIB] | | | | |
| | Local unresectable | BSC (if poor performance status) or systemic CT or reirradiation [cat IIB] or alternating electric field therapy [GBM - cat IIB] | | | | |
| Member Votes | | 4 of 4 votes | | 4 of 4 votes | | |

AG: Anaplastic glioma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; BSC: Best supportive care; cat: Category; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; GBM: Glioblastoma multiforme; KPS: Karnofsky performance score; MGMT: O-6-methylguanine-DNA methyltransferase; PCV: Procarbazine, lomustine and vincristine; PFS: Performance status; RMG: Recurrent malignant glioma; RT: Radiation therapy; TMZ: Temozolomide; yr: Year(s); [ ]: Recommendation