

Salvage Chemotherapy in Progressive High-grade Astrocytoma

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Abstract

Introduction: Despite aggressive multidisciplinary interventions, patients with high-grade astrocytomas experience tumour progression or recurrence. Treatment for this group of patients remains a formidable challenge. We describe our experience of salvage chemotherapy for these patients. **Materials and Methods:** A retrospective review of relevant clinical and radiographic information of patients who received at least one cycle of salvage chemotherapy for progressive high-grade astrocytoma at the National Cancer Center, Singapore, from March 2004 to September 2006, was conducted. Patients underwent regular assessment with clinical examination and magnetic resonance brain imaging to gauge response to salvage chemotherapy. Survival and progression free interval data were analysed via Kaplan-Meier method. **Results:** Twenty-four patients (13 glioblastomas, 11 anaplastic astrocytomas) had received chemotherapy as salvage treatment following progression of their high-grade astrocytoma. Among 20 patients assessable for tumour response, there were 4 patients with partial responses and 9 with stable responses. The 12-month survival rate for the entire group from time of onset of tumour progression was 49.6%. Eight patients had survived more than 12 months at the time of writing. Among patients with glioblastoma, the 12-month survival rate was 30% and the median survival was 11.2 months. For patients with anaplastic astrocytoma, the 12-month survival rate was 73%. **Conclusion:** Durable disease control and prolonged survival were seen in a significant portion of selected patients with progressive high-grade astrocytoma who received salvage chemotherapy.

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Introduction

High-grade astrocytoma includes glioblastoma multiforme (GBM) (World Health Organization grade 4) and anaplastic astrocytoma (AA) (WHO grade 3). These are the more common gliomas in adults.¹ Treatment of these highly aggressive neoplasms remains a challenge. The infiltrative nature of astrocytoma or location of tumour in the eloquent brain precludes a surgical cure. Radical radiation therapy and chemotherapy render tumour control for a variable period. When therapy fails, tumours progressively enlarge in size or recur, frequently in or adjacent to the initial location. Hau et al² reported a retrospective study of comparable patients with progressive high-grade astrocytoma that showed improved survival for patients who received re-intervention compared to those who received only symptomatic or palliative treatments.² Control of tumour is also important to reduce destruction of normal brain by tumour, minimise its accompanying

neurologic morbidity and subsequent negative impact on quality of life.^{3,4} However when tumour progresses, additional surgical and radiotherapy options are limited. Salvage chemotherapy is a controversial option. While some patients may substantially benefit from salvage chemotherapy, others may experience significant toxicity. Also, the optimal salvage chemotherapeutic regimen has yet to be identified. We describe our experience with salvage chemotherapy in patients whose high-grade astrocytoma had progressed or recurred following initial standard treatment.

Materials and Methods

Patients with primary brain tumours were referred from neurosurgeons to the Neuro-Oncology Clinic at the National Cancer Centre, Singapore, which was manned by 2 neuro-oncologists. All patients were followed up regularly with clinical assessment and magnetic resonance brain imaging

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(MRBI). Tumour progression includes progressively enlarging residual tumour that was previously stable and recurrence of new tumour in patients who were previously free of any evidence of residual disease. Progression of tumour was documented radiographically in all patients. At time of tumour progression, salvage treatment may include additional surgery, radiation therapy or chemotherapy. Decisions for surgery or additional radiation were made in consultation with neurosurgeons and radiation oncologists. Generally, surgery was offered if symptomatic improvement could be achieved, additional radiation may be offered depending on the location of the recurrence. Salvage chemotherapy was offered at the discretion of the primary neuro-oncologist. Patients who received salvage chemotherapy underwent regular assessment with clinical examination and MRBI to gauge response to treatment.

All patients who received salvage chemotherapy for high-grade astrocytoma were treated by the 2 neuro-oncologists at the Neuro-Oncology Clinic, National Cancer Centre. Relevant clinical, pathological and radiographic information were obtained retrospectively. Karnofsky performance scale (KPS) scores were also obtained. All patients with high-grade astrocytoma (astrocytoma WHO grades 3 and 4) who were treated with at least 1 course of salvage chemotherapy were included. Complete response (CR) was defined as disappearance of all enhancing tumours on contrast-enhanced MRBI, with patient receiving no corticosteroids and determined to be neurologically stable or improved. Partial response (PR) was defined as a greater than 50% reduction in the size (product of 2 largest perpendicular diameters) of enhancing tumour in a patient who was neurologically stable or improved while on a stable dose or reduced dose of corticosteroids. Progressive disease (PD) was defined by either a 25% increase in the size of enhancing tumour or appearance of any new tumour, or neurologic deterioration while on a stable or increasing dose of corticosteroids. Other responses were labelled as a stable response.⁵ Progression-free interval-1 (PFS-1) is defined as the time interval between initial diagnosis and first tumour progression. Progression-free interval-2 (PFS-2) is defined as the interval between first and subsequent progression. Survival is defined as the time interval between first tumour progression and death. Kaplan-Meier analysis for survival and PFS-2 was done with SPSS (version 10.1.3).

Results

Between March 2004 and September 2006, 24 patients had received chemotherapy as salvage treatment following progression of their high-grade astrocytoma. There were 13 patients with GBM and 11 with AA. The median age was 44.6 years (range, 21.2 to 61.8). Previous treatment included a diagnostic biopsy in 9 patients and debulking

resection in 15 patients. All patients underwent conventional external beam brain radiation therapy following surgery. All patients with GBM and 6 patients with AA received adjuvant chemotherapy concurrent with or immediately following their radiation treatments.

Tumour progression in all patients was documented on contrast-enhanced brain MRI. The median PFS-1 was 12.7 months (range, 3.8 to 121.6). Five patients with AA had PFI-1 <2 years. Two of these patients had rim-enhancing tumours with features suggestive of central necrosis on imaging, 2 patients had very extensive disease (1 had gliomatosis cerebri and the other had disease involving both frontal lobes and the corpus collosum) and 1 patient had a brainstem tumour with leptomeningeal dissemination at presentation. Four patients with GBM had PFI-1 between 12 and 24 months. One patient with GBM had PFI-1 of more than 36 months.

Of the 24 patients, 6 patients underwent a second resection. One patient received a second course of conventional radiation therapy prior to receiving salvage chemotherapy. Among patients who underwent a second surgical resection, 3 received salvage chemotherapy within 4 weeks; the remaining 3 received their treatments within 4 to 8 weeks. The median KPS score of these 24 patients was 70. Ten patients received temozolomide or temozolomide in combination with a second agent. Five patients received irinotecan. The other chemotherapy regimens used include PCV (lomustine, procarbazine, vincristine), edotecarin, carboplatin with etoposide, bevacizumab. Three patients discontinued treatment due to adverse effects. These included allergic rash in 1 patient, severe diarrhoea and vomiting in 1 patient and sepsis followed by severe deconditioning in the remaining patient. One patient stopped treatment after completing 12 months of chemotherapy; this patient remains free of disease progression. The remainder of patients who had ceased salvage chemotherapy did so because of disease progression.

Twenty patients were assessable for tumour response to salvage chemotherapy. Four patients who were not assessable for tumour response included 1 patient who had no measurable contrast-enhancing disease following the second surgical resection for progressive disease, 2 patients who discontinued chemotherapy prior to any assessment imaging and 1 patient who had yet to undergo imaging to assess tumour response at the time of writing. Four patients demonstrated partial response. Nine patients achieved a stable response.

Follow-up ranged between 2.4 and 42.7 months (mean, 13.3). Eleven patients had died (8 with GBM and 3 with AA). Using Kaplan-Meier survival analysis, the estimated 12-month survival rate for the whole group was 49.6% (Fig. 1). At the time of writing, 8 patients (33%) had

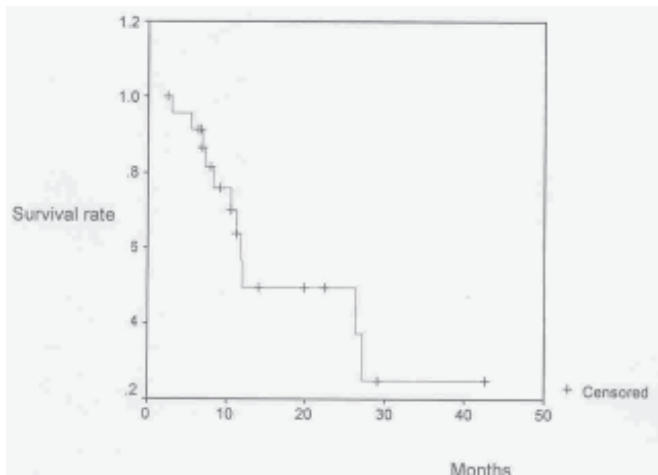


Fig. 1. Survival curve following progression of high-grade astrocytoma.

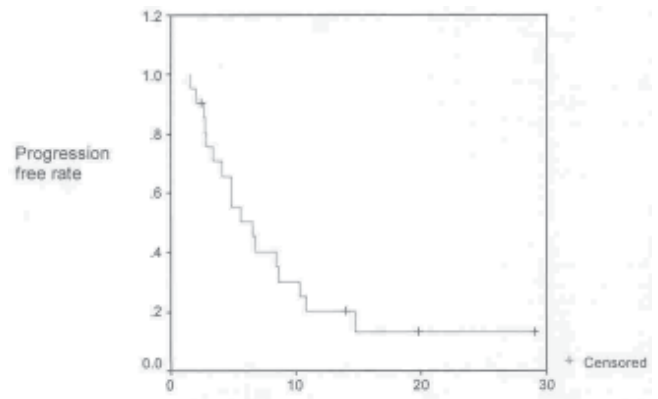


Fig. 2. Progression-free interval-2 (PFI-2).

survived more than 12 months after their tumour progression, another 8 patients are still alive with follow-up of 2.4 to 11.3 months. Among patients with GBM, the 12-month survival rate was 30% and the median survival was 11.2 months. For patients with AA, the 12-month survival rate was 73%, but the number of events was too small for median survival to be estimated.

Two patients who ceased chemotherapy because of intolerable side effects prior to re-assessment were excluded from assessment of PFI-2. At the end of the follow-up period, 4 patients (1 with GBM, 3 AA) remained alive and free of further disease progression at 2.4, 14, 19.8 and 29.1 months. The median PFI-2 was 6.5 months (range, 1.6 to 29.1; 95% confidence interval, 3.8 to 9.2 months) (Fig. 2). Seventeen per cent (4) of the patients had PFI-2 of at least 12 months and 25% had PFI-2 between 6 and 12 months. Survival and PFI-2 of patients according to tumour grade are presented in Table 1.

Table 1. Survival and Progression Free Interval-2 (PFI-2) for Patients with Glioblastoma and Anaplastic Astrocytoma

	GBM	AA
No. of patients	13	11
Median age (y)	50.1	39.4
Median KPS	80	70
Median PFI-1 (mo)	9	34.3
Median survival from tumour progression/recurrence (mo) (95% confidence interval)	11.2 (9.2-13.2)	Not available
Median PFI-2 (mo) (95% confidence interval)	4.8 (3.3-6.3)	10.3 (4.8-15.9)
6-months PFI-2 rate	27%	67%

AA: anaplastic astrocytoma; GBM: glioblastoma multiforme; KPS: Karnofsky performance scale; PFI: progression-free interval

Table 2. Survival and Progression-free Survival in Phase II Trials Involving Patients with Progressive High-grade Astrocytoma

	Salvage chemotherapy	Astrocytoma grade (WHO)	KPS	Median age (y)	Median survival	Median PFI	6-month PFI rate
Brandes AA et al ⁶	Temozolomide	GBM, WHO grade 4	Median KPS 80	48.4	30.3 w	11.7 w	24%
Jaeckle K et al ⁷	Temozolomide, cis-retinoic acid	GBM, WHO grade 4 AA, WHO grade 3	Median KPS 80	45	35 w 47 w	16 w 22 w	32 % 46%
Yung et al ⁸	Temozolomide	AA, WHO grade 3	≥70	42	14.2 m	5.5 m (24 w)	49%
Friedman et al ⁹	CPT-11 (irinotecan)	GBM, WHO grade 4 AA, WHO grade 3	≥60 ≥60	46	42 w >40 w	18 w 12 w	Unavailable Unavailable
Our group		GBM, WHO grade 4 AA, WHO grade 3	80 (median) 70 (median)	50.1 39.4	11.2 m (48 w)	4.8 m (20.9 w) 10.3 m (44.8 w)	36% 60%

AA: anaplastic astrocytoma; GBM: glioblastoma multiforme; KPS: Karnofsky performance scale; PFI: progression-free interval; WHO: World Health Organization

Serial KPS score was available for 16 patients during the time they were on salvage chemotherapy. KPS score improved in 1 patient who had a PR with salvage chemotherapy and deteriorated in 1 patient whose tumour progressed despite treatment. The remaining 14 patients demonstrated stable KPS scores.

Discussion

High-grade astrocytoma (GBM and AA) is a highly aggressive malignant primary brain tumour. Progressive high-grade astrocytoma is a formidable challenge. In this series, a selected group of patients, either relatively young or with good performance status received salvage chemotherapy at progression of their high-grade astrocytoma. This study has limitations. It is a retrospective study of patients who were treated in one institution. The number of patients was also relatively small, although the number of events (deaths or further tumour progression) was sufficient for important observations to be made.

The overall survival and progression-free intervals in this group of patients with progressive high-grade astrocytoma were comparable to reported phase II trials (Table 2). Lower histologic grade, younger age and good performance status are well-established independent prognostic factors for better outcome.¹⁰ The age and KPS of our patients with either grade 3 or 4 astrocytoma were similar to those seen in the phase II trials. Approximately half of our patients survived for at least 12 months following their first progression. Seventeen per cent had durable disease stability for more than 1 year.

Salvage chemotherapy was well tolerated by the majority of our patients. Three patients discontinued chemotherapy due to adverse effects. KPS scores remained stable during salvage chemotherapy. Four of 5 patients whose tumour had a PR did not demonstrate improvement in KPS scores. Possible reasons for this observation include irreversible brain damage by tumour prior to response, adverse effects of salvage chemotherapy or insensitivity of KPS. Although this report was unable to address this question in detail, the authors judged that neurologic deficits secondary to tumour effects were the main determinant of KPS in this group of patients. Other investigators had demonstrated the association of progression of high-grade glioma with deterioration of neurologic deficits and a sharp decline in quality of life.^{3,4}

Conclusion

Durable disease control and prolonged survival were seen in a significant portion of patients with progressive high-grade astrocytoma who received salvage chemotherapy. Careful patient selection may have contributed to this. These results, together with the preservation of the patients' performance status, support the use of salvage chemotherapy in selected patients with progressive high-grade astrocytoma.

REFERENCES

1. World Health Organization Classification of Tumors: Pathology and Genetics: Tumors of the Nervous System. In: Kleihues P, Cavenee WB, editors. Lyon, France: International Agency for Research on Cancer (IARC) Press, 2000.
2. Hau P, Baumgart U, Pfeifer K, Bock A, Jauch T, Dietrich J, et al. Salvage therapy in patients with glioblastoma: is there any benefit? *Cancer* 2003;98:2678-86.
3. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WK, et al. Effect of neurological dysfunction on health-related quality of life in patients with high-grade glioma. *J Neurooncol* 1997;34:263-78.
4. Osoba D, Brada M, Yung WK, Prados MD. Health-related quality of life in patients with anaplastic astrocytoma during treatment with temozolomide. *Eur J Cancer* 2000;36:1788-95.
5. 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.
6. Brandes AA, Ermani M, Basso U, Paris MK, Lumachi F, Berti F, et al. Temozolomide in patients with glioblastoma at second relapse after first line nitrosourea-procarbazine failure: a phase II study. *Oncology* 2002;63:38-41.
7. Jaeckle KA, Hess KR, Yung WK, Greenberg H, Fine H, Schiff D, et al; North American Brain Tumor Consortium. Phase II evaluation of temozolomide and 13-cis-retinoic acid for the treatment of recurrent and progressive malignant glioma: a North American Brain Tumor Consortium study. *J Clin Oncol* 2003;21:2305-11.
8. Yung WK, Prados MD, Yaya-Tur R, Rosenfeld SS, Brada M, Friedman HS, et al; Temodal Brain Tumor Group. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. *J Clin Oncol* 1999;17:2762-71. Erratum in: *J Clin Oncol* 1999;17:3693.
9. Friedman HS, Petros WP, Friedman AH, Schaaf LJ, Kerby T, Lawyer J, et al. Irinotecan therapy in adults with recurrent or progressive malignant glioma. *J Clin Oncol* 1999;17:1516-25.
10. Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Prados MD, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol* 1999;17:2572-8.