

Oligodendroglial tumor chemotherapy using “decreased-dose-intensity” PCV: A Singapore experience

Abstract—The authors propose “decreased-dose-intensity” PCV (procarbazine, lomustine [CCNU], and vincristine) chemotherapy for Asian patients with oligodendroglial tumors. In this study, all seven patients with oligodendroglioma (OD) and eight with anaplastic oligodendroglioma (AO) had objective responses or stable disease. Median progression-free survival was greater than 29 months (OD) and 36.5 months or greater (AO); 86% of patients with OD and 63% with AO remain progression-free. Twenty-four Common Toxicity Criteria Grade 3/4 adverse events were noted.

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Oligodendroglial tumors are among the most chemosensitive of human solid malignancies. In terms of cost and availability, PCV (procarbazine, lomustine [CCNU], and vincristine) chemotherapy is the most viable chemotherapeutic option for patients with oligodendroglial tumors in Asia. PCV-associated toxicity, particularly cumulative myelosuppression, is well described among white patients.^{1,2} There are no reports in the published literature describing Asian oligodendroglial PCV chemotherapy outcome. In our experience, most Asian patients cannot tolerate the toxicity associated with the Western “standard” PCV dose. We developed a “decreased-dose-intensity” PCV regimen for our Asian patients, and this study reports our experience.

Methods. From January 1998 to July 2005, 15 patients (53% male; median age 43 years) with histologically confirmed oligodendroglial tumors (7 oligodendroglioma [OD], 8 anaplastic oligodendroglioma [AO]) were treated at the National Cancer Centre, Singapore. PCV was administered based on an 8-week cycle as follows: day 1, 90 mg/m² CCNU PO; days 8 to 21, 84 mg/m² procarbazine PO; and days 1 and 28, 1.0 mg/m² vincristine IV (cap of 2.0 mg). Chemotherapy was intended for at least 6 to 8 cycles. Treatment was discontinued upon tumor progression or Grade 3/4 National Cancer Institute Common Toxicity Criteria (NCI-CTC) hematologic toxicity persistent beyond 4 weeks.

All patients underwent MRI scanning within 14 days before initiation of chemotherapy, after the second or third cycle, at the end of chemotherapy, when clinical progression was suspected, and at least 6 monthly follow-up intervals. Tumor size was measured via the product of the two largest perpendicular diameters. Metastasis along the ventricular lining or cortical surface was considered evidence of leptomeningeal disease (LMD). Postgadolinium T1-weighted images were used to measure enhancing tumors, and T2-weighted or fluid-attenuated inversion recovery images were used for non-contrast-enhancing tumors.

Conventional measures of response such as complete response

(CR), partial response (PR), stable disease, and progressive disease (PD) were used.³ The proportion of [CR + PR] constituted the objective response rate. Progression-free survival (PFS) was the period from initiation of chemotherapy to disease progression or death. Grade 3/4 Common Toxicity Criteria (NCI-CTC version 2.0) adverse events (AEs) were noted.

Results. Treatment outcome and PFS data are summarized in table 1. No patient had development of PD while undergoing chemotherapy. Five patients with OD were given up-front PCV because they all had clinically symptomatic, radiologically extensive, surgically unresectable, and thus “aggressive” low-grade ODs. We observed early (after 2 or 3 cycles of PCV) objective responses in 57% of patients with OD and 13% of patients with AO. Among patients with OD, median PFS was greater than 29 months (range of > 23 to > 40 months). Six of seven patients (86%) remain progression free, whereas one patient (13%) had development of disease progression at 26 months. Among patients with AO, median PFS was 36.5 months or greater (range of 20 to > 68 months). Five of eight patients (63%) remain progression free, whereas three patients (38%) had development of disease progression at 20, 36, and 37 months. LMD was present in two of these three patients before chemotherapy.

Dose reduction by the third cycle was necessary in 8 patients because of AEs, and all 15 patients underwent 25% or greater dose reduction of CCNU and procarbazine by the fifth cycle. Mean administered PCV doses were 80 mg/m² CCNU, 79 mg/m² procarbazine, and 1.0 mg/m² vincristine. The mean administered dose intensity for CCNU was 1.12 mg/m²/d, for procarbazine was 15 mg/m²/d, and for vincristine was 0.04 mg/m²/d. A total of 194 AEs in 102 cycles were recorded, 24 of which were Grade 3/4 in severity (table 2). Fifteen cycles in 5 patients were complicated by Grade 3/4 AEs. Treatment was discontinued in 1 patient after five cycles because of prolonged myelosuppression. No chemotherapy-related deaths were recorded.

Discussion. Compared with “standard,” 42-day PCV dose intensity (CCNU: 2.62 mg/m²/d; procarbazine: 20 mg/m²/d; vincristine: 0.07 mg/m²/d), our administered dose intensity was 57% reduced for CCNU, 24% reduced for procarbazine, and 43% reduced for vincristine. Unequivocal early responses were observed, highlighting the chemosensitive nature of these tumors in Asian patients. Objective response rates for our patients with OD tumors were comparable with other published studies (71% vs

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Table 1 Treatment profile and outcome (n = 15 patients)

Age, y/sex	Type of surgery	Postoperative treatment	Early chemotherapy response	End of chemotherapy response	PFS, mo
Oligodendroglioma					
58/F	Resection	PCV alone, 5 cycles	PR	PR	>23
46/M	Resection	PCV alone, 7 cycles	SD	SD	>24
52/F	Biopsy	PCV alone, 6 cycles	PR	PR	>29
55/F	Biopsy	PCV alone, 6 cycles	SD	PR	>32
45/F	Biopsy	PCV after RT, 6 cycles	SD	SD	>39
52/F	Resection	PCV alone, 7 cycles	CR	CR	>40
42/M	Resection	PCV salvage (after RT), 8 cycles	PR	PR	26
Anaplastic oligodendroglioma					
27/F	Resection	PCV alone, 6 cycles	SD	SD	>32
35/M	Resection	PCV after RT, 6 cycles	SD	SD	>32
31/M	Resection	PCV after RT, 8 cycles	CR	CR	>43
40/F	Resection	PCV alone, 7 cycles	SD	PR	>65
32/F	Biopsy	PCV after RT, 9 cycles	SD	SD	>68
18/M	Resection	PCV salvage (after RT), 7 cycles	SD	SD	20
40/M	Resection	PCV salvage (after RT), 8 cycles	SD	SD	36
52/M	Resection	PCV salvage (after RT), 7 cycles	SD	SD	37

PFS = progression-free survival; PVC = procarbazine, CCNU, and vincristine; PR = partial response; SD = stable disease; RT = radiation therapy; CR = complete response.

62% to 100%)³ but not for our patients with AO tumors (25% vs 59% to 77%).²⁻⁴ Two factors may have contributed to our lower response rate for patients with AO tumors. Two patients had LMD before PCV, whereas three patients received PCV chemotherapy as salvage therapy for tumor recurrence after previous radiation therapy (RT). Patients with LMD are reported to have lower response rates (47%) and 1-year PFS (34%).⁵ Lower response rates for patients who receive PCV following relapse after previous RT (59%) have also been reported.⁴ Median PFS values for our patients with OD (>29 months) and AO (>36.5 months) are comparable with published median PFS values (OD: >24 months; AO, 12.3 to 16.3 months).^{2,6}

Despite using decreased-dose-intensity PCV, 33% of patients and 15% of cycles were complicated by

Table 2 NCI-CTC Grade 3/4 adverse events in 102 chemotherapy cycles

Toxicity	Grade 3	Grade 4
Neutropenia	7	4
Leukopenia	6	2
Anemia	1	1
Neuropathy	1	0
Nausea/vomiting	1	0
Pain	0	1
Total	16	8

NCI-CTC = National Cancer Institute Common Toxicity Criteria.

Grade 3/4 AEs, as compared with 31% of patients⁵ and 7.7% of cycles⁴ in published reports.

Although CYP-450 polymorphisms have been demonstrated to impact efficacy and toxicity for cytotoxic drugs such as amonafide, doxorubicin, irinotecan, and 5-fluorouracil in different ethnic groups,⁷ published literature lacks specific information for CCNU, procarbazine, and vincristine metabolism. In clinical practice, Asian neuro-oncologists are aware that optimal cytotoxic drug doses for white patients are not optimal for Asian patients. Doses of oncology drugs are generally lower in Japan compared with those used in clinical trials in the United States.⁷ In a study involving Japanese patients with oligodendroglial tumors, patients received a lower dose (80 mg/m²) of MCNU (ranimustine) because of frequent dose reductions and dose delays experienced with the “standard” dose (110 to 130 mg/m²).⁸ Another Japanese study cycled ACNU (nimustine) every 8 weeks at a decreased dose (75 to 80 mg/m²)⁹ because of severe hematologic toxicity after a standard dose of 100 mg/m².¹⁰ Our study results are consistent with views that the optimal PCV chemotherapy dose for Asian patients is lower than that proposed by current regimens from Western countries.

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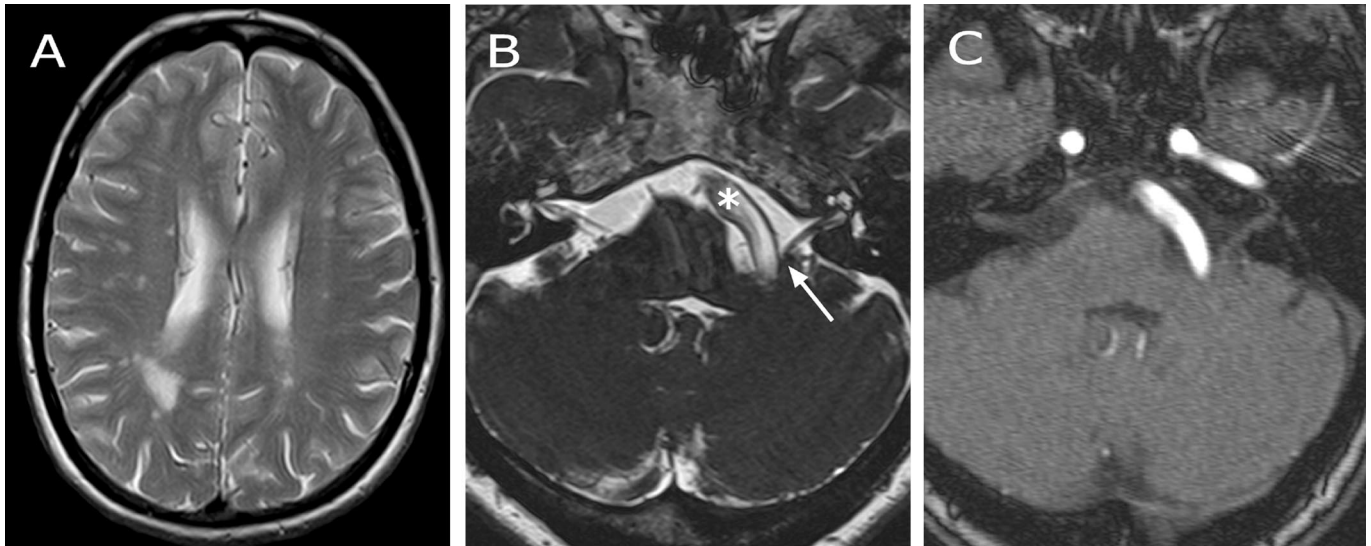


Figure. (A) T2-weighted axial MRI shows asymmetric, widespread, hyperintense white-matter lesions. (B, C) Three-dimensional-CISS imaging (B, three-dimensional Fourier transformation constructive interference in steady state) and three-dimensional time-of-flight MR-angiography (C) demonstrate left VIIIth cranial nerve compression (arrow) due to dolichoectasia of the basilar artery (asterisk).

Paroxysmal vertigo as the presenting symptom of Fabry disease

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A 50-year-old woman presented with a 10-year-history of paroxysmal attacks of severe rotational vertigo lasting seconds without hearing loss or tinnitus, occurring approximately once monthly. MRI revealed megadolichobasilar artery and white-matter lesions (figure, A).

Considering a positive family history for Fabry disease, a point mutation was found in the α -galactosidase-A gene. This enzyme

deficiency is a rare X-linked disorder of glycosphingolipid metabolism causing angiokeratoma, neuropathy, cornea verticillata, stroke, and renal or cardiac failure with high mortality in men.¹ X-chromosomal inactivation causes unspecific symptoms and partial forms in female heterozygotes. Our patient displayed cornea verticillata, but neither angiokeratoma nor acroparesthesia.

Cerebrovascular substrate deposition commonly affects the vertebrobasilar system resulting in dolichoectasia.² Paroxysmal vertigo most likely resulted from megadolichobasilar compression of the vestibulocochlear nerve (figure, B and C), although other causes of vertigo occur in Fabry disease.

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