Temozolomide for 1p19q co-deleted and partially deleted gliomas

- M.G. McNamara, H. Jiang, M.J. Lim Fat, S. Sahebjam, T.R. Kiehl, J. Karamchandani, C. Coire, C. Chung, B.A. Millar, N. Laperriere, W.P. Mason

Disclosure slide

- I have no conflicts of interest to declare.

Introduction

- Among gliomas, co-deletions of chromosomes 1p and 19q are associated with tumors with oligodendroglial components.
- Combined alterations have been observed in up to 70% of oligodendrogliomas and 50% of mixed oligoastrocytomas.
- Besides being a relevant diagnostic marker, 1p19q loss has been validated for its prognostic relevance in anaplastic oligodendroglial tumors and mixed oligoastrocytomas.

Cairncross G *et al*., 1998, JNCI 90: 1473-9, Cairncross G *et al*., 2013, J Clin Oncol 31: 337-43, van den Bent M *et al*., 2013, J Clin Oncol 31: 344-50.

Introduction

Glioma	WHO grade	Differentiation	Share histological features with:
Oligodendroglioma	II (low grade)	Well	Oligodendrocytes
Oligoastrocytoma	II (low grade)	Well	Mixed – oligodendrocytes and astrocytes
Anaplastic oligodendroglioma	III (high grade)	Undifferentiated (anaplastic)	Oligodendrocytes
Anaplastic oligoastrocytoma	III (high grade)	Undifferentiated (anaplastic)	Mixed – oligodendrocytes and astrocytes

Introduction

- Responses to procarbazine, lomustine, and vincristine (PCV) were first reported in small series of patients with recurrent oligodendroglioma and oligoastrocytoma in 1988 and 1992 respectively*.

*Cairncross G *et al*., 1988, Ann Neurol 23: 360-4, Kim L *et al*., 1992, J Neurosurg 85: 602-7.

Introduction

- These studies led to randomised phase III trials (RTOG trial 9402 and EORTC trial 26951) to clarify the role of PCV chemotherapy in anaplastic oligodendroglioma and anaplastic oligoastrocytoma*.

*Cairncross G *et al*., 2006, J Clin Oncol 24: 2707-14, van den Bent M *et al*., 2006, J Clin Oncol 24: 2715-22.

Introduction

- Long-term results of RTOG 9402 and EORTC 26951 indicated that patients whose tumours harboured a 1p19q co-deletion had benefit from early addition of PCV chemotherapy to radiotherapy:
  - a significant improvement in overall survival compared with early radiotherapy, even with salvage chemotherapy at tumour relapse*.

*Cairncross G *et al*., 2013, J Clin Oncol 31: 337-43, van den Bent M *et al*., 2013, J Clin Oncol 31: 344-50.

Introduction

- Long-term follow up of RTOG 9802 reported for patients with high-risk grade II gliomas (with less than gross total tumour resection or who were more than 40 years of age), radiotherapy plus PCV prolonged both progression-free and overall survival, compared to radiotherapy alone*.

*Buckner JC *et al*., 2014, J Clin Oncol 32: 5s (suppl abstr 2000).

Unanswered questions

- Whether up-front chemotherapy, omitting/deferring radiotherapy, in the desire to avoid late neurocognitive toxicity of radiotherapy should be the initial therapy for tumours with co-deleted 1p19q.

- Whether temozolomide, an oral agent with a better toxicity profile, can be substituted for PCV.

Objectives

- To retrospectively review outcomes in patients treated with up-front temozolomide alone in 1p19q co-deleted / partially deleted:
  - Oligodendroglioma
  - Oligoastrocytoma
  - Anaplastic oligodendroglioma
  - Anaplastic oligoastrocytoma

Methods

- Temozolomide was administered at a dose of 150-200 mg/m^2 (day 1-5, 28 day cycle).

- Radiotherapy was given to a dose of 59.4 Gy in fractions of 1.8 Gy.

Methods

- DNA was extracted and amplified by PCR using primers specific for microsatellite markers located on chromosomes 1p and 19q to assess allelic loss using loss-of-heterozygosity analysis*.

- Incomplete deletion - allelic loss on 1p19q but not at all informative loci.

*Cairncross G *et al*., 1998, JNCI 90: 1473-9.

Methods

- Estimates of progression-free and overall survival were calculated using the Kaplan-Meier method.
- Survival differences between groups were examined using log-rank test.
- Univariable and multivariable analyses were performed using Cox proportional hazard model.

Study population

- A total of 106 consecutive patients were included who presented to Princess Margaret Cancer Centre, Toronto, from December 1997 to December 2013.
- The median follow-up time for all patients was 5.1 years (range 0.1-16.3).
- As of December 2013, there were 64 (60%) progression-free survival events, 94 patients (87%) were still alive.

Patient characteristics

	All Patients (N=106)	Oligodendroglioma (N=42)	Oligoastrocytoma (N=8)	Anaplastic Oligodendroglioma (N=47)	Anaplastic Oligoastrocytoma (N=9)
Median age at diagnosis (range)	40 (19-66)	42 (24-58)	41 (28-66)	40 (19-63)	40 (30-59)
Male	58 (55%)	21 (50%)	6 (75%)	26 (55%)	5 (56%)
ECOG PS 0 1	 80 (75%) 26 (25%)	 36 (86%) 6 (14%)	 6 (75%) 2 (25%)	 33 (70%) 14 (30%)	 5 (56%) 4 (44%)
Seizure at presentation	79 (75%)	32 (76%)	7 (88%)	35 (74%)	5 (56%)
Previous low grade glioma	22 (21%)	8 (19%)	1 (12%)	11 (23%)	2 (22%)

Tumour

	All patients (N=106)	Oligodendroglioma (N=42)	Oligoastrocytoma (N=8)	Anaplastic oligodendroglioma (N=47)	Anaplastic oligoastrocytoma (N=9)
Location of tumour:					
Frontal lobe	**62 (58%)**	**25 (60%)**	**5 (62%)**	**29 (62%)**	**3 (33%)**
Contrast enhancement	**50 (47%)**	**10 (24%)**	**2 (25%)**	**33 (70%)**	**5 (56%)**
Extent of resection:					
Biopsy	**24 (23%)**	**15 (36%)**	**1 (12%)**	**7 (15%)**	**1 (11%)**
Partial	**73 (69%)**	**24 (57%)**	**5 (62%)**	**36 (77%)**	**8 (89%)**
Subtotal	**9 (8%)**	**3 (7%)**	**2 (25%)**	**4 (9%)**	**0**
1p loss alone	**4 (4%)**	**0**	**1 (12%)**	**3 (6%)**	**0**
19q loss alone	**9 (8%)**	**5 (12%)**	**1 (12%)**	**0**	**3 (33%)**
Co-deleted	**66 (62%)**	**29 (69%)**	**2 (25%)**	**32 (68%)**	**3 (33%)**
Incomplete	**27 (25%)**	**8 (19%)**	**4 (50%)**	**12 (26%)**	**3 (33%)**

Treatment

	All patients (N=106)	Oligodendroglioma (N=42)	Oligoastrocytoma (N=8)	Anaplastic oligodendroglioma (N=47)	Anaplastic oligoastrocytoma (N=9)
Up-front treatment	72 (68%)	12 (29%)	7 (88%)	44 (94%)	9 (100%)
Up-front temozolomide alone	52 (49%)	9 (21%)	5 (62%)	33 (70%)	5 (56%)
Median number of cycles (range)	12 (1-24)	12 (8-12)	12 (11-18)	12 (5-24)	12 (1-12)
Median time to treatment [days (range)]	66.5 (9-3575)	760 (22-3421)	58 (27-1876)	51 (9-3575)	55 (22-122)

Time to radiotherapy

- Median time to radiotherapy in all patients [N=47 (44%)] was 34.7 months (0.5-159.3).

Time to radiotherapy – oligodendroglioma / oligoastrocytoma

	Oligodendroglioma (Total N=42)	*Oligoastrocytoma (Total N=8)*
Radiotherapy: N (%)	**17 (40%)**	**6 (75%)**
Timing of radiotherapy:		
Up-front	**5 (29%)**	**2 (33%)**
First progression	**2 (12%)**	**1 (17%)**
Second progression	**9 (53%)**	**2 (33%)**
Third progression	**1 (6%)**	**0**
Median time to radiotherapy in months (range)	**43.2 (1.0-96.0)**	**43.4 (1.0-86.6)**

Time to radiotherapy – anaplastic oligodendroglioma / anaplastic oligoastrocytoma

	1p19q co-deleted / incomplete deletion (received temozolomide alone up-front) *(Total N=36)*
Radiotherapy: N (%)	**9 (25%)**
Timing of radiotherapy: **First progression** **Second progression** **Third progression**	 **4 (44%)** **3 (33%)** **2 (22%)**
Median time to radiotherapy in months (range)	**41.2 (16.3-93.2)**

Adverse events (patients receiving up-front temozolomide alone)

Adverse event	Grade 1/2	Grade 3	Grade 4
Thrombocytopenia	50%	2%	0
Fatigue	42%	2%	0
Nausea	42%	0	0
Neutropenia	33%	2%	0
Cognitive impairment	4%	0	0
Thrombo-embolic event	2%	0	0

Survival

Group	N	Med PFS mo (95% CI)	2yr PFS (%) (95% CI)	5yr PFS (%) (95% CI)	5yr OS (%) (95% CI)
All	106	46.3 (37.9-56.7)	81.1 (71.6-87.6)	34.0 (23.5-44.7)	90.9 (81.6-95.6)
Oligodendroglioma	42	46.1 (32.1-58.8)	79.1 (62.5-89)	32.0 (16.7-48.4)	90.3 (72.6-96.8)
Oligoastrocytoma	8	44.7 (26.2-58.8)	100 (100-100)	12.5 (0.7-42.3)	100 (100-100)
Anaplastic oligodendroglioma (AOD)	47	45.7 (30.1-63.6)	78.4 (62.5-88.2)	38.4 (22.0-54.5)	88.7 (72.2-95.7)
Anaplastic oligoastrocytoma (AOA)	9	Not reached	87.5 (38.7-98.1)	65.6 (15.7-90.9)	100 (100-100)
AOD / AOA co-deleted / incomplete (received up-front temozolomide alone)	36	46.3 (38.7-90.8)	86.0 (66.8-94.5)	43.0 (21.7-62.6)	96.0 (74.8-99.4)

Multivariable analysis of progression-free survival

Variable	Reference	Hazard ratio (95% CI, *P*)
ECOG PS 1	ECOG PS 0	2.63 (1.40-4.93, 0.003)
1p19q co-deletion / incomplete deletion	1p loss alone / 19q loss alone	0.43 (0.19-0.99, 0.047)

Conclusion

- Up-front temozolomide alone in 1p19q co-deleted / incompletely deleted anaplastic oligodendroglioma / anaplastic oligoastrocytoma resulted in favourable 5 year overall survival.
- May be a treatment option for this population.
- With similar PFS and OS patterns in low grade and anaplastic gliomas, molecular characteristics may be more important than grade.
- Results of the Phase III Intergroup Study of temozolomide alone versus radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy with adjuvant PCV chemotherapy in patients with 1p19q co-deleted anaplastic glioma are awaited.
- Isocitrate dehydrogenase-1 status is pending.

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