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Initial treatment patterns over time for anaplastic oligodendroglial tumors

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Anaplastic oligodendroglial tumors are rare neoplasms with no standard approach to treatment. We sought to determine patterns of treatment delivered over time and identify clinical correlates of specific strategies using an international retrospective cohort of 1013 patients diagnosed from 1981–2007. Prior to 1990, most patients received radiotherapy (RT) alone as initial postoperative treatment. After 1990, approximately 50% of patients received both RT and chemotherapy (CT) sequentially and/or concurrently. Treatment with RT alone became significantly less common (67% in 1980–1984 vs 5% in 2005–2007, $P < .0001$). CT alone was more frequently administered in later years (0% in 1980–1984 vs 38% in 2005–2007; $P < .0001$), especially in patients with 1p19q codeleted tumors (57% of codeleted vs 4% with no deletion in 2005–2007; $P < .0001$). Temozolomide replaced the

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combination of procarbazine, lomustine, and vincristine (PCV) among patients who received CT alone or with RT (87% vs 2% in 2005–2007). In the most recent time period, patients with 1p19q codeleted tumors were significantly more likely to receive CT alone (with temozolomide), whereas RT with temozolomide was a significantly more common treatment strategy than either CT or RT alone in cases with no deletion ($P < .0001$). In a multivariate polytomous logistic regression model, the following were significantly associated with type of treatment delivered: date (5-year interval) of diagnosis ($P < .0001$), 1p19q codeletion ($P < .0001$), pure anaplastic oligodendroglioma histology ($P < .01$), and frontal lobe predominance ($P < .05$). Limited level 1 evidence is currently available to guide treatment decisions, and ongoing phase III trials will be critical to understanding the optimal therapy.

Keywords: oligoastrocytoma, oligodendroglioma, PCV, temozolomide, 1p19q.

Anaplastic oligodendroglial tumors are rare malignant brain tumors for which the optimal therapeutic strategy is controversial. Historically, cytoreductive surgery followed by radiotherapy (RT) was the standard approach for all malignant gliomas. However, reports of oligodendroglial chemosensitivity that first emerged over 20 years ago[1] led to phase III trials by the Radiation Therapy Oncology Group (RTOG trial 9402)[2] and the European Organisation for Research and Treatment of Cancer (EORTC trial 26951)[3] testing the safety and efficacy of adding chemotherapy (CT) with the combination of procarbazine, lomustine, and vincristine (PCV) before[2] or after RT[3] following maximal safe surgical resection. These trials initially demonstrated improvements in progression-free survival (PFS) but not overall survival (OS) following RT and PCV as opposed to RT alone on early analysis. However, long-term follow-up of RTOG 9402 now demonstrates significantly longer survival from combined intensive PCV + RT over RT alone in 1p19q codeleted cases.[4–6]

However, the relatively long survival of patients with 1p19q codeleted tumors puts them at risk for delayed neurotoxicity from RT administered at diagnosis, leading many clinicians to favor CT alone, deferring RT until progression.[7] A recent German phase III trial (NOA-04) for anaplastic gliomas suggested noninferiority of deferred RT[8] but was underpowered for efficacy analyses restricted to oligodendrogliomas.[9] These phase III trials[2,3,8] and phase II studies[10] have not elucidated a single optimal treatment. Rather, several therapeutic options appear reasonable, including RT alone, CT alone with PCV or temozolomide (TMZ), and combined RT + CT (concurrently and/or sequentially) depending on clinical characteristics and molecular analyses of tumor tissue.

In a previous publication, we retrospectively captured the postoperative treatment strategies delivered to 1013 patients with anaplastic oligodendroglial tumors diagnosed over almost 3 decades (1981–2007).[11] Comparative outcomes are described elsewhere.[11] In the current report, patterns of treatment over time were determined and clinical correlates of specific strategies among patients in the retrospective cohort were analyzed.

Methods

Patients

We generated an international retrospective database of 1013 patients diagnosed with anaplastic oligodendroglioma or anaplastic oligoastrocytoma from 1981–2007 who were not treated in phase III trials and collected demographic, treatment, and survival data as reported previously.[11] To analyze differences in the postoperative initial treatment strategy delivered over time, we divided the data into 5-year intervals based on date of diagnosis: 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, and since 2005.

Statistical Analyses

Treatment patterns, patient demographics, and clinical data were summarized across the time intervals. Univariate trends in treatment administered over time were assessed via chi-square test. The clinical and pathological features associated with the likelihood of receipt of a particular treatment strategy, categorized as CT alone, RT alone, or CT + RT (concurrently and/or sequentially), were assessed using a polytomous logistic regression model. Three sets of odds ratios are reported along with 95% confidence intervals for receipt of: (1) CT alone versus RT alone; (2) CT + RT versus RT alone; and (3) CT + RT versus CT alone. All analyses were conducted and completed at Memorial Sloan-Kettering Cancer Center.

Results

Patient characteristics have been published previously.[11] Demographic information and initial postoperative treatments administered over time are shown in Tables 1 and 2. Until 1990, RT alone was the most frequently administered postoperative treatment. Beginning in 1990, approximately 50% of patients in each 5-year interval received both CT and RT, and treatment with RT alone became significantly less common (67% before 1985 vs 5% since 2005; $P < .0001$). Simultaneously, CT alone became a much more common approach (0% vs 38%; $P < .0001$ for this trend).

Among patients who received CT, either alone or with RT, TMZ replaced PCV (Tables 3 and 4) starting in approximately 2000. Among the 468 patients treated with CT (either alone or in combination with RT) since 2000, TMZ was the regimen used in 71% (333/468). This trend became even more pronounced in the last time period studied, from 2005–2007, with less than 2% receiving PCV ($P \leq .001$). In addition, concurrent TMZ with RT became much more frequent after

Table 1. Patient characteristics

	1980–1984 (*n* = 6)		1985–1989 (*n* = 28)		1990–1994 (*n* = 101)		1995–1999 (*n* = 294)		2000–2004 (*n* = 469)		2005–2007 (*n* = 115)	
	n	%	n	%	n	%	n	%	n	%	n	%
Age (y)												
Median	36		36		42		41		45		44	
Range	18–50		21–69		23–75		18–89		19–85		19–83	
Gender												
Men	4	66	17	61	60	59	170	58	257	55	65	57
Women	2	33	11	39	41	41	124	42	212	45	50	43
Histology												
Oligodendroglioma	4	67	15	54	54	53	189	64	264	56	61	53
Oligoastrocytoma	2	33	13	46	47	47	105	36	205	44	54	47
Prior low-grade glioma												
Yes	1	17	5	18	14	14	29	10	74	16	29	25
No	5	83	23	82	87	86	261	89	388	83	84	73
Unknown	0	0	0	0	0	0	4	1	7	1	2	2
Extent of resection												
Resection	3	50	19	68	88	87	248	84	397	85	101	88
Biopsy	1	17	4	14	10	10	32	11	57	12	12	10
Unknown	2	33	5	18	3	3	14	5	15	3	2	2
KPS												
≥70	5	83	19	68	69	68	228	78	413	88	103	90
<70%	1	17	4	14	11	11	35	12	40	9	10	9
Unknown	0	0	5	18	21	21	31	11	16	3	2	2
1p19q status												
1p19q codeletion	2	33	8	29	16	16	73	25	144	31	58	51
No 1p or 19q deletion	0	0	6	21	25	25	71	24	112	24	28	24
Other[a]	4	67	14	50	60	59	150	51	213	45	29	25
Lobe												
Frontal	5	83	13	46	49	49	164	56	265	57	73	63
Temporal	1	17	5	18	14	14	44	15	87	19	20	17
Parietal	0	0	3	11	13	13	36	12	56	12	13	11
Occipital	0	0	1	4	0	0	10	3	15	3	4	3
Other	0	0	1	4	8	8	14	5	41	9	5	4
Unknown	0	0	5	18	17	17	26	9	5	1	0	0
Hemisphere												
Right	4	67	6	21	49	49	141	48	210	45	56	49
Left	0	0	15	54	34	34	124	42	246	52	54	47
Bilateral	2	33	1	4	1	1	3	1	7	1	5	4
Unknown	0	0	6	21	17	17	26	9	6	1	0	0

[a]Includes unknown, discordant deletion, or partial deletion status.

Table 2. Initial postoperative treatment regimen

Initial Treatment	1980–1984 (*n* = 6%)	1985–1989 (*n* = 28%)	1990–1994[a] (*n* = 101%)	1995–1999[a] (*n* = 294%)	2000–2004[a] (*n* = 469%)	2005–2007 (*n* = 115%)
CT alone, *n* (%)	0 (0)	1 (4)	10 (10)	43 (15)	103 (22)	44 (38)
RT alone	4 (67)	15 (54)	30 (30)	65 (22)	80 (17)	6 (5)
CT + RT	1 (17)	11 (39)	51 (51)	144 (49)	262 (56)	59 (51)
Observation	1 (17)	1 (4)	7 (7)	32 (11)	17 (4)	6 (5)

Years refer to date of diagnosis; "CT + RT" indicates sequentially and/or concurrently; CT or RT "alone" refers to the initial treatment strategy, notwithstanding further therapy administered after disease progression(s).
[a]Receiving initial therapy other than those listed were 3, 10, and 7 patients diagnosed in 1990–1994, 1995–1999, and 2000–2004, respectively.

Table 3. Type of initial postoperative treatment received, categorized by 5-year time intervals and by 1p19q deletion

All Patients	1980–1984 (*n* = 6)	1985–1989 (*n* = 28)	1990–1994 (*n* = 101)	1995–1999 (*n* = 294)	2000–2004 (*n* = 469)	2005–2007 (*n* = 115)
RT alone, *n* (%)	4 (67)	15 (54)	30 (30)	65 (22)	80 (17)	6 (5)
CT alone						
TMZ	0 (0)	0 (0)	0 (0)	0 (0)	64 (14)	43 (37)
PCV	0 (0)	1 (4)	10 (10)	37 (13)	34 (7)	1 (1)
CT + RT						
TMZ + RT	0 (0)	0 (0)	0 (0)	10 (3)	169 (36)	57 (50)
PCV + RT	1 (17)	9 (32)	48 (48)	126 (43)	80 (17)	1 (1)
By deletion status						
1p19q codeletion	(*N* = 2)	(*N* = 8)	(*N* = 16)	(*N* = 73)	(*N* = 144)	(*N* = 58)
RT alone, *n* (%)	1 (50)	7 (88)	4 (25)	14 (19)	25 (17)	3 (5)
CT alone						
TMZ, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	36 (25)	32 (55)
PCV	0 (0)	0 (0)	1 (6)	7 (10)	12 (8)	1 (2)
CT + RT						
TMZ + RT	0 (0)	0 (0)	0 (0)	6 (8)	40 (28)	20 (34)
PCV + RT	1 (50)	1 (13)	8 (50)	30 (41)	18 (13)	0 (0)
No 1p19q deletion	(*N* = 0)	(*N* = 6)	(*N* = 25)	(*N* = 71)	(*N*= 112)	(*N* = 28)
RT alone, *n* (%)	0 (0)	2 (33)	11 (44)	15 (21)	20 (18)	2 (7)
CT alone						
TMZ	0 (0)	0 (0)	0 (0)	0 (0)	8 (7)	1 (4)
PCV	0 (0)	0 (0)	1 (4)	3 (4)	4 (4)	0 (0)
CT + RT						
TMZ + RT	0 (0)	0 (0)	0 (0)	1 (1)	49 (44)	22 (79)
PCV + RT	0 (0)	3 (50)	11 (44)	38 (54)	26 (23)	0 (0)
Other deletion[a]	(*N* = 4)	(*N* = 14)	(*N* = 60)	(*N* = 150)	(*N* = 213)	(*N* = 29)
RT alone, *n* (%)	3 (75)	6 (43)	15 (25)	36 (24)	35 (16)	1 (3)
CT alone						
TMZ	0 (0)	0 (0)	0 (0)	0 (0)	20 (9)	10 (34)
PCV	0 (0)	1 (7)	8 (13)	27 (18)	18 (8)	0 (0)
CT + RT						
TMZ + RT	0 (0)	0 (0)	0 (0)	3 (2)	80 (38)	15 (52)
PCV + RT	0 (0)	5 (36)	29 (48)	58 (19)	36 (17)	1 (3)

[a]Includes unknown, discordant deletion, or partial deletion status; TMZ, temozolomide; PCV, procarbazine, lomustine, and vincristine. For details, see Lassman et al.[11]

Table 4. Chemotherapy used concurrently or sequentially with radiotherapy

	1980–1984 (*n* = 1)	1985–1989 (*n* = 12)	1990–1994 (*n* = 61)	1995–1999 (*n* = 187)	2000–2004 (*n* = 365)	2005–2007 (*n* = 103)
TMZ, *n* (%)						
TMZ alone	0 (0)	0 (0)	0 (0)	0 (0)	64 (18)	43 (42)
TMZ → RT	0 (0)	0 (0)	0 (0)	0 (0)	20 (5)	6 (6)
TMZ + RT	0 (0)	0 (0)	0 (0)	0 (0)	49 (13)	39 (38)
RT → TMZ	0 (0)	0 (0)	0 (0)	10 (5)	100 (27)	12 (12)
PCV						
PCV alone	0 (0)	1 (8)	10 (16)	37 (20)	34 (9)	1 (1)
PCV → RT	1 (100)	2 (17)	19 (31)	40 (21)	35 (10)	0 (0)
PCV + RT	0 (0)	0 (0)	7 (11)	8 (4)	5 (1)	1 (1)
RT → PCV	0 (0)	7 (58)	22 (36)	78 (42)	40 (11)	0 (0)

Table 5. Multivariable polytomous logistic regression

	CT Alone vs RT Alone Odds Ratio (95% CI)	CT + RT vs RT Alone Odds Ratio (95% CI)	CT Alone vs CT + RT Odds Ratio (95% CI)	*P*-value
KPS at diagnosis <70 vs ≥70	1.62 (0.50, 5.25)	1.45 (0.56, 3.77)	1.11 (0.40, 3.08)	.67
Age	0.99 (0.96, 1.02)	0.99 (0.97, 1.02)	1.00 (0.98, 1.02)	.70
1p19q codeletion vs no deletion	3.06 (1.37, 6.84)	0.73 (0.40, 1.34)	4.19 (2.16, 8.13)	<.001
Biopsy vs resection	2.16 (0.79, 5.92)	0.90 (0.36, 2.24)	2.40 (1.07, 5.35)	.09
AO vs AOA Histology	1.46 (0.63, 3.34)	0.54 (0.29, 1.03)	2.69 (1.39, 5.18)	<.01
Frontal lobe vs other	1.62 (0.83, 3.16)	2.07 (1.18, 3.62)	0.78 (0.45, 1.35)	<.05
Bilateral vs unilateral	0.71 (0.08, 6.76)	1.23 (0.21, 7.34)	0.58 (0.10, 3.54)	.84
History of prior low grade (yes vs no)	1.15 (0.46, 2.84)	0.96 (0.44, 2.12)	1.19 (0.59, 2.40)	.89
Date (5-year interval) of diagnosis	3.18 (2.05, 4.92)	1.45 (1.06, 1.97)	2.20 (1.57, 3.19)	<.0001

AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma.

2000; prior to that, sequential RT/PCV (in either order) was the most common approach among patients who received combined modality therapy (Table 4).

Use of CT alone was restricted almost entirely to patients with 1p19q codeleted tumors; 57% of patients with codeleted tumors received CT alone vs 4% of those with no deletion in the most recent time period ($P < .0001$). By contrast, cases with no deletion received TMZ + RT as the most frequent therapy after 2000 (Table 3).

We fit a multivariate polytomous logistic regression model to examine factors associated with receipt of RT alone, CT alone, or CT + RT. We found that 1p19q codeletion ($P < .0001$), anaplastic oligodendroglioma histology ($P < .01$), frontal lobe predominance of the tumor ($P < .05$), and 5-year interval of diagnosis ($P < .0001$) were significantly associated with the type of treatment delivered (Table 5). Specifically, patients with codeleted tumors or "pure" oligodendrogliomas (rather than mixed oligoastrocytomas) were significantly more likely to receive CT alone compared with RT alone or CT + RT. Those with frontal tumors were more likely to receive CT + RT than RT alone but were not significantly more likely to receive CT alone than another strategy (Table 5).

Discussion

Anaplastic oligodendroglial tumors are rare primary brain tumors lacking a standard treatment approach for newly diagnosed patients. In the analysis presented here, clear treatment patterns over time emerged that paralleled the development of new therapies, such as TMZ for recurrent anaplastic astrocytoma, and chemoradiotherapy (with TMZ) for newly diagnosed glioblastoma. We found that the use of RT alone decreased significantly over time and that CT has become a standard component of initial treatment, either alone or in combination with RT. Integration of CT into initial therapy occurred concurrently with and despite upfront data from phase III trials demonstrating no improvement in OS from the addition of CT (with PCV) to RT in anaplastic oligodendroglial tumors.[2,3] Furthermore, TMZ replaced PCV as the CT regimen administered either alone or in combination with RT since 2000, shortly after TMZ was first FDA approved (accelerated) for recurrent anaplastic astrocytomas in 1999.[12] Level 1 evidence to support this transition for oligodendroglial tumors is lacking, and existing data[8] are controversial,[9,13] but the more favorable toxicity profile of TMZ likely underscored the immediate switch, as discussed elsewhere.[11]

We also observed that the most frequently administered initial postoperative therapy comprised a combination of CT and RT, with 49%–56% of patients diagnosed since 1990 receiving both. Randomized data to support such treatment for anaplastic oligodendroglial tumors are also lacking, but the successful phase III trial for glioblastoma by the EORTC and the National Cancer Institute of Canada published in 2005 has solidified this approach in the minds of many.[14] Whether results in glioblastoma (combining RT + TMZ) can and should be extrapolated to more indolent anaplastic (or low-grade) oligodendroglial tumors will be unknown until results from ongoing phase III studies are available.

Finally, among patients with 1p19q codeleted tumors, CT alone (almost universally TMZ) has been administered to 57% of patients since 2005. The recommendation to defer RT is based in part on the desire to avoid late neurocognitive toxicity of RT in such patients, analogous to the approach for low-grade glioma.[15] Notably, this is modestly higher than the frequency of 42% advised by surveyed neuro-oncologists in 2005,[7] suggesting that the trend to defer RT may be increasing. Prospective[8] and retrospective data[11] suggest that OS is not compromised by deferring RT in favor of CT alone. However, no appropriately powered randomized study has been conducted yet to support this approach in 1p19q codeleted anaplastic oligodendroglial tumors.

Two large phase III randomized trials are now accruing patients from across North America and Europe to compare initial treatment strategies for anaplastic gliomas with and without 1p19q codeletion. These are critically important studies, and we encourage enrollment. The phase III trial of CATNON (Concurrent and/or Adjuvant TMZ for 1p19q NON

deleted tumors) will test the efficacy of CT (with TMZ) during and/or after RT vs RT alone for patients with anaplastic tumors that do not harbor 1p19q codeletion (http://clinicaltrials.gov/ct/show/NCT00626990). Potentially more controversial is the CODEL (for "CO-DEL"etion) phase III trial, which examines the role of CT (with TMZ) alone initially by randomizing 150 patients to TMZ alone, RT alone, or RT + TMZ (http://clinicaltrials.gov/ct/show/NCT00887146). Subsequently, patients are randomized to compare OS for RT alone vs RT + TMZ, as was done by Stupp et al.[14] for glioblastoma. Our results raise the possibility that although a thoughtfully designed trial, CODEL may suffer from a lack of perceived clinical equipoise, which may hinder accrual. Many neuro-oncologists want to delay RT in patients with codeleted oligodendroglial tumors; it remains to be seen whether they will suspend judgment long enough for the CODEL trial to accrue nearly 500 patients overall. In addition, long-term follow-up of codeleted cases from RTOG 9402, incomplete at initial publication[2] but currently emerging, demonstrates that median survival doubles when the initial treatment combines intensive-PCV and RT.[4–6] This may also affect the future design of CODEL and other clinical trials for this disease.

Our study suffers several limitations, most importantly the retrospective data collection and small size of the oldest cohort (1984–1989). We also did not address how patterns of diagnosis have changed over time, or how this may have affected treatment decisions.[16] For example, oligoastrocytomas containing necrosis would now be characterized as glioblastoma,[17] an observation made by others regarding the potential interpretation of prospective trials as well.[3,18]

However, studies such as ours may become increasingly useful in neuro-oncology for relatively indolent cancers like oligodendrogliomas and low-grade gliomas, where new ideas and new treatments may emerge faster than traditional comparative phase III trials can be conducted. Although the data set was retrospective, clear trends in treatment patterns were identified that may guide clinical trial design.

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