# Survey of treatment recommendations for anaplastic oligodendroglioma

Lauren E. Abrey, David N. Louis, Nina Paleologos, Andrew B. Lassman, Jeffrey J. Raizer, Warren Mason, Jonathan Finlay, David R. MacDonald, Lisa M. DeAngelis, and J. Gregory Cairncross for the Oligodendroglioma Study Group (see Appendix)

*Memorial Sloan-Kettering Cancer Center, New York, NY, USA (L.E.A., A.B.L., L.M.D.); Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA (D.N.L.); Northwestern University, Evanston, IL, USA (N.P.); Northwestern University, Feinberg School of Medicine, Chicago, IL, USA (J.J.R.); Princess Margaret Hospital, Toronto, Canada (W.M.); Children's Hospital of Los Angeles, Los Angeles, CA, USA (J.F.); London Regional Cancer Centre, London, Canada (D.R.M.); and University of Calgary, Calgary, Canada (J.G.C.)*

**Anaplastic oligodendroglioma is a malignant brain tumor uniquely sensitive to treatment with both chemotherapy and radiotherapy. There are few prospective clinical trials for newly diagnosed patients and multiple approaches to the treatment of these patients. This study explored the recommended treatment offered by experts in neuro-oncology. A Web-based survey was developed and distributed to 800 members of the Society of Neuro-Oncology (SNO) who had an e-mail address listed with SNO. Questions addressed use of molecular genetic information and treatment recommendations. A total of 99 clinical SNO members (20%) responded. The majority reported practicing at an academic center in the United States. Two-thirds of respondents see more than five patients with newly diagnosed anaplastic oligodendroglioma annually. Molecular genetic testing was requested for more than 75% of patients, and the results significantly influenced treatment recommendations ($p = 0.000003$). Regardless of molecular genetic status, the most commonly recommended treatment was the use of concurrent temozolomide and radiotherapy followed by adjuvant temozolomide (18%–34%). The current survey demonstrates that although neuro-oncologists have embraced the use of molecular genetic studies in newly diagnosed anaplastic oligodendroglioma, treatment recommendations vary widely and are often independent of the molecular data.** *Neuro-Oncology 9, 314–318, 2007 (Posted to Neuro-Oncology [serial online], Doc. D06-00067, April 13, 2007. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2007-002)*

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Anaplastic oligodendroglioma was first recognized as a chemosensitive glial tumor in 1988.[1] In the 1990s, molecular genetic studies demonstrated that allelic loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) were important prognostic markers of chemosensitivity and longer survival.[2–7] Identification of the chemosensitivity and the prognostic role of molecular markers in anaplastic oligodendroglioma represents one of the most exciting and important discoveries in neuro-oncology in the last decade. However, at present, there is no defined standard of care for the management of anaplastic oligodendrogliomas or specific guidelines for integrating the results of molecular studies into a therapeutic plan.

Anaplastic oligodendroglioma is a relatively rare tumor, so large prospective studies take many years to accrue and patterns of clinical practice have evolved independently of prospective data. The current recommended management of anaplastic oligodendrogliomas by the National Comprehensive Cancer Network

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Address correspondence to Lauren E. Abrey, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA (abreyl@mskcc.org).

(NCCN) is maximal resection followed by focal radiotherapy (RT) with or without adjuvant chemotherapy. This recommendation is supported by the results of a Radiation Therapy Oncology Group (RTOG) 94-02 study which showed that neoadjuvant chemotherapy using procarbazine, lomustine (CCNU), and vincristine (PCV) administered prior to RT did not prolong patient survival significantly compared with postoperative RT alone. This lack of a difference in overall survival was attributed in part to the successful use of PCV at recurrence in those who received RT alone initially.[8] However, the addition of PCV prolonged disease-free survival for patients with 1p/19q deletion only, and this group of patients had a much longer overall survival regardless of treatment. Similarly, the recent results of European Organization for Research and Treatment of Cancer (EORTC) 26951 demonstrated that adjuvant PCV did not improve overall survival for patients with newly diagnosed anaplastic oligodendroglioma.[9] These data suggest that the NCCN guidelines still represent the standard of care, but it is not clear how often neuro-oncologists follow these guidelines or recommend other therapies.

Because there are a number of possible ways in which clinicians might integrate new or emerging data about oligodendroglial tumors into clinical practice, we developed a survey to assess current patterns of practice. We sent this survey to all members of the Society of Neuro-Oncology (SNO) to learn more about the ways in which experts in neuro-oncology were advising and managing their patients. SNO is a multidisciplinary organization of physicians and scientists with expertise in primary brain tumors with approximately 500 clinical members. This survey specifically addressed the availability and use of molecular studies for 1p and 19q, and treatment recommendations for patients with or without information regarding 1p and 19q status.

## Methods

In February 2005, surveys were e-mailed to all members of SNO. The survey was completed using a Web-link that automatically collated submitted information. Questions addressed several specific domains, including (a) demographic information of the respondent, (b) patient volume, (c) pathological evaluation including use of molecular genetic testing, and (d) usual treatment recommendations. We allowed three months for completion of the survey, and all members received two follow-up e-mails reminding them of the deadline for completion. Submitted responses are reported descriptively as a percentage of total respondents. Discrete variables were analyzed using $\gamma^2$ analysis with Yates correction applied for expected variables of less than 5.

## Results

Of the approximately 500 clinical members of SNO, 99 (20%) replied to the survey. Responses from nonclinicians were not included. Breakdown by specialty and relative percentage of SNO membership is listed in Table 1. A total of 88% of respondents identified themselves as having an academic practice, and 72% practiced within the United States. Respondents were equally divided regarding the number of new anaplastic oligodendroglioma patients seen annually: 37% reported seeing 1–5 per year, 33% reported seeing 6–10 per year, and 31% reported seeing more than 10 per year.

### *Pathology*

The majority of respondents rely on the neuropathologist at their institution for diagnosis and seek a second opinion in 25% or fewer of all cases. In contrast, 12% get a second opinion for more than 75% of their patients. Pathology, if referred for a second opinion, was most commonly sent to a reference neuropathologist at an academic medical center.

Molecular genetic testing for allelic loss of 1p and 19q was requested in more than 75% of patients with anaplastic oligodendroglioma by the majority of respondents (Table 2). However, one in five respondents request this test in fewer than half of anaplastic oligodendroglioma patients or never request molecular marker analysis. Reasons given for not testing for 1p/19q loss in anaplastic oligodendroglioma included (a) lack of tissue

**Table 1.** Respondents by specialty

| | Total Respondents | Percentage of SNO Members Responding to the Survey[a] |
|---|---|---|
| Neurosurgery | 30 | 17 |
| Neuro-oncology | 50 | 30 |
| Medical Oncology | 5 | 6 |
| Radiation Oncology | 12 | 10 |
| Other | 5 | 2 |

Abbreviation: SNO, Society for Neuro-Oncology.

[a]Calculated as number of subspecialists responding divided by SNO membership for that subspecialty.

**Table 2.** Reported molecular genetic testing

| | |
|---|---|
| **By Tumor Type** | |
| Anaplastic oligodendroglioma | 95% |
| Obtain in 76%–100% of patients | 75% |
| Obtain in 51%–75% of patients | 5% |
| Obtain in 1%–50% of patients | 15% |
| Never obtain | 5% |
| Mixed glioma (oligoastrocytoma) | 92% |
| Anaplastic astrocytoma | 33% |
| Low-grade oligodendroglioma | 14% |
| Glioblastoma | 7% |
| **By Methodology** | |
| FISH | 48% |
| LOH | 29% |
| Both FISH and LOH | 6% |
| Unsure/not answered | 17% |

Abbreviations: FISH, fluorescence in situ hybridization; LOH, loss of heterozygosity.

(39%), (b) not available (30%), (c) cost (20%), (d) lack of clinical utility (11%), and (e) other (11%). For other tumor types, there was variable use of 1p/19q testing.

Molecular genetic testing of 1p/19q was reported to be available at 64% of institutions; fluorescence in situ hybridization (FISH) was used more frequently than loss of heterozygosity (LOH) polymorphism analysis. Most respondents (62%) reported that they did not know the patient charge for this testing; 19% reported a charge of less than $500, 16% reported a charge between $500 and $1,000, and 3% reported a charge of more than $1,000.

### *Treatment Recommendations*

The survey asked respondents to indicate their preferred treatment for a patient with a newly diagnosed anaplastic oligodendroglioma, given a variety of genetic scenarios (Table 3). Overall, the most frequent recommendation made by approximately one-third of respondents was the concurrent administration of temozolomide and RT followed by adjuvant temozolomide when 1p/19q information was unavailable, both chromosomes were intact, or 1p was intact. If 1p status was unknown, or both 1p and 19q were intact, 86%–90% of respondents recommended RT as a component of treatment. If 1p was intact with associated loss of 19q, 80% recommended RT. For patients with 1p and 19q loss, respondents were more likely to recommend chemotherapy alone (42%) (with either temozolomide [34%] or PCV [8%]). RT was recommended as a component of therapy in only 56% of these patients.

If 19q was intact in the setting of 1p loss, 70% of respondents recommended RT, and only 26% recommended chemotherapy alone. Inclusion of RT was recommended more frequently for those patients with an unknown genetic status or in those patients with intact 1p and 19q, as compared with a patient with loss of 1p or 19q ($p = 0.000003$). Both 1p or 19q loss independently decreased the likelihood that RT would be recommended (1p LOH, $p = 0.000002$; 19q LOH, $p = 0.008$).

For patients with mixed oligoastrocytoma, the proportion of tumor reported to be oligodendroglial influenced the treatment in the same fashion as a pure anaplastic oligodendroglioma (Table 4). In addition, 43% reported that they would treat a patient with a mixed oligoastrocytoma and 1p/19q loss in an identical fashion as an anaplastic oligodendroglioma. One-third of respondents reported having a clinical trial available at their institution for patients newly diagnosed with an anaplastic oligodendroglioma.

## Discussion

This survey demonstrates there is no uniform approach to the management of anaplastic oligodendroglioma among academic neuro-oncologists and that experts in the field have been quick to adopt the use of molecular genetic testing. However, the results of genetic testing are not being used consistently to guide treatment decisions with the exception of 1p and 19q deletion, where there is a clear tendency, rightly or wrongly, to treat with chemotherapy initially and try to postpone RT. Although patients with anaplastic oligodendroglioma with 1p and 19q loss have an excellent prognosis if treatment includes RT at initial diagnosis, there are no robust data on the prudence of delaying RT in this subset of patients.

Pathology was rarely sent to an outside pathologist for a second opinion. This may reflect that the majority of respondents reported that they practiced at an academic medical center where they have access to a dedicated neuropathologist. However, this is a potentially important issue because several studies indicate significant discordance among neuropathologists in the diagnosis of an oligodendroglioma.[10–12] This highlights the need for central neuropathological review in oligodendroglioma clinical trials. Even this practice of central pathology review, though, guarantees uniformity only within a given study and does not eliminate variation from study to study. In this regard, reporting the combination of histological diagnosis and molecular genetic profiles may be helpful to improve the consistency and comparison of different clinical trials.

Molecular genetic assessment of allelic loss on 1p and 19q is both widely available and ordered by most respondents. The most common reasons given for not obtaining 1p/19q testing were lack of tissue or availability of testing; however, 11% were not confident that 1p/19q testing had clinical utility. The best available data suggest that there are at least four molecular subsets of anaplastic oligodendroglioma, each with distinct clinical outcomes.[13] In a retrospective analysis of patients with anaplastic oligodendroglioma who received PCV as the initial postoperative therapy (RT deferred),[6] patients

**Table 3.** Recommended treatment based on chromosomal analysis

| | Temo Followed by RT (%) | Concurrent Temo/RT Followed by Temo (%) | RT Followed by Temo (%) | Temo Alone (%) | RT Alone (%) | PCV and Then RT (%) | RT and Then PCV (%) | PCV Alone (%) | Other (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1p/19q unavailable | 12 | 32 | 22 | 11 | 7 | 9 | 4 | 0 | 4 |
| 1p/19q intact | 5 | 34 | 19 | 7 | 20 | 5 | 7 | 0 | 3 |
| 1p and 19q LOH | 11 | 18 | 11 | 34 | 4 | 7 | 5 | 8 | 3 |
| 1p LOH, 19q intact | 17 | 23 | 12 | 23 | 7 | 7 | 4 | 4 | 4 |
| 1p intact, 19q LOH | 11 | 31 | 14 | 14 | 11 | 8 | 5 | 3 | 4 |

Abbreviations: RT, radiotherapy; Temo, temozolomide; PCV, procarbazine, lomustine (CCNU), and vincristine; LOH, loss of heterozygosity.

**Table 4.** Mixed oligoastrocytoma

| Oligodendroglioma Fraction | Recommend Treating as AO |
|---|---|
| Up to 25% | 9% |
| 26%–50% | 20% |
| >50% | 21% |
| 1p/19q LOH | 43% |

Abbreviations: AO, anaplastic oligodendroglioma; LOH, loss of heterozygosity.

whose tumors harbored isolated, combined loss of 1p and 19q had the most favorable outcomes. These findings suggest that therapy may be rationally selected on the basis of molecular analysis, although there are no prospective data to validate treatment selection based on the molecular signature of a tumor.

It is much less clear whether molecular testing of other primary brain tumors is valuable for prognosis or treatment sensitivity. The most frequent other tumor that respondents report testing for 1p/19q loss is the mixed oligoastrocytoma. This may be useful to determine whether the tumor is biologically more akin to an oligodendroglioma than an astrocytoma. Those oligoastrocytomas with greater genetic similarity to pure oligodendroglioma might behave more favorably with regard to prognosis and therapy. Analysis of 1p/19q status may also be useful in differentiating small cell glioblastoma from anaplastic oligodendroglioma. However, there is no clear evidence that 1p/19q status determines prognosis or treatment sensitivity for glioblastoma or other malignant gliomas.[14]

Respondents report using FISH more often than LOH, and a few use array comparative genomic hybridization to determine chromosomal status. Most data suggest that FISH and LOH yield comparable results for 1p and 19q analysis, although the data are not 100% concordant. LOH has the advantage of detecting all allelic losses and being easy to interpret, but it is technically more complex and requires blood for comparative DNA analysis. FISH does not require additional clinical material and is technically less complex but may be more difficult to score than LOH. Overall, the cost for these two techniques is similar, but respondents reported a wide range of charges associated with assessment of 1p/19q. It is unknown whether third-party payers reimburse for these studies.

The tumor's molecular genetic status clearly influenced the recommended treatment. Patients with 1p loss were less likely to have RT recommended, whereas those with 1p intact were reportedly referred for RT 80% of the time. For patients with combined 1p and 19q loss, about one-third of respondents recommended chemotherapy alone. These patients have an excellent prognosis, with many surviving 10 years or longer. Thus, this cohort is at high risk for developing delayed neurocognitive toxicity as a consequence of RT; therefore, it might be reasonable to defer RT in an effort to optimize quality of life.

Despite the recommended NCCN guidelines and results of recent EORTC and RTOG trials strongly supporting the use of RT alone or as part of the initial management of anaplastic oligodendroglioma, our respondents recommended chemotherapy alone in 3%–32% of the scenarios presented. RT was incorporated into the treatment plan of 68%–95% of patient scenarios. The most frequently recommended therapy was concurrent administration of temozolomide and RT followed by adjuvant temozolomide. This regimen was recently reported by Stupp et al.[15] to offer a significant survival advantage for patients with glioblastoma as compared with RT alone, but the appropriate use of this regimen in the treatment of anaplastic oligodendroglioma is unknown.

Temozolomide was recommended over PCV by a ratio of nearly 5:1. Historically, PCV is the regimen most frequently reported in clinical studies of anaplastic oligodendroglioma, with radiographic response rates up to 75%; however, this regimen is associated with cumulative myelosuppression, nausea, vomiting, and weight loss. Studies suggest that temozolomide has efficacy in the treatment of recurrent oligodendroglioma, with response rates of 25%–56%.[16,17] It seems likely that these data, coupled with the more tolerable side-effect profile of temozolomide, have influenced the respondent's recommendations. However, the efficacy of temozolomide has never been directly compared with PCV for anaplastic oligodendroglioma.

Our results are limited by the fact that this was a survey of what clinicians report recommending in various clinical situations and therefore has potential recall bias. Also, a minority of clinical members of SNO responded to the survey. Therefore, actual clinical practice might not be accurately or completely reflected by these results. However, the 30% response rate among neuro-oncologists suggests that this survey reflects that range of practice at academic centers within the United States. A retrospective assessment of the actual practice patterns at several major neuro-oncology centers in the United States and Canada is currently being conducted by the Oligodendroglioma Study Group.

Hypothesis-driven prospective clinical trials for newly diagnosed anaplastic oligodendroglioma are critical to assess new treatment paradigms and to delineate appropriate ways to tailor treatment recommendations based on molecular genetic information. Given the relative scarcity of patients with newly diagnosed anaplastic oligodendroglioma, international collaboration will be critical to the successful conduct of planned trials. In lieu of the results of planned and ongoing studies, it may be useful to outline specific recommendations for the management of anaplastic oligodendroglioma by either meta-analysis or an expert consensus interpretation of the available literature.[18]

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**Appendix.** Oligodendroglioma Study Group

| Member | Affiliation |
|---|---|
| Lauren E. Abrey, M.D. | Memorial Sloan-Kettering Cancer Center |
| J. Gregory Cairncross, M.D. | University of Calgary |
| Lisa M. DeAngelis, M.D. | Memorial Sloan-Kettering Cancer Center |
| Jonathan Finlay, M.D. | Children's Hospital of Los Angeles |
| Peter Forsyth, M.D. | Tom Baker Cancer Center |
| Andrew B. Lassman, M.D. | Memorial Sloan-Kettering Cancer Center |
| Frank Lieberman, M.D. | University of Pittsburgh |
| David N. Louis, M.D. | Massachusetts General Hospital/Harvard Medical School |
| David R. MacDonald, M.D. | London Regional Cancer Centre |
| Warren Mason, M.D. | Princess Margaret Hospital |
| Nina Paleologos, M.D. | Northwestern University |
| Edward Pan, M.D. | Florida Hospital Cancer Institute |
| Jeffrey J. Raizer, M.D. | Northwestern University/Feinberg School of Medicine |
| Steven Rosenfeld, M.D. | Columbia University |
| David Schiff, M.D. | University of Virginia |
| Susan Weaver, M.D. | Albany Medical College |

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