

Response Criteria for Phase II Studies of Supratentorial Malignant Glioma

By David R. Macdonald, Terrance L. Cascino, S. Clifford Schold, Jr, and J. Gregory Cairncross

We suggest "new" response criteria for phase II studies of supratentorial malignant glioma and favor rigorous criteria similar to those in medical oncology, with important modifications. Four response categories are proposed: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Response in this scheme is based on major changes in tumor size on the enhanced com-

puted tomographic (CT) or magnetic resonance imaging (MRI) scan. Scan changes are interpreted in light of steroid use and neurologic findings. We advocate careful patient selection, emphasize pitfalls in the assessment of response, and suggest guidelines to minimize misinterpretations of response.

J Clin Oncol 8:1277-1280. © 1990 by American Society of Clinical Oncology.

LEVIN ET AL in the early computed tomographic (CT)-scan era proposed response criteria for patients with malignant (ie, anaplastic) glioma receiving chemotherapy.¹ These criteria introduced rigor to clinical studies of brain tumor. Following their lead, we suggest new criteria based on modern scanning and a fuller appreciation of the influence of steroids on neurologic findings and brain tumor images. Pediatric oncologists who treat brain tumor have developed response criteria similar to those advocated here.²

Response criteria for brain tumor have evolved slowly, in part because neuro-oncologists have lacked experience with responding tumors. Medical oncologists learned quickly the meaning of response by "starting with lymphoma." Neuro-oncologists have struggled with the concept of response because chemotherapy has had little impact on the common malignant glioma of adults, namely glioblastoma multiforme. However, neuro-oncologists have recently observed significant responses to chemotherapy in several uncommon brain tumors (eg, oligodendroglioma, lymphoma, medulloblastoma) and as a result of these "successes" have a new perspective on the range of responses (and nonresponses) that are possible with systemic therapies for brain tumor.

For most disease sites in oncology, response is defined as a $\geq 50\%$ reduction in tumor size. The usual measure of "size" is the largest cross-sectional area (largest cross-sectional diameter \times largest diameter perpendicular to it). Medical oncologists adopted this definition because treatments that produced only small reductions in tumor size in phase II studies did not lead to

meaningful disease control or prolong life in definitive phase III trials. Neuro-oncologists on the other hand, not wanting to overlook effective drugs, often accept minor scan improvements or stable disease as evidence of antitumor activity, arguing that the blood-brain barrier and slow debris-clearing mechanisms in the brain, make brain tumor a "special" case. Because promising brain tumor treatments are advanced to phase III studies that are expensive, require large numbers of patients, and take years to complete, we have reservations about lenient definitions of response.

We suggest that neuro-oncologists adopt uniform, rigorous response criteria similar to those in general oncology. Uniform criteria facilitate communication and comparison of results. Rigorous criteria guard against overinterpretation of minor nontreatment-related clinical and scan changes. Our criteria stress imaging and steroid requirements and deemphasize, but do not ignore, clinical considerations. There are four "response" categories: complete response (CR): disappearance of all enhancing tumor on consecutive CT or magnetic resonance imaging (MRI)

From the Departments of Clinical Neurological Sciences and Oncology, University of Western Ontario and London Regional Cancer Centre, London, Ontario; the Department of Neurology, Mayo Clinic, Rochester, MN; and the Department of Medicine (Neurology), Duke University Medical Center, Durham, NC.

Submitted January 3, 1990; accepted March 12, 1990.

Address reprint requests to J. Gregory Cairncross, MD, London Regional Cancer Centre, 790 Commissioners Rd, East, London, Ontario, Canada N6A 4L6.

© 1990 by American Society of Clinical Oncology.

0732-183X/90/0807-0019\$3.00/0

scans at least 1 month apart, off steroids, and neurologically stable or improved. Partial response (PR): $\geq 50\%$ reduction in size of enhancing tumor on consecutive CT or MRI scans at least 1 month apart, steroids stable or reduced, and neurologically stable or improved. Progressive disease (PD): $\geq 25\%$ increase in size of enhancing tumor or any new tumor on CT or MRI scans, or neurologically worse, and steroids stable or increased. Stable disease (SD): all other situations.

Response in this scheme demands a sustained (ie, ≥ 1 month) and significant (ie, $\geq 50\%$) reduction in the size of the enhancing tumor on CT or MRI scans. We suggest that size be considered the tumor's largest cross-sectional area. Volume measurements are technically difficult in many glioma patients and may not be the wisest choice for response assessment.³ A less rigorous definition of size reduction (eg, $\geq 25\%$ reduction in area) may be acceptable, but insisting on a $\geq 50\%$ reduction gives a noticeably smaller tumor and "room for error." Error is unavoidable in any measurement, but its impact will be greater when attempting to detect smaller differences, rather than larger ones.⁴ A more rigorous definition of size reduction (eg, $\geq 50\%$ reduction in diameter) may also be acceptable, but we think this may be too stringent. Judging by experience with oligodendroglioma⁵ and primitive neuroectodermal tumor⁶ in which unequivocal, prolonged CT responses to chemotherapy have been observed, we are confident that CT and MRI scans will demonstrate response when response occurs. Likewise, experience with glioblastoma multiforme demonstrates that CT and MRI detect nonresponse when tumors are resistant.

Steroid use must be considered in response assessment. By themselves, these drugs improve symptoms and signs, maintain clinical improvement for extended periods even at low or reduced doses, and substantially decrease the size of some malignant gliomas on CT scans.⁷ These benefits mimic treatment effects making it difficult for neuro-oncologists to assess the tumor's response to concurrent therapies. Response assessment is considerably easier in the minority of patients who do not require steroids for symptom control. The neurologic examination may be helpful in

assessing response, but many patients have "fixed" deficits that will not improve even with successful treatment.

The SD category is a guide to continue treatment, but we are reluctant to call stable patients responders; others may disagree. Virtually all patients in the SD category are receiving two treatments, a steroid and an investigational agent. Neuro-oncologists are "on thin ice" attributing clinical stability and minor scan improvement to chemotherapy when steroids are so predictably effective. For this reason, response in our scheme downplays clinical changes and demands a significant reduction in tumor size. When new drugs halt the growth of previously enlarging tumors for sustained periods without the benefit of steroids, then stable disease may signify antitumor activity.

Tumor progression is defined by increasing tumor size, new areas of tumor, or unequivocal neurologic deterioration. Provided the investigator carefully excludes nontumor-related causes of clinical or radiologic worsening (ie, pseudoprogression), either is evidence of treatment failure. Examples of pseudoprogression include premature steroid reduction, steroid myopathy, frequent seizures, and systemic disturbances such as infection, pulmonary emboli, metabolic encephalopathy (ie, hyponatremia, hyperglycemia), or anticonvulsant toxicity. The neurologic examination is not a reliable measure of response, but it can be an important and valid measure of progression. Patients requiring escalating steroid doses to maintain neurologic function, in the absence of significant CT worsening (ie, $< 25\%$ increase or no change), may have early tumor progression but are included in the stable category. These patients warrant early reevaluation.

When is response assessed, how is its duration measured, and when can treatment failure be declared? In our experience, CR can occur within 2 months, and time to maximum response can be as long as 6 to 12 months. Murovic et al reported that time to CR may range from 9 to 151 weeks.⁸ We suggest that patients be assessed for response after two courses of treatment, that responding and stable patients continue treatment, that duration of response be the interval between the start of treatment and the first clinical or radiologic sign of tumor progression, and that tumor

progression be declared no sooner than 1 month after the first course of treatment.

Rigorous response criteria must be coupled with careful patient selection. First, central pathology review by an experienced neuropathologist is recommended for all protocol patients. Second, malignant gliomas are a heterogeneous group of tumors and may differ in their response to cytotoxic drugs.⁵ Failure to consider this in study design and analysis makes it difficult to compare studies and possible to overlook important responses in low frequency subtypes of anaplastic glioma hidden in larger groups.⁵ We suggest that phase II studies of malignant glioma focus on a single tumor type or establish separate accrual goals for each type included in the trial. Third, investigational drugs should be reserved for patients with better function (eg, Karnofsky score ≥ 60) as those with severe disability may not live long enough to be assessable for response. Finally, investigational agents should be restricted to patients with limited prior chemotherapy. Insufficient bone marrow reserve, or resistance to multiple drugs, may prevent a "fair test" of a new compound in heavily pretreated patients. We suggest that phase II studies of anaplastic glioma exclude patients who have previously received chemotherapy for recurrent tumor.

In addition to steroids, there are other peculiarities of CNS tumors that increase the potential for false-positive and, to a lesser degree, false-negative responses. The investigator must be aware of these pitfalls. Factors mimicking response include delayed clinical and CT improvement (similar false-positives and false-negatives may occur with gadolinium-enhanced MRI) following surgery or radiotherapy, spontaneous resolution of postoperative or hemorrhage-related CT enhancement,⁹ spontaneous resolution of CT enhancing radiation effects¹⁰ and apparent CT improvement due to changes in scanning technique (eg, immediate scan, low-dose contrast). Factors contributing to false-negative responses include misdiagnosis (eg, radiation necrosis) and apparent CT worsening due to changes in scanning technique (eg, delayed scan, high-dose contrast). The following guidelines are intended to minimize errors in the interpretation of response: Delay investigational treatment following major

tumor resection unless there is unequivocal residual tumor on CT or MRI scans. Delay investigational treatment following conventional radiotherapy or adjuvant chemotherapy for 2 months and preferably until there is scan-documented, enlarging tumor. Rebiopsy before investigational treatment following interstitial radiotherapy (eg, radiation necrosis), long periods of tumor control after initial treatment (eg, change in tumor type) or whenever there is doubt about diagnosis. Delay investigational treatment for 2 weeks and obtain a new baseline scan following the introduction of steroids or a major change in steroid dose. Keep steroid dose stable for 2 weeks during periods critical for response evaluation. Use uniform scanning technique (ie, scanner, patient position, dose of contrast, injection/scan interval).

No criteria are perfect or apply to all situations, and we foresee some limitations with these. The designation CR poses a potential problem in that the scan rarely normalizes and small enhancing abnormalities of uncertain significance may persist on CT scans (and presumably MRI scans) following successful treatment.¹¹ With experience, we may equate "major" PR (eg, $\geq 90\%$ reduction in tumor size) with "complete" response. Similar concerns have been raised in general oncology. In lymphoma, minor persistent abdominal scan abnormalities negating CR have proved not to be tumor when rebiopsied.¹² In this situation, where the scan has underestimated response, major partial responders may have the same prognosis as complete responders. Most malignant gliomas enhance following contrast; some do not.¹³ Our criteria are not suitable for the assessment of nonenhancing malignant tumors. Perhaps a $\geq 50\%$ reduction in the size of the hypodense area is a reasonable definition of PR but normalization of the scan (ie, CR) is unlikely as surgical defects and gliosis produce permanent low-density abnormalities in most cases. We think our criteria are an acceptable definition of response for heterogeneously enhancing tumors (ie, tumors containing enhancing and nonenhancing regions). More anaplastic areas of these tumors usually enhance, and enhancing regions may be easier to measure than nonenhancing ones.

Two additional points merit comment. First, response criteria are important in nonstudy situations. Glioma patients who are not eligible for a study or refuse investigational treatment can be offered nonprotocol chemotherapy. Response assessment is important for their management (ie, is treatment working, or not?) and the same criteria and guidelines can be used. Second, the clinical trial is a special patient care situation.

The physician investigator must be certain that the clinical trial is properly designed and executed. Careful patient selection and rigorous response criteria are essential elements of the successful "clinical experiment."

ACKNOWLEDGMENT

The authors thank Dr Leslie Levin for helpful discussions, Drs Ian Tannock and Charles Moertel for reviewing the manuscript, and Pat Gray for preparing the manuscript.

REFERENCES

1. Levin VA, Wilson CV, Crafts D, et al: Criteria for evaluating patients undergoing chemotherapy for malignant brain tumor. *J Neurosurg* 47:329-335, 1977
2. Zeltzer PM, Friedman HS, Norris DG, et al: Criteria and definition of response and relapse in children with brain tumor. *Cancer* 56:1824-1826, 1985
3. Chisholm RA, Stenning S, Hawkins TD: The accuracy of volumetric measurement of high-grade gliomas. *Clin Radiol* 40:17-21, 1989
4. Warr D, McKinney S, Tannock I: Influence of measurement error on assessment of response to anticancer chemotherapy: Proposal for new criteria of tumor response. *J Clin Oncol* 2:1040-1046, 1984
5. Cairncross JG, Macdonald DR: Successful chemotherapy for recurrent malignant oligodendroglioma. *Ann Neurol* 23:360-364, 1988
6. Lefkowitz I, Packer R, Siegel K, et al: Results of treatment of children with recurrent primitive neuroectodermal tumors—medulloblastoma (PNET/MB) with CCNU, cis-platinum (CPDD) and vincristine (VCR). *Proc Am Soc Clin Oncol* 6:71, 1987 (abstr)
7. Cairncross JG, Macdonald DR, Pexman JHW, et al: Steroid-induced CT changes in patients with recurrent malignant glioma. *Neurology* 38:724-726, 1988
8. Murovic J, Turowski K, Wilson CB, et al: Computerized tomography in the prognosis of malignant cerebral gliomas. *J Neurosurg* 65:799-806, 1986
9. Cairncross JG, Pexman JHW, Rathbone MP: Post-surgical contrast enhancement mimicking residual brain tumor. *Can J Neurol Sci* 12:75, 1985
10. Cascino TL, Kimmel DW, Dinapoli RP, et al: Report of four cases with a resolving syndrome which otherwise simulates recurrent brain tumor. *Neurology* 38:306, 1988 (abstr, suppl 1)
11. Friedman HS, Schold SC, Djang WT, et al: Criteria for termination of phase II chemotherapy for patients with progressive or recurrent brain tumor. *Neurology* 39:62-65, 1989
12. Surbone A, Longo DL, De Vita VT Jr, et al: Residual abdominal masses in aggressive non-Hodgkins lymphoma after combination chemotherapy: Significance and management. *J Clin Oncol* 6:1832-1837, 1988
13. Chamberlain MC, Murovic J, Levin VA: Absence of contrast enhancement on CT brain scans of patients with supratentorial malignant gliomas. *Neurology* 38:1371-1373, 1988