VOLUME 23 · NUMBER 22 · AUGUST 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma

Lauren E. Abrey, Tracy T. Batchelor, Andrés J.M. Ferreri, Mary Gospodarowicz, Elisa J. Pulczynski, Emanuele Zucca, Justine R. Smith, Agnieszka Korfel, Carole Soussain, Lisa M. DeAngelis, Edward A. Neuwelt, Brian Patrick O'Neill, Eckhard Thiel, Tamara Shenkier, Fransesc Graus, Martin van den Bent, John F. Seymour, Philip Poortmans, James O. Armitage, and Franco Cavalli

From the Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted January 25, 2005; accepted April 11, 2005.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Lauren E. Abrey, MD, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; e-mail: abreyl@mskcc.org.

0732-183X/05/2322-5034/$20.00

DOI: 10.1200/JCO.2005.13.524

ABSTRACT

Standardized guidelines for the baseline evaluation and response assessment of primary CNS lymphoma (PCNSL) are critical to ensure comparability among clinical trials for newly diagnosed patients. The relative rarity of this tumor precludes rapid completion of large-scale phase III trials and, therefore, our reliance on the results of well-designed phase II trials is critical. To formulate this recommendation, an international group of experts representing hematologic oncology, medical oncology, neuro-oncology, neurology, radiation oncology, neurosurgery, and ophthalmology met to review current standards of reporting and to formulate a consensus opinion regarding minimum baseline evaluation and common standards for assessing response to therapy. The response guidelines were based on the results of neuroimaging, corticosteroid use, ophthalmologic examination, and CSF cytology. A critical issue that requires additional study is the optimal method to assess the neurocognitive impact of therapy and address the quality of life of PCNSL survivors. We hope that these guidelines will improve communication among investigators and comparability among clinical trials in a way that will allow us to develop better therapies for patients.

J Clin Oncol 23:5034-5043. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Primary CNS lymphoma (PCNSL) is a rare subtype of non-Hodgkin's lymphoma (NHL) that is confined to the brain, eyes, and leptomeninges. For a rare tumor, PCNSL has generated enormous research efforts and numerous publications. This disproportionate interest may be explained by the fact that the overall incidence of PCNSL in the immunocompetent population has been increasing during the last several decades, and it is one of the few malignant primary brain tumors that is sensitive to treatment.[1] PCNSL is sensitive to both chemotherapy and radiotherapy, but the overall response rates and long-term survival are significantly inferior to the results achieved in similar subtypes of extranodal NHL.

Since 1978, there have been more than 40 prospective clinical trials and large institutional series published reporting a variety of treatment algorithms for PCNSL. Unfortunately, the results reported in these predominantly phase II trials are difficult to compare to determine the optimal therapeutic approach for an individual patient. There have been numerous calls to undertake a large, definitive, phase III study, but this has been unsuccessful because of the difficulty identifying the most important question to address as well as the relative rarity of patients available to be enrolled onto such a trial. The only phase III study published to date was terminated after 7

years because of failure to accrue the necessary number of patients.[2] As a result, the ability to compare ongoing phase II trials is critical to improving our understanding and treatment of this disease.

The International Primary CNS Lymphoma Collaborative Group is composed of an international and multidisciplinary group of investigators working to further our understanding of this rare type of NHL (Appendix).[3] A subcommittee of the International Primary CNS Lymphoma Collaborative Group met on March 3, 2004, in Barcelona, Spain, and at the 2004 Annual Meetings of the American Society of Clinical Oncology and American Society of Hematology, to outline a consensus opinion regarding the recommended baseline evaluation for all patients, to standardize response criteria and outcome measures for patients enrolled onto clinical trials, and to review clinical issues unique to PCNSL. This report is restricted to immunocompetent patients with PCNSL and does not address the unique or particular issues raised in the immunocompromised population.

BACKGROUND

A review of 16 published articles and seven ongoing clinical trials highlights the need for consistent baseline evaluation, response criteria, and reporting.[2,4-18] Tables 1 and 2 list details of baseline evaluation, eligibility guidelines, response criteria, and data reported in these articles and ongoing trials. Of the published articles, only 12 required definitive histology review for inclusion, two allowed patients with typical radiographic features of PCNSL to be included, and two did not comment specifically on histology. Eight of the published articles did not require a complete extent-of-disease evaluation to exclude systemic lymphoma or document involvement of eyes or CSF in all patients. Systemic work-up was variable: chest, abdomen, and pelvis computed tomography (CT) was used in five studies, chest and abdominal CT was used in two studies, abdominal CT was used in five studies, abdominal and pelvis CT was used in one study, abdominal ultrasound was used in one studies, and bone marrow biopsy was used in 11 studies. Detailed ophthalmologic evaluation, including slit-lamp examination, was reported in 13 studies, and 15 studies reported baseline CSF cytology. Four of the published articles required measurable tumor burden for study entry. Eight studies reported performance status using the Karnofsky scale, five studies reported performance status using Eastern Cooperative Oncology Group (ECOG) criteria, one study reported performance status using WHO criteria,

Table 1. Baseline Evaluation in Published Reports and Ongoing Clinical Trials

Reference	Age (years)	PS/Minimum	CXR	CT	MRI Brain	CSF Studies	Eye Examination	BM Biopsy
Mead et al[2]	Adult	WHO	—	CA	—	Yes	Yes	—
Bessell et al[4]	< 70	ECOG	—	CAP	Yes	Yes	Yes	Yes
Bessell et al[5]	< 70	ECOG	—	CAP	Yes	Yes	Yes	Yes
Hoang-Xuan et al[6]	≥ 60	KPS > 30	Yes	A	Yes	Yes	Yes	Yes
Abrey et al[7]	—	KPS	Yes	A	Yes	Yes	Yes	Yes
DeAngelis et al[8]	—	KPS	—	CAP	Yes	Yes	Yes	Yes
Batchelor et al[9]	≥ 18	KPS, > 50	—	CAP	Yes	Yes	Yes	—
O'Neill et al[10]	≥ 18	ECOG 0-3	Yes	AP	Yes	Yes	Yes	Yes
Wu et al[11]	—	ECOG	—	—	Yes	Yes	—	Yes
O'Brien et al[12]	—	ECOG 0-3	—	CAP	Yes	Yes	Yes	Yes
DeAngelis et al[13]	—	—	Yes	A	Yes	Yes	Yes	Yes
Nelson et al[14]	> 18	KPS > 30	Yes	A	CT	Yes	—	Yes
Sandor et al[15]	—	—	Yes	A	Yes	Yes	Yes	—
Herrlinger et al[16]	> 18	KPS > 40	Yes	A US	Yes	—	—	—
Poortmans et al[17]	16-65	KPS > 30	—	—	Yes	Yes	Yes	—
Pels et al[18]	18-75	KPS	—	CA	Yes	Yes	Yes	Yes
IELSG 20	18-75	ECOG 0-3	—	CA	Yes	Yes	Yes	Yes
RTOG 0227	—	Zubrod 0-2	—	—	Yes	Yes	Yes	—
OHSU	16-75	ECOG 0-3	—	CAP	Yes	Yes	Yes	—
Tübingen	≥ 18	KPS > 20	Yes	A US	Yes	Yes	Yes	—
MSKCC	≥ 18	KPS	Yes	CAP	Yes	Yes	Yes	Yes
Transtasman	18-75	ECOG 0-3	—	CAP	Yes	Yes	Yes	—
NABTT 2109	≥ 18	KPS > 50	Yes	CAP	Yes	Yes	Yes	—

Abbreviations: PS, performance status; CXR, chest x-ray; CT, computed tomography; MRI, magnetic resonance imaging; BM, bone marrow; KPS, Karnofsky performance status; C, chest; A, abdomen; P, pelvis; US, ultrasound; ECOG, Eastern Cooperative Oncology Group; IELSG, International Extranodal Lymphoma Study Group; RTOG, Radiation Therapy Oncology Group; OHSU, Oregon Health Sciences University; MSKCC, Memorial Sloan-Kettering Cancer Center; NABTT, New Approach to Brain Tumor Therapy.

Table 2. Design and Response Assessment in Published Reports and Ongoing Clinical Trials

Reference	Design	Primary End Point	Response Criteria	Sample Size		Median Follow-Up
				Planned	Actual	
Mead et al[2]	Randomized	OS	—	NA	53	5 years
Bessell et al[4]	Series	—	M	NA	31	4.1 years
Bessell et al[5]	Series/phase II	—	M	NA	57	59 months, 17 months
Hoang-Xuan et al[6]	Phase II, 2 stage	RR	Other	31-50	50	3 years
Abrey et al[7]	Series	—	Other	NA	52	33 months
DeAngelis et al[8]	Phase II	2-year OS	Other	NA	102	56 months
Batchelor et al[9]	Phase II, 2 stage	RR	M	25	25	25 months
O'Neill et al[10]	Phase II	OS	Other	30	50	21 months
Wu et al[11]	Series	RR	Other	NA	44	15 months
O'Brien et al[12]	Phase II	2-year OS	Other	30	46	24 months
DeAngelis et al[13]	Series	—	M	NA	31	—
Nelson et al[14]	Phase II	—	Other	NA	41	> 3.3 years
Sandor et al[15]	Phase II	RR	Other	NA	14	3.3 years
Herrlinger et al[16]	Phase II	CRR	M	105	37	—
Poortmans et al[17]	Phase II, 2 stage	RR	Other	50	52	27 months
Pels et al[18]	Phase II	TTF	Other	NA	65	26 months
IELSG 20	Phase II, 2 stage	CRR	Cheson		39	NA
RTOG 0227	Phase I/II	MTD/2-year OS	Other	52-64		NA
OHSU	Phase II	Toxicity; efficacy	Other	180		NA
Tübingen	Phase II	CRR	M	20		NA
MSKCC	Phase II	2-year PFS	Other	30		NA
Transtasman	Phase II	OS, 2-year OS	Other	53		NA
NABTT 2109	Phase II, 2 stage	CRR	Other	27-53		NA

Abbreviations: OS, overall survival; NA, not available; M, MacDonald criteria; RR, response rate; TTF, time to treatment failure; CRR, complete response rate; MTD, maximum tolerated dose; IELSG, International Extranodal Lymphoma Study Group; RTOG, Radiation Therapy Oncology Group; OHSU, Oregon Health Sciences University; MSKCC, Memorial Sloan-Kettering Cancer Center; NABTT, New Approach to Brain Tumor Therapy.

and two did not report performance status. Four reported results of the mini-mental status examination (MMSE), but none reported on quality of life.

In contrast, the seven ongoing studies all require histologic diagnosis and only one allows patients with typical radiographic features to participate without definitive histology. Six require a minimum performance status—two using the Karnofsky scale and four using the ECOG or Zubrod scale. Two require measurable tumor burden at study entry. Six of the ongoing trials include routine evaluation of MMSE and quality of life. All require systemic evaluation but use different methods: four require CT of chest, abdomen, and pelvis; one requires abdominal ultrasound; one requires CT of chest and abdomen; and only two require bone marrow biopsy. All require baseline CSF evaluation and detailed ophthalmologic examination including slit lamp.

Predetermined primary end points were only reported in 11 of the published articles, but are stipulated for all of the active trials. However, the planned end points are variable, ranging from response rate to overall survival. All reported trials have included a measure of overall survival (methods were varied or unspecified), 12 include progression-free survival, and two include disease-free survival. Most studies (10 published, five ongoing) specified their own particular method of response assessment; five published manuscripts used the Macdonald criteria[19] for response assessment despite the fact that these were developed for the assessment of malignant gliomas and do not adequately assess the multicompartment distribution of PCNSL. Median follow-up of reported patients was often short. Seven studies reported patients with an average follow-up of less than 30 months and two reports did not specify length of follow-up.

This overview highlights the fact that although most investigators or cooperative groups are following similar general principles, the information being generated is difficult to compare or to apply to an individual patient presenting for treatment. Although the treatment of PCNSL has improved significantly in the last decade, additional advances and interpretation of new therapies will depend on investigators reporting data that are consistent and comparable.

INTERNATIONAL WORKING GROUP RECOMMENDATIONS

Baseline Evaluation

Pathology. All patients enrolled onto a clinical trial for PCNSL should have histopathologic confirmation of the

diagnosis. This is critical because there is a subset of patients in whom a presumptive diagnosis of PCNSL is made on the basis of magnetic resonance imaging (MRI) appearance and tumor response to corticosteroids. However, tissue diagnosis is essential because there are other intracranial processes, such as multiple sclerosis, sarcoidosis, and occasional gliomas, that have a similar appearance and transient response to corticosteroids. The diagnostic procedure of choice for PCNSL is a stereotactic needle biopsy because patients derive no clinical benefit from surgical resection and the deep-seated nature of most lesions increases the risk of surgical complications. If there is evidence of ocular or CSF involvement, a vitrectomy or CSF cytology may establish the tissue diagnosis. Time from pathologic diagnosis to initiation of treatment should be specified in all reports of prospective clinical trials.

Whenever possible, the tumor should be characterized by immunophenotype. It is unknown if different immunophenotypes confer a different prognosis or response to therapy. If there is a large enough number of patients with a specific immunophenotype in a given trial, subset analysis may be possible. Furthermore, our current understanding of the molecular classification of PCNSL lags behind the understanding of other types of NHL; therefore, every effort should be made to use available clinical/pathologic material to improve our understanding of this tumor. Characterizing the basic molecular and genetic abnormalities of PCNSL will foster the future development and application of target-specific therapies in this disease.

Clinical evaluation. The baseline evaluation of any newly diagnosed patient with PCNSL should include a comprehensive physical and neurologic examination. Particular attention should be paid to examination of peripheral lymph nodes in all patients and the testes in older men. Age and performance status are the two most widely documented prognostic variables and must be recorded in every patient. The ECOG performance scale has been used in the only prognostic model of PCNSL and is the accepted standard for the International Prognostic Index in systemic NHL[20]; therefore, this is the recommended measure of performance status. However, because individual institutions or cooperative groups may prefer to use the Karnofsky performance status, a table showing approximate equivalent values for the two scales is included (Table 3).

Evaluation of cognitive function is important at baseline, and follow-up assessments are critical both to gauge the benefit of therapy as well as to monitor for treatment-related neurocognitive decline. At this point, there is no standard battery of neuropsychological testing; therefore, at a minimum we recommend baseline and serial scoring of MMSE in all patients. Finally, because response assessment is affected by glucocorticoid administration, it is important to record corticosteroid dosing at baseline and at each evaluation.

Table 3. Equivalent KPS and ECOG Scores[21]

KPS	ECOG
90-100	0
70-80	1
60-70	2
30-50	3
20-10	4
0	5

Abbreviations: KPS, Karnofsky performance status; ECOG, Eastern Cooperative Oncology Group.

Laboratory evaluation. Baseline laboratory evaluation should include serum lactate dehydrogenase in all patients and determination of adequate hepatic and renal function in those who will receive high-dose methotrexate. Elevated serum lactate dehydrogenase has been identified as an independent prognostic variable in a large retrospective series by the International Extranodal Lymphoma Study Group and subsequently used in the construction of a prognostic model.[22] A creatinine clearance greater than 50 to 60 mL/min is necessary to ensure adequate excretion of high-dose methotrexate; furthermore, one study has suggested that rapid clearance of methotrexate may be a poor prognostic variable.[23] All patients should be tested for HIV infection given the increased risk of PCNSL in this population.

Extent-of-disease evaluation. Thorough evaluation to determine the full extent of disease is critical before the initiation of therapy to ensure that the patient receives appropriate therapy and to determine clinical trial eligibility. This evaluation includes studies of the CNS, body, and bone marrow. Optimal imaging of the brain parenchyma requires a gadolinium-enhanced MRI scan. Contrast-enhanced CT scans may be substituted in patients in whom MRI is medically contraindicated (eg, cardiac pacemaker) or unavailable. All patients should have a lumbar puncture for CSF cytology unless medically contraindicated. Total protein has been identified as an important prognostic factor and should be analyzed in all patients[22]; CSF protein levels should only be assessed on lumbar puncture samples because ventricular CSF has a lower normal value. CSF should be sampled before or 1 week after surgical biopsy to avoid false-positive results; a minimum of 3 mL and ideally 10 mL should be sent for cytologic evaluation.[24] Additional CSF studies that may be helpful include cell count,

beta$_2$-microglobulin, immunoglobulin H gene rearrangement, and flow cytometry. A recent report suggests that flow cytometry is more sensitive than routine cytology to assay for occult leptomeningeal lymphoma.[25] A detailed ophthalmologic examination, including dilated fundus examination, should be done to exclude vitreous, retinal, or optic nerve involvement. Fluorescein angiography may be helpful to confirm lymphomatous involvement of the retina. Color photography of the posterior pole of the eye should be obtained in those patients with ocular involvement to follow and document response to therapy. Involvement of the spinal cord parenchyma is sufficiently rare that gadolinium-enhanced MRI of the total spine is warranted only in patients with spinal symptoms.

Occult systemic disease has been reported in up to 8% of patients initially thought to have isolated PCNSL.[14,26-28] As a result, complete systemic staging is warranted in every patient. CT scan of the chest, abdomen, and pelvis, and bone marrow biopsy with aspirate are the recommended staging procedures. Testicular ultrasound may be considered in older men to exclude an occult testicular lymphoma metastatic to brain. In the future, body positron emission tomography imaging may be incorporated into the evaluation of systemic disease.

Response assessment. Gadolinium-enhanced MRI scans are the standard for the evaluation of bulky parenchymal brain disease. Either unidimensional or cross-sectional measurements may be used to assess response accurately; all clinical trials should specify the type of measurement used.[29] Studies should be performed approximately every 2 months during active therapy or at the time the therapeutic modality is changed. Imaging should be performed no longer than two months after completion of all planned therapy to assess overall treatment response. All complete responses (CRs) should be confirmed by repeat imaging.

Detailed ophthalmologic examination with dilated fundus examination, slit-lamp examination and color photography of the posterior pole, and lumbar puncture for cytology are required only if these studies were initially positive or if clinically indicated by new symptoms or signs. Lumbar puncture for CSF cytology is necessary to confirm cytologic response observed in the ventricular CSF. CR in the eyes or CSF should be confirmed by repeat evaluation.

Response criteria. The following criteria were developed on the basis of anatomic and radiographic definitions (Table 4). As additional radiographic, laboratory, or functional studies become more widely available and are demonstrated to have predictive value, they may be recommended as well.

CR requires the following:

(1) Complete disappearance of all enhancing abnormalities on gadolinium-enhanced MRI.

(2) No evidence of active ocular lymphoma as defined by absence of cells in the vitreous and resolution of any previously documented retinal or optic nerve infiltrates. Chronic changes of the retinal pigment epithelium in the setting of a prior retinal or optic nerve infiltrate does not preclude the definition of a CR. All patients with initial involvement of the eyes on baseline evaluation should have a detailed follow-up evaluation including dilated fundus examination and color photographs of the posterior pole of the eye. Repeat ophthalmologic evaluation is not required for patients without evidence of ocular lymphoma at baseline or interval development of ocular symptoms.

(3) Negative CSF cytology. Given the reported disparity between cytologic specimens obtained from the ventricular system as opposed to lumbar puncture, it is recommended that a negative CSF cytology be confirmed from both spaces in patients with an Ommaya reservoir.[30] Patients without significant CSF abnormalities at baseline do not require repeat CSF evaluation provided they have not developed interval symptoms that suggest leptomeningeal dissemination. Although baseline CSF total protein may have prognostic importance, the value of CSF total protein after therapy is unknown.

Table 4. Response Criteria for Primary Central Nervous System Lymphoma

Response	Brain Imaging	Corticosteroid Dose	Eye Examination	CSF Cytology
CR	No contrast enhancement	None	Normal	Negative
CRu	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
PD	25% increase in lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: CNS or systemic			

Abbreviations: CR, complete response; CRu, unconfirmed complete response; RPE, retinal pigment epithelium; PR, partial response; PD, progressive disease.

(4) At the time a CR is determined, the patient should have discontinued use of all corticosteroids for at least 2 weeks. Rare exceptions may be made for those patients receiving corticosteroids for another diagnosis (eg, panhypopituitarism).

CR/unconfirmed (CRu) includes those patients who fulfill the criteria for CR with the following features/limitations:

(1) Any patient who fulfills all criteria for CR but continues to require corticosteroid therapy at any dose should be considered an unconfirmed CR. This is critical because corticosteroids may be oncolytic in treating occult tumor. In addition, corticosteroids may decrease gadolinium enhancement on MRI.

(2) Some patients will have a small but persistent enhancing abnormality on MRI related to biopsy or focal hemorrhage. It is often difficult to ascertain whether this represents a residual nidus of tumor or scar tissue. Adjunctive radiologic studies such as single-photon emission computed tomography or positron emission tomography may be helpful, but often the nature of these abnormalities may only be determined by observing the patient with serial scans. If the type of abnormality does not change or slowly involutes over time without therapy and corticosteroids, it is reasonable to categorize it as a CR.

(3) Patients with a persistent minor abnormality on follow-up ophthalmologic examination (persistent nonmalignant cells in the vitreous, alteration of the retina/optic nerve that is not consistent with tumor infiltration) may be considered a CRu if this abnormality is unlikely to represent ocular lymphoma.

Partial response (PR) requires all of the following:

(1) A $\geq$ 50% decrease in the contrast-enhancing lesion seen on MRI as compared with baseline imaging.

(2) Corticosteroid dose is irrelevant to the determination of PR.

(3) Ophthalmologic examination should show a decrease in the vitreous cell count or retinal/optic nerve cellular infiltrate but may continue to show persistent malignant or suspicious cells. Color photos of the posterior pole of the eye should be obtained to document improvement in retinal/optic nerve infiltrates.

(4) CSF cytologic examination may be negative or continue to show persistent malignant or suspicious cells in patients with a $\geq$ 50% decrease in the primary brain lesion. In the setting of primary leptomeningeal lymphoma, PR is not recognized; all patients should be categorized as CR, CRu, stable disease, or progressive disease.

(5) No new sites of disease.

Stable disease is defined as less than a PR but is not progressive disease.

Progressive disease requires the following:

(1) A more than 25% increase in the contrast-enhancing lesion seen on MRI as compared with baseline or best response (comparison should be made to the smallest of multiple lesions).

(2) Progression of ocular disease as indicated by an increase in the vitreous cell count or progressive retinal or optic nerve infiltration.

(3) Appearance of any new lesion or site of disease (ocular, leptomeningeal or systemic) during or at the end of therapy.

Relapsed disease (only applicable to patients with a prior CR, CRu) requires the following:

(1) Appearance of any new lesion.

End Points

The major end points reported for clinical trials should include event-free survival (time to treatment failure), which includes failure or death as a result of any cause, progression-free survival, and overall survival (Table 5). Overall survival and event-free survival are measured from entry onto a trial until death as a result of any cause or until death or progression of disease, respectively. Progression-free survival for all patients is calculated from the time of entry onto a study until disease progression or death as a result of PCNSL. Secondary end points such as response, response duration, disease-free survival, or cause-specific survival may also be included, provided that the other end points have been reported. Disease-free survival is calculated for the subset of patients in CR or CRu from the first assessment documenting a response to the date of disease progression.

Table 5. End Point Definitions*

End Point	Response Category	Definition	Point of Measurement
Overall survival	All patients	Death as a result of any cause	Entry onto trial
Event-free survival	All patients	Failure or death as a result of any cause	Entry onto trial
Progression-free survival	All patients	Disease progression or death as a result of PCNSL	Entry onto trial
Disease-free survival	CR, CRu	Time to relapse	First documentation of response
Response duration	CR, CRu, PR	Time to relapse or progression	First documentation of response

Abbreviations: PCNSL, primary CNS lymphoma; CR, complete response; CRu, unconfirmed complete response; PR, partial response.
*Adapted from Cheson et al.[28]

Follow-Up

The manner in which patients are observed after treatment may vary considerably depending on regional practices, enrollment on clinical trials, and whether treatment was delivered with palliative or curative intent. Good clinical judgment is the most important factor to determine follow-up. However, a number of laboratory and imaging studies are usually performed on a routine basis. In general, the benefit of surveillance studies to detect early relapse is controversial, and no studies have examined this in PCNSL.

For patients enrolled onto clinical studies, time points for monitoring disease status should be standardized. Patients enrolled onto clinical trials should be reassessed after completion of therapy, at a minimum of every 3 months for 2 years, then every 6 months for 3 years, and annually for at least 5 years, for a total of 10 years of follow-up.[31] Given that first recurrences rarely occur beyond the 5-year time point in PCNSL, continued risk of relapse beyond 10 years from initial diagnosis is low; however, surviving patients should continue to be monitored for treatment-related neurotoxicity and other late adverse effects of therapy. Minimum testing at follow-up should include history, physical examination including an MMSE, and gadolinium-enhanced MRI scan of the brain. Patients with initial involvement of the eyes or spinal fluid should undergo repeat ophthalmologic or CSF evaluation as clinically indicated. Additional blood tests or imaging studies may be added as appropriate to an individual trial or clinical situation.

UNIQUE AND FUTURE ISSUES FOR PCNSL

One of the most significant issues influencing the development of new therapies for PCNSL is concern about the cognitive impact of current therapies. Current data suggest that the most effective approach combining high-dose methotrexate and whole-brain radiation leads to a potentially unacceptable risk of treatment-related neurotoxicity. For patients with ocular lymphoma, ocular radiation is believed by many experts to lead to an unacceptable risk of ocular toxicity.[32-34] A mandate is to document prospectively the impact of our therapies on patient cognition, neurologic function, and quality of life. This area has been understudied and often underreported. Although most of the ongoing clinical trials are collecting quality-of-life data, few prior studies have reported long-term outcomes. Furthermore, many published trials have relatively brief durations of follow-up that may underestimate the long-term impact of therapy and overestimate disease control. Therefore, evaluation of cognitive function at baseline is important to characterize disease-related neuropsychological impairments, and follow-up assessments are critical both to gauge the benefit of therapy as well as to monitor for treatment-related neurocognitive decline. At this point, there is no standard battery of neuropsychological tests that is widely used, but measures of psychomotor speed, executive, and memory abilities have been shown to be sensitive to detect treatment effects in this population and should be incorporated into all prospective clinical trials.[35,36] Despite its low sensitivity, the MMSE is suggested as the minimum requirement at baseline and serial follow-up for all patients. Careful follow-up of neurologic function, especially gait and neuroimaging changes, is also critical.

The other priority in PCNSL is to better understand the molecular biology and genetic profile of this tumor. Current information suggests that PCNSL is likely similar to but distinct from germinal center type diffuse large B-cell lymphoma. The availability of tissue specimens has made full characterization of PCNSL difficult, but new techniques may allow accurate assessment of small samples. Carefully planned efforts are underway in the United States and Europe to collect available tumor specimens and form tissue banks for detailed analysis.

Acknowledgment

We thank Molly Dorfman for all of her efforts in coordinating this international group of investigators, and Judy Lampron for her editorial assistance.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Appendix

IPCG Members	Affiliation
Abrey, Lauren	Memorial Sloan-Kettering Cancer Center
Armitage, James O.	University of Nebraska Medical Center
Baars, Joke W.	Antoni van Leeuwenhoek ZHS
Batchelor, Tracy	Massachusetts General Hospital
Bessell, Eric	Nottingham City Hospital
Betensky, Rebecca	Harvard School of Public Health
Bierman, Philip Jay	University of Nebraska Medical Center
Blay, Jean-Yves	Hopital Edouard Herriot
Borisch, Bettina	HUG Geneva Switzerland
Cavalli, Franco	Oncology Institute of Southern Switzerland
Chan, Chi-Chao	National Eye Institute
Child, Tony	The General Infirmary at Leeds
Colombat, Philippe	Service d'oncologie medicale
Connors, Joseph M.	BC Cancer Agency Vancouver Clinic
D'Addario, Giannicola	Kantonsspital St Gallen
DeAngelis, Lisa M.	Memorial Sloan-Kettering Cancer Center
Delattre, Jean-Yves	CHO Pitie-Salpetriere
Desablens, Bernard	Maladies du Sang
Doolittle, Nancy	Oregon Health and Science University
Doorduijn, Jeannette K.	Erasmus MC, Daniel den Hoed
Dorfman, Molly	Massachusetts General Hospital
Ferreri, Andrés	San Raffaele Scientific Institute
Fine, Howard	National Institutes of Health
Finke, Jurgen	University of Freiburg Medical Center
Gilles Salles	Centre Hospitalier Lyon-Sud
Girinsky, Théo	Institut Gustav Roussy
Glasmacher, Axel	University of Bonn
Glass, Jon	Fox Chase Cancer Center
Gospodarowicz, Mary	Princess Margaret Hospital
Graus, Francesc	Hospital Clinic/Barcelona
Grigg, Andrew	Royal Melbourne Hospital
Grossman, Stuart	Johns Hopkins Oncology Center
Guttenberger, Roland	Freiburg, Germany
Haaxma-Reiche, Hanny	University Hospital Groningen
Hansen, Mads	Rigshospitalet
Harris, Nancy	Massachusetts General Hospital
Herrlinger, Ulrich	University of Tuebingen
Hoang-Xuan, Khé	CHO Pitie-Salpetriere
Hochberg, Fred	Massachusetts General Hospital
Hodson, Dan	West Anglia Cancer Network Lymphoma Group
Hofer, Silvia	Deutsche Kultur Und Familie
Illerhaus, Gerald	University of Freiburg Medical Center
Jahnke, Kristoph	Charite Universitatsmedizin Berlin
Jean Pierre, Armand	Institut Gustav Roussy
Kluin-Nelemans, Hanneke	Universitair Ziekenhuis Groningen
Korfel, Agnieszka	Charite–Universitaetsmedizin Berlin
Laperriere, Normand	The Gerry & Nancy Pencer Brain Tumor Centre
Lister, Andrew	St Bartholomew's Hospital
Levy-Clarke, Grace	National Eye Institute
Lugtenburg, Elly	University Hospital Rotterdam
Marcus, Robert	West Anglia Cancer Network Lymphoma Group
Mason, Warren	Princess Margaret Hospital
Neuwelt, Edward A.	Oregon Health and Science University
O'Brien, Peter	Newcastle Mater Hospital
O'Neill, Brian P.	Mayo Clinic and Foundation
Ossenkoppele, Gert van	Vrije Universiteit Medisch Centrum
Pels, Hendrik	Neurologische Klinik
Ponzoni, Maurilio	S. Raffaele H. Scientific Institute
Poortmans, Philip	Dr Bernard Verbeeten Instituut
Pulczynski, Elisa	University Hospital Aarhus

(continued on following page)

Appendix (continued)

IPCG Members	Affiliation
Raemaekers, John	Radboud U Nijmegen Medical Center
Raizer, Jeffrey	Northwestern University
Reni, Michele	S. Raffaele H. Scientific Institute
Rosenthal, Mark	Royal Melbourne Hospital
Rosta, András	Országos Onkológiai Intézet
Rozewicz, Cynthia M.	European Organization for Research and Treatment of Cancer
Rubenstein, James L.	University of California, San Francisco
Scepanovic, Danijela	Clinical Centre of Montenegro
Schiff, David	University of Virginia
Schlegel, Uwe	University of Bochum
Schmidt-Wolf, Ingo	University of Bonn
Sebban, Catherine	Centre Leon Berard
Seymour, John	Peter MacCallum Cancer Centre
Shenkier, Tamara	BC Cancer Agency Vancouver Clinic
Soussain, Carole	CHG-Meaux
Stupp, Roger	University Hospital CHUV
Swinnen, Lode	The Bunting-Blaustein Cancer Research Building
Teodorovic, Ivana	European Organization for Research and Treatment of Cancer
Thiel, Eckhard	Charite–Universitaetsmedizin Berlin
Thomas, José	UZ-Gasthuisberg
Tsang, Richard	Princess Margaret Hospital
van den Bent, Martin	European Organization for Research and Treatment of Cancer
van Glabbeke, Martine	European Organization for Research and Treatment of Cancer
van Hoof, Achiel	AZ St Jan
van Imhoff, Gustaaf	Universitair Ziekenhuis Groningen
Weller, Michael	University of Tuebingen
Yahalom, Joachim	Memorial Sloan-Kettering Cancer Center
Zucca, Emanuele	Oncology Institute of Southern Switzerland

Abbreviation: IPCG, International Primary CNS Lymphoma Collaborative Group.

REFERENCES

1. Olson JE, Janney CA, Rao RD, et al: The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: A surveillance, epidemiology, and end results analysis. Cancer 95:1504-1510, 2002

2. Mead GM, Bleehen NM, Gregor A, et al: A medical research council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: Cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Cancer 89:1359-1370, 2000

3. Ferreri AJ, Batchelor T, Zucca E, et al: International Collaborative Group Against Primary CNS Lymphomas. J Clin Oncol 21:1649-1650, 2003

4. Bessell EM, Graus F, Lopez-Guillermo A, et al: CHOD/BVAM regimen plus radiotherapy in patients with primary CNS non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 50:457-464, 2001

5. Bessell EM, Lopez-Guillermo A, Villa S, et al: Importance of radiotherapy in the outcome of patients with primary CNS lymphoma: An analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. J Clin Oncol 20:231-236, 2002

6. Hoang-Xuan K, Taillandier L, Chinot O, et al: Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: A multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. J Clin Oncol 21:2726-2731, 2003

7. Abrey LE, Yahalom J, DeAngelis LM: Treatment for primary CNS lymphoma: The next step. J Clin Oncol 18:3144-3150, 2000

8. DeAngelis LM, Seiferheld W, Schold SC, et al: Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 20:4643-4648, 2002

9. Batchelor T, Carson K, O'Neill A, et al: Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: A report of NABTT 96-07. J Clin Oncol 21:1044-1049, 2003

10. O'Neill BP, O'Fallon JR, Earle JD, et al: Primary central nervous system non-Hodgkin's lymphoma: Survival advantages with combined initial therapy? Int J Radiat Oncol Biol Phys 33:663-673, 1995

11. Wu HG, Kim IH, Ha SW, et al: Survival improvement with combined radio-chemotherapy in the primary central nervous system lymphomas. J Korean Med Sci 14:565-570, 1999

12. O'Brien P, Roos D, Pratt G, et al: Phase II multicenter study of brief single-agent methotrexate followed by irradiation in primary CNS lymphoma. J Clin Oncol 18:519-526, 2000

13. DeAngelis LM, Yahalom J, Thaler HT, et al: Combined modality therapy for primary CNS lymphoma. J Clin Oncol 10:635-643, 1992

14. Nelson DF, Martz KL, Bonner H, et al: Non-Hodgkin's lymphoma of the brain: Can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 23:9-17, 1992

15. Sandor V, Stark-Vancs V, Pearson D, et al: Phase II trial of chemotherapy alone for primary CNS and intraocular lymphoma. J Clin Oncol 16:3000-3006, 1998

16. Herrlinger U, Schabet M, Brugger W, et al: German Cancer Society Neuro-Oncology Working Group NOA-03 multicenter trial of single-agent high-dose methotrexate for primary central nervous system lymphoma. Ann Neurol 51:247-252, 2002

17. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H, et al: High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. J Clin Oncol 21:4483-4488, 2003

18. Pels H, Schmidt-Wolf IG, Glasmacher A, et al: Primary central nervous system lymphoma: Results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. J Clin Oncol 21:4489-4495, 2003

19. Macdonald DR, Cascino TL, Schold SC Jr, et al: Response criteria for phase II studies of

supratentorial malignant glioma. J Clin Oncol 8:1277-1280, 1990

20. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 329:987-994, 1993

21. Buccheri G, Ferrigno D, Tamburini M: Karnofsky and ECOG performance status scoring in lung cancer: A prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer 32A:1135-1141, 1996

22. Ferreri AJ, Blay JY, Reni M, et al: Prognostic scoring system for primary CNS lymphomas: The International Extranodal Lymphoma Study Group experience. J Clin Oncol 21:266-272, 2003

23. Glantz MJ, Cole BF, Glantz LK, et al: Cerebrospinal fluid cytology in patients with cancer: Minimizing false-negative results. Cancer 15:733-739, 1998

24. Ferreri AJ, Guerra E, Regazzi M, et al: Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. Br J Cancer 90:353-358, 2004

25. Hegde U, Filie A, Little RF, et al: High incidence of occult leptomeningeal disease detected by flow cytometry in newly diagnosed aggressive B-cell lymphomas at risk of central nervous system involvement: The role of flow cytometry versus cytology. Blood 105:496-502, 2005

26. O'Neill BP, Dinapoli RP, Kurtin PJ, et al: Occult systemic non-Hodgkin's Lymphoma in patients initially diagnosed as primary central nervous system lymphoma: How much staging is enough? J Neuro-oncol 25:67-71, 1995

27. Ferreri AJM, Reni M, Zoldan MC, et al: Importance of complete staging in non-Hodgkin's lymphoma presenting as a cerebral mass lesion. Cancer 77:827-833, 1996

28. Loeffler JS, Ervin TJ, Mauch P, et al: Primary lymphomas of the central nervous system: Patterns of failure and factors that influence survival. J Clin Oncol 3:490-494, 1985

29. Shah G, Kesari S, Xu RH, et al: Comparison of 1D, 2D, 3D and volumetric parameters in measuring tumor response in high-grade gliomas in adults. Presented at Am Soc Clin Oncol Annual Meeting, New Orleans LA, June 4-8, 2004

30. Chamberlain MC, Kormanik PA, Glantz MJ: A comparison between ventricular and lumbar cerebrospinal fluid cytology in adult patients with leptomeningeal metastases. Neuro-oncol 3:42-45, 2001

31. Hoffman PM, McKelvie P, Hall AJ, et al: Intraocular lymphoma: A series of 14 patients with clinico pathological features and treatment outcomes. Eye 17:513-521, 2003

32. Chan C-C, Wallace DJ: Intraocular lymphoma: Update on diagnosis and management. Cancer Control 11:285-295, 2004

33. Brady LW: Ocular complications of high-dose radiotherapy. Oncology 10:981-982, 1996

34. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol 17:1244, 1999

35. Correa DD, DeAngelis LM, Shi W, et al: Cognitive functions in survivors of primary central nervous system lymphoma. Neurology 62: 548-555, 2004

36. Neuwelt EA, Guastadisegni PE, Varallyay P, et al: Imaging changes and cognitive outcome in primary CNS lymphoma after enhanced chemotherapy delivery. AJNR Am J Neuroradiol 26:258-265, 2005