Primary leptomeningeal lymphoma

International Primary CNS Lymphoma Collaborative Group report

Jennie W. Taylor, MD
Eoin P. Flanagan, MD
Brian P. O'Neill, MD
Tali Siegal, MD
Antonio Omuro, MD
Lisa DeAngelis, MD
Joachim Baehring, MD
Ryo Nishikawa, MD
Fernando Pinto, MD
Marc Chamberlain, MD
Khe Hoang-Xuan, MD
Alberto Gonzalez-Aguilar, MD
Tracy Batchelor, MD, MPH
Jean-Yves Blay, MD
Agnieszka Korfel, MD
Rebecca A. Betensky, PhD
Maria-Beatriz S. Lopes, MD
David Schiff, MD

Correspondence to
Dr. Schiff:
davidschiff@virginia.edu

ABSTRACT

Objective: To evaluate clinical presentation, optimal diagnostic evaluation and treatment, and outcome in primary leptomeningeal lymphoma, a rare form of primary CNS lymphoma without parenchymal or systemic involvement.

Methods: The International Primary CNS Lymphoma Collaborative Group, a multidisciplinary group of physicians with a particular interest in primary CNS lymphoma, retrospectively identified cases of lymphoma isolated to the leptomeninges as diagnosed by CSF cytology, flow cytometry, or biopsy, without systemic or parenchymal brain/spinal cord lymphoma or immunodeficiency.

Results: Forty-eight patients were identified, with median age at diagnosis of 51 years and median Eastern Cooperative Oncology Group performance status of 2. Presenting symptoms were multifocal in 68%. Leptomeningeal enhancement was seen in 74% and CSF profile was abnormal in all cases. CSF cytology detected malignant lymphocytes in 67%. Flow cytometry identified monoclonal population in 80%, as did receptor gene rearrangement studies in 71%. Sixty-two percent had B-cell lymphoma, 19% T-cell, and 19% unclassified. Treatment varied and included fractionated radiotherapy (36%), systemic chemotherapy (78%), and intra-CSF chemotherapy (66%), with 66% receiving ≥ 2 modalities. Seventy-one percent had a favorable clinical response; ultimately, 44% received salvage treatment. Median overall survival was 24 months, with 11 patients still alive at 50 months follow-up.

Conclusion: Primary leptomeningeal lymphoma is a rare form of primary CNS lymphoma. Patients usually present with multifocal symptoms, with evidence of leptomeningeal enhancement and diagnostic CSF analysis. Although treatment is highly variable, patients have a better prognosis than previously reported and a subset may be cured. *Neurology*® 2013;81:1690-1696

GLOSSARY

CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; IPCG = International Primary CNS Lymphoma Collaborative Group; LP = lumbar puncture; PCNSL = primary CNS lymphoma; PD = progressive disease; PLML = primary leptomeningeal lymphoma; PR = partial response; SD = stable disease.

Leptomeningeal seeding from lymphoma occurs in 6% to 8% of patients with systemic non-Hodgkin lymphoma. It arises almost exclusively in aggressive lymphoma subtypes, particularly diffuse large B-cell lymphoma, or with transformation of indolent lymphomas to a higher grade.¹ Leptomeningeal metastases portend a very poor prognosis, with median overall survival of only 4 to 5 months.¹ This is true if the relapse is isolated to the CNS or concordant with progressive systemic disease.

Leptomeningeal dissemination is often seen in primary CNS lymphoma (PCNSL), a rare CNS-restricted variant of non-Hodgkin lymphoma with >90% of the diffuse large B-cell lymphoma subtype. The combination of CSF analysis and neuroimaging detects meningeal involvement in 7% to 42% of patients.^{2,3} Interestingly, the leptomeningeal involvement does

From the Massachusetts General Hospital (J.W.T., T.B., R.A.B.), Boston; Mayo Clinic (E.P.F., B.P.O.), Rochester, MN; Hadassah Hebrew University Medical Center (T.S.), Jerusalem, Israel; Memorial Sloan-Kettering (A.O., L.D.), New York, NY; Yale University (J.B.), New Haven, CT; Saitama Medical University (R.N.), Japan; Kings College Hospital (F.P.), London, UK; University of Washington (M.C.), Seattle; LOC National Expert Center (K.H.-X., A.G.-A.), APHP, UPMC, Pitie-Salpetriere, Paris; Centre Leon Berard (J.-Y.B.), Lyon, France; Campus Benjamin Franklin (A.K.), Charite Universitätsmedizin Berlin, Germany; Department of Biostatistics (R.A.B.), Harvard School of Public Health, Boston, MA; and University of Virginia (M.-B.S.L., D.S.), Charlottesville.

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not appear to be prognostic, with median overall survival ranging from 14 to 60 months depending on treatment response.^{3,4}

However, primary leptomeningeal lymphoma (PLML) without synchronous parenchymal brain/spine or systemic disease is rare. The estimated incidence of PLML is 7% of all PCNSLs, which itself comprises approximately 2% of all primary brain tumors and 0.8% of all lymphomas.⁵ There are few case reports or small series,^{5–23} with the largest published case series consisting of 9 patients. In that series, the median age at diagnosis was 57 years, all patients had abnormal CSF, and the median survival was only 8 months. With the increasing incidence of PCNSL, as well as advances in diagnosis and treatment leading to longer survival, the current study sought to characterize the clinical features, diagnostic evaluation, treatment, and outcome of PLML in the modern era.

METHODS Patients. Under the auspices of the International Primary CNS Lymphoma Collaborative Group (IPCG), a multidisciplinary group of physicians with a particular interest in PCNSL, we retrospectively ascertained patients fulfilling criteria for PCNSL isolated to the leptomeninges. PLML was defined as lymphomatous involvement of the leptomeninges as diagnosed by positive CSF cytology, flow cytometry or gene rearrangement, or meningeal biopsy. Patients were excluded if there was synchronous systemic or parenchymal CNS lymphoma, any history of lymphoma, or development of systemic or parenchymal CNS lymphoma within 6 months of PLML diagnosis. Patients were also excluded if there was a history of AIDS, organ transplantation, or other causes of immunosuppression. A neuropathologist (M.-B.L.) reviewed all available pathology reports centrally to confirm the diagnosis of PLML.

Statistical analysis. Statistical analysis included use of the Kaplan-Meier method to estimate progression-free and overall survival and Cox regression models for univariate analysis with age as a continuous variable and performance status, lymphoma subtype, and treatment as dichotomous variables. A multivariate model was not applied given the small number of patients.

Standard protocol approvals, registrations, and patient consents. Detailed information was collected by chart review after institutional review board approval at each institution.

RESULTS Forty-eight patients at 12 IPCG sites across 6 countries between 1981 and 2011 met inclusion criteria. Nineteen patients (40%) were diagnosed before 2000, 8 (17%) before 1990, and 11 (23%) between 1991 and 2000. Median age at diagnosis was 51 years (range, 6–84 years) with median onset of symptoms 2 months (range, 0–30 months) before diagnosis (table 1). The majority of patients were men with median Karnofsky performance status of 70 (range, 40–90) and Eastern Cooperative Oncology Group (ECOG) of 2 (range, 1–4) at diagnosis. Diffuse

Table 1 Age, sex, performance status, and pathologic diagnosis in primary leptomeningeal lymphoma (n = 48)

Median age, y (range)	51 (6–84)
Sex, % (n)	
Men	62 (30)
Women	38 (18)
Median performance status (range)	
ECOG	2 (1–4)
KPS	70 (40–90)
Lymphoma subtype, % (n)	
B-cell	62 (30)
T-cell	19 (9)
Other	19 (9)
MALT	2 (1)
Lymphoblastic	2 (1)
Lymphoma, not otherwise specified	15 (7)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; MALT = mucosa-associated lymphoid tissue.

large B-cell lymphoma was the most common diagnosis, with T-cell lymphoma diagnosed in 9 (19%), and one case each of marginal zone and lymphoblastic lymphoma, both diagnosed by meningeal biopsy. Seven samples (15%) were not analyzed with flow cytometry, gene rearrangement studies, or immunohistochemistry and were therefore diagnosed as lymphoma not otherwise specified. Patients were included only if the systemic workup, including body imaging, was negative for lymphoma. Thirty-seven patients underwent bone marrow biopsy, all negative for lymphoma.

Presenting signs and symptoms. Thirty-three patients (68%) presented with multifocal symptoms and signs. Twenty-eight (58%) had cranial neuropathies, with 15 (31%) a cranial nerve VI palsy and 8 (17%) cranial nerve VII palsy. Spinal symptoms were recorded in 23 (48%) with 17 (35%) demonstrating leg weakness on initial examination. Twenty-one (44%) presented with headache, 12 (25%) ataxia, and 12 (25%) encephalopathy. Ten patients (21%) had bowel and bladder dysfunction and 4 (8%) had seizure as their presenting symptom.

Diagnostic studies. Forty-seven patients had neuroimaging reviewed by the IPCG physician; imaging from one patient was unavailable for review. Forty patients (85%) had MRI and 7 (15%) CT only. Twenty-three (49%) had only brain imaging, 8 (17%) only the spine, 11 (23%) brain and spine, and 5 (11%) had normal imaging without location specified. Imaging was abnormal in 38 patients (81%) (table 2). Leptomeningeal enhancement of the spinal cord occurred in 15 of 19 (79%) (figure 1).

Table 2 Percentage of significant imaging and pathologic findings in primary leptomeningeal lymphoma

Imaging findings	%	No.
Abnormal findings	81	38/47
Leptomeningeal enhancement	74	34/47
Cerebral convexities	38	13/34
Posterior fossa	29	10/34
Cranial nerves	32	11/34
Spinal cord	79	15/19
Hydrocephalus	9	3/34
Normal	19	9/47
Pathologic findings	% Diagnostic	No.
Cytology	67	30/45
Flow cytometry	80	20/25
Molecular markers: IgH or TCR gene rearrangement	71	15/22

Abbreviations: IgH = immunoglobulin heavy-chain; TCR = T-cell receptor.

All 48 patients underwent CSF analysis. All 40 patients with CSF profiles available for review had abnormal profiles. Median CSF glucose was 47 mg/dL (range, 10–150 mg/dL), protein 235 mg/dL (range, 13–1,317 mg/dL), and white blood cell count 96/mm³ (range, 1–1,160/mm³) with 90% lymphocytes (range, 0%–100%). Nineteen of the 35 tested patients (54%)

had hypoglycorrachia, defined as glucose <50 mg/dL; 35 of 39 (92%) had elevated CSF protein ≥55 mg/dL; and 35 of 38 (92%) had a leukocytosis of >5 cells/mm³. Thirty of 45 patients (67%) had positive cytology. Moreover, 20 of 25 patients (80%) had a monoclonal B- or T-cell population detected by flow cytometry, and 15 of 22 (71%) by immunoglobulin heavy-chain or T-cell receptor gene rearrangement (table 2). CSF was diagnostic for lymphoma after a median of 2 lumbar punctures (LPs) (range, 0–5), whereas 16 patients (33%) required a meningeal biopsy for diagnosis. A neuropathologist (M.-B.L.) reviewed and confirmed the cytology, flow cytometry, or biopsy reports for 26 patients (54%).

Treatment and outcome. Patients received a variety of treatments, including radiation, systemic chemotherapy, or CSF-directed chemotherapy (table 3). Treatment was known for 47 patients and unknown for one patient. Thirty-one (66%) received ≥2 treatment modalities as initial therapy: 20 (43%) the combination of systemic and intra-CSF chemotherapy; 4 (9%) the combination of radiation and intra-CSF chemotherapy; 1 (2%) radiation and systemic chemotherapy; and 6 (13%) received all 3 modalities. Nine patients (19%) received only systemic chemotherapy, 6 (13%) radiation alone, and 1 (2%) intra-CSF chemotherapy only.

The majority of patients (68%) received high-dose methotrexate as the backbone of their initial treatment regime; other drugs included alkylating agents—procarbazine or temozolomide—in 15 (32%); rituximab, cytarabine, vincristine in 11 (23%) each; cyclophosphamide in 7 (15%); and doxorubicin in 6 (13%). Seventeen patients (36%) received radiation at diagnosis. Intra-CSF chemotherapy was included in the treatment plan of 31 patients (66%)—with 11 (23%) receiving methotrexate alone, 7 (15%) cytarabine alone, 8 (17%) receiving both, and 5 (11) receiving intra-CSF treatment with unspecified drug.

Clinical follow-up was available for 45 patients, and response was based on the assessment of the treating IPCG physician. Twenty-one patients (47%) achieved a clinical complete response (CR), 11 (24%) a partial response (PR), 2 (5%) stable disease (SD), and 11 (24%) had progressive disease (PD). Thirty-five patients had radiographic follow-up: 22 (63%) achieved CR, 8 (23%) PR, 2 (6%) SD, and 3 (9%) had PD. In the CSF, 27 of 33 patients (82%) had documented clearance of malignant cells. Twenty-six patients had imaging and CSF monitoring at follow-up, with 18 (69%) achieving CR in both. Six patients (13%) had progressive leptomeningeal disease during or immediately after completion of initial therapy, and did not receive further treatment before death.

Twenty patients (44%) went on to receive salvage therapy after relapse (18 [40%] relapsed in the CNS

Figure 1 MRI of a 66-year-old man with primary leptomeningeal lymphoma of the lumbar spine

T1-weighted contrast-enhanced sagittal image demonstrating leptomeningeal enhancement of multiple lumbar and sacral nerve roots of the cauda equina (arrow).

Table 3 Percentage of treatments up-front and at recurrence in primary leptomeningeal lymphoma

	Initial treatment		Salvage treatment	
	% of cases	n = 47	% of cases	n = 20
Radiation	36	17	60	12
WBRT	19	9	10	2
Craniospinal	15	7	20	4
Focal + WBRT	2	1	30	6
Systemic chemotherapy	78	36	70	14
Methotrexate-based	70	32	30	6
Other	9	4	40	8
Intra-CSF chemotherapy	66	31	50	10
Methotrexate-based	43	20	15	3
Other	23	11	35	7

Abbreviation: WBRT = whole-brain radiation therapy.

and 2 [4%] systemically) (table 3). At relapse, 3 patients (15%) received the combination of radiation and systemic and intra-CSF chemotherapy; 6 (30%) radiation and systemic chemotherapy; 3 (15%) systemic and intra-CSF chemotherapy; and 1 (5%) radiation and intra-CSF chemotherapy. Three (15%) received intra-CSF therapy alone, 2 (10%) radiation alone, and 2 (10%) systemic chemotherapy alone. Of the 8 patients (40%) who received systemic chemotherapy without high-dose methotrexate, the following agents were used: cytarabine in 7 (35%); vincristine in 6 (30%); cyclophosphamide and rituximab in 4 (20%) each; etoposide in 3 (15%); and an alkylating agent in 2 (10%). Seven of the 10 who were treated with intra-CSF chemotherapy received cytarabine alone, 2 (10%) methotrexate alone, and 1 (5%) both agents. Based on the clinical assessment of the treating physician, 4 (20%) achieved a CR, 3 (15%) PR, 2 (10%) SD, and 11 (55%) had PD. Nineteen had follow-up MRIs: 7 (37%) had radiologic CR, 2 (11%) PR, 2 (11%) SD, and 8 (42%) PD. Complete

clearance of CSF was noted in 5 of 14 patients (36%) with follow-up LP.

Median progression-free survival for the entire cohort was 8 months (95% confidence interval [CI] 6–34 months), and median overall survival was 24 months (lower limit of 95% CI 15; upper limit not estimable) (figure 2), with most patients dying of progressive leptomeningeal disease. Median follow-up (i.e., time to death or censoring) was 48 months (95% CI 37–84 months), and 11 patients were still alive at 50 months follow-up, suggesting that a subset may be cured.

In univariate analysis, no factor predicted survival; age, B-cell vs T-cell subtype, positive cytology, positive flow cytometry or testing for flow, and initial treatment modality—i.e., any form of radiation, systemic methotrexate, or intrathecal chemotherapy—were not significant predictors of survival. Although performance status at diagnosis was also not a significant outcome predictor, there was a trend (hazard ratio 0.39) toward worse survival in patients with an ECOG performance status of 3 or 4 compared with those who had a performance status of 1. This suggests a possible worse outcome in patients with a poor performance status at diagnosis, although the small sample size likely limited detection of significance. Diagnosis before 1990 did not predict survival, but diagnosis before 2000 had a trend toward a significant correlation with worse outcome (hazard ratio 2.1, $p = 0.078$).

DISCUSSION While leptomeningeal involvement of lymphoma can occur as a late manifestation of systemic lymphoma or synchronously with PCNSL, lymphoma isolated to the leptomeninges is exceedingly rare. The biological basis of lymphomatous involvement isolated to the subarachnoid space is not understood; nor are the factors that predict response to treatment or site of relapse. One hypothesis considers homing of systemically generated lymphomatous cells to the leptomeninges, although the

Figure 2 Kaplan-Meier curves for progression-free survival (A) and overall survival (B)

mechanisms of malignant transformation, the point of access to the CNS, and the origin of the cells remain insufficiently studied.¹⁶

Similar to other processes affecting the leptomeninges, patients with PLML present with symptoms and signs referable to multiple levels of the neuraxis, with a high prevalence of cranial nerve palsies and lumbosacral radiculopathies.²⁴ Symptom onset in PLML is typically rapid; we observed a median of 2 months from onset to diagnosis. However, as in our series, some patients have a more indolent course with symptom onset ranging from 3 to 7 years.^{12,14}

Establishing the diagnosis of leptomeningeal involvement from lymphoproliferative disorders can be challenging. MRI has a reported sensitivity of 20% to 37.5% for detection of leptomeningeal seeding from PCNSL and hematologic disorders, compared with 85% for solid malignancies.^{25,26} Eighty-one percent of our patients in the current study had abnormal neuroimaging even though complete neuraxis imaging was performed in only 23% of patients. While some patients only underwent CT, the radiographic appearance of lymphoma, with iso- to hyperdensity on CT and homogeneous contrast enhancement, makes underdiagnosis of parenchymal brain lymphoma in these patients relatively unlikely. Contrast MRI of the entire neuraxis to define total tumor burden should be performed before initiating treatment and is an important tool in evaluating treatment response in these patients. Even when neuroimaging is abnormal, histologic confirmation is essential for PLML and typically comes from the CSF.

In PLML, the CSF profile is always abnormal, and findings may include leukocytosis, elevated protein concentration, and hypoglycorrhachia. Definitive diagnosis may be established by detection of malignant lymphocytes on cytology, or a monoclonal population by flow cytometry or gene rearrangement studies, which may be more sensitive. Nonetheless, there are patients with a positive cytology despite negative flow cytometry, suggesting that a combined approach will yield best results.²⁷ Repeat LP may be needed because the sensitivity of cytology ranges from 20% to 80% for detecting leptomeningeal metastases from hematologic malignancies.²⁵ Positive CSF cytology is dependent on the proportion of malignant cells in the sample (a threshold of 5% is needed for detection) and the integrity of the sample.^{28,29} Therefore, we suggest obtaining and sending CSF for cytology, flow cytometry, and gene rearrangement studies,³⁰ and to repeat the analysis if initial results are suspicious but not definitive. Despite these efforts, a diagnosis from CSF may not be possible and meningeal biopsy, preferably corresponding to an area of enhancement seen on MRI, may be required.³¹

The current study supports previous observations that PLML has a higher representation of T-cell

lymphoma than PCNSL, 19% in our cohort.^{8,16} However, PLML still accounts for only 2% to 5% of cohorts of T-cell-related PCNSL, emphasizing its rarity.^{15,16} Demonstration of T-cell receptor gene rearrangement, as confirmed in one of our patients, can differentiate a true T-cell lymphoma from reactive T lymphocytes, which may accompany a B-cell malignancy.^{32,33} While knowing the tumor type is important for some therapeutic decisions, such as whether to incorporate rituximab into the treatment protocol, prognosis and treatment response do not seem to differ between B-cell and T-cell subtypes.¹⁶ Treatment in the current cohort varied widely although 46% of patients received multimodal therapy while 39% received systemic chemotherapy alone. Response rates were high, with 71% achieving at least a clinical PR and 82% with documented clearance of malignant cells from their CSF. Although 44% relapsed and required salvage treatment, 35% of patients who received salvage therapy achieved at least a clinical PR. No clinical predictors were identified for long-term survival.

The most notable finding in this cohort was the median overall survival of 24 months, which significantly exceeds that previously reported.⁵ We cannot determine in our cohort whether the improved outcome is attributable to aggressive multimodal treatment, or whether more conservative initial treatment would have similar results. Based on univariate analyses, no potential predictors of outcome were significantly associated with outcome, although some important data were missing. The marginally significant association with worse outcome among those diagnosed before 2000 is difficult to interpret given the small sample size. Symptom duration before diagnosis was similar between the current cohort and that previously reported by Lachance et al.,⁵ making it unlikely that time to diagnosis accounts for the disparity in outcome. While treatment varied significantly, outcomes were better than previously reported and appeared independent of initial treatment. Almost one-fourth of our cohort was alive after 50 months of follow-up, suggesting that a subset of these patients may be cured. The role of intra-CSF chemotherapy and radiation in the treatment of PLML is unclear, although frequently used in the current retrospective series. A phase I study of intraventricular rituximab and methotrexate for recurrent B-cell CNS lymphoma demonstrated safety and high response rates; further studies are warranted, and such an approach may be of particular interest in PLML.³⁴ Our study suggests that patients with PLML may benefit from aggressive therapy similar to other forms of PCNSL, with high-dose methotrexate as the primary backbone treatment.

AUTHOR CONTRIBUTIONS

Jennie W. Taylor contributed to study design, drafting/revising the manuscript, and data analysis. Eoin P. Flanagan, Brian P. O'Neill, Tali Siegal, Antonio Omuro, Lisa DeAngelis, Joachim Baehring, Ryo Nishikawa, Fernando Pinto, Marc Chamberlain, Khe Hoang-Xuan, Alberto Gonzalez-Aguilar, Tracy Batchelor, Jean-Yves Blay, Agnieszka Korfel, and Rebecca A. Betensky contributed to acquisition of data, drafting/revising the manuscript, and data analysis. Maria-Beatriz S. Lopes contributed to drafting/revising the manuscript and data analysis. David Schiff contributed to study design, acquisition of data, study supervision, drafting/revising the manuscript, and data analysis.

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DISCLOSURE

J. Taylor and E. Flanagan report no disclosures. B. O'Neill serves on the scientific advisory boards of the V Foundation, Sontag Foundation, and Advance Brain Cancer Cure (ABC2). He serves as a member of the editorial advisory board of *Neuro-Oncology* and the *Journal of Neuro-Oncology*. He receives honoraria for his textbook *Principles of Neuro-Oncology*. He receives research support as principal investigator/director of T32NS 07494-8, P50CA 108961-7, and P30CA 15083-38; site principal investigator for 28XS094-1 (The Cancer Genome Atlas Program); and principal investigator of ABC2-1 (Advance Brain Cancer Cure). T. Siegal has received funding for travel, honoraria and research support from Roche, Schering-Plough, and Merck Serono pharmaceutical companies, and served on the advisory board and as a consultant for Roche and Schering-Plough. A. Omuro served on the scientific advisory board for Roche and Novocure. He has received funding by NIH grants 3P30CA008748-47S2 and 1U01CA137443-01. He has received institutional support through the MSKCC Department of Neurology Research and Development Fund to conduct clinical research and research support for conduction of clinical trials from the B*Cured Foundation, CERN Foundation, Roche/Genentech, Sanofi, Plexxikon, Tactics Therapeutics, and Merck. L. DeAngelis serves on the scientific advisory board for NFLPA. She serves on the editorial boards for *Neurology*, *Neuro-Oncology*, *Journal of Neuro-Oncology*, *CNS Oncology*, and *British Medical Journal*. She has received royalties from Oxford University Press for *Neurologic Complications of Cancer*. She has received research support from NIH KL2 award for Babak Navi (mentor). J. Baehring serves on the advisory board of Genentech. He has received honoraria from SigmaTau for lectures and round table discussions. R. Nishikawa serves on the advisory board of Hoffmann-La Roche Ltd. He has received honoraria for lectures and writings from MSD K.K., Chugai Pharmaceutical Co. Ltd., and Nobelpharma Co. Ltd. F. Pinto, M. Chamberlain, K. Hoang-Xuan, and A. Gonzalez-Aguilar report no disclosures. T. Batchelor serves as a consultant or advisor for Merck & Co., Inc., Roche, Kirin Pharmaceuticals, Spectrum, Champions Biotechnology, Advance Medical, and Novartis. He has received honoraria from UpToDate, Inc., Robert Michael Educational Institute LLC, Educational Concepts Group, Research to Practice, Immedex, Oakstone Medical Publishing, and American Society of Hematology. He has received research funding from Pfizer, AstraZeneca, Millennium, and NIH. J. Blay reports no disclosures. A. Korfel serves on the advisory board for Mundipharma and Riemser. She has received funding for travel from Mundipharma, Pfizer, Roche, and Riemser. She has received commercial research support from Mundipharma, Pfizer, Roche, and Riemser. R. Betensky has served on NIH Study Sections. She has received NIH funding for research (R01CA075971, R03CA165070, UL1RR025758, P50NS051343, P30CA006516, P50AG005134, P01AG036694, R01NS070834, R01AG026484, R33 DK074099, R01CA057683). She has received funding for travel to meetings for 2 Institute of Medicine Committees, for scientific conferences, and for seminars sponsored by consulting networks. She has served as associate editor for *Biostatistics*. She has consulted for Columbia

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