The Cancer and Leukemia Group B Lymphoma Committee
Bruce D. Cheson and George P. Canellos

Abstract

The malignant lymphomas include at least 30 entities that are distinct with respect to histology, immunology, genetics, clinical features, and outcome following therapy. The clinical behavior of these diseases ranges from indolent but generally incurable to aggressive and frequently fatal yet potentially curable with appropriate chemotherapy or chemotherapy-antibody regimens. Over the past 50 years, the Cancer and Leukemia Group B (CALGB) Lymphoma Committee has conducted a series of clinical trials that have contributed to an improvement in outcome for patients with a number of the more common lymphoma subtypes.

The World Health Organization has classified approximately 30 neoplastic diseases of the hematopoietic and lymphoid tissues (1). The Cancer and Leukemia Group B (CALGB) Lymphoma Committee highlight below clinical trials that have resulted in improved patient outcome for the more frequent lymphoma subtypes.

Hodgkin’s Lymphoma

Hodgkin’s lymphoma represents one of the successes of modern oncology. Patients with limited stage disease were traditionally treated with radiation therapy as the primary modality. Although the majority of patients were cured, systemic therapy was required for those that developed a recurrence. CALGB investigators (2) conducted a randomized trial in 113 patients whose disease had progressed after primary radiation therapy. The study involved a comparison among 1-(2-chloroethyl)-3-cyclohexyl-L-nitrosourea, vinblastine, procarbazine, doxorubicin, prednisone; Adriamycin, bleomycin, vincristine, and streptozotocin; and a regimen that alternated between the two regimens. Although there were no major differences in efficacy among the various treatment strategies, an important observation was that almost half of the patients remained failure free at 5 years, and 60% remained alive.

Currently, most patients who present with advanced-stage disease can be cured with conventional doses of multiagent chemotherapy. For those with stage III disease, chemotherapy plus radiotherapy was often used, although the optimal approach was poorly defined. CALGB investigators conducted a small trial in which patients with stage III disease were randomized to four weekly doses of vinblastine and one dose of mechlorethamine hydrochloride followed by no additional therapy involved field radiation therapy or total nodal irradiation (3). The patients were followed to a maximum of 10 years. The combined modality approaches produced a longer disease-free survival than chemotherapy alone. Although radiation therapy plays less of a role in the current management of this subgroup of patients given the greater efficacy of contemporary chemotherapy regimens, this study provided important information about the use of combined modality treatment at the time it was published.

The mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) combination chemotherapy regimen provided the first evidence for cure in a substantial proportion of patients with stage III and IV Hodgkin’s lymphoma. Nevertheless, over the decades since the introduction of MOPP, other regimens were developed to improve on the efficacy of MOPP while attempting to reduce its toxicities, particularly infertility and secondary malignancies (4–8). Nissen et al. (7) conducted a randomized study comparing MOPP with several modifications of the MOPP regimen; in one, 1,3-bis(2-chloroethyl)-1-nitrosourea was substituted for the nitrogen mustard (BOPP), another eliminated the procarbazine (MOP), and another omitted the alkylating agent (OPP). The three drug combinations were clearly inferior with respect to response rate and survival. BOPP and MOPP were comparable, although the former was felt to have less treatment-associated toxicity. Other regimens substituting 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea for nitrogen mustard or vinblastine for vincristine were highly effective but with considerable hematotoxicity (8).

Based on the work of Bonadonna et al., the Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) and MOPP/ABVD regimens received considerable interest (9, 10). However, their efficacy compared with the standard MOPP regimen remained to be determined. CALGB conducted a pivotal comparison of MOPP, ABVD, and MOPP/ABVD (11). The study included 361 eligible patients and reported an overall response rate of 93%, including 77% complete remissions; both complete and overall response rates favored the anthracycline containing regimens. Moreover, the failure-free survival at 5 years was 50% for MOPP, 61% for ABVD, and 65% for MOPP-ABVD. In addition, MOPP was associated with greater toxicities and, as a result of this trial, was virtually abandoned as initial chemotherapy for Hodgkin’s lymphoma. Subsequent data on a MOPP/ABV hybrid regimen were sufficiently encouraging to lead to a subsequent trial of ABVD versus the MOPP/ABV hybrid (12, 13). The two regimens showed comparable efficacy; however, the lower toxicity with ABVD, especially with regard to acute pulmonary and hematologic toxicity and second malignancies,
established ABVD as the current standard chemotherapy therapy for patients with advanced-stage Hodgkin’s lymphoma (14).

### Follicular Non-Hodgkin’s Lymphoma

Before the introduction of rituximab, no evidence supported the use of one chemotherapy regimen over another in the treatment of patients with follicular or low-grade non-Hodgkin’s lymphoma (NHL). Moreover, considerable controversy existed as to whether initial combination chemotherapy was superior to treatment with a single alkylating agent. In a prospective trial, CALGB randomly assigned 228 patients to either oral cyclophosphamide at 100 mg/m² or cyclophosphamide-Adriamycin-vincristine-prednisone (CHOP)/bleomycin for 2 years or until toxicity was prohibitive. In the latter regimen, bleomycin was discontinued at a cumulative dose of 60 units/m², and the Adriamycin was discontinued after 450 mg/m². With 20 years of follow-up, failure-free and overall survival were comparable between the arms. In an unplanned subset analysis, patients with what was then called follicular mixed lymphoma experienced a longer survival with the combination regimen. However, this finding has not been consistently observed in other studies. Nevertheless, the prolonged follow-up reported in this study clearly showed that more intensive treatment did not necessarily confer meaningful clinical benefit in these diseases, similar to other reports (15, 16).

### Diffuse Large B-Cell Lymphoma

For decades, the CHOP regimen had been the standard therapy for patients with previously untreated, advanced-stage diffuse large-B-cell lymphoma (17). Numerous attempts were made to improve on the efficacy of this combination by adding other agents that were presumed to be non–cross-resistant and with nonoverlapping toxicities (18–20). The CALGB developed one such regimen in which the dose of methotrexate and the role of bleomycin were evaluated in the context of the other agents in CHOP (21). In CALGB 7851, 177 patients with diffuse large-B-cell lymphoma and 97 with other aggressive histologies received three cycles of CHOP every 3 weeks with or without bleomycin. Those patients who experienced a response were randomized for the next three cycles to receive high-dose methotrexate with leucovorin rescue or to no additional therapy. There was no benefit to the addition of either bleomycin or high-dose methotrexate. Other combinations were studied in patients who were refractory to CHOP or similar regimens (22). These data suggested that the addition of other drugs would not add to the activity of CHOP as had already been proposed (23). Further confirmation of the role of CHOP was provided by a national high-priority trial in which the CALGB participated with the Southwest Oncology Group; CHOP was compared with methotrexate, bleomycin, Adriamycin, cyclophosphamide, vincristine, dexamethasone (MACOP-B); methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin (MACOP-B); and prednisone, methotrexate, Adriamycin, cyclophosphamide, etoposide, vincristine, prednisone, methotrexate (ProMACE/CytoBOM). Outcomes with the various regimens were similar, except with less toxicity in the CHOP arm, further establishing CHOP as the standard of care for patients with aggressive NHL (24).

### High-Grade NHL

Burkitt’s leukemia is rare but may manifest as a highly aggressive form of acute lymphoblastic leukemia (L3). In addition, a small fraction of adult lymphomas are of the small noncleaved morphology. Based on data from pediatric trials suggesting benefit from high-intensity, short-course chemotherapy in patients with this histology, the CALGB conducted protocol 9251 (25). The patient population included 24 patients with acute lymphoblastic leukemia and 51 patients with small noncleaved cell NHL. They were treated with an intensive multagent regimen, including cyclophosphamide and prednisone followed by ifosfamide, high-dose methotrexate, vincristine, dexamethasone, doxorubicin, etoposide, cytarabine, and central nervous system prophylaxis with either triple intrathecal therapy or central nervous system irradiation. Of the 54 eligible patients, 43 attained a complete remission, and 28 (52%) were alive and in continuous complete remission with a median follow-up of 5.1 years. The original regimen was associated with considerable neurotoxicity related to the radiation and was subsequently modified to reserve cranial irradiation for patients with bone marrow or central nervous system disease, begin irradiation after completion of chemotherapy, and reduce the number of doses of intrathecal chemotherapy. Evaluation of a subsequent cohort of patients suggested that the frequency and severity of neurologic toxicities was substantially decreased (26).

### Current Studies and Future Directions

The CALGB Lymphoma Committee is pursuing a number of novel directions in its clinical trials. The Committee is committed to testing new chemotherapy regimens in patients with Hodgkin’s lymphoma. Although >90% of patients with low-risk disease may be cured with radiation or combination chemotherapy, there are long-term toxicities associated with these approaches. Gemcitabine has been shown to have a high level of activity in patients with relapsed and refractory Hodgkin’s lymphoma and is thus a potentially important agent for the initial treatment of this disease (27). The Committee developed a combination of doxorubicin, vinblastine, and gemcitabine that is being used as the initial therapy of low-risk patients. The role of positron emission tomography will also be evaluated in this trial. In relapsed patients, the Committee is building on its encouraging prior results with a regimen composed of liposomal doxorubicin, vinorelbine, and gemcitabine, which achieved responses in 58% of relapsed and refractory patients who had not received a prior autologous stem cell transplant and in 68% of those who had progressed after that procedure. The new protocol uses the same chemotherapy but also incorporates an anti-CD30 monoclonal antibody (28). Although the single-agent data with such antibodies in Hodgkin’s lymphoma has been modest, the expectation is that it will enhance the activity of the chemotherapy agents (29, 30).

Protocols evaluating doublets of biological agents without chemotherapy are actively accruing previously untreated patients with follicular NHL. The first of these combinations is rituximab and the anti-CD80 monoclonal antibody galiximab based on encouraging phase II data in previously treated patients (31). Upon completion of this trial, the next
doublet will be rituximab and oblimersen, a bcl-2 antisense oligonucleotide that adds to the activity of other agents in lymphoid malignancies (32). Studies of new agents will also be conducted in patients with relapsed follicular lymphoma. An agent of interest is lenalidomide, a second-generation immunomodulatory agent with activity in patients with 5q–myelodysplastic syndrome (33), multiple myeloma, and chronic lymphocytic leukemia (34). To date, there are no data in patients with NHL. The current CALGB protocol for patients with follicular NHL who have relapsed after chemotherapy plus rituximab is a randomized study of either rituximab as a single agent, lenalidomide, or a combination of the two drugs.

Diffuse large B-cell lymphoma can be distinguished into three genetically distinct subtypes by microarray analyses (35). Molecular profiling may also be used to identify appropriate therapy for select patients. Thus, the current CALGB study for previously untreated patients with diffuse large B-cell lymphoma involves a comparison between R-CHOP and the infusional R-EPOCH regimen developed by National Cancer Institute investigators (36). However, the critical questions in this study will be addressed by DNA microarray analyses on biopsy samples from all patients. These include a prospective validation of the prognostic subsets of diffuse large B-cell lymphoma, to assess the use of molecular profiling for pathologic diagnosis, identification of the molecular signature patterns that correlate best with outcome following either infusional R-EPOCH or bolus R-CHOP therapy and to potentially identify new therapeutic targets using molecular profiling.

The treatment of patients with mantle cell lymphoma has been frustrating, with high response rates to standard chemotherapeutic regimens but eventual relapse in virtually all patients. One of the most promising new agents in the treatment of mantle cell lymphoma is the proteasome inhibitor bortezomib, which induces responses in 30% to 50% of patients with relapsed or refractory disease (37, 38). Following encouraging results with an intensive front-line strategy, including rituximab and autologous stem cell transplantation, CALGB has decided to incorporate bortezomib into the treatment strategy (39). Response rates to any one of a variety of chemotherapy regimens are high in mantle cell lymphoma; however, the durability of such responses is disappointing. Therefore, the current front-line protocol for patients with mantle cell lymphoma will test the optimal delivery schedule for bortezomib as a maintenance strategy. For patients who progress after an initial therapy, the doubling of lenalidomide and bortezomib is being evaluated. In addition, a phase II/III program is under development that will focus on new proapoptotic agents in patients with refractory lymphomas of various histologies.

A major goal of the Committee is to incorporate a correlative or translational research study into every protocol. All patients entered onto the diffuse large B-cell protocol (CALGB 50303) will undergo core biopsies for fresh frozen lymph node tissue to be submitted for DNA microarray analysis. For protocols involving other histologies, tissue microarrays are being prepared, and samples of genomic DNA from peripheral blood mononuclear cells are being collected to correlate receptor pharmacomerisms with clinical outcome. By emphasizing the importance of correlative science, the Committee hopes to better understand the biology of the various histologic and biological subtypes of malignant lymphoma and to more rationally develop treatment strategies, leading to an improved outcome for patients with these diseases.

References


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