Fifty Years of Clinical Research by the Leukemia Committee of the Cancer and Leukemia Group B

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Abstract

Progress in the care of patients with leukemia has been one of the great success stories in the field of oncology, and clinical research in leukemia has been the “flagship” of the Cancer and Leukemia Group B since the inception of this organization. Lessons learned from the founders’ emphasis on childhood and adult leukemia have been extended broadly over the past 50 years to virtually all types of malignant diseases, and the Leukemia Committee has continued to provide leadership and key contributions. The Leukemia Committee is focused on the individualization of treatment based on distinctive biological and clinical characteristics with the aim of increasing efficacy and decreasing nonspecific toxicity. Our clinical trials in leukemia and myeloma have shifted from primarily empirically derived comparisons of different chemotherapeutic regimens to testing novel concepts such as the role of dose intensity, inhibition of specific mechanisms of drug resistance, the use of hematopoietic growth factors and monoclonal antibodies, and the utility of targeted agents. The Cancer and Leukemia Group B was the pioneer among the cooperative groups in the creation of centralized tissue repositories and the incorporation of correlative laboratory studies as an integral feature of clinical trials, a practice now termed “translational research.” Considerable effort has focused on the identification of important pretreatment characteristics, such as morphologic features, immunophenotype, chromosomal abnormalities, and molecular defects, which are significantly associated with outcome in multivariable analyses and which enhance our understanding for the complex biology of these diseases.

The Early Days

During the first decade of its existence, the Acute Leukemia Group B (ALGB), which was later to become the Cancer and Acute Leukemia Group B (CALGB), focused solely on extending the survival of patients with acute leukemia—at that time a uniformly fatal disease. The ALGB was initially both an intramural and extramural enterprise at the National Cancer Institute. In 1954, James F. Holland designed the first randomized clinical trial at the National Cancer Institute (1). By the time the study was activated, Holland had moved to RPMI in Buffalo, New York. Emil (Tom) Frei III became the head of the ALGB and led the Group until 1965.

This first pioneering study targeted childhood leukemia and attempted to replicate experiments in mice that showed that the combination of two drugs (a purine analogue and a folic acid analogue) was more successful than either drug used separately. Protocol 01 was a comparative trial of continuous versus intermittent methotrexate together with daily 6-mercaptopurine that opened on May 16, 1955 and closed 17 months later (2). Sixty-five patients were enrolled at three institutions in two cities. This eight-page protocol was remarkable for many of the attributes found in modern clinical trials. There were clearly stated eligibility and exclusion criteria, required prestudy tests, a plan for randomization, provisions for central morphology review, a description of anticipated toxicities, recommended supportive care measures, and detailed criteria for response assessment. However, in contrast to current leukemia trials, this study included all forms of acute leukemia as well as children and adults with both newly diagnosed and previously treated disease. In addition, it lacked a background section to justify the treatment plan as well as a statistical section. The study results, published in the December 1, 1958 issue of Blood, showed no difference in the frequency of remission for the two treatment programs but a significantly longer survival for the continuous treatment (2).

Importantly, data from this trial suggested that the best predictor of survival was the posttreatment bone marrow result. In fact, at the first meeting of the ALGB in Boston in 1956, Sidney Farber already raised the issue of common standards, response criteria, and definitions for clinical trials (1). Prior to this point, clinical end points had been determined by the number of leukemia blast cells left circulating in the blood. The ALGB proposed a definition for complete remission (CR) in leukemia of <5% residual blasts in the marrow that has since become the worldwide standard for all future trials. To this criterion was added the disappearance of clinical symptoms of leukemia, such as fever, infection, and bleeding, and the recovery of normal hematopoiesis.

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Maintenance chemotherapy was another concept that was introduced by Emil J. Freireich, Frei, and the ALGB in acute lymphoblastic leukemia (ALL). In protocol 03, a phase III trial which began in July 1959, investigators randomized children to receive either placebo or 6-mercaptopurine after the induction of remission with prednisone. The study ended in April 1960 when it was shown that 6-mercaptopurine yielded significantly longer remissions (3).

Combination chemotherapy for leukemia that relied on a mechanistic understanding of drug action and pharmacology was inaugurated by Frei, Holland, and colleagues based on sound experimental data developed by Skipper and others. The ALGB showed that the combination of 6-mercaptopurine and methotrexate gave a higher remission rate than either one separately, although the combination did not result in longer survival (4). While Freireich and Frei and others at the National Cancer Institute were developing the VAMP regimen [vinristine, amethopterin (methotrexate), mercaptopurine, and prednisone] in 1962, the ALGB added cyclophosphamide and carmustine [1,3-bis(2-chloroethyl)-1-nitrosourea] to the same four drugs in protocol 6313 (the 13th study in 1963). Both regimens yielded unprecedented results and provided the cornerstones for modern curative regimens for ALL.

During the five decades since these pioneering studies, the Leukemia Committee has been chaired by Emil Frei, James Holland, Peter H. Wiernik, O. Ross McIntyre, Charles A. Schiffer, and most recently, Richard A. Larson. Many others who became leaders in the treatment of leukemia and myeloma, such as Oliver J. Glidewell, Rose Ruth Ellison, Richard T. Silver, Edward S. Henderson, Fred Rosner, Janet Cuttner, Arthur Sawitsky, Kanti R. Rai, Robert A. Kyle, Morton Coleman, Robert Cooper, Harvey D. Preisler, Robert L. Capizzi, Robert J. Mayer, Richard M. Stone, Jonathan E. Kolitz, Bayard L. Powell, Wendy Stock, and John C. Byrd, chaired important studies. A total of 197 trials in leukemia and myeloma were activated during these 50 years, including 98 randomized phase III studies. In addition, as described elsewhere in this issue, the CALGB was the pioneer among the cooperative groups in the creation of centralized tissue repositories and the incorporation of correlative laboratory studies as an integral feature of clinical trials, a practice now termed “translational research.”

Current Activities and Research Themes

Subsequently, the Committee’s portfolio expanded to include acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), myelodysplastic syndromes (MDS), chronic myelogenous leukemia (CML), adult ALL, chronic lymphocytic leukemia (CLL), hairy cell leukemia, and multiple myeloma. Research themes have emphasized randomized trials to optimize combination chemotherapy for biologically distinctive subsets of leukemia, the use of intensive dose escalation of individual agents to overcome resistance, and the introduction of new drugs, typically first in relapsed disease and then into frontline treatment. Leukemia studies have been designed and conducted in close collaboration with other CALGB committees, such as Pathology, Leukemia Correlative Science, Transplant, and Lymphoma. Considerable effort has focused on the identification of important pretreatment characteristics, such as morphologic features, immunophenotype, chromosomal abnormalities, and molecular defects, which are significantly associated with outcome in multivariable analyses and which enhance our understanding for the complex biology of these diseases.

Particularly in recent phase III studies, the Leukemia Committee has promoted the use of minimally restrictive eligibility requirements in part to increase the access of patients to novel therapies but also to make the results more generalizable and thus applicable to less highly selected patients than typically permitted on clinical trials (5). There has also been increasing collaboration between the CALGB, Eastern Cooperative Oncology Group, Southwest Oncology Group, and the National Cancer Institute of Canada Clinical Trials Group. This has allowed more rapid accrual to intergroup studies in rare diseases such as APL and relapsed ALL as well as more common diseases such as CLL and myeloma. The CALGB has also partnered with industry to develop important new chemotherapy drugs. These include azacitidine for MDS and nelarabine for T-cell ALL, two drugs which gained Food and Drug Administration approval based, in large part, on data from CALGB trials (studies 8421, 8921, and 9221 and 19801, respectively).

The hypotheses currently being tested are that (a) better outcomes are achieved when treatment is individualized and based on pretreatment clinical and biological disease characteristics; (b) inhibitors of drug efflux mechanisms and anti-apoptotic pathways can overcome inherent drug resistance in leukemia cells; (c) escalating chemotherapy drugs to their maximal tolerated dose can overcome drug resistance in leukemia cells; (d) autologous hematopoietic stem cell transplantation is safe and effective for patients with acute leukemia; (e) the immune system can be activated in a way to prolong disease-free survival; (f) inhibiting signaling pathways with small molecules and targeting surface antigens with antibodies will lead to increased leukemia cell kill; and (g) cytogenetic remissions are important end points in treating leukemia but molecular remissions are even more important for disease-free survival. The following will highlight some of the more recent research accomplishments of the group, many of which have had an important effect on advancing the standard of care as well as future research directions.

Highlights from Clinical Studies in AML

The CALGB defined the modern standard management of adults with AML: 3 days of an anthracycline plus 7 days of cytarabine by continuous infusion (3 + 7) for induction followed by high-dose cytarabine for postremission consolidation. Beginning with CALGB study 7721, a series of randomized comparative studies were conducted in the 1970s and early 1980s that failed to show additional benefit from the substitution of Adriamycin for daunorubicin, the addition of 6-thioguanine to 3 + 7, prolonging the duration of cytarabine infusion to 10 days, or doubling of the dose of cytarabine to 200 mg/m²/d (6). Increasing patient age was found to have a significant effect on outcome in many of these studies, prompting the subsequent development of separate clinical trials for younger and older (>60 years) patients with AML.

Although most previously untreated adults with primary AML enter CR when treated with cytarabine and an anthracycline, such responses are often not durable. Intensive
postremission therapy may prolong these remissions. In the prospective cytogenetic study, CALGB 8461 (8). Patients were categorized into one of three cytogenetic groups: (a) core binding factor type [t(8;21), inv(16), or t(16;16)]; (b) normal; and (c) other abnormal karyotype (including chromosomal deletions or additions, abnormalities of chromosome band 11q23, and complex karyotypes). There were 57 patients with core binding factor type AML, 140 patients with normal karyotype AML, and 88 patients with other cytogenetic abnormalities. The effect of cytarabine dose on long-term remission was most marked ($P < 0.001$) in the core binding factor type AML group; after 5 years, 78% of those receiving 3 g/m$^2$ were still in CR compared with 57% of those receiving 400 mg/m$^2$ and 16% of those receiving 100 mg/m$^2$. Among those with a normal karyotype, after 5 years, 40% of those receiving 3 g/m$^2$ were still in CR compared with 37% of those receiving 400 mg/m$^2$ and 20% of those receiving 100 mg/m$^2$ ($P = 0.01$). In contrast, cytarabine at all doses produced only a $\leq 21\%$ chance of long-term continuous CR for patients with other cytogenetic abnormalities. This study showed that the curative effect of cytarabine intensification varies significantly among cytogenetic groups. Pretreatment cytogenetics became an important part of postremission treatment planning in more recent studies.

Older patients with AML are less likely to enter remission than younger adults, in part because of a higher mortality rate related to severe myelosuppression. Sargramostim [granulocyte-macrophage colony-stimulating factor (GM-CSF)] and filgrastim [granulocyte colony-stimulating factor (G-CSF)] have been shown to shorten the duration of neutropenia and decrease infectious complications when administered after chemotherapy to patients with lymphomas and solid tumors. CALGB study 8923 was one of the earliest randomized trials to evaluate these drugs in patients with AML; 388 patients $>60$ years old (median, 68 years) who had newly diagnosed primary AML were randomly assigned to receive placebo or GM-CSF (5 $\mu$g/kg/d i.v. over a period of 6 hours) in a double-blind manner, beginning the day after the completion of remission induction chemotherapy (9).

The CR rate was 51% among the 193 patients assigned to GM-CSF and 54% among the 195 assigned to receive placebo ($P = 0.61$). The reasons for failure (early death, death during marrow hypoplasia, and persistent leukemia), the incidence of severe or lethal infection, and the incidence of regrowth of leukemia (2% overall) were similar in the two groups. The median duration of neutropenia was slightly shorter ($P = 0.02$) in the patients who received GM-CSF (15 days) than in those who received placebo (17 days), but the clinical effect was minimal because the growth factor failed to lower the treatment-related mortality rate or improve the rate of CR. The results of this trial and other similar studies with G-CSF provided evidence against the routine use of hematopoietic growth factors during remission induction in AML.

Relapse remains a major problem in older patients with AML. Of 205 patients who achieved CR on CALGB 8923, 169 were medically well and were randomized to receive either lower-dose cytarabine alone or a combination of higher-dose cytarabine and mitoxantrone (10). After a median follow-up of 7.7 years, the median disease-free survival times were 11 and 10 months for those randomized to cytarabine or cytarabine/mitoxantrone, respectively, with corresponding rates of relapse, excluding deaths in CR, of 77% and 82%. Because cytarabine/

![Fig. 1. Probability of survival for all patients (A) and patients $\leq 60$ years old (B) according to the dose of cytarabine in CALGB study 8525 (7). Only AML patients in CR who underwent postremission randomization are included. The $P$ values are for the differences among the three treatment groups. The median follow-up was 52 months. Tick marks, surviving patients. Reprinted with permission from Mayer et al. (7).](image-url)
mitoxantrone was more toxic, we concluded that this more intensive therapy had no benefit in the postremission management of older patients with AML. These results emphasized the need to develop novel therapeutic strategies for these patients.

More recently, the CALGB has explored strategies to overcome multiple mechanisms of treatment resistance in AML, including chemotherapy dose escalation, inhibition of drug efflux mediated by P-glycoprotein and other membrane transporters, addition of interleukin-2 mediated immunotherapy, inhibition of the antiapoptotic effects of BCL2, and more intensive postremission consolidation chemotherapy including hematopoietic stem cell transplantation. CALGB study 9222 failed to show any advantages between two different nonmyeloablative chemotherapy regimens when given at conventional doses for postremission therapy (11). CALGB studies 9420 and 9720 investigated the addition of valspodar (PSC-833), an inhibitor of P-glycoprotein, to remission induction chemotherapy in patients >60 years old but found no benefit (12, 13).

Characteristically, P-glycoprotein is more commonly overexpressed in blasts from relapsed or refractory patients and in older adults in whom AML follows MDS. However, we hypothesized that the inhibition of multidrug resistance in a small subset of AML stem cells present at diagnosis would overcome primary (subclinical) drug resistance and reduce the relapse rate in younger patients. We further hypothesized that dose escalation of chemotherapy drugs to myeloablative levels followed by autotransplantation of first remission stem cells would reduce the relapse rate. Finally, we proposed that an autologous host-versus-leukemia effect could be initiated using daily low doses and pulses of higher-dose interleukin-2 and that this would improve disease-free survival in first CR.

CALGB study 9621 was a large dose-escalation study of daunorubicin, etoposide, and cytarabine with or without PSC-833 in patients <60 years old with untreated AML (14). Doses selected for phase III testing were daunorubicin 90 mg/m² and etoposide 100 mg/m² each for 3 days in cytarabine-daunorubicin-etoposide, and daunorubicin and etoposide each 40 mg/m² in cytarabine-daunorubicin-etoposide-PSC-833. Intolerable mucosal toxicity occurred at higher doses of cytarabine-daunorubicin-etoposide-PSC-833. Although the design of this study precluded direct comparisons, there was an apparent advantage for receiving cytarabine-daunorubicin-etoposide-PSC-833 with respect to disease-free survival and overall survival in patients ≤45 years old, despite the significantly lower doses of daunorubicin and etoposide given in cytarabine-daunorubicin-etoposide-PSC-833 compared with cytarabine-daunorubicin-etoposide. In the subsequent phase III trial (CALGB 19808), however, there was no difference in CR rate (77% and 78%), disease-free survival, or overall survival for the 302 patients randomly assigned to cytarabine-daunorubicin-etoposide or cytarabine-daunorubicin-etoposide-PSC-833. This series of studies not only showed that patients with AML could tolerate significantly higher doses of daunorubicin than had previously been used but also showed no benefit from inhibition of P-glycoprotein with valspodar.

**Highlights from Clinical Studies in AML**

Oral tretinoin [all-trans retinoic acid (ATRA)] induces CR in APL. The North American intergroup trial (CALGB 9191) was designed to test whether induction therapy with ATRA was superior to chemotherapy alone and whether maintenance treatment with ATRA improved outcome (15, 16). Of the 174 patients treated with chemotherapy, 120 (69%) had a CR, as did 124 of the 172 (72%) given ATRA (P = 0.56). However, the 5-year disease-free survival and overall survival were longer with ATRA induction than with chemotherapy (69% versus 29%, and 69% versus 45%, respectively). Based on both induction and maintenance randomizations, the 5-year disease-free survival was 16% for patients randomized to chemotherapy followed by observation, 47% for chemotherapy followed by ATRA, 55% for ATRA followed by observation, and 74% for ATRA followed by ATRA. Treatment with ATRA, a WBC count <2000/µL, and absence of bleeding were each significantly associated with improved survival. Thus, this trial showed that ATRA as induction or maintenance treatment improves disease-free and overall survival compared with chemotherapy alone and should be included as part of the standard treatment of APL.

More recently, the CALGB led the second North American intergroup APL study (CALGB 9710). This large randomized phase III trial for adult and pediatric patients evaluated the benefit of arsenic trioxide as initial postremission therapy, followed by a second randomization to test two different ATRA-containing maintenance regimens. This was the first randomized study to test arsenic trioxide in APL patients in first remission. Over 580 patients were enrolled by five cooperative groups (CALGB, Southwest Oncology Group, Eastern Cooperative Oncology Group, Children’s Oncology Group, and the National Cancer Institute of Canada Clinical Trials Group). Molecular detection of PML/RARα was done in three central laboratories that standardized their methods to confirm the diagnosis of APL at study entry and to follow minimal residual disease during and after treatment. The results are scheduled to be released by the Data and Safety Monitoring Board in 2006.

**Highlights from Clinical Studies in MDS**

Patients with high-risk MDS have high mortality from bone marrow failure or transformation to AML. Supportive care has been standard therapy. Since the 1980s, the CALGB systematically evaluated the use of lower-dose azacitidine in patients with high-risk MDS, culminating in CALGB study 9221, which was a randomized trial comparing supportive care plus azacitidine (75 mg/m² s.c. for 7 days every 28 days) with supportive care only (17). Quality of life was assessed by centrally conducted telephone interviews at baseline and days 50, 106, and 182 (18). Azacitidine treatment resulted in significantly higher response rates, improved quality of life, reduced risk of leukemic transformation, and improved survival compared with supportive care. Responses occurred in 60% of patients on the azacitidine arm (7% CR; 16% partial response, 37% improved) compared with 5% (improved) receiving supportive care only (P < 0.001). Median time to leukemic transformation or death was 21 months for azacitidine compared with 13 months for supportive care (P = 0.007). Transformation to AML occurred as the first event in 15% of patients on the azacitidine arm and in 38% receiving supportive care (P = 0.001). The landmark ancillary quality of life assessments provided a novel way to determine clinical benefit and showed that randomization to azacitidine treatment.
Comparatively few randomized phase III trials have been conducted in adults with ALL. The CALGB has conducted four such trials, the first of which was CALGB study 7612, which compared the results of adding daunorubicin, which was a relatively new agent at that time, to an otherwise identical induction program consisting of vincristine, prednisone, and L-asparaginase in untreated adults with ALL (19). A CR was observed in 38 patients (83%) treated with daunorubicin compared with 25 (47%) receiving vincristine, prednisone, and L-asparaginase alone (P = 0.003), establishing the role of an anthracycline in induction therapy. The high response rate attributable to the use of the anthracycline was confirmed by the subsequent nonrandomized treatment of 78 additional patients, in whom a CR rate of 76% was attained. Central nervous system prophylaxis and maintenance therapy was employed in 103 patients achieving CR. Maintenance consisted of cycles of 6-mercaptopurine and methotrexate with periodic reinforcement with vincristine and prednisone. Maintenance therapy proved to be minimally toxic. The average duration of CR was 15 months and was not affected by the induction regimen. Approximately 25% of responders remained in continuous CR for 36 months. The failure of the daunorubicin-containing program to produce a higher percentage of long-term survivors, despite the higher CR rates achieved, was thought to be due to the use of postremission therapy that was weak in intensity and dependent on reinforcement with vincristine and prednisone. These data clearly established the increased effectiveness of vincristine, prednisone, L-asparaginase, and daunorubicin in adults with ALL. The results supported the concept of an intensive, rather than a conservative, chemotherapy approach as the most appropriate strategy for adult ALL.

The goal of CALGB study 8811 was to evaluate a more intensive chemotherapy program for adults with untreated ALL and to examine prospectively the effect of clinical and biological characteristics on the outcome (20). One hundred ninety-seven patients (16-80 years old; median, 32 years) received cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase; 167 patients (85%) achieved a CR. A CR was observed in 38 patients (83%) treated with daunorubicin compared with 25 (47%) receiving vincristine, prednisone, and L-asparaginase alone (P = 0.003), establishing the role of an anthracycline in induction therapy. The high response rate attributable to the use of the anthracycline was confirmed by the subsequent nonrandomized treatment of 78 additional patients, in whom a CR rate of 76% was attained. Central nervous system prophylaxis and maintenance therapy was employed in 103 patients achieving CR. Maintenance consisted of cycles of 6-mercaptopurine and methotrexate with periodic reinforcement with vincristine and prednisone. Maintenance therapy proved to be minimally toxic. The average duration of CR was 15 months and was not affected by the induction regimen. Approximately 25% of responders remained in continuous CR for 36 months. The failure of the daunorubicin-containing program to produce a higher percentage of long-term survivors, despite the higher CR rates achieved, was thought to be due to the use of postremission therapy that was weak in intensity and dependent on reinforcement with vincristine and prednisone. These data clearly established the increased effectiveness of vincristine, prednisone, L-asparaginase, and daunorubicin in adults with ALL. The results supported the concept of an intensive, rather than a conservative, chemotherapy approach as the most appropriate strategy for adult ALL.

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Morbidity and mortality due to infections remains a major problem, particularly in older patients. In CALGB study 9111, we randomly assigned 198 adults with untreated ALL to receive either placebo or G-CSF (5 μg/kg/d) s.c., beginning 4 days after starting the same intensive remission induction chemotherapy developed in CALGB 8811 and continuing until the neutrophil count was ≥1,000/μL for 2 days (21). Patients initially assigned to G-CSF then continued to receive G-CSF through two monthly courses of consolidation therapy. Patients assigned to placebo received no further study drug. The results are shown in Table 1. Patients in the G-CSF group had significantly shorter durations of neutropenia (<1,000/μL) and thrombocytopenia (<50,000/μL) and fewer days in the hospital (median, 22 versus 28 days; P = 0.02). The patients assigned to receive G-CSF had a higher CR rate and fewer deaths during remission induction than did those receiving placebo (P = 0.04). Of importance was the observation that there was no apparent adverse effect of administering G-CSF concurrent with intermittent cytotoxic therapy on this study. Despite a 6- to 9-day reduction in the duration of neutropenia after consolidation chemotherapy, the patients in the G-CSF group did not complete the planned first 3 months of chemotherapy any more rapidly than did the patients in the placebo group. Overall toxicity was not lessened by the use of G-CSF. After a median follow-up of 4.7 years, there were no significant differences in either disease-free survival (P = 0.53) or overall survival (P = 0.25) for the patients assigned to G-CSF (medians, 2.3 and 2.4 years, respectively) compared with those assigned to placebo (medians, 1.7 and 1.8 years, respectively). Thus, adults who received intensive...
chemotherapy for ALL benefited from G-CSF treatment but its use did not markedly affect the ultimate outcome.

In a cytogenetic companion study (CALGB 8461), we showed that karyotype continued to represent a significant prognostic factor in adult ALL patients even after treatment became more intensive (22). A total of 256 patients had adequate pretreatment cytogenetic analyses: 67 before 1988 and 189 subsequently. The CR rate for the whole group was 80%. Patients with t(9;22), t(4;11), −7, or +8 had significantly lower probabilities of continuous CR and survival than patients with a normal karyotype (38% and 37%) or patients with other cytogenetic abnormalities (52% and 49%; P < 0.001 for each comparison). When analyzed by treatment period, the CR rate before CALGB study 8811 was 63%; subsequently, it was 86% (P < 0.001) with the greatest benefit being seen in patients with cytogenetic abnormalities other than t(9;22), t(4;11), −7, or +8. In multivariate analyses, karyotype retained its prognostic significance for disease-free survival but not for survival; it remained the most important factor for disease-free survival. We concluded that cytogenetic analysis at diagnosis should be used to guide treatment decisions in adults with ALL and that allogeneic stem cell transplantation should be pursued in patients with high-risk karyotypes.

In efforts to improve further on these results, more recent studies have focused on scheduling postremission therapy into discrete “treatment blocks,” allowing the intercalation of newer immunotherapeutic approaches with monoclonal antibodies, imatinib mesylate for Ph+ patients, novel chemotherapy agents (such as nelarabine for T-cell ALL), and modifications of the central nervous system prophylaxis. In addition, short but intensive regimens were designed for the subgroup of patients with mature B-cell, Burkitt-type ALL (23).

Table 1. Hematologic recovery after chemotherapy and clinical outcome by randomized treatment assignment for 198 adults with ALL enrolled on CALGB study 9111 (21)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Median days (IQR)</th>
<th>G-CSF (n = 102)</th>
<th>Placebo (n = 96)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction course I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery to ANC&gt;1,000/μL</td>
<td>16 (15-18)</td>
<td>22 (19-29)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Duration of neutropenia</td>
<td>13 (10-16)</td>
<td>20 (15-27)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Recovery to platelets &gt;50,000/μL</td>
<td>16 (14-20)</td>
<td>19 (15-23)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Duration of thrombocytopenia</td>
<td>14 (9-17)</td>
<td>17 (11-22)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Fever &gt;38.5 °C</td>
<td>3 (1-5)</td>
<td>3 (2-7)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>22 (18-29)</td>
<td>28 (22-33)</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

No. patients (%)

| Died during induction             | 5 (5)             | 11 (11)         |
| Refractory disease                | 8 (8)             | 11 (11)         |
| CR                                | 89 (87)           | 74 (77)         | 0.04* |

Abbreviations: IQR, interquartile range (25-75th percentiles); ANC, absolute neutrophil count.

*P value using χ² test for trend for the three outcomes.

Highlights from Clinical Studies in CLL

Fludarabine was initially approved for use in patients with relapsed CLL. In CALGB study 9011, conducted between 1990 and 1994, we compared the efficacy of fludarabine, fludarabine plus chlorambucil, and chlorambucil alone in the primary treatment of CLL (24). The results of this randomized phase III intergroup study, coordinated by the CALGB, were presented at the plenary session at the annual meeting of the American Society of Hematology and showed a significant advantage in progression-free survival for patients with untreated symptomatic CLL who received fludarabine alone or in combination. Assignment of patients to the combination group was stopped when a planned interim analysis revealed excessive toxicity and a response rate that was not better than the rate with fludarabine alone. Between the other two groups, the response rate was significantly higher for fludarabine than for chlorambucil. Among 170 patients treated with fludarabine, 20% had a CR and 43% had a partial response compared with 4% and 33%, respectively, for 181 patients treated with chlorambucil (P < 0.001 for both comparisons).

The median duration of remission and the median progression-free survival in the fludarabine group were 25 and 20 months, respectively, whereas both values were 14 months in the chlorambucil group (P < 0.001 for both comparisons). The median overall survival among patients treated with fludarabine was 66 months, which was not significantly different from the overall survival in the other two groups (56 months with chlorambucil and 55 months with combined treatment), reflecting the benefit of fludarabine when used to rescue patients after relapse. Subsequent analyses focusing on complications of treatment showed that severe infections and thrombocytopenia were more frequent with fludarabine than with chlorambucil (P = 0.08) and that therapy-related AML/MDS was more commonly seen in the combination therapy arm. Overall, however, toxic effects were tolerable with both single-drug regimens.

Subsequent trials in CLL conducted worldwide have built on this therapeutic benefit from fludarabine. Recent CALGB studies have shown that rituximab has clinical activity and modulates antiapoptotic proteins associated with drug resistance in CLL. CALGB study 9712 was a randomized phase II study to determine the efficacy, safety, and optimal schedule of administration of rituximab with fludarabine in previously untreated CLL patients (25). Patients were randomized to receive either six monthly courses of fludarabine concurrently with rituximab followed 2 months later by 4 weekly doses of rituximab for consolidation therapy, or fludarabine alone for 6 months followed 2 months later by rituximab consolidation therapy. A total of 104 patients were randomized to the concurrent (n = 51) and sequential (n = 53) regimens. During the induction portion of treatment, patients receiving the concurrent regimen experienced more grade 3 or 4 neutropenia (74% versus 41%) and grade 3 or 4 infusion-related toxicity (20% versus 0%) compared with the sequential arm. The consolidation rituximab therapy was tolerated well in both arms. The overall response rate with the concurrent regimen was 90% (47% CR and 43% partial response) compared with 77% (28% CR and 49% partial
response) with the sequential regimen. After a median follow-up time of 23 months, the median response duration and survival had not been reached for either regimen.

We then retrospectively compared the treatment outcome of patients with similar clinical characteristics enrolled on CALGB studies 9712 (n = 104) and 9011 (n = 178; ref. 26). In multivariable analyses controlling for pretreatment characteristics, the patients receiving fludarabine and rituximab had a significantly better progression-free survival (P < 0.0001) and overall survival (P = 0.0006) than patients receiving only fludarabine therapy. Two-year progression-free survival probabilities were 67% versus 45% and 2-year survival probabilities were 93% versus 81%. Infectious toxicity was similar between the two treatment approaches. These comparative data are retrospective and could be confounded by differences in supportive care or dissimilar enrollment of genetic subsets on each trial. The current CALGB study 10101 is extending the significant clinical activity of the fludarabine/rituximab regimen by the addition of the anti-CD52 monoclonal antibody alemtuzumab as a postinduction therapy.

### Highlights from Clinical Studies in CML

Before imatinib became the standard treatment for CML, patients with chronic-phase disease were treated with IFN-based regimens, some of which were piloted in large CALGB studies. In CALGB study 8583, we investigated whether interferon (IFN) would reduce the proportion of bone marrow Ph+ cells in chronic-phase CML by treating 107 previously untreated patients daily with recombinant α-2b IFN at 5 × 10^6 IU/m² s.c. (27). Forty-three (50%) patients achieved at least a partial hematologic remission (24 CR and 39 partial response). The median time to response for the 63 responders was 3.4 months with a median duration of remission of 52 months. The median overall survival was 66 months. The percentage of cytogenetic responders among all patients was 29% (31 of 107 patients). The median time to first cytogenetic response was 9 months. A major dose reduction of IFN (≥50%) was required at some time during treatment in 38% of patients; 26% required 10% to 49% dose reductions; and 36% had minor dose reductions of <10%. No association was observed between dose received and the attainment of a cytogenetic response. These data provided confirmation that major cytogenetic responses to IFN occur in 20% to 38% (95% confidence interval) of chronic-phase CML patients.

The research goal in CML has been to increase the complete cytogenetic response rate in newly diagnosed patients who are not candidates for allogeneic hematopoietic cell transplantation. The availability of sensitive molecular methods for detecting cells that contain the BCR/ABL fusion gene has made this a model disease for establishing genetic response end points and for studying minimal residual disease. CALGB 9013 was a phase II trial that evaluated intermittent courses of IFN plus low-dose cytarabine in 88 previously untreated patients with CML in chronic-phase (28). Fifty-five (63%) patients had a complete hematologic response and 10 (11%) had a partial hematologic response. Median time to best response was 5.3 months. Median survival for all patients from study entry was 81 months; the 5-year survival probability was 65%. When 28 patients were censored at the time of bone marrow transplantation, the median survival was 82 months. Sixty-three patients had adequate follow-up cytogenetic studies: 10 had a complete cytogenetic response and 23 a partial response (50-99% normal cells; CALGB criteria). Cytogenetic responders had significantly longer survival than nonresponders (P = 0.01) using a landmark analysis at 18 months. Quantitative Southern blot analyses of blood were found to be equivalent to cytogenetic analyses of marrow specimens for monitoring responses (29).

### Future Directions

The Leukemia Committee of the CALGB is focused on the individualization of treatment based on distinctive biological and clinical characteristics with the aim of increasing efficacy and decreasing nonspecific toxicity. Major challenges for future clinical trials are a direct result of our increasing knowledge of the key biological drivers in leukemia cell proliferation and survival. Each leukemic disorder can now be divided into more homogeneous, but much smaller, subsets. There is currently no shortage of exciting new agents to test, each of which may inhibit a specific pathway or alter the expression of a uniquely mutated gene. Rapid identification of the underlying molecular defect at diagnosis will be required to assign patients to appropriate clinical trials. Greater collaboration among cooperative groups both in North America and abroad is required to enroll sufficient numbers of patients to evaluate new targeted therapies rapidly and rigorously. CALGB leukemia trials have developed many of the standards of care for patients with acute and chronic leukemias, have established rigorous methods for evaluating new treatment approaches, and have revealed much of the cytogenetic and molecular heterogeneity of these diseases. Armed with this knowledge and experience, the next 50 years of CALGB leukemia research will undoubtedly produce a dramatic increase in the fraction of patients with leukemia who can be cured.

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