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HIGHLIGHTS

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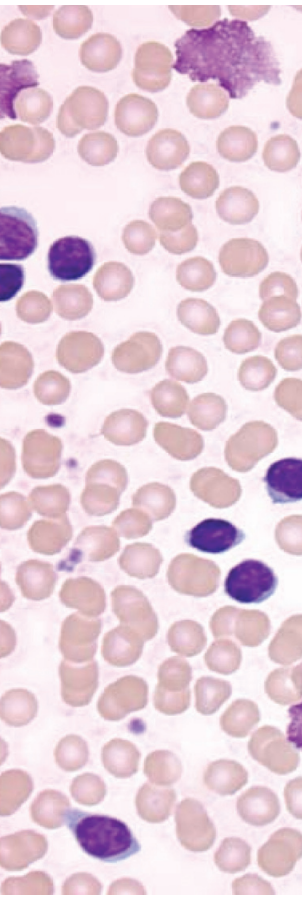

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MEDICAL COMMUNICATIONS

PIM Postgraduate Institute for Medicine

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CONTINUING MEDICAL EDUCATION

GOAL

The goal of this activity is to describe recent developments in the management of patients with chronic lymphocytic leukemia (CLL), particularly through a review of recently presented and published clinical research data.

TARGET AUDIENCE

This activity is intended for hematologists, oncologists, and other physicians who are involved in the treatment of patients with CLL.

STATEMENT OF NEED

CLL, also known as chronic lymphoid leukemia, affects more than 20,000 people in the United States and Western Europe each year. It is expected that this number will increase to more than 23,000 by the year 2010. The disease results from an acquired injury to the DNA of a single cell in the bone marrow. This injury is not present at birth. As of today, scientists do not understand the cause of the change in the DNA. Unlike the other three major types of leukemia, CLL is not associated with high doses of radiation or benzene exposure.

The disease is very uncommon in individuals under 45 years of age. Ninety-five percent (95%) of patients are over the age of 50 at the time of diagnosis. Long-term survival has not changed over the past several decades. RAI staging of the disease is very helpful in treatment because, at its earlier stages, it may have no effect on a person's well-being. When symptoms occur, treatment is indicated, although optimal therapy has yet to be defined.

Alkylating agents and purines with or without monoclonal antibodies remain the therapy of choice and are administered initially with or without prednisone. This protocol is followed by combination therapy when results fail. Prognosis continues to be based on investigational studies that evaluate the use of cell surface immunophenotypes and immunoglobulin heavy chain variable region (IgV_H) mutational states. Several agents are being researched for treatment of refractory CLL. The hallmark unmet need in the management of CLL is for therapies that will extend survival.

This activity consists of a review of the clinical aspects of CLL and various treatment strategies for patients with de novo and refractory disease. Ongoing clinical trials evaluating the safety and efficacy of novel therapeutic agents are reviewed through an analysis of recently presented and published clinical research data.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Review the current and various treatment regimens for CLL and their side effects.
- Explain why newer regimens and agents are needed.
- Discuss recent advancements in the first-line therapy options for treating CLL patients.
- Review data from recent clinical trials of novel treatments for relapsed/refractory CLL.
- Describe the ways in which humanized monoclonal antibodies can improve outcomes.

SPONSORSHIP

This activity is jointly sponsored by CJP Medical Communications (CJP) and Postgraduate Institute for Medicine (PIM). It is funded by an unrestricted educational grant from Genentech, Inc.

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PIM's reviewer, Linda Graham, RN, and Marc Weathersby, Vice President, CJP Medical Communications, have no real or apparent conflicts to disclose.

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This ***Grand Rounds in Hematology*** monograph, *Improving the Treatment of Hematologic Malignancies: Chronic Lymphocytic Leukemia*, is based on our selection of key abstracts from the ASH meeting in December 2006 and related publications in the following areas of chronic lymphocytic leukemia (CLL): new advances in prognosis, approaches to frontline therapy including the use of chemoimmunotherapies, management of the relapsed refractory patient, and, finally, novel drugs for the treatment of CLL. In each area we will not only provide the key points of each work, but also discuss what the results of these advances provide in our overall counseling, evaluation, and treatment options for CLL patients. We believe that the rapidly increasing information base in CLL necessitates this review and hope that our perspective provides a sound basis for individuals involved in the care of patients with CLL. Thus this review is designed to provide a relevant body of knowledge that is both informative and practical for the hematologist/oncologist in their overall management of CLL.

CLL affects more than 20,000 people in the United States and Western Europe each year. It is expected that this number will increase to more than 23,000 by the year 2010. It is currently believed that the disease results from a yet to be described critical genetic change in the B-cell progenitors found in the bone marrow. There may be a requirement for a second "hit" such as may occur from a yet to be defined environmental exposure that finally induces the clinical disease of CLL. Prognosis continues to be based on the use of both traditional and more novel investigational risk parameters that include the measurement of CD38, ZAP-70 , fluorescent in situ hybridization (FISH) defects, and immunoglobulin heavy chain variable region (IgV_H) mutational status. At the time of this report, however, the exact contributions and merits of these prognostic variables are still being evaluated for time to treatment, response to therapy, and prediction of response duration.

Long-term survival has not changed over the past several decades, and though there are dramatic increases in the induction of overall responses for previously untreated patients to greater than 90% and complete responses of 40% to 70%, there is as yet no curative approach. Alkylating agents and purine nucleoside analogues in combination with rituximab (so called chemoimmunotherapy) is the therapy of choice for previously untreated CLL. The failure of upfront therapy in CLL unfortunately leaves the clinician with less effective therapies in terms both of overall response and duration of that response.

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CONTENTS

Fludarabine versus Fludarabine Cyclophosphamide as First-Line Therapy

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BACKGROUND

The optimal first line therapy for patients with chronic lymphocytic leukemia (CLL) remains to be defined. Historical studies suggest that single agent fludarabine offers a superior progression-free survival than alkylating agent–based regimens.

APPROACH

The study by Flinn and colleagues details the findings of a randomized phase III trial by the North American Intergroup comparing fludarabine monotherapy (F) to combination therapy with fludarabine and cyclophosphamide (FC) [1]. The trial randomized 278 previously untreated patients (median age, 61 years) with CLL meeting the NCI working group criteria for initiating treatment to single agent fludarabine (25 mg/m^2 intravenously on days 1 though 5) or combination therapy with fludarabine (20 mg/m^2 intravenously on days 1 through 5) and cyclophosphamide (600 mg/m^2 intravenously on day 1). Patients with autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, or a creatinine clearance < 40 mL/min were excluded from participation. The fludarabine dose in both arms was reduced for patients with a creatinine clearance < 70 mL/min. Cycles were repeated every 4 weeks (maximum of 6 cycles). Patients randomized to the FC combination received growth factor support with filgrastim and prophylaxis against herpes zoster; such treatment was optional in the F arm.

RESULTS

The primary endpoint of the trial was the complete remission (CR) rate. Patients randomized to the FC combination had a CR rate of 23.4% compared to 4.6% ($P < .0001$) in those randomized F alone. The overall response rate also favored the FC combination (74.3% versus 59.5%; $P = .013$). In stepwise logistic regression, the estimated odds of achieving CR increased 6.9-fold in patients randomized to FC combination therapy.

Progression-free survival (PFS) was also evaluated as a secondary endpoint (Figure 1). The median PFS in FC-treated patients was 31.6 months compared to 19.2 months in fludarabine-treated patients. Limited follow-up precludes evaluation of differences in overall survival. No differences in the 2-year survival rate have been observed to date (79% for FC, 80% for F).

As expected, greater toxicity was observed among patients treated with combination therapy. Overall, 50% of patients on the FC arm experienced ≥ grade 3 nonhematologic toxicity compared to 33% in the F arm ($P = .007$). Despite this difference, no increase in rates of infection occurred between arms ($P = .812$).

SUMMARY

The results of this trial suggest that the FC combination achieves a superior CR rate and PFS than F monotherapy for patients well enough to receive aggressive treatment. These results confirm the findings of a recently reported randomized trial by the German CLL Study Group evaluating an FC combination with a slightly different dose/schedule [2] . Follow-up trials evaluating the benefit of the addition of rituximab to the FC platform are underway.

REFERENCES

1. Flinn IW, Neuberg DS, Grever MR, et al. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. *J Clin Oncol.* 2007;25:793-798.
2. Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood.* 2006;107:885-891.

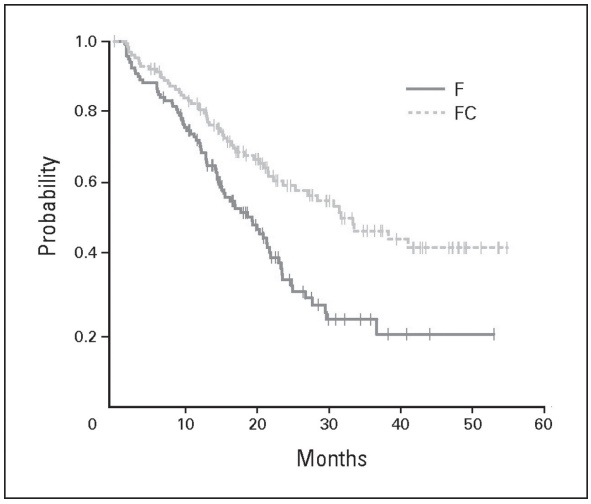

Figure 1. Progression-free survival by treatment arm. Using the Kaplan-Meier method, the progression-free survival duration was computed from random assignment until documented progression of disease or death without progression. F, fludarabine-alone arm; FC, fludarabine plus cyclophosphamide arm. Reprinted from [1] with permission from the American Society of Clinical Oncology.

Pentostatin, Cyclophosphamide, and Rituximab (PCR)

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BACKGROUND

This paper, by Kay and colleagues [1], (and the accompanying abstract by Dr. Shanafelt [2]) presented the final results of a phase II study of pentostatin, cyclophosphamide, and rituximab (PCR) in 64 patients with previously untreated chronic lymphocytic leukemia (CLL). The results of this study were subsequently published as a plenary paper in *Blood* [3]. This paper demonstrated that PCR was well tolerated and clinically active in previously untreated CLL patients, with overall response (OR), complete response (CR), and nodular partial response (nPR) rates of 91%, 41%, and 22%, respectively. Median progression-free survival (PFS) was 33 months.

Although combination regimens using fludarabine (fludarabine and rituximab [FR]; fludarabine, cyclophosphamide, and rituximab [FCR]) have become the mainstay of upfront therapy for CLL, fludarabine is associated with significant toxicities, most notably myelosuppression and immunosuppression, particularly of T- and B-lymphocytes. Less common but potentially severe toxicities include autoimmune hemolytic anemia and immune thrombocytopenia purpura. The investigators and others have demonstrated that pentostatin is also active against CLL, and pentostatin may be less toxic than fludarabine. Therefore, the investigators examined the use of the PCR regimen as upfront therapy for previously untreated CLL.

APPROACH

Sixty-four patients with previously untreated CLL were enrolled. The median age was 62.5 years, and 53% were Rai stage III or IV. Risk stratification showed that 71% of patients had unmutated immunoglobulin heavy chain variable region (IgV_H), 34% were positive for ZAP-70, 36% had a complex karyotype, 22% had loss of 11q22, and 5% had loss of 17p13. Patients received pentostatin 2 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 on day 1, and rituximab 375 mg/m^2 on day 1 (100 mg/m^2 on day 1 and 375 mg/m^2 on days 3 and 5 of cycle 1) every 21 days for up to 6 cycles. Filgrastim was administered beginning on day 3. Patients received allopurinol for 15 days of cycle 1 for tumor lysis prophylaxis, and patients received TMX/SMZ and acyclovir prophylaxis for 12 months.

RESULTS

Therapy was well tolerated. The most common grade 3 to 5 toxicities were neutropenia (44%), thrombocytopenia (21%), and nausea (10%). Six patients developed grade 3+ infection, and only 5 patients required transfusion of blood products. Two patients with comorbid illnesses died during the study. The OR rate was 91%, including 41% CR, 22% nPR, and 27% PR. With a median follow-up of 31 months, median PFS was 33 months. Among patients who achieved CR or nPR, median PFS was superior in patients who were able to achieve a flow cytometry negative bone marrow (defined as ≤ 1% residual CD5+/CD19+ cells). The ability to achieve CR or nPR was not affected by any high-risk genetic or biological factor, with the exception that all 3 patients with del (17p13.1) failed to achieve CR or nPR.

SUMMARY

The PCR regimen was well tolerated and clinically effective in patients with previously untreated CLL, with 63% of patients achieving CR or nPR. Importantly, this regimen also found that attaining ≤ 1% CD5$^+$/CD19$^+$ B-cells as shown with FCR results in improved PFS [4]. Similarly, as shown with FR, PCR was able to achieve CR and nPR in patients with high-risk genetic or biological factors, with the exception of del (17p13.1) [5]. Abstract #36 [2], which is also reviewed in this issue, demonstrated that PCR is well tolerated by patients ≥ age 70 and patients with impaired renal function. Thus, further investigation of this active regimen is warranted.

REFERENCES

1. Kay N, Geyer S, Call T, et al. Combination chemoimmunotherapy with patients with pentostatin, cyclophosphamide and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B-chronic lymphocytic leukemia. *Blood*. 2006;108. Abstract 35.
2. Shanafelt TD, Byrd JC, Geyer SM, et al. The pentostatin, cyclophosphamide, and rituximab regimen (PCR) is highly active and well tolerated regardless of patient age, creatinine clearance, and performance status: analysis of a multi-center phase II trial. *Blood*. 2006;108. Abstract 36.
3. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. *Blood*. 2007;109:405-411.
4. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23:4079-4088.
5. Byrd JC, Gribben JG, Peterson BL, et al. Select high-risk genetic features predict earlier progression following chemoimmunotherapy with fludarabine and rituximab in chronic lymphocytic leukemia: justification for risk-adapted therapy. *J Clin Oncol*. 2006;24:437-443.

Pentostatin, Cyclophosphamide, and Rituximab (PCR) for Elderly Patients

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BACKGROUND

This paper compared the toxicity and clinical activity of the pentostatin, cyclophosphamide, and rituximab (PCR) regimen in previously untreated chronic lymphocytic leukemia (CLL) patients ≥ age 70 with toxicity and response data obtained in previously untreated CLL patients < age 70 [1]. (The overall results of this study were presented in abstract #35 at the December ASH 2006 meeting, and a summary of that abstract can be found elsewhere in this issue [2].) This paper demonstrated that PCR was as effective and well tolerated in patients ≥ age 70 as the regimen was in younger patients < age 70, with the only notable exception being that a higher percentage of older patients required a dose delay longer than 1 week.

Although aggressive combination regimens such as fludarabine, cyclophosphamide, and rituximab (FCR) have achieved complete response (CR) rates of more than 70% in previously untreated CLL patients, the median age of patients in many studies is significantly lower than the median age of CLL patients as a whole. The median age of CLL patients at first treatment is approximately 70 years of age, but the median age of patients in the upfront FCR study was 58 years. Previous studies have shown that patients ≥ age 70 tolerate aggressive regimens, including FCR, more poorly than younger patients (Ferrajoli, Leuk Lymphoma 46: S86).

APPROACH

Sixty-four patients with previously untreated CLL received pentostatin 2 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 on day 1, and rituximab 375 mg/m^2 on day 1 (days 1, 3, and 5 of cycle 1 only) every 21 days for up to 6 cycles. Filgrastim was administered beginning on day 3. Patients received allopurinol for 15 days of cycle 1 for tumor lysis prophylaxis, and patients received TMX/SMZ and acyclovir prophylaxis for 12 months. Median age was 62.5 years (range, 38-80 years), with 46 patients being younger than age 70 and 18 patients being older than age 70.

RESULTS

Patients ≥ age 70 received a similar number of cycles (median 6 versus 6, mean 5.6 versus 5.3) as younger patients. A similar percentage of older patients required dose reduction (13% versus 11%), although more older patients required a dose delay > 1 week (28% versus 7%, $P = .03$). Grade 3 to 4 hematologic (61% versus 48%), infectious (6% versus 11%), and other nonhematologic toxicities (22% versus 28%) were similar in older and younger patients. Grade 3 to 4 thrombocytopenia was similar in both groups (17% versus 22%). A higher percentage of patients ≥ age 70 developed grade 3 to 4 neutropenia (56% versus 35%), but this was not statistically significant ($P = .16$). The only significant finding with respect to renal function was that patients with a creatinine clearance (CrCl) < 70 mL/min (n = 25) were more likely to require dose reduction (24% versus 5%) than patients with CrCl ≥ 70 mL/min (n = 39). The overall and complete response rates were similar in patients ≥ age 70 and < age 70 (83% versus 93% and 39% versus 41%, respectively). Event-free survival (EFS) was identical for older and younger patients ($P = .98$). Similarly, no differences in response rates or EFS were observed based on CrCl.

SUMMARY

The PCR regimen was well tolerated and clinically effective in patients with previously untreated CLL, regardless of age, renal function, or performance status. Although FCR has achieved the best phase II results of any upfront chemotherapy regimen for the treatment of CLL, patients ≥ age 70 tolerate FCR more poorly than younger patients. The findings of abstract #36 [1] indicate that PCR should be considered for previously untreated CLL patients ≥ age 70, who constitute approximately half of all patients requiring initial treatment of their CLL. The contribution of prophylactic antibiotics and filgrastim to this tolerability is unclear, but it would be prudent to use prophylactic antibiotics and G-CSF as prescribed in this study in order to ensure the reproducibility of these results in more elderly (≥ age 70) community CLL patients.

REFERENCES

1. Shanafelt TD, Byrd JC, Geyer SM, et al. The pentostatin, cyclophosphamide, and rituximab regimen (PCR) is highly active and well tolerated regardless of patient age, creatinine clearance, and performance status: analysis of a multi-center phase II trial. *Blood*. 2006;108. Abstract 36.
2. Kay N, Geyer S, Call T, et al. Combination chemoimmunotherapy with patients with pentostatin, cyclophosphamide and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B-chronic lymphocytic leukemia. *Blood*. 2006;108. Abstract 35.

Molecular Prognostic Parameters and Response to Therapy

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BACKGROUND

Molecular characteristics of the chronic lymphocytic leukemia (CLL) B-cell have proven to be powerful predictors of overall survival in patients with CLL.

APPROACH

The study by Grever and colleagues evaluated whether these characteristics predicted response to therapy and/or progression-free survival (PFS) among patients treated with fludarabine-based therapy as part of the North American Intergroup Trial [1]. The investigators assessed immunoglobulin heavy chain variable region (IgV_H) mutation status, CD38 protein expression, ZAP-70, apoptosis-related protein levels, and cytogenetic abnormalities as assessed by fluorescent in situ hybridization (FISH) in 235 consenting patients treated with either fludarabine monotherapy or combination therapy with fludarabine and cyclophosphamide and prospectively evaluated association with clinical outcome. All prognostic assays were performed on baseline pretreatment specimens. The hierarchical classification developed by Dohner and colleagues was used to evaluate the prognostic implications of cytogenetic abnormalities on FISH.

RESULTS

None of the molecular prognostic characteristics evaluated predicted complete remission (CR) rates. Unfavorable cytogenetic abnormalities—del (17p13.1) or del (11q22.3)—on FISH analysis predicted for shorter PFS (all $P \leq .006$). The median PFS times for patients with del (17p13.1) or del (11q22.3) were 10.8 months and 21.5 months, respectively (Figure 1). Mutation of p53 in the absence of del (17p13.) on FISH analysis was not associated with shorter PFS. No other prognostic parameter (IgV_H, ZAP-70, CD38, apoptosis-related protein levels) predicted PFS.

In regression models accounting for type of therapy received (fludarabine versus fludarabine-cyclophosphamide combination), cytogenetic analysis by FISH substantially impacted modeling of PFS. The presence of del (17p13.1) (hazard ratio 3.528; $P = .0002$) and del (11q22.3) (hazard ratio 1.904; $P = .0063$) was associated with shorter duration of response.

Importantly, treatment allocation to combination therapy with fludarabine and cyclophosphamide combination therapy did not overcome the shorter PFS observed in patients with del (17p13.1) or del (11q22.3).

SUMMARY

The results of this study demonstrate that unfavorable cytogenetic abnormalities on FISH analysis, such as del (17p13.1) or del (11q22.3), identify CLL patients unlikely to have durable benefit from fludarabine-based therapies. Alternative treatment strategies for patients with these cytogenetic defects are under evaluation and could lead to tailored treatment strategies in the future.

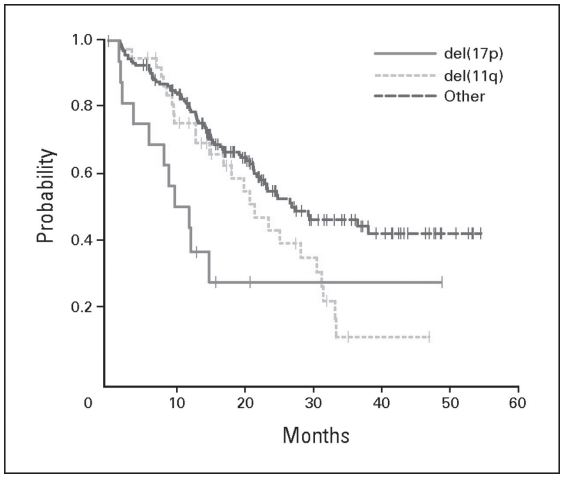

Figure 1. Progression-free survival for the high-risk cytogenetic abnormalities del (17p) and del (11q) in both treatment arms (n = 235). The *P* value for the comparison of del (17p), del (11q), and other cytogenetic anomalies is .0006 by the log-rank test. Reprinted from [1] with permission from the American Society of Clinical Oncology.

REFERENCE

1. Grever MR, Lucas DM, Dewald GW, et al. Comprehensive assessment of genetic and molecular features predicting outcome in patients with chronic lymphocytic leukemia: results from the US Intergroup Phase III Trial E2997. *J Clin Oncol.* 2007;25:799-804.

Alemtuzemab Consolidation

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BACKGROUND

This paper, by Schweighofer and colleagues, presented long-term follow-up results [1] of a previously published, prospective, randomized GCLLSG study examining the use of alemtuzumab as consolidation after initial fludarabine-based therapy [2]. The paper demonstrated the durability of the clinical benefit achieved by consolidation alemtuzumab. With a median follow-up of 48 months, median progression-free survival (PFS) had not been reached in the alemtuzumab arm, compared to a median PFS of 20.6 months in the control arm.

APPROACH

Patients in complete or partial remission after induction therapy with fludarabine or fludarabine/cyclophosphamide were randomized to no further treatment or consolidation therapy with alemtuzumab 30 mg intravenously thrice weekly for up to 12 weeks.

RESULTS

The study was stopped prematurely after enrollment of 21 patients (10 in control arm, 11 in alemtuzumab arm) due to increased hematologic and infectious toxicity in the alemtuzumab arm. Six of 11 patients in the alemtuzumab arm experienced grade 4 hematologic toxicity, and 7 of 11 patients developed grade 3 to 4 infections, including 4 patients who reactivated cytomegalovirus (CMV). However, 2 of 11 patients converted from a partial to a complete remission with alemtuzumab, and 5 of 6 tested patients achieved a molecular remission. With a median follow-up of 48 months, 8 of 10 patients in the control arm have relapsed with a median PFS of 20.6 months. In marked contrast, only 3 of 11 patients in the alemtuzumab arm have relapsed, and median PFS has not been reached yet.

SUMMARY

In conclusion, the use of alemtuzumab as consolidation therapy after initial fludarabine-based induction therapy achieved molecular remissions and resulted in improved long-term PFS. However, the use of alemtuzumab therapy in this setting also resulted in increased hematologic and infectious toxicity, particularly CMV reactivation. Thus, while alemtuzumab clearly is able to improve molecular remissions and thereby improve PFS in the consolidation setting, the optimal dose, schedule, and timing of alemtuzumab consolidation remains to be defined in order to minimize the infectious toxicity of alemtuzumab in this setting. Multiple groups are studying the dose and schedule for use of consolidation alemtuzumab including GCLLSG in its ongoing CLL2i trial and CALGB in the CALGB 9712 trial that administers fludarabine and rituximab followed by alemtuzumab consolidation. The M.D. Anderson Cancer Center has combined alemtuzumab with fludarabine, cyclophosphamide, and rituximab (CFAR) and is studying this regimen in the upfront setting. It is hoped that the findings of these ongoing studies will refine the use of alemtuzumab consolidation after fludarabine-based induction so that the infectious complications described in this GCLLSG paper are reduced or significantly eliminated.

REFERENCES

1. Schweighofer C, Ritgen M, Eichhorst B, et al. Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukemia (CLL) in first remission: long-term follow-up of a randomized phase III trial of the German CLL Study Group (GCLLSG). *Blood*. 2006;108. Abstract 33.
2. Wendnter CM, Ritgen M, Schweighofer CD, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission: experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). *Leukemia*. 2004;18:1093-1101.

Cyclophosphamide, Fludarabine, Alemtuzumab, and Rituximab (CFAR) for Relapsed Disease

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BACKGROUND

The paper given by Wierda et al presented updated results of a single institution phase II study of a novel combination regimen consisting of cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR) in 79 patients with relapsed chronic lymphocytic leukemia (CLL) [1]. The study demonstrated that the addition of alemtuzumab did not increase hematologic or infectious toxicity beyond that observed historically with a combination of fludarabine, cyclophosphamide, and rituximab (FCR) at the same institution, and overall and complete response rates of 65% and 24% were observed in this heavily treated population.

The M.D. Anderson Cancer Center has piloted the FCR regimen for treatment of both relapsed and previously untreated CLL. A previously published study of FCR in 177 patients with relapsed CLL had observed overall and complete response rates of 73% and 25%, respectively [2]. The investigators sought to build upon these findings by adding the anti-CD52 antibody alemtuzumab to FCR, given alemtuzumab's activity in patients with high-risk cytogenetic abnormalities and its ability to clear bone marrow disease.

APPROACH

Seventy-nine patients with relapsed CLL were enrolled. The median age was 58 years, and the median number of prior therapies was 3 (range, 1-14). Prior therapies included FCR (58%), combination therapy with fludarabine and cyclophosphamide (FC) (13%), rituximab (90%), and alemtuzumab (19%). Forty percent of patients were refractory to their last fludarabine regimen. Patients received alemtuzumab 30 mg intravenously on days 1, 3, and 5; rituximab 375 mg/m^2 or 500 mg/m^2 intravenously on day 2; fludarabine 25 mg/m^2 intravenously on days 3-5; and cyclophosphamide 250 mg/m^2 intravenously on days 3 through 5 every 28 days for up to 6 cycles. Tumor lysis prophylaxis consisted of allopurinol on days 1 through 7 of cycle 1. Patients received TMP-SMZ and valacyclovir or valganciclovir as prophylaxis, and cytomegalovirus (CMV) antigen was monitored before each cycle of therapy. Patients also received pelfilgrastim.

RESULTS

Patients received a median of 3 cycles of therapy. Hematologic and infectious toxicity was similar to that observed previously with FCR at the same institution. Grade 3 to 4 neutropenia and thrombocytopenia was observed in 89% (71% grade 4) and 59% (35% grade 4) of patients, respectively. Infectious toxicity included major infection in 11% of patients, minor infection in 28% of patients, fever of unknown origin in 36% of patients, and zoster in 6% of patients. Three of 30 patients (10%) who received prophylactic valganciclovir developed CMV reactivation, compared to 25 of 48 patients (52%) who received prophylactic valcyclovir. The overall response (OR) rate was 65%, with 24% of patients achieving a complete response (CR) and 4% a nodular partial response (nPR). OR and CR rates were 74% and 36%, respectively, for fludarabine sensitive patients (n = 47), compared to only 49% and 6%, respectively, for fludarabine refractory patients (n = 31). Median progression-free survival (PFS) was 27 months for patients who achieved a CR, compared to 10 months for patients who achieved a partial response (PR). Median overall survival was 7 months for nonresponders, 18 months for patients achieving a PR, and not reached after 3 years for patients attaining a CR. Eight of 34 patients who achieved a flow cytometry negative bone marrow relapsed, compared to 11 of 14 patients with persistent marrow CLL by flow cytometry.

SUMMARY

CFAR showed significant promise in this heavily treated population with relapsed CLL. Despite the addition of alemtuzumab, hematologic and infectious toxicity was not greater than what would be expected with FCR alone. However, CMV reactivation was observed in more than 50% of patients who received valacyclovir as antiviral prophylaxis. The use of valganciclovir reduced the incidence of CMV reactivation to 10%, and frequent CMV monitoring and prophylactic valganciclovir must be used with this regimen. While CFAR was more effective in patients who responded to their most recent fludarabine regimen (OR, 74%; CR, 36%), some activity was observed in fludarabine refractory patients (OR, 49%; CR, 6%). Based on these promising findings, the investigators are pursuing a phase II study of CFAR as initial therapy for patients with previously untreated CLL.

REFERENCES

1. Wierda WG, O'Brien S, Faderl S, et al. Combined cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR), an active regimen for heavily treated patients with CLL. *Blood*. 2006;108. Abstract 31.
2. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23:4070-4078.

Fludarabine, Cyclophosphamide, and Rituximab (FCR)-Lumiliximab for Relapsed Disease

Reviewed by:

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BACKGROUND

Byrd and colleagues presented a paper with updated results of an industry-sponsored phase I/II study of an anti-CD23 monoclonal antibody (lumiliximab; IDEC-152) given in combination with fludarabine, cyclophosphamide, and rituximab (FCR) to 31 patients with relapsed chronic lymphocytic leukemia (CLL) [1]. The paper compared these results to previously published results obtained with the FCR regimen in relapsed CLL and concluded that the addition of lumiliximab may improve the clinical activity of FCR.

A previously published phase I study (Byrd et al, Clin Cancer Res, in press) had administered lumiliximab as a single agent in doses ranging from 125 mg/m^2 weekly to 500 mg/m^2 thrice weekly for 4 weeks. Toxicity was acceptable, with only 16% grade 3 to 4 adverse events and minimal myelosuppression. Although no clinical responses were observed in the 152-20 study, reduction of the peripheral lymphocyte count and nodal disease were seen in 91% and 52% of patients, respectively. Based on these data, as well as preclinical studies demonstrating synergism of lumiliximab with fludarabine and rituximab, the same investigators pursued a phase I/II study (152-30) of lumiliximab in combination with FCR in patients with relapsed CLL.

APPROACH

The investigators elected to give lumiliximab at a dose of 500 mg/m^2 in the 152-30 study, based on the finding that CD23 binding sites were saturated at doses of 375 mg/m^2 to 500 mg/m^2 given weekly. Thirty-one patients with relapsed CLL were enrolled in this combination study. The median age of patients was 58 years, and 74% of patients were Rai stage I/II. The median number of prior therapies was 2 (range, 1-9), and 60% of patients had received prior rituximab. Patients received lumiliximab at a dose of 375 mg/m^2 (n = 3) or 500 mg/m^2 (n = 28), in combination with standard dose FCR every 28 days for up to 6 cycles. Patients received rituximab 50 mg/m^2 on day 1, 325 mg/m^2 on day 3, lumiliximab 50 mg/m^2 on day 2, and 325 mg/m^2 or 450 mg/m^2 on day 4 during cycle 1. Patients received rituximab 500 mg/m^2 and lumiliximab 375 mg/m^2 or 500 mg/m^2 on day 1 during cycles 2 through 6. Fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 were administered on days 2 through 4 of cycle 1 and days 1 through 3 of cycles 2 through 6.

RESULTS

Therapy was well tolerated, with the most common toxicities being nausea (77%), fever (61%), chills (55%), neutropenia (55%), and fatigue (48%). Twenty patients (65%) experienced a grade 3 to 4 adverse event. The overall response rate was 71%, with 52% of patients achieving a complete response (CR). One of 4 patients with del (17p13.1) achieved a partial response, and 6 of 8 patients with del (11q22.3) responded, including 5 patients who achieved CR. A retrospective comparison of these results with historical results obtained with FCR in 177 patients with relapsed CLL at the M.D. Anderson Cancer Center suggested that the addition of lumiliximab to FCR improved the CR rate (52% versus 25%) without increasing hematologic or other toxicity [2]. Response data are summarized in Table 1. Patients in the 2 studies were well matched with respect to demographics, with the notable exceptions being that the MDACC FCR group included a higher percentage of Rai stage III/IV patients (50% versus 26%) and a higher percentage of rituximab-naïve patients (88% versus 40%).

Table 1

	152-30 (L + FCR) (n = 31 patients)	FCR (n = 177 patients)
Overall response	22 (72%)	130 (73%)
Complete response	16 (52%)	45 (25%)
Partial response	3 (10%)	85 (48%)
Unconfirmed partial response	3 (10%)	—

SUMMARY

The addition of the anti-CD23 antibody lumiliximab to FCR did not increase toxicity beyond that observed historically with FCR. Although it must be emphasized that this was a retrospective comparison, this paper presented intriguing results that suggest that the addition of lumiliximab to FCR may improve the CR rate. Based on these promising findings, Biogen IDEC is sponsoring a large, international, prospective, randomized phase III study of FCR with or without lumiliximab in relapsed CLL.

REFERENCES

1. Byrd JC, Castro J, O'Brien S, et al. Comparison of results from a phase 1/2 study of lumiliximab (anti-CD23) in combination with FCR for patients with relapsed CLL with published FCR results. *Blood*. 2006;108. Abstract 32.
2. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23:4070-4078.

Lenalidomide for Relapsed/Refractory Disease

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BACKGROUND

Few effective salvage therapies are available for patients with relapsed/refractory chronic lymphocytic leukemia (CLL), particularly those with fludarabine refractory disease or unfavorable cytogenetic abnormalities such as del (17p13.1) or del (11q22.3). Alternative drugs with nonoverlapping mechanisms of action need to be tested for such patients.

APPROACH

The phase II studies by Chanan-Kahn and colleagues [1] and Ferrajoli et al [2] evaluated the efficacy of lenalidomide for patients with relapsed/refractory CLL who had previously received purine nucleoside analogue–based therapy. Lenalidomide is a thalidomide analogue with numerous potential biologic effects including immunomodulation, antiangiogenic activity, and effects on tumor cell microenvironment. This agent was recently approved by the FDA for treatment of patients with previously treated multiple myeloma and individuals with the myelodysplastic syndrome associated with 5q-.

In the first trial, Chanan-Khan treated 45 patients (median age, 64 years) with relapsed/refractory CLL with lenalidomide [1]. Patients had received a median of 3 prior therapies (range, 1-10), and 51% had fludarabine refractory disease. The initial treatment dose for the first 29 patients was the traditional multiple myeloma schedule (25 mg orally every day for days 1-21 of 28-day cycle). After 2 of the first 29 patients experienced tumor lysis syndrome, the starting dose was changed to 5 mg/day (days 1-21 of 28-day cycle) and increased by 5 mg every 2 weeks to a maximum dose of 25 mg. The final 16 patients enrolled on protocol also received a 2-week course of prednisone (20 mg daily for 7 days followed by 10 mg daily for 7 days) to prevent tumor flare reactions. Patients remained on active treatment until they achieved a molecular complete remission (CR) or experienced disease progression. At the time of progression, patients were continued on lenalidomide with the addition of rituximab (375 mg/m^2 on days 1, 8, and 15 of the first combination cycle and days 1 and 15 of subsequent cycles).

RESULTS

The overall response rate by intent to treat analysis was 47% (21 of 45), with 9% (4 of 45) of patients achieving a CR. Notably, 3 of the 4 CR patients achieved a molecular remission by polymerase chain reaction analysis. Among individuals with del (11q22.3) on fluorescent in situ hybridization (FISH), 47% responded to therapy. Three patients experienced progressive disease and had rituximab added to the lenalidomide treatment. All 3 patients experienced a partial response.

The most common hematologic toxicities were thrombocytopenia (45% ≥ grade 3) and neutropenia (70% ≥ grade 3). The most common nonhematologic toxicity was fatigue, which occurred in 73% of patients (10% ≥ grade 3). Of interest, 58% of patients experienced a tumor flare reaction (8% ≥ grade 3) with sudden, tender enlargement of the lymph nodes or liver/spleen in conjunction with fever and/or increase in white blood cell count. Lenalidomide therapy was continued during flare reactions, and symptoms were treated with ibuprofen 400 mg every 6 hours for the duration of the reaction. Overall, 5% of patients experienced ≥ grade 3 infectious complications, and 15% experienced neutropenic fever. Two patients (5%) developed pulmonary embolism.

APPROACH

In the second lenalidomide trial by Ferrajoli et al [2], 35 patients (median age, 64 years) with relapsed/refractory CLL were treated with continuous daily oral lenalidomide with a starting dose of 10 mg/day. Dose escalation in 5 mg increments was permitted at 4-week intervals up to a maximum dose of 25 mg/day. Patients had received a median of 4 prior treatments (range, 1-15), all had previously received at least 1 purine nucleoside analogue–containing regimen, and 26% had fludarabine refractory disease. Overall, 60% (21 of 35) of patients had either del (11q22.3) or del (17p13.1) by FISH.

RESULTS

At the time of presentation, 35 patients had received at least 3 months of therapy and were considered evaluable for response. The median daily dose of lenalidomide at 3 months was 10 mg/day. The overall response rate among these individuals was 37% (13 of 22), with 2 patients (6%) achieving a CR. Time to response was prolonged in some patients. An additional 10 patients (29%) had stable disease and remained on treatment at the time of presentation

The most common hematologic toxicities were thrombocytopenia (14% ≥ grade 3) and neutropenia (17% ≥ grade 3). Fatigue was the most common nonhematologic toxicity, occurring in 38% of patients (9% ≥ grade 3). Other common nonhematologic toxicities included rash (29%) and diarrhea (17%). Similar to the findings of Chanan-Khan [1], 35% (12 of 35) of patients experienced a tumor flare reaction. One patient (3%) developed deep venous thromboses.

Correlative studies performed in conjunction with the trial included evaluation

of an extensive array of cytokine and soluble receptors. Measured plasma vascular endothelial growth factors (VEGF) levels declined from baseline in 4 patients achieving a response. No clear changes were observed among 12 other cytokines and soluble receptors evaluated.

SUMMARY

The results of these 2 trials demonstrate that lenalidomide has single agent activity in patients with relapsed/refractory CLL, including individuals with fludarabine refractory disease and unfavorable cytogenetic abnormalities such as del (11q22.3). The optimal dose, schedule, and timing for lenalidomide use in patients with CLL are the subjects of ongoing studies.

REFERENCES

1. Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. *J Clin Oncol*. 2006;24:5343-5349.
2. Ferrajoli A, O'Brien SM, Faderl SH, et al. Lenalidomide induces complete and partial responses in patients with relapsed and treatment-refractory chronic lymphocytic leukemia (CLL). *Blood*. 2006;108. Abstract 305.

Flavopiridol for Relapsed/Refractory Disease

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BACKGROUND

Effective treatments are needed for chronic lymphocytic leukemia (CLL) patients with unfavorable cytogenetic abnormalities, particularly those with del (17p13.1). Although flavopiridol induces *p53* independent apoptosis in vitro, prior studies using a 24- to 72-hour continuous intravenous infusion did not achieve the plasma concentration necessary for in vitro apoptosis and lacked clinical activity.

APPROACH

After pharmacokinetic modeling, investigators at Ohio State University determined that flavopiridol by intravenous bolus (IVB) followed by continuous 4-hour intravenous infusion (CIVI) would overcome plasma protein binding and achieve the plasma concentrations necessary to induce leukemic cell apoptosis. Byrd and colleagues recently reported the results of the first 42 patients with relapsed refractory CLL/small lymphocytic leukemia (SLL) treated on a phase I trial of flavopiridol using this pharmacokinetically-derived administration schedule [1].

RESULTS

In the present report, Lin et al [2] updated the results of this trial after treatment of an additional 16 patients with a focus on response to treatment by cytogenetic abnormalities. In aggregate, 58 patients (median age, 60 years) with relapsed CLL/SLL were treated with 1 of 4 dose schedules. Patients had received a median of 4 prior therapies (range, 1-14), and 48 patients were refractory to or intolerant of fludarabine. Cohort 1 (n = 20) patients were treated with 30 mg/m^2 IVB followed by 30 mg/m^2 CIVI. Cohort 2 (n = 3) patients were treated with 40 mg/m^2 IVB followed by 40 mg/m^2 CIVI. Cohort 3 (n = 14) patients were treated with the Cohort 1 schedule for cycle 1, with dose escalation to 30 mg/m^2 IVB followed by 50 mg/m^2 with cycle 2 if severe tumor lysis syndrome (TLS) was not observed. Cohort 4 (n = 14) patients were also treated with the Cohort 1 schedule for the first dose of cycle 1, with does escalation to 30 mg/m^2 IVB, followed by 50 mg/m^2 with the second dose of cycle 1 if severe TLS was not observed. Patients in all cohorts were treated every week for 4 consecutive weeks followed by 2 weeks off.

Life threatening TLS is the dose limiting toxicity of flavopiridol using this administration schedule. TLS was experienced during either the first or second cycle by all 3 patients in cohort 2, one of whom died due to hyperkalemia-induced cardiac arrhythmia. All subsequent patients enrolled in the study were treated as inpatients for the first 5 doses of flavopiridol in conjunction with hydration, prophylactic rasburicase, prophylactic phosphate-binders, urine alkalization, hourly potassium monitoring, and the ability to perform emergent dialysis within 1 hour. Pretreatment leukocyte count appeared to be a risk factor for hyperacute TLS. TLS requiring dialysis occurred in 5 of 8 (63%) patients with leukocyte count $\geq 200 \times 10^9$/L, compared to 1 of 34 (3%) patients with leukocyte count $< 200 \times 10^9$/L [1].

At the time of presentation, 26 of 52 (50%) evaluable patients had achieved a partial response. The median progression-free survival (PFS) of all responders was 11 months (range, 5-29 months). Using this administration schedule, flavopiridol appeared to be equally effective in all biologic risk groups including those with del (17p13.1) (overall response rate [ORR] = 47% [9 of 19]; PFS, 10 months), del (11q22.3) (ORR = 81% [17 of 21]; PFS, 11 months), complex karyotype (ORR = 48% [13 of 27]; PFS, 10 months), or bulky disease (ORR = 54% [21 of 39]).

SUMMARY

The results of this trial demonstrate that flavopiridol administered according to the pharmacokinetically-derived schedule of Byrd and colleagues is active in patients with heavily pretreated CLL including those with del (17p13.1) or del (11q22.3), other poor risk cytogenetic features (complex karyotype), or bulky disease. Life threatening tumor lysis is the dose limiting toxicity and requires comprehensive prophylactic measures and intensive inpatient monitoring during the initial treatment cycles.

REFERENCES

1. Byrd JC, Lin TS, Dalton JT, et al. Flavopiridol administered using a pharmacologically derived schedule is associated with marked clinical efficacy in refractory, genetically high-risk chronic lymphocytic leukemia. *Blood*. 2007;109:399-404.
2. Lin TX, Heerema NA, Fischer B, et al. Flavopiridol is active in genetically high-risk, relapsed chronic lymphocytic leukemia (CLL): analysis of 56 patients by cytogenetic abnormality. *Blood*. 2006;108. Abstract 302.

SUMMARY

Improving the Treatment of Hematologic Malignancies: Chronic Lymphocytic Leukemia

Guest Editor

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This monograph selected several recent papers or abstracts (presented at the December 2006 ASH meeting) that touched on areas of both prognosis and therapy for chronic lymphocytic leukemia (CLL). We wished to focus on both treated and untreated CLL because this particular set of patients has increasing treatment options for the practicing physician to consider. In terms of prognosis, we also have described the implications for using novel risk parameters in both determining the potential for a given patient to respond and also how durable that response will be. What are the take home messages from this new information that can be used by the clinician?

The abstracts and papers focused on 3 general themes: first line therapy, prognostic parameters in relation to response to therapy, consolidation, and maintenance therapy, and, finally, treatment approaches for relapsed/refractory CLL. Dr Lin reviewed the newer approach of pentostatin-based protocol, which shows very high overall response (OR) rates and significant albeit less complete response (CR) rates than have been reported for fludarabine, cyclophosphamide, and rituximab (FCR). However, Dr Lin's review also pointed out that the pentostatin, cyclophosphamide, and rituximab (PCR) regimen may be "kinder and gentler" than fludarabine-based protocols particularly for the elderly patient. Dr. Shanafelt reviewed the efficacy of fludarabine/cyclophosphamide (FC) versus fludarabine (F) for previously untreated patients and highlighted an important aspect: Clearly FC is superior to F alone, but the CR levels appear to be far less than CIT regimens such as FR, FCR, and PCR. In addition, the use of computed tomography scans for response evaluation can significantly downgrade the level of responses seen compared to the use of the rapidly outdated NCI-96 criteria as shown by Eichhorst's work from the GLLSG trial reported recently in *Blood*.

In regard to prognostic parameters, several points are worth emphasizing. The PCR treatment approach as well as the FC therapy study by Grever et al show that CR- and nodular partial response (nPR)-type responses are not precluded by the presence of high-risk parameters with the exception of del (17p13.1) and that prediction of response duration may depend on CD38 expression levels as well as high-risk fluorescent in situ hybridization (FISH) defects such as del (17p13.1) or del (11q22.3). The value of doing risk stratification analysis is pointed out by the finding in the PCR trial reported by Kay that patients with del (11q22.3) fared as well as non–del (11q22.3) patients in terms of PFS. This latter aspect provides additional rationale that further work on the role of prognostic parameters with these and other even more novel parameters in the setting of clinical trials will continue to refine our prognostic abilities.

The paper reviewed by Lin on alemtuzumab therapy for consolidation of fludarabine treatment highlighted and reinforced the known potency of that former drug to clear out bone and blood marrow for CLL patients. However, the real question here is does the added reduction in CLL burden balance with the considerable increase in infectious complications seen in this CLL cohort? Thus the achievement of minimal reacting dose and improved PFS status found using alemtuzumab must be proven to be capable of outweighing the negative impact of the CLL patients' ability to resist the onslaught of serious infectious complications. As pointed out by Dr. Lin, there is considerable ongoing effort in clinical trial settings to determine the proper dose and schedule for alemtuzumab in CLL.

Finally both Drs. Lin and Shanafelt reviewed several options for relapsed/refractory CLL. This is a very robust area of research in CLL and is filling a truly unmet need: what to do with frontline failures of CLL therapy? Fortunately, we now have multiple options available with agents that are nonoverlapping mechanisms of action for these patients. Thus the addition of alemtuzumab to FCR (so called CFAR) or the addition of lumiliximab and anti-CD23 monoclonal antibody to the FCR regimen has resulted in significant increases in CR and/or OR levels for cohorts of CLL patients who had been previously treated. Which one to choose is not obvious yet because these 2 trials are nonrandomized studies, and, in the case of CFAR, it appears to be highly immunosuppressive with cytomegalovirus (CMV) reactivation a relatively common occurrence. In addition, both approaches would require a clinician to use fludarabine for patients who have already been exposed to this drug in the past. Two very different options for treatment of relapsed/refractory CLL are found in the papers reviewed by Drs. Lin and Shanafelt on lenalidomide and flavopiridol. In these latter cases, there is not only evidence that they are effective in heavily pretreated CLL cohorts with OR levels in the 40% to 50% range, but also that they can work in CLL patients with high-risk parameters including del (17p13.1). This latter group of studies in relapsed refractory CLL sets the stage for future exploration of unique combinations of combination therapies that have the promise of giving potent treatment options for the most difficult cohort of CLL patients.

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1. Is the following statement TRUE or FALSE? According to results presented by Wierda et al, cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR) combination therapy is not effective as salvage therapy in patients with high-risk cytogenetics.
   A. True
   B. False

2. In the study by Chanan-Khan and colleagues, lenalidomide monotherapy was associated with responses in which of the following subgroups?
   A. Patients with 11q deletions
   B. Patients with bulky disease
   C. Fludarabine-refractory patients
   D. All of the above

3. Lin and colleagues found that flavopiridol was active among patients with relapsed chronic lymphocytic leukemia (CLL) with which of the following adverse features?
   A. 17p deletion
   B. 11q deletion
   C. Complex karyotype
   D. Bulky disease
   E. All of the above

4. In the US Intergroup trial of single agent fludarabine versus fludarabine and cyclophosphamide, how much did combination therapy improve progression-free survival (PFS)?
   A. < 6 months
   B. 1 year
   C. 2 years
   D. Combination therapy did not prolong PFS

5. In the US Intergroup trial of single agent fludarabine versus fludarabine and cyclophosphamide, del (17p13.1) and del (11q 22.3) predicted what outcome relative to those without these abnormalities:
   A. Lower complete response (CR) rate and shorter PFS
   B. Lower CR rate but equivalent PFS
   C. Equivalent CR rate but shorter PFS

6. Wierda and colleagues showed that the combination of (CFAR) was effective as salvage therapy for relapsed CLL. However, 52% of patients on prophylactic valacyclovir reactivated cytomegalovirus (CMV). What percentage of patients on prophylactic valganciclovir reactivated CMV?
   A. 50%
   B. 30%
   C. 10%
   D. 0%

7. Byrd and colleagues presented results of a phase I/II study of the anti-CD23 fludarabine, cyclophosphamide, and rituximab (FCR) and the monoclonal antibody lumiliximab (FCR + L) and compared the results to historical results with FCR in relapsed patients. Which of the following is true?
   A. The overall response rate (ORR), but not the CR rate, was higher to FCR + L than to FCR
   B. The CR rate, but not the ORR, was higher to FCR + L than to FCR
   C. Both the CR rate and ORR were higher to FCR + L than to FCR
   D. There was no difference in CR rate or ORR between FCR + L and FCR

8. The German CLLSG presented follow-up data on 21 patients who were randomized to observation or consolidation alemtuzumab after initial fludarabine-based therapy. With 48 months' follow-up, the median PFS of patients in the observation arm was 20.6 months. What was the median PFS of patients in the alemtuzumab arm?
   A. 23 months
   B. 31.5 months
   C. 39 months
   D. Not reached

9. Kay and colleagues reported findings of a phase II study of pentostatin, cyclophosphamide, and rituximab (PCR). What were the CR rate, ORR, and median PFS?
   A. 41% CR, 91% OR, 33 months
   B. 55% CR, 91% OR, 24 months
   C. 66% CR, 96% OR, not reached
   D. 55% CR, 91% OR, 24 months

10. Shanafelt and colleagues compared the response to and toxicity of PCR in younger patients < 70 years of age and older patients > 70. Which of the following is true?
    A. CR rate and ORR were worse in older patients.
    B. ORR was the same, but CR rate was inferior in older patients.
    C. Older patients received fewer median cycles of therapy than younger patients.
    D. More older patients required dose reduction and dose delay > 1 week
    E. More older patients required dose delay of > 1 week.

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