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Chronic Lymphocytic Leukemia: Current and Emerging Treatment Approaches

Part 1 of a 3-part series on Recent Advances in the Treatment of Hematologic Malignancies

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Abstract

The focus in oncology continues to shift toward therapy based around a clear understanding of genetic abnormalities and their connection with prognosis and response to therapy. Chronic lymphocytic leukemia is a prime example of a malignancy benefiting from not only important new treatment options, but also the identification and clarification of numerous prognostic markers. This monograph presents the most current information about the various cytogenetic and immunologic abnormalities that have been identified and their association with prognosis. In addition, recent treatment advances, including newly approved agents, are discussed. Finally, this monograph provides clarification regarding how to now integrate the plethora of information about various prognostic markers into clinical practice so that clinicians caring for patients with chronic lymphocytic leukemia can make the most informed decisions regarding treatment approach.

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Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, hematologists, and oncology nurses involved in treating patients with chronic lymphocytic leukemia (CLL).

Statement of Need/Program Overview: Much has occurred and been presented at the various major hematology and oncology meetings over the past year regarding the emergence of new data impacting new standards of care for CLL. These emerging data may not be fully understood by practicing hematologists/oncologists in the community setting. A one-year retrospective Clinical Roundtable Monograph is the ideal vehicle through which community-based physicians can learn about these recent advances.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of existing and emerging agents in the natural history of CLL.
- Review the results of clinical trials evaluating various therapies in the treatment of CLL.
- Identify future research directions for various therapies in CLL.

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The Natural History of CLL and New Prognostic Markers

Kanti R. Rai, MD

As clinicians who treat chronic lymphocytic leukemia (CLL) are well aware, the natural history of this disease follows one of three courses:

(i) A proportion of patients show few signs of this disease, with little to no adverse effects. There also is virtually no shortening of overall survival expectation nor of quality-of-life because of CLL among these patients. These patients are considered to be in the low-risk category of CLL.

(ii) A significant minority of CLL patients, however, experience an aggressive course following diagnosis, with rapid development of symptoms and other stigmata of the disease. Need for initiating therapeutic intervention becomes obvious soon after the diagnosis and these patients suffer an early death either from complications of treatment or from the disease itself. This group is considered high-risk.

(iii) The third group runs a middle ground between the two listed above. Following a varying period of “inactivity,” some symptoms and signs of disease become evident. The overall survival (OS) of these patients is certainly longer than of high-risk group and are therefore considered intermediate-risk CLL.

In recent years, various studies have explored the molecular biology and genetics underlying the abnormally prolonged survival of the leukemic lymphocytes of CLL. These studies demonstrate that the Bcl-2 gene, which is expressed in CLL, increases leukemic cell survival by inhibiting apoptosis.^{1,2} Interestingly, long before the discovery of Bcl-2 and the concept of apoptosis, Galton and Dameshek hypothesized that CLL is a disease of progressively increasing accumulation of leukemic lymphocytes.^{3,4} Based solely on clinical observation of the natural history of CLL in a large number of patients, they postulated (simultaneously and independently of each other) that CLL lymphocytes live long because they are nonfunctional and immunologically incompetent.

Applying prognostic criteria to individual patients is difficult. Clinical stage, lymphocyte doubling time, and pattern of lymphocytic infiltration in bone marrow biopsies have been the traditional markers for predicting the course of CLL (Table 1). However, these criteria often do not prove effective with individual patients, and clinicians are left with little direction about what criteria would work better. The Binet and Rai staging systems have proven accurate in assigning patients to prognostic groups, but again these have often proven unsatisfactory when dealing with individual patients.^{4,5}

Over the last two decades, however, researchers have identified four new prognostic markers. These include (1) CD38 expression on leukemic lymphocytes; (2) immunoglobulin variable region heavy chain gene mutation (IgV_H) status of CLL lymphocytes; (3) ZAP-70 expression; and (4) fluorescent in situ hybridization (FISH) and cytogenetic abnormalities (Table 2). These markers have varying levels of usefulness in terms of clinical application.⁷

CD38 coexpression on leukemic cells is associated with a poor prognosis.^{8,9} Such patients typically require treatment earlier than those without CD38 expression and also have a shorter survival time. Patients with somatic hypermutation in their IgV_H genes tend to have excellent survival and clinical

Table 1. “Older” Prognostic Markers in CLL

Marker	Prognosis	
	Good	Worse
Clinical stage	Low	Higher
Lymphocyte doubling time	Slow	Rapid
Pattern of lymphocyte infiltration (BM Bx)	Non-diffuse	Diffuse

CLL=chronic lymphocytic leukemia.

cal prognoses, whereas those without this mutation tend to have poor prognoses.⁹⁻¹¹

ZAP-70 expression was first identified by investigators at the National Institutes of Health through a microarray analysis of a large number of CLL patients.¹² They found 15 or so genes—ZAP-70 among them—that differed between samples from patients with mutated versus unmutated CLL. The protein associated with the ZAP-70 gene is a tyrosine kinase that is normally active in T cells but also has expression in some CLL patients. Subsequently, several investigators showed that CLL patients with ZAP-70 expression fared worse than those without this marker.^{13,14}

With regard to FISH cytogenetics, Dohner and colleagues found that del(13q) was associated with a very good prognosis among CLL patients.¹⁵ In addition, patients with no other abnormalities detected by FISH also tend to have a good prognosis. These markers are associated with a median life expectancy of 10–12 years or more. By contrast, patients with del(17p) or p53 mutations typically have a survival

Table 2. “Newer” Prognostic Markers in CLL

Marker	Prognosis	
	Good	Worse
IgV _H Gene	Mutated	Unmutated
ZAP-70 expression	Negative	Positive
CD38 expression	Negative	Positive
Cytogenetic (FISH)	del(13q)	del(11q), del(17p)
	Normal	Trisomy 12 ?

CLL=chronic lymphocytic leukemia; FISH=fluorescence in situ hybridization.

time of less than 3 years. Del(11q) is also associated with a similarly short survival time.

Trisomy 12 was once considered the most common cytogenetic abnormality in CLL, but the group of German investigators found that this mutation was present in only 15% of the patient samples tested.¹⁶ The prognosis of these patients fell somewhere between the poor prognosis associated with del(17p) and del(11q) and the good prognosis associated with del(13q).

But when it comes time to assess a patient's prognosis, oncologists often run into a strange predicament: any given patient might test positive for one or two “good” markers but also one or two “bad” markers. To which should the clinician award primacy in order to ensure the best care of the patient? Recent studies are providing some clues.

First, a study by Rassenti and colleagues shows that when it comes to determining prognosis, ZAP-70 appears to trump all other markers such as mutation status and CD38 expression.¹⁴ But there are also studies showing that mutation status is the most important marker, so clearly more data are needed.

In newly diagnosed CLL patients, del(17p) seems to be irrelevant, as this mutation most commonly arises following exposure to cytotoxic drugs.¹⁷ Approximately 15–20% of CLL patients develop del(17p) mutations following treatment, and these patients tend to have a poor prognosis.¹⁸

An Eastern Cooperative Oncology Group (ECOG) clinical trial comparing fludarabine plus cyclophosphamide (FC) versus fludarabine alone for the treatment of CLL included ZAP-70 and FISH mutation analyses.¹⁹ Interestingly, the investigators found that these markers were not predictive of overall survival time but rather of progression-free survival (PFS).

A new and ambitious Cancer and Leukemia Group B (CALGB) study for the treatment of newly diagnosed CLL will enroll only those patients exhibiting poor prognostic markers such as ZAP-70 positivity or FISH cytogenetics.¹⁸ These patients will be randomized to either observation (the current standard of care for newly diagnosed patients) or chemoimmunotherapy. The primary endpoint of this study

is the time at which treatment (or additional treatment) becomes necessary for any patient on either arm. The ECOG and Southwest Oncology Group have also joined this interesting study, which will enroll over 2,000 patients. However, this study will take at least 10 years to complete.

In summary, the issue of prognostic markers for CLL will likely be resolved in the next 5–10 years. Ongoing studies are expected to provide accurate and reliable data about how to integrate these markers into the management of individual patients with CLL.

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Recent Developments in the Treatment of CLL

Bruce D. Cheson, MD

The advent of immunochemotherapy has led to dramatic improvements in the treatment of CLL. Namely, fludarabine-based regimens incorporating rituximab with or without cyclophosphamide (FCR and FR, respectively) are associated with overall response rates (ORRs) of 90% or higher, with most patients achieving complete remissions (CRs).^{1,2} These data in comparison with historical controls suggest that new treatments are prolonging the survival of patients with CLL.

Nevertheless, CLL remains incurable, and many patients, particularly those over age 65 or 70, are unable to tolerate some of these otherwise effective regimens.³ Other patients do not respond to FR or FCR, or they progress after treatment. Thus there is a compelling need for additional CLL treatment options, in both the frontline and second-line settings.

There is a great deal of interest in new biologic therapies. The median age of CLL patients at presentation is approximately 70 years, and many of these patients are better suited to biologic-based treatments than to aggressive chemotherapy regimens. The monoclonal antibody alemtuzumab was initially approved by the US Food and Drug Administration (FDA) for the treatment of relapsed and refractory CLL but was recently approved for newly diagnosed patients as well.⁴ This agent is associated with a response rate of more than 30% in relapsed or refractory patients, of approximately 80% when given as initial therapy, and is well tolerated when administered subcutaneously.⁵ However, alemtuzumab carries a substantial risk of potentially life-threatening opportunistic infections, particularly among previously treated patients.⁶ Antimicrobial prophylaxis is essential for patients undergoing alemtuzumab therapy and screening for cytomegalovirus and other infections should also be routine.

Although not approved in this setting, rituximab is often used to treat CLL, as mentioned above. Since this agent is well tolerated and active in the first-line setting, there has been considerable interest in developing more effective anti-CD20 monoclonal antibodies, and several of these are currently in clinical trials. Of these second-generation agents, ofatumumab is the furthest along in clinical development. This agent binds to a different epitope than rituximab, and is therefore hypothesized to have improved antibody-dependent cell-mediated cytotoxicity and/or complement-dependent cytotoxicity. A phase I/II study by Coiffier and colleagues found ofatumumab to be well tolerated in patients with relapsed or refractory CLL⁷;

based on these findings it will likely continue to the next stage of clinical trial study.

Another monoclonal antibody being tested in CLL is lumiliximab. This anti-CD23 agent has shown some activity in phase I and II studies, but not enough to induce complete or partial responses (PRs).⁸ Following on from encouraging historical comparisons with the FCR regimen, a phase III study comparing FCR with or without lumiliximab for previously treated CLL is now ongoing.⁹

Lenalidomide is an increasingly popular choice for CLL treatment. Studies suggest that lenalidomide is an antiangiogenic agent, targets the tumor microenvironment, and may also kill cells directly.¹⁰ B-cell malignancies such as CLL have defects not only in the malignant cells themselves but also in the surrounding microenvironment and with angiogenesis, which may explain why lenalidomide is proving effective in the treatment of CLL.

There have been two key studies of lenalidomide in this setting. Chanan-Khan and colleagues administered lenalidomide at 25 mg/day for 21 of 28 days.¹¹ Nonresponding patients had rituximab added to their regimens. The ORR among relapsed or refractory CLL patients was 47%, with a CR rate of 9%. In the 3 patients whose disease progressed following an initial response, response was reinduced by retreatment with lenalidomide plus rituximab. Ferrajoli and colleagues administered lenalidomide at a starting dose of 10 mg/day for 28 days, with doses increased by 5 mg per 28-day cycle to a maximum of 25 mg/day.¹² In this study the ORR was 32%, with a 7% CR rate. Whether the discrepancies between these two studies reflect differences in the patient population has not been determined. However, it appears that lenalidomide is effective in patients with del(11q) mutations but works less well in patients with del(17p) mutations. This agent is being incorporated into several frontline CLL studies.

Other new drugs of interest include flavopiridol, a semisynthetic flavone derivative. Oncologists have been studying this agent for years, but an effective schedule of administration was only recently developed. Byrd and colleagues reported a 45% PR rate in their study of flavopiridol in the treatment of CLL, even among patients with adverse cytogenetics.¹³ However, flavopiridol is also associated with a high likelihood of tumor lysis syndrome and associated renal problems. More stringent patient selection is helping to reduce these side effects.

Bendamustine is a particularly noteworthy new treatment for CLL, having just recently been approved by the

FDA.¹⁴ The structure of this drug is unique; it appears to have an alkylating agent on one side and a structure similar to a purine analog on the other. This agent is known to act as an alkylator, but whether it also exhibits purine analog function is not yet known. Several phase I and II studies found PR rates among treatment-naïve CLL patients receiving bendamustine ranging from 65% to 90%.^{15,16}

These encouraging findings led to a phase III trial by the German CLL Study Group comparing bendamustine to chlorambucil in previously untreated patients.¹⁷ A total of 305 patients received either chlorambucil 0.8 mg/kg orally on days 1 and 15 of a 28-day cycle or bendamustine at a dose of 100 mg/m² intravenously on days 1 and 2 of a 28-day cycle, with treatment lasting for 6 cycles for both arms. Reporting their findings at the 2007 ASH annual meeting, Knauf and colleagues noted an ORR of 68% for the bendamustine group and 39% for the chlorambucil group ($P<.0001$). The CR rates were 29% and 2%, respectively, and PFS was 21.7 months versus 9.3 months, respectively ($P<.001$). Side effects were similar between the two groups, save for a higher occurrence of neutropenia among patients treated with bendamustine. Following these positive results, several ongoing studies are evaluating bendamustine in combination with other agents to see if this approach might further improve outcomes. Table 3 summarizes response rates associated with some of the most common new agents in the treatment of CLL.

CLL is characterized by an overexpression of Bcl-2 and its family members, which leads to impairment of programmed cell death. Thus, targeting the apoptotic pathways is another promising therapeutic avenue for CLL (Table 4). The most widely studied anti-Bcl-2 agent is oblimersen sodium. In a phase III study comparing FC with or without oblimersen, the rate of CR plus nodular PR for the oblimersen-containing arm was significantly greater than the rate seen among patients receiving FC alone (17% vs 7%; $P=.025$).¹⁸ Adverse reactions associated with oblimersen were modest, including a nonsignificant increase in thrombocytopenia. A number of other Bcl-2 antagonists, including obatoclax, ABT-737, and AT-101, are in preclinical and early clinical development.¹⁹

In summary, there is a wealth of new chemotherapy and targeted agents now available for the treatment of CLL. One of the next steps in CLL treatment is to develop combination strategies based on solid scientific rationale. The goal of these efforts is to improve the CR rate in previously untreated patients, leading to prolonged responses and survival or perhaps even cure. Among relapsed patients, the goal of current research is to improve responses to well-tolerated therapies and to ensure that these responses are durable and associated with a good quality of life and prolonged survival.

Table 3. Activity of “New” Agents in Relapsed/Refractory CLL/SLL

Drug	CR, %	ORR, %
Bendamustine	7–36	64–94
Flavopiridol	0	43
Lenalidomide	6–13	37–38

CLL=chronic lymphocytic leukemia; CR=complete response rate; ORR=overall response rate; SLL=small lymphocytic leukemia.

Table 4. Apoptosis as a Therapeutic Target

Drug	Target
Oblimersen	Bcl-2
Obatoclax	Bcl-2 family
YM155	Survivin
AT-101	Bcl-2, Bcl-XL, MCL1
ABT-737	Bcl-2, Bcl-XL, NOXA
APO2L/TRAIL	DR4, DR5
Agonistic monoclonal antibodies	DR4, DR5

DR4 = TRAIL-R1 (approved gene name TNFRSF10A); DR5 = TRAIL-R2 (approved gene name TNFRSF10B).

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Incorporating Prognostic Factors Into Treatment Decisions

Susan O'Brien, MD

There is confusion among academic and community-based practitioners about how best to incorporate new findings about prognostic factors and therapy advances into the treatment of our patients with CLL. For example, as Dr. Rai noted, when a patient exhibits two prognostic factors—one good and one bad—which takes priority in predicting outcome?

Data regarding prognostic factors are only now being applied prospectively, and the findings are still somewhat inconsistent. For example, in a study comparing fludarabine with or without cyclophosphamide, mutation status did not correlate with PFS, whereas in the CALGB study of fludarabine with or without rituximab, this correlation was observed.^{1,2} However, the fact that one of these studies was of chemotherapy alone and the other included a biologic agent makes interpreting the results even more difficult.

Further, testing for ZAP-70 is not easily done outside of a major research center. Thus far, the flow assays have proven unreliable outside of academic laboratories. Some laboratories have begun using immunostaining to test for ZAP-70 because staining the bone marrow is fairly simple.³ However, there are less data available on this method, and it can only be used on marrow containing mostly CLL and not normal lymphocytes.

When it comes to analyzing prognostic factors, it is important to remember that the current recommended approach for early-stage asymptomatic CLL is no therapeutic intervention, even if the patient has high-risk features.⁴ There are no data supporting earlier treatment intervention

in patients with high-risk features. Therefore clinicians need to consider whether conducting these expensive tests is worthwhile if the patient will be observed rather than treated no matter what the tests show. Currently the primary reason to test for various prognostic factors is to enable clinicians to inform patients whether their disease appears to be low-risk or high-risk.

Once a patient requires therapy there is still a question of which tests should actually influence treatment choices. I think clearly FISH is the answer to that question. It is important to know if 17p deletions are present. Data show that this marker correlates with poorer outcomes regardless of what other prognostic factors might be present.⁵ In addition, readily available FISH tests make confirming the presence of del(17p) fairly simple.

However, the exact treatment recommended for patients with del(17p) has not been fully clarified. More defined are the treatments that do not work in such patients. For example, fludarabine and alkylating agents are not as effective in patients with del(17p) mutations compared to those without this mutation (Table 5). Alemtuzumab has been found to be effective among del(17p) patients with refractory CLL.⁶ However, a multicenter study of frontline alemtuzumab, while confirming these findings, also found that the median PFS among previously untreated CLL patients with del(17p) was just 10.7 months (Table 6).⁷ Thus alemtuzumab may be a reasonable choice for patients with this prognostic factor, but it is by no means an optimal treatment.

Table 5. Fludarabine Versus FC (N=235) E2997 Genomic Analysis

Feature	Fludarabine (n=113)		FC (n=122)	
	No.	PFS, mo	No.	PFS, mo
del(17p)	9	9	10	12
del(11q)	16	15	24	25
Trisomy 12	27	21	21	NR
Normal	20	14	17	NR
del(13q)	38	23	43	NR

FC=fludarabine/cyclophosphamide; NR=not reached; PFS=progression-free survival.

Adapted from Grever et al.¹

With the uncertain benefits of currently available drugs, younger and otherwise healthy CLL patients with del(17p) may be good candidates for allogeneic stem cell transplantation.⁸ Because del(17p) is known to be associated with poor outcomes following therapeutic interventions, a transplant may be the best approach for patients able to tolerate this procedure.

β 2 microglobulin is another useful measure to include in treatment considerations for CLL patients. The test for this prognostic factor is easy, cheap, and reliable, and provides useful information. Studies have found that serum β 2-microglobulin is an independent predictor of PFS in patients with CLL, particularly in the early stages of the disease.^{9,10}

Testing for del(11q), which is usually found along with del(17p) on CLL FISH panels, may also be useful. Emerging data are showing that the alkylating agents may be particularly effective in patients with this mutation. Thus, if a clinician were deciding between, say, FR, FCR, or a combination of pentostatin plus cyclophosphamide and rituximab (PCR), it would be useful to use FISH testing to determine whether the patient has the 11q deletion. If so, FCR or PCR would be the better treatment option.

Regarding retesting for prognostic markers, there is no evidence supporting repeat tests in untreated asymptomatic patients. Mutation status will not change throughout the course of the disease and although the data are somewhat conflicting it appears that significant changes in ZAP-70 status do not occur either. However, relapsing patients who require retreatment should be retested by FISH since acquisition of abnormalities such as del(11q) and del(17p) are common in disease progression.

Table 6. CAM307: PFS by Cytogenetic Abnormality and Treatment Arm*

Deletion	Alemtuzumab		Chlorambucil		P value for PFS†
	N	Median PFS, mo	N	Median PFS, mo	
del(17p)	11	10.7	10	2.2	.2034
del(11q) [no del(17p)]	23	8.5	31	8.5	.3895
Trisomy 12 [no del(17p), no del(11q)]	24	18.3	10	12.9	.0815
Normal	25	19.9	26	14.3	.3477
Sole del(13q)	33	24.4	34	13.0	.0107

*Data presented according to hierarchical model of Döhner (*NEJM*. 2000;343:1910-1916).

†P value is calculated using log-rank test.

Adapted from Hillmen P, et al. *Blood*. 2006;108(11):93a. Abstract 301.

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Question & Answer Forum

The faculty answer further questions about the management of chronic lymphocytic leukemia.

What is the role of computed tomography scanning in staging and prognosis?

Bruce Cheson The role of computed tomography (CT) scanning in the staging and prognosis of CLL patients has not yet been clearly determined. A report by Montserrat and colleagues suggests that for Rai stage 0 disease if a CT scan shows nodal involvement the disease is likely to progress more like Rai stage 1.¹ Right now, however, there is not enough evidence to support CT scanning outside of a clinical trial setting.

Kanti Rai I agree that right now CT scanning should not be part of CLL staging or prognosis outside of a clinical trial. If a node or the spleen is palpable by physical examination, that is a sufficient indicator of the stage of disease and level of tumor burden. Stage 0 and stage 1 patients have distinctly different survival statistics, and implementing CT scans in all stage 0 patients would cause too much confusion with little to no benefit in treatment decision making.

In what combination regimens is bendamustine now being studied?

BC A phase I trial of bendamustine plus lenalidomide is now getting underway. When the maximum tolerated dose of this combination is identified, rituximab will then be added. The addition of this antibody may increase the toxicities of all the drugs, and so this trial will remain at the phase I level until the maximum tolerated doses for all three agents are identified. Other studies will pursue the same combination but in a different sequence: bendamustine plus rituximab followed later by lenalidomide. Interestingly, bendamustine is also being studied in other hematologic malignancies, such as non-Hodgkin lymphoma, where it is being combined with bortezomib plus rituximab.

Much of the interest in bendamustine stems from the fact that CLL patients who relapsed following treatment with

FR or FCR had no further treatment options. Bendamustine is an effective agent for such patients, is not cross-resistant with alkylating agents, and may have activity in patients with adverse cytogenetic factors. Thus this agent not only adds significantly to the therapeutic armamentarium, it also provides a foundation on which to build other regimens for patients who have relapsed after prior therapies.

Could you elaborate on the issue of lenalidomide dosing?

Susan O'Brien As mentioned earlier, the response rates in the study by Chanan-Khan et al, in which patients received lenalidomide at a dose of 25 mg, were higher than in the study by The University of Texas M. D. Anderson Cancer Center, in which lenalidomide was started at a dose of 10 mg and escalated gradually from there. However, comparing two small trials is never a reliable basis for treatment decisions. The absolute comparability of the patients in these studies could also have impacted the response rates. With caution, I would say that there may be a dose-response correlation, but the ideal dose has not yet been clearly determined.

BC I agree. There really is no solid evidence for the dose-response effect with lenalidomide. And unfortunately, patients with CLL seem to tolerate agents such as lenalidomide and oblimersen worse than patients with lymphoma or solid-tumor malignancies. Some CLL patients have experienced tumor lysis syndrome with lenalidomide doses as low as 2.5 mg/day. The optimal dose has not yet been determined, nor has the optimal schedule.

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Chronic Lymphocytic Leukemia: Current and Emerging Treatment Approaches

CME Post-Test: Circle the correct answer for each question below.

- The Bcl-2 gene is associated with:
 - Prolonged leukemic cell survival
 - Shortened leukemic cell survival
 - CLL that progresses very slowly
 - Poor tolerance of alkylating agents in the treatment of CLL
- Traditional prognostic markers in CLL include which of the following?
 - Age at diagnosis
 - Gender
 - Lymphocyte doubling time
 - None of the above
- CLL patients with ZAP-70 expression fare _____ those without ZAP-70 expression.
 - better than
 - worse than
 - the same as
 - No data exist about this prognostic marker in CLL
- In a trial comparing FC versus fludarabine alone for the treatment of CLL, ZAP-70 and FISH mutation analyses were predictive of:
 - overall survival
 - complete response rate
 - partial response rate
 - progression-free survival
- Lenalidomide may be effective in the treatment of CLL because:
 - This disease is associated with defects in the tumor microenvironment, which is a target of lenalidomide
 - Lenalidomide targets CD20, which is expressed by all CLL patients
 - This agent is antiangiogenic, and CLL is characterized by defects in angiogenesis
 - Both A and C
- Flavopiridol has elicited promising responses in CLL, but is also associated with a high likelihood of:
 - tumor lysis syndrome
 - renal problems
 - Both A and B
 - Neither A nor B
- In a phase III trial of bendamustine versus chlorambucil in the treatment of CLL, the PFS among patients receiving bendamustine was:
 - 21.7 months
 - 9.3 months
 - 12 months
 - 6 months
- Data show that ____ correlates with poorer outcomes, regardless of what other prognostic factors might be present.
 - trisomy 12
 - del(11q)
 - del(17p)
 - All of the above
- β 2-microglobulin is an independent predictor of _____ in patients with CLL.
 - response to alkylating agents
 - PFS, particularly in the early stages of disease
 - PFS, particularly in the later stages of disease
 - response to alemtuzumab
- Relapsing patients who require re-treatment should be retested by FISH since acquisition of which of the following abnormalities is common in disease progression?
 - Del(11q)
 - Del(17p)
 - Both A and B
 - ZAP-70

Evaluation Form: Chronic Lymphocytic Leukemia: Current and Emerging Treatment Approaches

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

- Describe the importance of existing and emerging agents in the natural history of CLL. 1 2 3 4 5
- Review the results of clinical trials evaluating various therapies in the treatment of CLL. 1 2 3 4 5
- Identify future research directions for various therapies in CLL. 1 2 3 4 5

Overall Effectiveness of the Activity

The content presented:

- Was timely and will influence how I practice 1 2 3 4 5
- Enhanced my current knowledge base 1 2 3 4 5
- Addressed my most pressing questions 1 2 3 4 5
- Provided new ideas or information I expect to use 1 2 3 4 5
- Addressed competencies identified by my specialty 1 2 3 4 5
- Avoided commercial bias or influence 1 2 3 4 5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity. _____

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