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Accurate Reporting of Adverse Events in Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

Abstract

The treatment of lymphomas such as non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) has greatly advanced, especially over the last decade, with notable improvements in patient responses and survival times. However, adverse events remain an important, and often overlooked, issue in the management of these patients. Treatment of these malignancies is made additionally complex due to the occurrence of related severe cytopenias and other side effects. New agents to treat NHL and CLL are currently in clinical development; many of these are targeted agents with the added benefit of not producing the same adverse events (such as hematologic toxicity) observed with older cytotoxic chemotherapies. However, even these newer agents must be incorporated with caution into the clinical setting, as they have their own unique toxicity profiles and can even cause off-target effects when used at high doses. As these agents advance through clinical trials, clinicians must be able to recognize and manage associated adverse events. This monograph addresses these important points, with experts discussing adverse events due to the malignancies themselves as well as their associated treatments. Proper reporting of adverse events is critical, as are proper clinical trial design and long-term follow-up.

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Current Treatment of Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

Kanti R. Rai, MD

The topic of adverse events in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) is an extremely important one, although it is often neglected by clinicians in this field. Although the focus is generally on improving patient responses, achieving complete remissions, and increasing patient survival, many investigators do not carefully consider the long-term impact of cumulative toxicities and quality of life in treated patients.

Frontline Treatment of Indolent NHL

Indolent NHL, exemplified by follicular lymphomas, is generally not life-threatening when it is initially diagnosed. One initial approach to a patient with advanced-stage, asymptomatic follicular lymphoma is observation alone, or watchful waiting.[1] This strategy is based on the results of several studies that demonstrated a lack of advantage among patients who were treated with initial chemotherapy. Young and colleagues compared watchful waiting with aggressive upfront chemotherapy (prednisone, methotrexate, doxorubicin, and cyclophosphamide, plus etoposide and mechlorethamine, vincristine, procarbazine, and prednisone [ProMACE-MOPP]) followed by total nodal irradiation.[2] They found that only 15% of patients in the observation arm experienced disease progression, but there was no long-term follow-up of these data. Brice and colleagues conducted a prospective, randomized study in patients (N=193) with newly diagnosed follicular lymphoma and low tumor burden.[3] Similar overall response rates were achieved among patients whose treatment was delayed until disease progression, compared with patients treated with immediate prednimustine or interferon alpha (70% vs 78% and 70%, respectively). The 5-year overall survival (OS) rates were also similar among the 3 treatment arms (78%, 70%, and 84%, respectively). Long-term results (median follow-up, 16 years) of a randomized, controlled trial by Ardeshna and colleagues showed that in patients (N=309) with asymptomatic advanced-stage, low-grade NHL, there was no difference in median OS between patients treated with upfront systemic therapy (10 mg/day continuous chlorambucil) or observation with delay of chemotherapy until disease progression (5.9 years vs 6.7 years; P=.84).[4]

More recently, Ardeshna and associates evaluated the strategy of watchful waiting since the introduction of rituximab.[5] This approach was tested in a prospective, randomized, international Intergroup trial, which compared upfront rituximab (2 doses: 375 mg/m^2/week for 4 weeks followed by observation, or 375 mg/m^2/week for 4 weeks followed by maintenance rituximab 375 mg/m^2 every 2 months) with watchful waiting among patients (N=463) with asymptomatic stage II–IV nonbulky follicular lymphoma. Upfront rituximab treatment resulted in a significant delay in the need to initiate therapy at 3 years compared with watchful waiting (80% and 91% vs 48% for rituximab induction and rituximab induction plus maintenance vs watchful waiting). This delay led to a significantly decreased need for treatment at 3 years among patients who received rituximab induction plus maintenance compared with patients in the observation group (hazard ratio [HR], 0.20; 95% confidence interval [CI], 0.13–0.29; P<.001), as well as for patients who received rituximab induction only compared with

observation (HR, 0.37; 95% CI, 0.26–0.56; *P*<.001). Additionally, a greater proportion of patients in the induction-plus-maintenance and induction-only rituximab treatment arms achieved a 3-year progression-free survival (PFS) compared with observation alone (81% and 60% vs 33%). Importantly, however, this analysis was not able to demonstrate a significant difference in the 3-year OS among the 3 treatment arms. Thus, until longer follow-up data become available, watchful waiting is still the recommended upfront approach for these patients.

According to the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, the appearance of one of a number of possible factors may trigger the initiation of treatment for patients with indolent NHL. These factors include involvement of 3 or more nodal sites, each with a diameter of 3 cm or more; any nodal or extranodal tumor mass with a diameter of 7 cm or more; B symptoms; splenomegaly; pleural effusions or peritoneal ascites; cytopenias; or leukemia.[6]

Rituximab, either as a single agent or as part of a combination regimen, is currently the most important initial therapy once treatment is initiated. Several clinical studies have established the efficacy of single-agent rituximab in patients with follicular lymphoma. Colombat and colleagues reported promising results in patients (N=50) with low tumor burden follicular lymphoma, in which single-agent rituximab therapy was associated with a 73% overall response rate.[7] Many of these patients also achieved a molecular response, and a significant association was observed between molecular and clinical responses (*P*<.001). A similar overall response rate (72%) was reported by Witzig and colleagues in another study of patients (N=37) with grade 1 stage III/IV follicular lymphoma; of these, 36% were complete responses.[8] More recently, Martinelli and colleagues reported results of a randomized trial of patients with follicular lymphoma (N=202), in which patients were initially treated with single-agent rituximab. If their disease did not progress, patients were randomized to either observation or prolonged rituximab therapy.[9] After a median follow-up of 9.5 years, the median event-free survival rate was significantly improved among patients who received prolonged rituximab compared with patients who did not receive rituximab (24 vs 13 months; *P*<.001). The 8-year event-free survival rate was 27% in patients who received prolonged rituximab and 5% in patients who did not.

Whereas single-agent rituximab may reduce the tumor burden in indolent NHL patients, even better outcomes may be achieved when rituximab is combined with chemotherapy. For example, in a study of newly diagnosed follicular lymphoma patients with high tumor burdens (N=428), Hiddemann and colleagues compared cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) alone versus CHOP plus rituximab (R-CHOP).[10] The R-CHOP patients achieved a 60% reduced relative risk for treatment failure, a significantly prolonged time to treatment failure (*P*<.001), and a significantly higher overall response rate (96% vs 90%; *P*=.011). Additionally, a superior OS was reported among patients treated with R-CHOP compared with CHOP alone (2-year OS: 95% vs 90%; at 3 years, 6 vs 17 patients had died; *P*=.016). The addition of rituximab to cyclophosphamide, vincristine, and prednisone (R-CVP) is also superior to cyclophosphamide, vincristine, and prednisone (CVP) alone, as shown in a study by Marcus and colleagues.[11] In this study of patients (N=321) with previously untreated stage III or IV follicular lymphoma, R-CVP resulted in significantly improved outcomes compared with CVP alone, including median time to progression (34 vs 15 months; *P*<.0001), overall response rate (81% vs 57%; *P*<.0001), and estimated 4-year OS (83% vs 77%; *P*=.0290).

Rummel and colleagues presented results from the StiL (Study Group Indolent Lymphomas) trial, a randomized, multicenter, open-label, phase III study that compared frontline therapy with bendamustine plus rituximab versus R-CHOP in patients (N=549) with follicular, mantle cell, marginal zone, and Waldenström's lymphomas.[12] The median PFS was significantly prolonged among patients treated with bendamustine plus rituximab compared with R-CHOP (54.9 vs 34.8 months; *P*=.00012). When this analysis was restricted to only patients with follicular lymphoma, the difference remained significant (*P*=.0281). Importantly, this study also demonstrated that the safety profile for the bendamustine plus rituximab combination was superior to R-CHOP, with significantly lower rates of neutropenia, leukocytopenia, alopecia, paresthesias, and infectious complications. Based on this outcome, the current evidence suggests that the optimal initial treatment of indolent NHL is bendamustine plus rituximab.

Frontline Treatment of CLL

Compared with indolent NHL, the frontline treatment of CLL has undergone even more dramatic changes over the last decade. Historically, treatment for newly diagnosed CLL was either single-agent fludarabine or chlorambucil. This approach gradually changed to the combination of fludarabine plus rituximab, largely based on the Cancer and Leukemia Group B (CALGB) 9712 trial.[13] This randomized, phase II trial in patients (N=104) with symptomatic, previously untreated CLL, reported by Byrd and colleagues, demonstrated that concurrent treatment with fludarabine plus rituximab was superior to sequential treatment with fludarabine followed by rituximab. A higher overall response rate

was achieved with concurrent treatment versus sequential therapy (90% vs 77%).

More recently, an advancement in frontline therapy for CLL has been the 3-drug combination of fludarabine, cyclophosphamide, and rituximab (FCR). In a phase II trial for the frontline treatment of CLL patients (N=300) by Tam and colleagues, an impressive 95% overall response rate was achieved at a median follow-up of 6 years.[14] A phase III trial by Hallek and colleagues compared the FCR combination with fludarabine plus cyclophosphamide (FC) in a prospective, randomized setting among patients (N=817) with previously untreated CLL.[15] After a median 3-year follow-up, an intent-to-treat analysis showed improved outcomes in patients receiving FCR versus patients receiving FC (without rituximab). FCR patients had higher overall response rates (90% vs 80%, respectively; $P<.0001$) and complete response rates (44% vs 22%, respectively; $P<.0001$), as well as increased 3-year PFS (65% vs 45%, respectively; $P<.0001$) and 3-year OS (87% vs 83%, respectively; $P=.01$) with the FCR combination versus fludarabine plus cyclophosphamide alone. It should be noted that in this larger study, FCR was associated with a lower rate of complete remission than in the previous phase II trial. This difference likely occurred because the larger, multicenter study was closer to a real-world setting compared with the earlier phase II study that was from a single institution.

Bendamustine has also been approved as frontline therapy in CLL. Its role in combination with rituximab in patients with relapsed disease was recently investigated in a phase II study from the German CLL Study Group.[16] In the 62 evaluable patients, overall response was 77.4%, with complete remission in 14.5% and partial response in 62.9%. Stable disease was observed in 17.7% of patients, and 4.8% experienced progressive disease. The efficacy of the bendamustine/rituximab combination in the frontline setting remains to be determined. The German CLL Study Group is currently conducting a randomized, phase III trial comparing FCR and bendamustine plus rituximab in previously untreated CLL patients. The results of that study, known as the CLL-10 trial, will be of great interest to the investigators as well as the clinicians.

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Considerations in Clinical Trial Design for Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

Jonathan W. Friedberg, MD

The development of drugs for the treatment of hematologic malignancies in the modern era has become more complex than ever before. In the previous era of conventional cytotoxic chemotherapy, the paradigm for drug development was to escalate the dosage until the maximum or dose-limiting toxicity was reached. This dose was then used throughout clinical development.

For hematologic malignancies, including CLL and indolent NHL, this traditional drug development paradigm has presented particular challenges. Because of the nature of these diseases, patients often present with severe cytopenias and other symptoms that may be considered "serious adverse events" even before initiating therapy. A challenge in clinical trials, therefore, is how to best differentiate drug-related adverse events from symptoms of the underlying malignancy.

Critical to making this determination is having accurate contemporaneous controls for comparison. Additionally, it is necessary to realize that the expected rate of baseline cytopenia will vary according to the particular patient population. For example, CLL patients with advanced-stage disease or prior alemtuzumab exposure will probably have a different cytopenia profile than CLL patients with newly diagnosed disease. Therefore, comparing patient cohorts to historical controls is especially problematic in this situation. For this reason, an increased emphasis has been placed on the use of contemporaneous controls in the setting of randomized phase II and III trials, in order to more accurately evaluate the toxicity profile of a novel therapy. A recent example of this approach was shown by Hess and colleagues, who conducted a randomized, phase III trial comparing temsirolimus with investigator's choice of therapy for the treatment of relapsed or refractory mantle cell lymphoma.[1] The inclusion of the investigator's choice was important because it provided a contemporaneous control arm to better evaluate both the safety and efficacy of temsirolimus.

When designing clinical trials for CLL and indolent NHL, it is important to clearly define a dose-limiting toxicity. Because neutropenia and thrombocytopenia are frequently expected throughout the natural history of these diseases, they should not themselves be considered dose-limiting toxicities. Many sponsors have defined a hematologic toxicity as dose-limiting only when it is severe and out of proportion to what would be expected. Examples of this might include a certain incidence or duration of *febrile* neutropenia, or a severity of thrombocytopenia that requires transfusion support.

Fortunately, many of the new agents under clinical development for these malignancies are not expected to have the same toxicity profile as the more conventional cytotoxic chemotherapies. This has given the entire community a reason to consider how best these newer agents and combinations should be developed for CLL and indolent NHL, particularly in the era of targeted therapy. One important difference with targeted agents is that escalating the drug to the maximally tolerated dose may not in actuality be the most appropriate strategy. In fact, dose escalations of targeted agents may frequently lead to more off-target effects, limiting the utility of the agent. Thus, there has been a movement toward using laboratory-based correlative endpoints to define an optimal biologic dose that should be used in clinical development, with the hope that this dose would spare the patient from experiencing significant toxicity while maximizing efficacy against the tumor.

Phase 0 clinical trials, a concept conceived to address the development of these targeted agents, present a paradigm shift for early cancer drug development.[2] To date, there have been limited phase 0 trials conducted in hematologic malignancies. Phase 0 trials can test, in a very small number of patients, whether a particular target is inhibited at low doses. Thus, in this newer era of targeted therapy, the focus of drug development is not to determine the maximally tolerated dose of a drug according to its toxicity, but to define a biologically active dose. As these agents advance through development, unexpected toxicities frequently appear, even at very low doses, especially when the drug is administered as part of a combination regimen.

A final important concept to consider is that a particular agent at a particular dose may be considered safe in one hematologic malignancy but not another. For example, lenalidomide has been shown to be safely administered at doses up to 25 mg/day in patients with aggressive lymphomas.[3] However, among patients with

CLL, cases of life-threatening tumor lysis syndrome have been reported at lenalidomide doses of only one-tenth (2.5 mg/day) that strength.[4] Therefore, it is not wise to extrapolate safety and dosage considerations from experience with one hematologic malignancy (for example, multiple myeloma) to another hematologic malignancy (for example, CLL or NHL). Instead, careful dose titration studies must be performed in the various lymphoma histologies.

Summary

In this modern era of drug development, it is challenging to develop cytotoxic agents and novel combinations in diseases such as CLL and indolent NHL that are associated with cytopenias. Clever clinical trial designs are required in order to best define what a dose-limiting toxicity is for these diseases. It is hoped that in this new era of targeted agents, in which more emphasis is placed on achieving biologically active doses instead of maximally-tolerated doses, patients will experience fewer treatment-related adverse events with preservation of efficacy.

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Adverse Events in Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma: Importance of Accurate Reporting and Long-Term Follow-Up

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Research in the fields of both CLL and NHL has resulted in the clinical development of several new agents with promising early results. Clinicians are frequently faced with a situation in which a new treatment looks promising initially but requires longer follow-up, not only to assess the durability of responses, but to identify the potential long-term complications. For example, secondary malignancies may not develop until 5–7 years (or later) following treatment. Similarly, drugs that are particularly immunosuppressive may elicit associated long-term effects such as infectious complications. Rituximab-associated B-cell depletion and fludarabine-associated B-cell and T-cell depletion may persist for months or even years following treatment.

The initial results from the phase III StiL trial are promising—it appears that the combination of bendamustine plus rituximab resulted in significantly improved PFS and complete response rates compared with R-CHOP for patients with advanced CD20-positive lymphomas (including CLL and NHL).[1] Importantly, these improvements were accompanied by a superior toxicity profile of bendamustine plus rituximab compared with R-CHOP, including fewer incidences of alopecia ($P<.001$), myelosuppression (neutropenia: 10.7% vs 46.5% [$P<.0001$]; leukocytopenia: 12.1% vs 38.2% [$P<.001$]; and need for granulocyte colony stimulating factor, 4.0% vs 20.0% [$P<.0001$]), paresthesias ($P<.001$), and infections ($P=.0025$). However, these patients must be followed over the long-term, to confirm this superiority over time. Further, because bendamustine (like cyclophosphamide) is an alkylating agent and therefore damages DNA, it does have the potential to result in the development of secondary malignancies over time.[2] Reports suggest that up to 4% of patients treated with bendamustine have developed secondary malignancies, including myelodysplastic syndrome, myeloproliferative disorders, chronic myelomonocytic leukemia, colorectal cancer, and lung cancer.[3-5]

The FCR regimen is particularly difficult to administer in elderly patients, who make up the primary CLL population. In a prospective, multicentered, phase III trial that compared FCR with FC in treatment-naïve CLL patients (median age, 61 years), approximately one-quarter (26%) of the patients in the FCR arm were unable to complete the full 6 courses of therapy.[6] However, this rate was still lower than the 34% of patients in the FC arm who were unable to complete all 6 treatment cycles.

Because fludarabine is primarily excreted through the kidneys, its dosage must be reduced by 20–50% in patients with mild or moderate to severe renal impairment.[7] In contrast, full doses of bendamustine can be administered (with caution) to patients even with mild or moderate renal impairment.

Based on early data, it appears that bendamustine also has an improved toxicity profile when compared with fludarabine-based regimens in CLL. For example, in a prospective phase II trial, frontline treatment with bendamustine plus rituximab in CLL patients was associated with lower rates of myelosuppression (14.6% leukopenia, 6.5% neutropenia, 6.1% thrombocytopenia, and 4.9% anemia) than what was reported in a randomized phase III trial with frontline FCR (24% leukopenia, 34% neutropenia, 7% thrombocytopenia, and 5% anemia).[6,8]

In a long-term follow-up of the US Intergroup Study E2997 phase III trial, presented by Smith and colleagues at the 2010 American Society of Hematology (ASH) meeting, an increase in the incidence of secondary malignancies was associated with the addition of cyclophosphamide to fludarabine.[9] The E2997 study randomized 278 patients with newly diagnosed CLL to treatment with fludarabine alone or FC, both administered in 6 cycles. At a median follow-up of 6.4 years, 4.7% (n=13) of all patients were observed to have a secondary malignancy, reported as a therapy-related myeloid neoplasm. However, after using cumulative incidence methodology and adjusting for a competing risk of death, the difference between the fludarabine-alone and FC arms did not reach statistical significance (4.6% vs 8.2%; $P=.18$). A majority (77%) of the patients who had developed a therapy-related myeloid neoplasm received all 6 treatment cycles. Interestingly, chromosomal abnormalities were apparent in 10 of the 12 patients whose cytogenetic analysis was available, suggesting that fludarabine-induced DNA damage may have led to the secondary malignancy.

Unfortunately, many of the US-based trials evaluating bendamustine did not include long-term follow-up as part of the study design. Although phase I and II trials are specifically designed to assess the toxicity of a particular therapy, they usually enroll only a limited number of patients, and many toxicities may not become apparent in small populations. Phase III trials include many more patients and thus can offer better insight into the toxicity profile of a particular therapy. However, it is often not until the agent gains widespread use among thousands of patients in the community that new and unexpected adverse events may emerge. For example, although published clinical trial data do not suggest that neurotoxicity is associated with bendamustine use, real-world clinical experience now suggests the potential for severe, life-threatening neurologic toxicity in a bendamustine-treated patient with no other attributable cause. Therefore, it is necessary to pay close attention to not only data reported from clinical trials but also data from those reporting structures that are available to community physicians. These reporting structures provide physicians with an ability to present case-by-case experiences with potential drug-related adverse events that have no other clear etiology. As multiple similar incidences are reported, patterns may begin to emerge that will help to establish a causal relationship between the therapy and the adverse event.

Clinical studies such as the German CLL 10 trial and the German StiL trial will offer an important opportunity to not only assess the short-term adverse events of these drugs, but their long-term toxicity profiles as well.[10,11] It is critical that these patients be followed over the long-term, especially as high rates of durable responses in both CLL and indolent NHL (eg, follicular lymphoma) have caused these malignancies to be treated more as chronic diseases. CLL is more of a disease of elderly patients, whereas indolent NHL, such as follicular lymphoma, can affect younger patients who have a life expectancy of multiple decades. Treatments in indolent NHL thus require particular consideration of long-term effects.

It is critical to assess what long-term complications may result from the use of these drugs in NHL and CLL patients. However, it is often not clear which agent is associated with a long-term effect, especially among patients who undergo a complicated succession of therapies. For example, a typical patient may have received frontline therapy with R-CHOP, followed by a bendamustine-based treatment, and subsequent radioimmunotherapy. If such a patient develops a secondary myelodysplasia, it is not possible to determine which of these therapies (or combination of therapies) was the causative agent. Clinicians must remain alert for problems that might occur in the long-term.

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Discussion: How to Improve Reporting of Adverse Events in Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

Kanti R. Rai, MD Improvement in the reporting of adverse events in CLL and NHL patients requires a continual emphasis on this issue from clinical investigators and practitioners. Many times, the reporting of adverse events is almost totally neglected.

This is often a reflection of the almost fractured way in which our clinical practice is performed today. A patient may be seen in a physician's clinic, at which time the physician may order initiation of a particular treatment. The patient then goes either to the physician's chemotherapy unit, where experienced, trained oncology nurses take over, or to a hospital bed outpatient chemotherapy unit, again, where very experienced nurses take over. Following the treatment, the patient goes home. The patient may return for a laboratory check, to ensure that neutrophil, platelet, and hemoglobin levels are all adequate, but it is not routine for the patient to regularly return to see the physician.

A great deal of emphasis is placed on physical examination to monitor response. An NHL patient should be examined to identify a reduction in lymph node size, and a CLL patient should be examined to identify a reduction in total lymphocyte levels as well as a reduction in the size of the spleen or lymph nodes. In contrast, there are very few opportunities in which a clinician repeatedly sits down with the patient and asks simple questions such as, "How do you feel?", "How have you been eating?", "Has your weight been fluctuating?", and "Are you experiencing any other symptoms that we should know about?" Even when the patient volunteers this information, it is often not adequately recorded in his or her chart. I believe that to truly improve adverse event reporting in these malignancies, there needs to be a change in the habits of clinicians, with a focus on paying attention to these seemingly mundane issues.

Bruce D. Cheson, MD I completely agree that it is up to the physician and the physician's team—particularly the nurse—to help collect these data. I also think that it is incumbent on the pharmaceutical companies to provide some type of structured database to more formally collect these events. These companies already have representatives out in the field, who can communicate with the nursing staff to find out if any unexpected toxicities have been reported. These can then be reported back to the company, and made known to study investigators.

Some pharmaceutical companies already have in place structured reporting mechanisms. However, these seem to be underutilized by the US Food and Drug Administration. I believe it is in the best interest of our patients for all involved—from the physician and nurse to the pharmaceutical company—to capture these data both for the benefit of the patient and the education of the clinician. As we are doing this, we need to consider that any adverse events reported may or may not actually be related to the therapeutic agent, so as not to condemn a drug too quickly for an unrelated toxicity.

Jonathan W. Friedberg, MD I particularly agree that one must be careful to either not over-report or under-report any potential drug-related toxicities. However, I think that in the era of targeted therapies, it is even more critical for physicians to report what may be perceived as uncommon or rare toxicities. For example, leukocytosis and liver toxicity are beginning to emerge as rarely experienced adverse events of some targeted agents; however, these only became apparent with vigilant reporting by investigators. The only way to better understand these types of toxicities is with enhanced reporting by physicians once these drugs have been approved and become more widely available. Even after new drug approval, constant dialogue among sponsors, investigators, and patients regarding these toxicities is critical.

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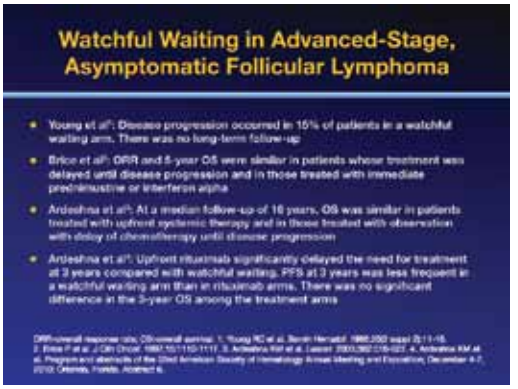

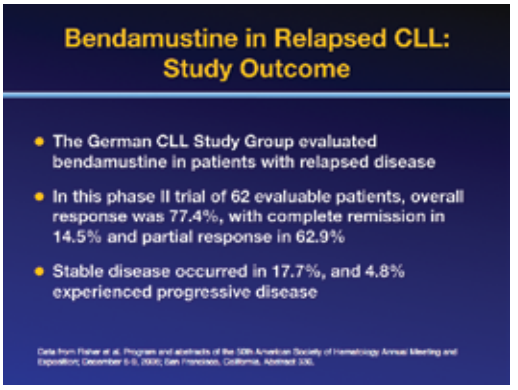

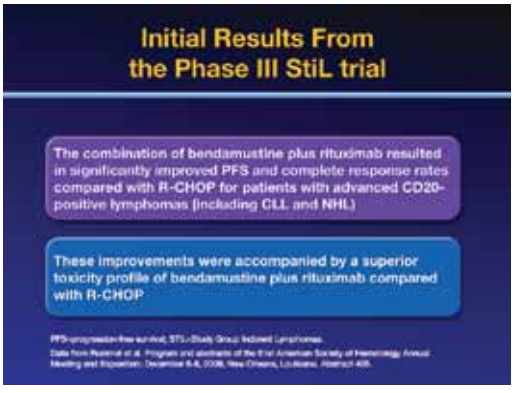

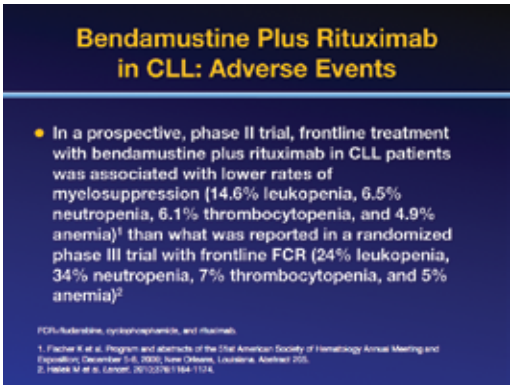

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