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Recent Advances in the Management of Hematologic Malignancies

Highlights from the 51st Annual Meeting
of the American Society of Hematology
New Orleans, Louisiana
December 5–8, 2009

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Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, nurses, hematologists, and other health care professionals involved in the management of patients with hematologic malignancies.

Statement of Need/Program Overview: Current research efforts in hematologic malignancies—including lymphoma, leukemia, myeloma, and myelodysplastic syndromes—are focusing on new agents, new potential roles for already approved therapies, biomarkers that enable identification of the patient subgroups most likely to respond to a particular therapy, cytogenetics and other prognostic factors to help predict outcome and guide treatment decisions, and the exploration of new modalities, such as radiolabeled antibodies. The annual meeting of the American Society of Hematology (ASH) is one of the premier outlets for the release of new clinical data on these various efforts, and as such it is an extremely important event for oncologists. With the multitude of presentations made at this meeting, there is a need for supplementary materials that distill information, cull the most important breakthrough findings, and summarize data for subsequent integration into clinical care.

Educational Objectives

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

- Integrate prognostic factors into treatment decisions for patients with hematologic malignancies, including lymphoma, leukemia, myelodysplastic syndromes, and multiple myeloma
- Identify factors influencing the choice of treatment for patients with myelodysplastic syndromes and leukemia
- Describe the most recent data on treatment options for both newly diagnosed and recurrent multiple myeloma

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Recent Advances in the Management of Hematologic Malignancies

Highlights from the 51st Annual Meeting
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Studies presented at the 2009 meeting of the American Society of Hematology (ASH) offered important new data that may change clinical practice. The meeting provided information in areas including chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS), follicular lymphoma, diffuse large B-cell non-Hodgkin lymphoma (NHL), mantle cell lymphoma, and multiple myeloma.

Chronic Lymphocytic Leukemia

The optimal treatment for CLL has been the subject of debate for many years. Fludarabine was the standard of care for decades until the advent of the fludarabine-rituximab regimen from Byrd and colleagues and the fludarabine-cyclophosphamide-rituximab (FCR) regimen developed by Keating and coworkers.[1,2] At the 2008 ASH meeting, Hallek and associates from the German CLL Study Group (GCLLSG) presented preliminary data showing that FCR prolonged progression-free survival (PFS) in patients with CLL who had not received any prior therapy.[3] At the 2009 ASH meeting, these investigators updated those results and demonstrated an apparent survival advantage for FCR when compared with fludarabine-cyclophosphamide (FC).[4] In this study, physically fit patients with active, previously untreated CLL were randomized to receive either FC (n=409) or FCR (n=408). Both treatment arms were well-balanced with respect to sex, age, stage, genomic aberrations, and immunoglobulin variable region heavy chain (IgV_H) gene status. Median age was 61 years (range, 30–81 years), and 25.7% of patients were female. Binet classification was 4.9%, 64.1%, and 31% for stages A, B, and C, respectively. Dr. Hallek, on behalf of the GCLLSG, presented the most recent data from the intent-to-treat analysis that showed not only higher response rates and longer PFS with FCR versus FC, but also a significantly improved overall survival (Figure 1). The overall response rate (ORR) for patients treated with FCR was 95.1% versus 88.4% for those receiving FC (P<.01). Median PFS was 51.8 months with FCR versus 32.8 months with FC (P<.001). The overall survival rate at 3 years was 87.2% with FCR versus 82.5% with FC (P=.012). Cox regression analyses demonstrated that FCR treatment predicts for a better PFS (hazard ratio [HR], 0.479; P<.001) and overall survival (HR, 0.581; P=.009) than FC. Consistent with the preliminary reports from this trial, there were more hematologic adverse events associated with FCR

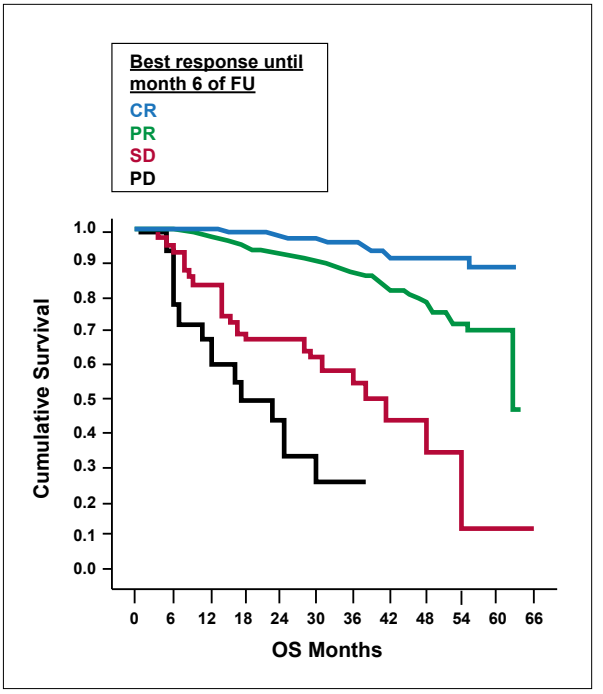

Figure 1. OS and type of response in previously untreated patients with advanced chronic lymphocytic leukemia.

CR=complete response; FU=follow-up; OS=overall survival; PR=partial response; PD=progressive disease; SD=stable disease.

Data from Hallek M et al.[4]

treatment than with FC; grade 3/4 neutropenia occurred in 33.7% and 21.0% of patients, respectively (P<.0001). However, the reported grade 3/4 infection rate was not significantly different (25.5% with FCR and 21.5% with FC; P=.18). Treatment-related mortality rates were similar for both regimens. Dr. Hallek's presentation also included a multivariate analysis on the study data to evaluate factors that might predict outcome in this patient group. FCR was particularly effective in some genetically defined subgroups—del(11q), del(13q), and trisomy 12—but not effective in the prevention of early relapse and death of patients with a del(17p). Conversely, the presence of del(17p), FC (vs FCR) therapy, and an elevated serum $ß_2$ microglobulin level were the strongest predictors for treatment failure. Both these observations warrant further evaluation, but the authors concluded that they might herald the development of patient-specific therapy for CLL. Overall, this paper is particularly significant because it represents the first data from a randomized trial that support the current use of FCR in CLL.

Bendamustine, an alkylating agent/antimetabolite hybrid, has been showing considerable promise in several hematologic malignancies. Bendamustine was approved by the US Food and Drug Administration (FDA) for use in CLL on the basis of a randomized, phase III study in previously untreated CLL patients,[5] in which it was associated with a higher complete response (CR) and ORR and a longer PFS compared with chlorambucil. The GCLLSG previously undertook a preliminary study in 48 relapsed and refractory patients with mantle cell or low-grade lymphoma evaluating bendamustine in combination with rituximab and reported an ORR of 77% with 15% CRs, data which supported further evaluation of this combination in other malignancies.[6] At ASH, Fischer and colleagues from the GCLLSG presented data from a multicenter phase II trial designed to assess the efficacy and toxicity of bendamustine in combination with rituximab in 117 patients with previously untreated CLL.[7] Bendamustine and rituximab were administered every 28 days for up to 6 treatment cycles: cycle 1 consisted of bendamustine 90 mg/m^2 on days 1–2 plus rituximab 375 mg/m^2 on day 0, and cycles 2–6 consisted of bendamustine 90 mg/m^2 on days 1–2 plus rituximab 500 mg/m^2 on day 0. The primary endpoint was ORR, and the secondary endpoints were response duration, event-free survival, minimal residual disease in peripheral blood and bone marrow, CR, and toxicity. The median follow-up time was 15.4 months, and the median PFS had not yet been reached. The mean number of treatment cycles was 5 (583 total treatment cycles). The ORR was 90.9%, with 32.7% clinical CRs. A further analysis of response with respect to cytogenetics demonstrated an ORR of 90.5% in 21 patients with the 11q deletion, 89.5% in 19 patients with chromosome 12 trisomy, and 88.9% in patients with unmutated IgV_H. The most common adverse events of grade 3/4 or higher during treatment included myelosuppression with infection and leucopenia, which occurred during 14.6% of treatment cycles (N=583), and neutropenia, thrombocytopenia, anemia, and infection, each of which occurred during 5.0–6.0% of treatment cycles. Treatment-related mortality occurred in 3.4% of patients. Minimal residual disease was assessed by 4-color flow cytometry after completion of treatment; 58% of patients achieved minimal residual disease negativity in blood, and 28% achieved minimal residual disease negativity in bone marrow. Dr. Fischer concluded that this study demonstrates the potential place for bendamustine in the treatment of CLL; in combination with rituximab, it is effective and safe as first-line treatment. Based on these encouraging phase II data, the GCLLSG is presently investigating the efficacy of bendamustine and rituximab in comparison with fludarabine-based immunochemotherapy (FCR) in the first-line treatment of CLL within a randomized phase III trial (CLL10 protocol).

The advent of rituximab heralded a new era in the treatment of CLL and led to the development of novel human and humanized anti-CD20 antibodies. Ofatumumab (huMax-CD20) is a human anti-CD20 that has recently been approved by the FDA for patients with CLL who are refractory to fludarabine and alemtuzumab. The approval was based on a study in 59 patients refractory to both fludarabine and alemtuzumab, in which a response rate of 58% was reported.[8] Ofatumumab is now being investigated in a more upfront setting. Dr. Wierda and colleagues reported on a study in which 61 previously untreated patients with CLL received standard fludarabine plus cyclophosphamide in combination with 300 mg for the first dose followed by either 500 mg (A) or 1,000 mg (B) of ofatumumab on day 1 for 6 further cycles.[9] The ORRs were comparable for both groups (77% group A, 73% group B) with 32% and 50% CRs, respectively. PFS was not reported because the follow-up duration was too short at the time of the meeting. Dr. Wierda reported that there were no grade 3/4 infusion reactions with ofatumumab, and grade 3/4 infections were reported in only 11 patients in the period during treatment and for up to 30 days thereafter. The response data do not compare favorably to published results with fludarabine-rituximab or FCR. The authors suggested that this discrepancy is explained by the fact that the patients in this trial are in a higher risk category than those in prior studies, especially with respect to $ß_2$ microglobulin levels.

Combination therapy is the standard of care for the treatment of relapsed and refractory CLL. Since fludarabine and alemtuzumab both have demonstrated single-

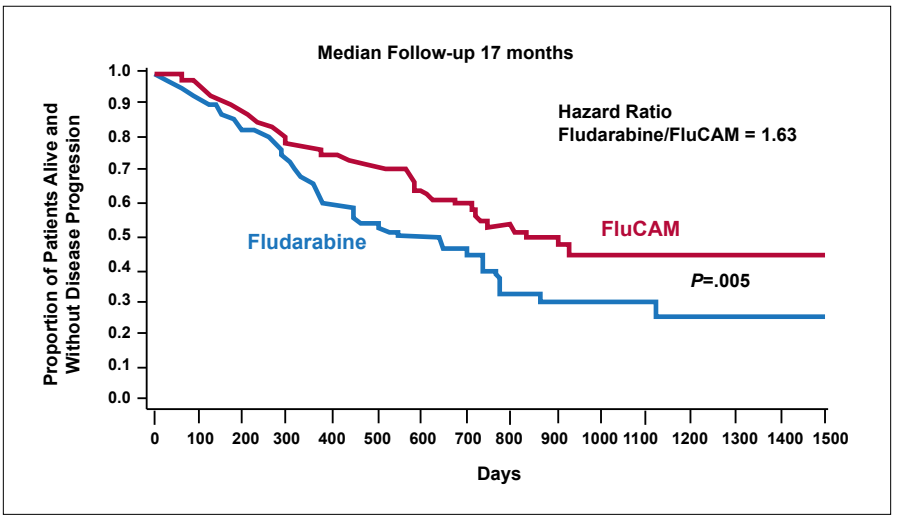

Figure 2. Response to alemtuzumab plus fludarabine compared with fludarabine monotherapy in relapsed/refractory chronic lymphocytic leukemia patients (median follow-up 17 months).

FluCAM=fludarabine, phosphate, and alemtuzumab.

Data from Engert A et al.[10]

agent activity in this disease, there has been interest in combining these agents. Alemtuzumab is an anti-CD52 monoclonal antibody with a reported response rate of 33% when used as a single agent in CLL patients who are refractory to fludarabine and alkylating agents. At ASH, Dr. Engert presented a study designed to compare fludarabine with fludarabine plus alemtuzumab for the second-line treatment of patients with relapsed or refractory CLL.[10] Patients (N=335) were randomized to receive fludarabine plus alemtuzumab or fludarabine alone. The primary endpoint was PFS, and the secondary endpoints included ORR, CR, overall survival, minimal residual disease, quality of life, and safety. The combination of fludarabine and alemtuzumab was superior to fludarabine alone; PFS was 29.6 months versus 20.7 months, respectively (*P*=.005). However, this benefit was limited to patients with Rai stage III–IV disease. The ORR was significantly higher (*P*<.001), as was the CR (*P*=.002), with fludarabine plus alemtuzumab compared with fludarabine monotherapy (Figure 2). The combination of fludarabine and alemtuzumab was well tolerated; there was no increase in overall deaths or grade 3/4 infectious complications compared with fludarabine alone. Cytomegalovirus infection was observed only in the combination arm of the study. This presentation represented a planned interim analysis of the study; final data are expected later in 2010.

Lenalidomide monotherapy has been demonstrated to be effective in relapsed and refractory CLL, with a reported ORR of 32–47%. Myelosuppression is the most common adverse effect; however, the therapy is associated with tumor-flare reaction and tumor lysis syndrome.[11] Rituximab also has single-agent activity and a favorable toxicity profile in CLL and synergistic activity when combined with other agents. Since these 2 agents have different mechanisms of action with different toxicities, when used in combination, they might exhibit synergistic activity. Dr. Ferrajoli and colleagues reported on a phase II study designed to evaluate the combination of lenalidomide and rituximab in patients with relapsed CLL.[12] All patients received rituximab (375 mg/m^2) intravenously on days 1, 8, 15, and 22 of cycle 1, and then once every 4 weeks during cycles 3–12. Lenalidomide was given orally at a dose of 10 mg/day starting on day 9 of cycle 1 and continued daily for 12 cycles. Each cycle consisted of 28 days of treatment. During the first 2 weeks of therapy, allopurinol at a dose of 300 mg/day was prescribed as prophylaxis for tumor lysis. Study endpoints included response and safety, particularly non-hematologic toxicities. In addition, the effect of the therapy on circulating T cells was evaluated. Sixty patients were enrolled in the study, and 44 were evaluable (median age, 63 years; range, 44–83 years). This lenalidomide and rituximab combination was active in patients with relapsed CLL (Table 1). The ORR after 12 cycles was 64%, which was higher and occurred more rapidly than with lenalidomide monotherapy, but with exclusively partial remissions. The median overall survival had not been reached; the 12-month overall survival was 95%, and median time to treatment failure was 12 months. The most common grade 3/4 hematologic adverse events were neutropenia (119/379 courses; 31%), thrombocytopenia (17/379 courses; 5%) and anemia (2/379 courses; <1%). Importantly, there was no increase in toxicity compared with previous studies of single-agent lenalidomide. Of interest was that rituximab appeared to reduce the frequency of the lenalidomide-associated tumor flare reaction. Dr. Ferrajoli and colleagues also evaluated the effect of the combination therapy on the distribution of circulating B-, T-, and NK-cell subsets. There were significant decreases in the percentage of $CD19^+CD20^+$

Table 1. Response to the Combination of Lenalidomide and Rituximab in Patients With Relapsed CLL

Patient Characteristics		Total N	nPR N (%)	PR N (%)	OR N (%)
Age	0–65 yr	23	4 (17)	11 (48)	15 (65)
	>65 yr	14	2 (14)	8 (57)	10 (71)
Rai stage	0–II	22	5 (23)	11 (50)	16 (73)
	III–IV	15	1 (7)	8 (53)	9 (60)
Number of prior treatments	1–2	22	4 (18)	11 (50)	15 (68)
	3–9	15	2 (13)	8 (53)	10 (67)
FISH	Del (17)p	9	3 (33)	3 (33)	6 (67)
	Del (11)q	10	1 (10)	6 (60)	7 (70)
	Trisomy 12	6	0 (0)	4 (67)	4 (67)
	Del 13	5	0 (0)	4 (80)	4 (80)
	Negative	7	2 (29)	2 (29)	4 (57)
IgV_H status	Mutated	10	0 (0)	6 (60)	6 (60)
	Unmutated	26	6 (23)	12 (46)	18 (69)
ß$_2$ microglobulin	0–4 mg/L	20	3 (15)	11 (55)	14 (70)
	>4 mg/L	16	3 (19)	8 (50)	11 (69)
All patients		37	6 (16)	19 (51)	25 (68)

Data from Ferrajoli A et al.[12]

CLL=chronic lymphocytic leukemia; FISH=fluorescent in situ hybridization; IgV_H=immunoglobulin variable region heavy chain; nPR=nodular partial response; OR=overall response; PR=partial response.

B cells along with significant increases in the percentages of $CD4^+$ T, $CD8^+$ T, $CD4^+CD25^{hi}CD127^-$ regulatory T cells and $CD3^-CD16^+CD56^+$ NK cells after 3 cycles of therapy (paired sample t test). This interesting combination merits further study.

Chronic Myelogenous Leukemia

Imatinib is currently the standard of care for patients with CML. In patients who achieve a durable response, overall survival is excellent, with disease progression most common during the initial 3 years of therapy. Patients who progress typically have a poor overall survival.[13] Nilotinib is a relatively new agent that acts as a selective inhibitor of *BCR-ABL* kinase. It has demonstrated activity in patients with CML who have progressed after imatinib or were intolerant of prior imatinib, and it has also been effective as initial treatment for these patients.[14] Dr. Saglio and colleagues presented a late-breaking abstract pertaining to the results from an international phase III trial designed to evaluate efficacy and safety of nilotinib 300 mg or 400 mg twice daily versus imatinib 400 mg once daily in patients newly diagnosed with chronic-phase Ph-positive CML.[15] Patients (N=846) were randomized to 1 of the 3 treatments groups on a 1:1:1 basis and followed for up to 5 years. All of the patients were in chronic-phase Ph-positive CML within 6 months of diagnosis, were 18 years or older, and had an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2. Patients in the 3 treatment groups were similar with respect to age (median ages, 47 years [range, 18–85 years), 47 years [range, 18–81 years], and 46 years [range, 18–80]) and time from diagnosis (<31 days). Sokal risk (%) was similar for each group (33% low, 36% intermediate, and 28% high for all 3 treatment groups). The primary endpoints of the study were major molecular response as evidenced by at least a 3-log reduction in the *BCR-ABL* transcript and complete cytogenetic response (CCyR) demonstrated as no Ph-positive metaphases out of 20 or more. Secondary endpoints were the time to reach, and durability, of major molecular response and CCyR; event-free survival; PFS; time to accelerated phase/blast crisis; and overall survival with a 5-year follow-up. Twelve months after initiation of treatment, there were significantly higher rates of major molecular response and CCyR with nilotinib versus imatinib in both the 300-mg twice daily and

Table 2. Phase III ENEST Study Comparing Nilotinib and Imatinib Safety and Efficacy in Patients With Newly Diagnosed CML

Treatment	Subjects Achieving 1-Yr MMR by 3-Mo Intervals, %				*P* Value vs Imatinib at Month 12
	Mo 3	Mo 6	Mo 9	Mo 12	
Nilotinib 300 mg BID	9	33	43	44	<.0001
Nilotinib 400 mg BID	5	30	38	43	<.0001
Imatinib 400 mg QD	1	12	18	22	

Treatment Arm	Subjects Achieving 1-Yr MMR by Sokal Score, %		
	Low	Intermediate	High
Nilotinib 300 mg BID	41	51	41
Nilotinib 400 mg BID	53	40	32
Imatinib 400 mg QD	26	23	17

Treatment Arm	Subjects Achieving CCyR, %		*P* Value vs Imatinib
	6 Mos	12 Mos	
Nilotinib 300 mg BID	67	80	<.0001
Nilotinib 400 mg BID	63	78	<.0005
Imatinib 400 mg QD	45	65	

Data from Saglio G et al.[15]

CCyR=complete cytogenetic response; CML=chronic myeloid leukemia; ENEST=Evaluating Nilotinib Efficacy and Safety in Clinical Trials in Newly Diagnosed Patients; MMR=major molecular responses.

400-mg twice daily arms, and higher rates of major molecular response at month 12 with nilotinib versus imatinib in both the 300-mg twice-daily and 400-mg twice-daily arms across all Sokal risk groups (Table 2). There were also significantly higher rates of CCyR at month 12 with nilotinib versus imatinib in both comparative treatment arms, and the best molecular response at any time was observed in the nilotinib treatment groups. The disease progression rate for patients receiving nilotinib 300 mg twice daily was 0.7% (*P*=.0095 vs imatinib), and for those receiving nilotinib twice daily, the rate was 0.4% (*P*=.0037 vs imatinib). The rate for imatinib was 3.9%. None of the patients who achieved major molecular response showed disease progression, but 3 patients who achieved CCyR (all on imatinib) did. Additional follow-up is needed to determine if these results should alter the treatment of these patients.

Imatinib revolutionized the treatment of CML, but not all patients respond to tyrosine kinase inhibition. Omacetaxine, formerly known as *homoharringtonine*—a drug that was tested in CML in the 1980s but then dropped with the advent of the tyrosine kinase inhibitors—is now seeing a potential new application in patients with the T315I mutation and patients who have failed to respond to tyrosine kinase inhibition. Dr. Cortes-Franco presented a paper describing a single-arm, multicenter phase II/III study that enrolled 81 patients who had the T3151 mutation and had previously failed imatinib treatment.[16] Of these patients, the majority (n=49) had chronic-phase disease, and the remainder either had accelerated-phase disease (n=17) or blast-phase disease (n=15). The drug was administered subcutaneously in 2 phases, induction and maintenance. Induction therapy was omacetaxine 1.25 mg/m^2 twice daily for 14 days every 28 days and, following a complete hematologic response, patients received maintenance omacetaxine 1.25 mg/m^2 twice daily for 7 days every 28 days. Overall, the therapy was very well tolerated, with myelosuppression, particularly thrombocytopenia, the most common type of grade 3/4 adverse event (71% among patients with chronic-phase disease).

In the chronic-phase disease cohort, the rate of complete hematologic response was 86%, and the rate of major cytogenetic response was 27% (9 complete, 4 partial). In the accelerated-stage setting (n=17), 1 patient achieved a CCyR. Cortes-Franco and colleagues also reported a separate analysis from this study investigating the activity of omacetaxine in imatinib-resistant patients who have the

BCR-ABL T315I mutation. In this analysis, they showed that the T31I clone decreased in 57% of CML patients.[17] These results are remarkable because this study shows the best response to date in this patient population and may lead to a place for omacetaxine in combination therapy in the future.

Jabbour and colleagues from MD Anderson Cancer Center presented an intriguing paper that investigated the baseline factors predictive of cytogenetic response in CML patients who received dasatinib after prior failure of imatinib.[18] Data were collected from 3 clinical trials of dasatinib in patients with chronic-phase CML: SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials of Dasatinib–C (START-C) (n=387), SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials of Dasatinib–R (START-R) (n=101), and CA180-034 (n=662). All patients in these studies who had received at least 1 dose of dasatinib were included in the current analysis, except those with T315I mutations. The dasatinib dose range was 50–70 mg twice daily, 100 mg once daily, or 140 mg once daily, and all patients had experienced resistance to dasatinib. Univariate and multivariate logistic regression analyses were undertaken to evaluate patient baseline and treatment characteristics as predictive factors for cytogenetic response. Independent favorable prognostic factors were identified for both major cytogenetic response and CCyR, and others were identified that predicted major or complete cytogenetic response but not both (Table 3). Although these data are encouraging, further analysis is needed to determine whether these or other factors are predictive for survival, ideally in a prospective clinical trial.

Acute Myelogenous Leukemia

AML patients aged 60 years or older typically have a poor prognosis, and newer agents with limited toxicity are needed. Lenalidomide has considerable activity in MDS, suggesting that it may have a place in the treatment of AML as well. Dr. Vij and colleagues presented data from a phase II study evaluating lenalidomide as initial treatment for AML in patients older than 60 years.[19] In this study, lenalidomide was given as 50 mg/day for 28 days for 2 cycles, followed by low-dose lenalidomide (10 mg/day) for a further 12 cycles. Thirty-three patients, median age 71 years (range, 60–88 years), were enrolled in the study. Seventy percent had de novo AML, 21% had transformed disease, and 9% had AML secondary to prior therapy. CR/incomplete response was achieved in 10 out of 33 (30%) patients in the intent-to-treat population (7 achieved CR, and 3 achieved incomplete response). All patients who achieved CR had received at least 2 cycles of therapy, and the overall CR rate among 22 patients who had received at least 2 cycles was 45%. Overall, the therapy was well-tolerated; the most common grade 3/4 toxicities in all patients (responders and non-responders) were thrombocytopenia, anemia, and leucopenia. Disease progression was the primary reason for discontinuing treatment (n=20, 60%). Only 8 (24%) patients discontinued therapy due to intolerance/toxicity, and 1 patient was reported to have completed more than 369 days of treatment.

Sapacitabine is a novel 2'-deoxycytidine nucleoside analogue that causes irreparable single-strand breaks in DNA, leading to G2 cell cycle arrest. This oral agent has activity in relapsed/refractory AML and may present a treatment option for older patients with AML who are less likely than younger patients to achieve a response, have higher rates of adverse effects to medication, and typically have a higher probability of relapse. Kantarjian and colleagues presented results from a study designed to assess safety and efficacy of 3 different sapacitabine doses in elderly patients with untreated AML or AML in first relapse.[20] Patients (N=60) were randomized 1:1:1 to receive either 200 mg twice daily for 7 days every 3–4 weeks (Arm A), 300 mg twice daily for 7 days every 3–4 weeks (Arm B), or 400 mg twice daily for 3 days per week for 2 weeks every 3–4 weeks (Arm C). There was no limit on the maximum number of cycles. The primary efficacy endpoint was 1-year survival. Secondary efficacy endpoints included response rates, duration of response, transfusion requirements, and duration of hospitalization. Patients received a median of 3 sapacitabine cycles. Dose reductions were more common in the sapacitabine 300 mg and 400 mg arms. Dr. Kantarjian reported that 1-year survival and response rates were highest for patients in groups A and C. A subgroup analysis of 1-year survival data indicates that the 200 mg twice daily dose of sapacitabine administered for 7 days is more effective for AML patients with an antecedent hematologic disorder, whereas the 400 mg twice daily dose given for 3 days in 2 consecutive weeks is more effective for de novo AML. These 2 doses are undergoing further clinical evaluation. Sapacitabine is well-tolerated; the most common adverse events included cytopenias, fatigue, gastrointestinal symptoms, pyrexia, and edema, most instances of which were mild to moderate.

Myelodysplastic Syndromes

The effectiveness of hypomethylating agents in patients with higher-risk MDS is well established, but the safety and efficacy of these agents in patients with lower-risk MDS is not well defined. Decitabine is a potent hypomethylating agent with activity in higher-risk MDS at low doses.[21] Subcutaneous low-intensity decitabine is safe and active in patients with low- or intermediate-1–risk MDS, and once-daily dosing is superior to once-weekly dosing.

Table 3. Independent Prognostic Factors With Predictive Benefit for Outcome in CP-CML Patients Treated With Dasatinib: An Analysis of 3 Clinical Trials

Factor	Odds Ratio (95% CI) of Responding	
	MCyR (range; *P* value)	CCyR (range; *P* value)
Age	1.019 (1.006–1.003; *P*=.006)	1.015 (1.002–1.029; *P*=.021)
% Ph+ cells	1.045 (1.030–1.060; *P*<.0001)	1.034 (1.025–1.044; *P*<.0001)
Time from CML diagnosis to initial dasatinib dose	1.129 (1.062–1.200; *P*=.0001)	1.130 (1.060–1.205; *P*=.0002)
Duration of imatinib therapy	0.986 (0.973–0.999; *P*=.031)	0.982 (0.970–0.995; *P*=.006)
Prior CyR with imatinib	0.399 (0.274–0.580; *P*>.0001)	0.432 (0.298–0.625; *P*<.0001)
Imatinib resistance	3.413 (1.898–6.136; *P*<.0001)	4.530 (2.647–7.751; *P*<.0001)
Prior SCT	2.906 (1.483–5.694; *P*=.02)	2.304 (1.158–4.584; *P*=.017)
Splenomegaly	2.406 (1.201–4.820; *P*=.013)	2.081 (1.019–4.251; *P*=.044)
Prior interferon	1.398 (0.933–2.094; *P*=.104) Not predictive	1.842 (1.244–2.727; *P*=.002)
Presence of blasts in PB	0.986 (0.530–1.834; *P*=.964) Not predictive	1.842 (1.244–2.727; *P*=.002)

Data from Jabbour E et al.[18]

CCyR=complete cytogenetic response; CI=confidence interval; CP-CML=chronic phase chronic myeloid leukemia; CyR=cytogenetic response; MCyR=major cytogenetic response; PB=peripheral blood; Ph+=Philadelphia chromosome–positive; SCT=stem cell transplantation.

However, a controlled evaluation of the daily decitabine regimen in patients with low/intermediate-1–risk MDS was needed to support dosing recommendations in this patient population. Garcia-Manero and associates reported promising interim data from a randomized phase II study of very low dose subcutaneous decitabine given daily or weekly times three in patients with lower risk MDS.[22] Fifty-four patients were randomized by Bayesian methodology to receive decitabine 20 mg/m^2 subcutaneously either daily for 3 days or weekly times 3 every 4 weeks. Baseline characteristics were skewed between the groups due to Bayesian randomization. The primary endpoint of the study was a comparison of activity, safety, and tolerability between the 2 decitabine dosing schedules. Secondary study endpoints included hematologic improvement, transfusion requirement, cytogenetic response, and overall survival. Patients received a median of 5 cycles of therapy (range, 1–11+).

Dr. Garcia-Manero reported higher rates of response with daily decitabine compared with the weekly regimen (Table 4).[23] The median time to initial response was 92.9 days (range, 1–365 days) with daily dosing versus 84.6 days (range, 1–337 days) with weekly dosing, and the duration of responses was markedly longer for patients who received daily versus weekly decitabine; the median duration of response for the daily regimen for patients who experienced a CR was 142.0 days (range, 112–282 days; n=3) and 115.5 days (range, 29–202 days) for patients achieving a partial response. The rates of transfusion independence were comparable between arms, as were changes from baseline in hemoglobin, neutrophil count,

Table 4. Results From a Randomized Phase II Study of Very Low Dose SQ Decitabine Administered Daily or Weekly Times 3 in Patients With Lower Risk MDS

Outcome, %	Daily Decitabine (n=32)	Weekly Decitabine (n=22)
Overall improvement*	21.9	9.1
CR	9.4	0
Marrow CR	0	4.5
PR	6.3	4.5
Hematologic improvement	6.3	0
SD	46.9	72.7

*Responses scored according to the International Working Group 2006 criteria.

Data from Garcia-Manero G et al.[22]

CR=complete response; MDS=myelodysplastic syndromes; PR=partial response; SD=stable disease; SQ=subcutaneous.

and platelet count across all decitabine dosing cycles. The median duration of survival had yet to be reached at a median follow-up of 4.5 months. PFS was more than 451 days for the daily regimen (median not reached) versus 358 days for the weekly regimen (P=.3132). There were higher rates of treatment-related hematologic adverse events with the weekly versus daily decitabine, with low rates of non-hematologic toxicity in both arms. A subanalysis was undertaken in 8 patients to evaluate global DNA hypomethylation using bisulfite repetitive-element polymerase chain reaction and pyrosequencing. Data were too limited to draw any conclusions at this point. However, Dr. Garcia-Manero reported that responses were observed with daily decitabine even in patient subgroups with poor prognosis and short median survival according to previously defined prognostic categories.[23]

Azacitidine, another hypomethylating agent, extends overall survival in high-risk or International Prognostic Scoring System (IPSS) intermediate-2–risk MDS patients[24] and is currently approved in the United States for use as a subcutaneous injection of 75 mg/m^2/day for 7 consecutive days every 28 days or as an intravenous injection following the same dosing schedule.[25] There has never been a direct comparison of differences in overall survival associated with the 2 routes of administration of azacitidine in a controlled setting, and consequently the AVIDA registry was established to evaluate azacitidine dosing patterns and efficacy in the community oncology setting. Sekeres and colleagues presented an interim analysis of this prospective, longitudinal, multicenter data registry of community-based US patients with MDS treated with azacitidine.[26] Electronic data were collected for the AVIDA registry at baseline and then quarterly after treatment initiation. Information collected included age, body mass index, bone marrow blast percentage, IPSS cytogenetic abnormality outcome category, disease duration, dosing schedule, hemoglobin, IPSS risk, platelets, prognosis, race, recent infection, and sex. Patients were categorized according to administration method (≥51% doses) and most common dosing schedule (number of days), IPSS MDS subtype risk level, and treatment period. Study endpoints included the average azacitidine dose maintained/treatment cycle, dose cycle delay lasting more than 28 days (yes/no), hematologic improvement as per International Working Group 2006 criteria,[27] and overall survival. A univariate Cox proportional hazards model was developed to investigate the relationship between overall survival and dosing administration route or baseline parameters, and 1-way analysis of variance and general linear models were used to compare the impact of dose per cycle for each administration route. Finally, a multivariate analysis was applied to all baseline characteristics relative to the dosing route.

The demographics of the 331 patients reported in the database were similar between the subcutaneous and intravenous administration groups (P value was not significant for all characteristics). The median duration of treatment was 4 cycles (range, 1–23), and the median follow-up was 5 months (range, 0–24). A total of 154 patients discontinued participation in the registry for several reasons: adverse events (n=10), patient choice (n=19), lost to follow-up (n=7), physician choice (n=37), death (n=53 [15% subcutaneous and 17% intravenous]) and "other" (n=21). The route of administration was very similar in the community setting: 43% of patients received azacitidine subcutaneously and 57% by intravenous infusion. The analysis showed that the route of administration did not significantly affect overall survival (85% vs 83%) or hematologic improvement (24.8% vs 24.1%) for subcutaneous and intravenous administration, respectively. Azacitidine was dosed at similar frequencies irrespective of the route of administration, although the FDA-approved dosing regimen of 7-consecutive-day cycles was not adhered to, apparently without impact on patient outcome. The traditional IPSS remains the relevant prognostic tool in MDS patients treated with azacitidine. Other factors (eg, age, sex, body mass index) may also provide prognostic information, but a relationship was not seen in the current study. There was no significant difference for dose cycle delay between the 2 routes of administration, but factors associated with an increased likelihood of dose cycle delay were identified as baseline higher bone marrow blast percentage, male sex, IPSS cytogenetic abnormality outcome category, presence of del(5q) cytogenetic abnormality, and nonconsecutive therapy dosing schedule. Patients on IV azacitidine received a lower average dose/treatment cycle than those receiving subcutaneous therapy (~10 mg less), and baseline factors associated with increased likelihood of lower average dose/treatment cycle were sex (female -23.3 mg, adjusted for body mass index), older age (-0.6 mg/year), lower body mass index, and lack of cytologic abnormalities. Various azacitidine dosing regimens were found in use in the community setting, but most patients (~80%) received the same dosing schedule across all treatment cycles. Only 17.5% of patients received the FDA-approved azacitidine dosing schedule (the 7-consecutive-day cycle), whereas the majority (52%) received less than 7 days of azacitidine per dosing cycle. This pattern differed depending on IPSS risk status; most lower-risk patients (58%) received less than the 7-day dosing cycle. In contrast, most IPSS higher-risk patients (61%) received either 7-nonconsecutive-day cycles, 7-consecutive-day cycles, or greater than 7-day dosing cycles.

The anti-angiogenic agent lenalidomide has demonstrated substantial activity in patients with MDS, espe-

Table 5. Relative Effectiveness of 2 Doses of Lenalidomide on Independence From RBC Transfusion in Patients With Low-Risk or Int-1–Risk MDS With Del5q: Results From the Phase III Trial MDS-004

RBC Transfusion Independence	Lenalidomide 5 mg	Lenalidomide 10 mg	Placebo
Modified ITT	n=46	n=41	n=51
≥26 wks	41%*	56%*	6%
≥8 wks	50%*	61%*	8%
ITT	n=69	n=69	n=67
≥26 wks	33%*	54%*	6%
≥8 wks	48%*	61%*	8%

*P<.001 vs placebo.

Data from Fenaux P et al.[29]

Int=intermediate; ITT=intention to treat; MDS=myelodysplastic syndromes; RBC=red blood cell.

cially those with chromosome 5q deletion, for which it is FDA-approved. In a phase II study (MDS-003), this agent resulted in red blood cell transfusion-independence of 8 consecutive weeks in 67% of patients, and a CCyR was achieved in 45% of patients.[28] However, the optimal dose for lenalidomide from this study was unclear, and a controlled study (MDS-004) was designed to compare the efficacy and safety of 2 doses (5 and 10 mg) versus placebo.[29] Low- or intermediate-1–risk patients as stratified according to the IPSS were enrolled in this multicenter, randomized, double-blind, placebo-controlled phase III study. All patients had chromosome 5q deletion and were red blood cell transfusion–dependent (defined as <56 consecutive days without a transfusion within the previous 112 days). The median age of the patients in years (range) was 66 (40–86), 68 (36–84), and 70 (39–85) for the lenalidomide 5 mg (n=46), 10 mg (n=41), and placebo (n=51) cohorts, respectively. The median time from diagnosis in years (range) was 3 (0–17), 3 (0–15), and 2 (0–14) for the lenalidomide 5 mg, 10 mg, and placebo cohorts, respectively. In the modified intent-to-treat analysis, the primary endpoint was red blood cell transfusion independence for at least 26 weeks and an increase in hemoglobin from baseline exceeding 1 g/dL. Secondary endpoints included cytogenetic response according to International Working Group 2000 criteria; CR was defined as absence of chromosome 5q31 abnormality, and partial response was defined as more than a 50% reduction of chromosome 5q31 abnormality. Dr. Fenaux reported that significantly higher rates of red blood cell transfusion independence were achieved with either lenalidomide dose versus placebo (Table 5).[29] Age, sex, French-American-British classification, IPSS risk, time from diagnosis, cytogenetic profile, baseline platelet count, and baseline cytopenias did not affect achievement of red blood cell transfusion independence for at least 26 weeks. The median number of cycles of lenalidomide necessary to achieve red blood cell transfusion independence for at least 26 weeks was approximately 1 for both treatment groups (5 mg: 3.3 weeks; 10 mg: 4.3 weeks). The maximum median hemoglobin increase in responders was similar in the 5 mg and 10 mg lenalidomide dose cohorts (5.1 and 6.3 g/dL, respectively). However, the cytogenetic response rates were highest with 10 mg lenalidomide, with no patients in the placebo arm showing a response. The incidence of AML progression was similar between treatment groups; 2-year progression to AML in all lenalidomide patients was 7.7% (7% and 10% for the 10 mg and 5 mg dose, respectively) versus 9% for placebo. Lenalidomide was well tolerated in the study, with the most common adverse events being neutropenia and thrombocytopenia. Dr. Fenaux concluded that the findings from this study support the use of lenalidomide at a starting dose of 10 mg/day, with dose reduction or interruption as required.

Clofarabine is a second-generation deoxyadenosine nucleoside analogue with demonstrated clinical activity as a frontline single-agent therapy in older patients with AML.[30] Faderl and colleagues evaluated the efficacy and safety of oral clofarabine in 32 patients with higher-risk MDS in a phase I/II study with IPSS intermediate-1–risk, intermediate-2–risk, or high-risk MDS or chronic myelomonocytic leukemia.[31] Patients received oral clofarabine daily for 5 days every 4–6 weeks. The initial dose was 40 mg/m^2, which was decreased to 30 mg/m^2 and eventually to 20 mg/m^2 because of toxicities, which included infection and renal insufficiency. Hematopoietic growth factor support was permitted. An ORR of 43% was reported, of which 25% were CRs. Response rates were lower among the 20 patients who failed previous hypomethylating therapy, with an ORR of 30% (10% CR). The therapy was associated with significant toxicity, including grade 3/4 transaminase elevations in 22% of patients and acute renal failure in 13% of patients. A large proportion of patients in this study (63%) had received prior therapy with a hypomethylating agent, representing a significant unmet medical need. However, even with the apparent activity of clofarabine in this population, the toxicity profile at these doses is a concern, and further studies are warranted at lower doses and with alternate schedules.

Follicular Lymphoma

Rituximab has been integrated into many chemotherapy regimens, not only improving complete and overall

response rates, but also prolonging overall survival to the extent that it is the first agent that is generally considered when developing a combination therapy in NHL. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the most widely used regimen for many of these patients.[32] However, recent data suggest an important role for bendamustine, a bifunctional alkylating agent. Studies from East Germany and the United States have generated impressive data demonstrating that single-agent bendamustine is highly active in relapsed and refractory patients, with overall responses in 70–80% of patients.[33] The addition of rituximab increases response rates in follicular and mantle cell lymphoma to over 90%, the majority being CRs.[33,34] Such observations led to the comparison of R-CHOP with bendamustine-rituximab in a randomized, controlled phase III trial by the Study Group for Indolent Lymphomas (StiL) in Germany. Dr. Rummel presented the final results of this study on behalf of StiL at the 2009 ASH meeting.[35] Data on 513 evaluable patients with follicular lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, and other indolent histologies were presented. The primary objective of the study was to show non-inferiority of bendamustine-rituximab when compared with R-CHOP for first-line treatment of advanced lymphomas. Secondary endpoints were response rates, time to next treatment, event-free survival, overall survival, and safety. Analysis of the primary endpoint showed that bendamustine-rituximab is superior to R-CHOP for PFS in the overall population: 54.9 versus 34.8 months (P=.00012). An analysis by histology showed that bendamustine-rituximab is superior to R-CHOP in follicular lymphoma (P=.0281), mantle cell lymphoma (P=.0146), and Walderströms lymphoma/lymphoplasmacytic lymphoma (P=.0024). Bendamustine-rituximab was at least comparable to R-CHOP in all measurements of the secondary endpoints and was superior to R-CHOP for CR (39.6% vs 30.0%, respectively; P=.26) and time to next treatment (not reached vs 37.5 months, respectively; P=.001). Comparison of adverse events revealed a much improved safety profile for bendamustine-rituximab versus R-CHOP for neutropenia (10.7% vs 46.5%; P<.0001), leukocytopenia (12.1% vs 38.2%; P<.0001), and granulocyte colony-stimulating factor administered (4.0% vs 20.0%; P<.0001). Other adverse events were also reduced significantly, including alopecia (P<.001), neuropathy (P<.001), and infectious complications (P=.0025). These data clearly support the use of bendamustine-rituximab as frontline therapy in lymphoma and represent a significant advance in the management of those patients with a follicular histology.

Bendamustine is now being combined with several other agents, especially bortezomib, to enhance efficacy. Fowler and colleagues presented the phase II data of the Velcade, Rituximab, Treanda in Combination for Relapsed Lymphoma (VERTICAL) trial, which examined this combination in 63 patients with relapsed and refractory follicular lymphoma receiving 5 cycles of bendamustine 90 mg/m^2 for days 1 and 2, with rituximab 375 mg/m^2 on days 1, 8, 15, and 22 of the first cycle and day 1 of each subsequent cycle, and bortezomib 1.6 mg/m^2 weekly for 4 weeks; the combination was delivered at 5-week intervals.[36] The median age of the patients was 58 years (range, 42–83 years), and the median time from diagnosis was 50 months (range, 7–273). The ORR was 80%, with 47% CR, and the regimen was generally well-tolerated, with no evidence of cumulative hematologic toxicity. Assessment of long-term outcome is ongoing, and future randomized trials are planned. Friedberg and colleagues presented data from a study with a similar combination, but with a bortezomib dose of 1.3 mg/m^2 on days 1, 4, 8, and 11, with 6 cycles given at 4-week intervals.[37] The reported ORR was 84%, with 52% CR. These data are encouraging but need to be confirmed in a randomized trial to determine if either of these regimens is superior to bendamustine-rituximab alone.

An alternative approach for the frontline therapy of follicular lymphoma is the use of "doublets" of monoclonal antibodies and other biological agents. Fowler and colleagues presented data on 30 patients treated with rituximab and lenalidomide,[38] with an 84% ORR and 79% CR/unconfirmed CR. A confirmatory trial is being planned by the Cancer and Leukemia Group B (CALGB).

New anti-CD20 monoclonal antibodies are also being investigated in NHL. Initial studies suggested activity for ofatumumab in relapsed and refractory follicular lymphoma; however, its activity in rituximab-resistant patients was unknown. Hagenbeek and colleagues presented data on ofatumumab in 116 patients with grade 1 or 2 follicular NHL resistant to at least 4 doses of rituximab either because of failure to respond to a rituximab-based regimen or progression within 6 months of such therapy.[39] Ofatumumab was administered at 300 mg for the first dose, followed by 500 mg or 1,000 mg for weekly doses 2–8. The ORR at the 1,000 mg dose was 10%, 22% in patients resistant to rituximab monotherapy, and only 9% in those refractory to chemoimmunotherapy. The median PFS was 6 months.

Lenalidomide, a second-generation immunomodulatory drug, is also being evaluated in NHL. Single-agent data in indolent and aggressive NHL has suggested response rates of 20–30%, and a 53% response rate has been reported in mantle cell lymphoma.[40] This oral agent is being combined with other active drugs, including rituximab and bendamustine. Gandhi and colleagues reported data from a preclinical study evaluating how in vitro treatment of NHL cell lines and cells from primary follicular lymphoma with lenalidomide and rituximab

affects cell surface signaling, CD20 expression, and subsequent cytotoxicity.[41] This study showed that treatment of follicular lymphoma cell lines with the 2 agents leads to synergistic antiproliferative effects and to cytotoxicity via non–immune-mediated mechanisms. In addition, lenalidomide does not alter CD20 expression on the cell surfaces and can potentiate rituximab-induced cell death through a mechanism that involves Bcl-2 phosphorylation. These data are consistent with clinical findings showing that the combination of the 2 agents appears to be at least additive, if not synergistic.

Diffuse Large B-Cell NHL and Mantle Cell Lymphoma

Diffuse large B-cell lymphoma is the most common NHL in North America. For decades, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) had been the standard regimen until 2002, when the Groupe d'Etude des Lymphomes de l'Adulte (GELA) first published data demonstrating an increase in CR rate and a prolongation of survival from the addition of rituximab. Data from several other groups supported those conclusions, and R-CHOP has become the international standard. Pfreundschuh and colleagues from the German High-grade Lymphoma Study Group published data with CHOP and cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone (CHOEP) that suggested an advantage for delivering the regimens on an every 14 day cycle (CHOP-14) rather than the standard 21 day cycles (CHOP-21).[42] They proposed that R-CHOP-14 should be the new standard. However, at the 2009 American Society of Clinical Oncology (ASCO) meeting, Cunningham and associates reported an early interim analysis of a direct comparison of R-CHOP-14 with R-CHOP-21 and found comparable response rates with no evidence of a difference in patient outcome, although the follow-up was relatively short.[43] At ASH, the GELA group reported the preliminary data from a similar comparison, which again suggested a lack of benefit from the more intensive treatment.[44] This planned interim analysis showed no statistically significant difference in efficacy between R-CHOP given every 14 days versus every 21 days. R-CHOP-21 is associated with numerically superior responses, and R-CHOP-14 is associated with greater hematologic toxicity and hospitalization. The final analysis is expected later in 2010.

Novel agents continue to be investigated for clinical activity in aggressive lymphomas. Pixantrone dimaleate, a novel aza-anthracenedione, is one such compound in clinical development. It has a similar chemical structure as mitoxantrone and anthracyclines and acts by reducing the formation of reactive oxygen species. It has demonstrated encouraging safety and activity in heavily pretreated patients with aggressive/indolent NHL in phase I and II studies.[45] Pettengell and colleagues presented data from a study that assessed efficacy and safety of pixantrone in patients with relapsed aggressive NHL who had failed at least 2 previous regimens, at least 1 of which contained an anthracycline.[46] Patients (n=140) were randomized to receive either weekly pixantrone 85 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, for up to 6 cycles, or an investigator's choice of a comparator single agent (oxaliplatin, vinorelbine, ifosfamide, etoposide, or mitoxantrone; gemcitabine or rituximab were permitted only in the United States). An independent review of the intent-to-treat population showed a CR/unconfirmed CR rate of 20% in the pixantrone arm compared with 5.7% in the comparator arm (P=.021). In the pixantrone arm, there were 8 confirmed CRs, versus none in the comparator group. However, the use of such single agents is not generally considered standard of care. The study reached its endpoint, but additional data will have to confirm its superiority to other anthracyclines in this setting.

Multiple Myeloma

Recent developments in therapeutics for multiple myeloma with new agents and combinations that have improved patient outcome are leading to a general questioning of the role of transplant in the early stages of the disease. Optimal treatment options are still evolving for patients with newly diagnosed and more advanced disease. A combination of bortezomib, melphalan, and prednisone (VMP) has demonstrated superior efficacy compared with melphalan and prednisone alone,[47] and a VMP-thalidomide combination (VMPT) has been shown to produce high response rates in relapsed/refractory patients.[48] In addition, VMPT demonstrated improved response rates, although the PFS was similar to that seen with VMP in elderly patients with newly diagnosed multiple myeloma.[49]

A promising new approach for the treatment of elderly patients with newly diagnosed disease was presented at the plenary session of this meeting by Dr. Mateos and colleagues from the Spanish Myeloma Group, who described final results from a phase III study in which VMP and bortezomib, thalidomide, and prednisone (VTP) were compared as induction therapy followed by maintenance bortezomib and thalidomide (VT) or bortezomib and prednisone (VP).[50] This study was designed to demonstrate decreased toxicity with comparable efficacy of the regimen in the context of published data from the phase III Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment With Melphalan and Prednisone (VISTA) trial, which compared VMP

to melphalan and prednisone as first-line therapy in this patient population.[51] In the study presented at ASH, 260 patients were randomized to one of the induction regimens, and both cohorts were subsequently randomized to maintenance therapy with either VP (n=87) or VT (n=91).[50] A comparison of ORR for each cohort following induction showed similar results for VMP and VTP (80% vs 81%, respectively; Table 6). However, of note, patients who received VMP induction therapy followed by VP maintenance had significantly longer median PFS versus VTP followed by VT maintenance (32.0 vs 26.5 months, respectively; HR, 1.6; *P*=.008). Median PFS for both cohorts had yet to be reached at the time of the meeting. These findings are significant for the myeloma community because they support the data from the VISTA study that demonstrate the effectiveness of VMP as an induction regimen in the newly diagnosed elderly patient. In addition, this study demonstrates the potential of bortezomib in maintenance therapy in this patient population.

A prospective, randomized phase III study in the elderly myeloma population was reported by Palumbo and colleagues.[52] In this study, induction treatment with VMPT followed by maintenance with VT (n=254) was compared to induction with VMP followed by no maintenance (n=257). Palumbo and colleagues reported that the estimated 3-year PFS rate was significantly higher with VMPT followed by VT versus VMP alone (60% vs 42%, respectively; *P*=.007) and that the estimated 3-year time to next therapy was significantly higher with VMPT followed by VT versus VMP alone (75% vs 60%, respectively; *P*=.0029). However, the estimated 3-year overall survival rates were similar for both treatment arms (89.2% vs 88.8%, respectively; *P*=.96). In the induction phase, VMP resulted in a higher incidence of hematologic toxicity than did VTP for grade 3 neutropenia (37 vs 28%, respectively; *P*=.02) and subsequent infections (7% vs <1%). There were no significant differences in thrombocytopenia or anemia. Grade 3/4 cardiac complications were more frequent with VMPT followed by VT versus VMP alone (10% vs 5%, respectively; *P*=.04), but the rates of infection, sensory neuropathy, and deep vein thrombosis/pulmonary embolism were similar between treatment arms. Overall, the superior efficacy of VMPT with VT maintenance with acceptable toxicity compared to VMP alone presents an attractive approach to treating newly diagnosed disease in the elderly, particularly because the use of melphalan prior to transplant is not an issue in this population.

Palumbo and colleagues presented a second paper describing a phase III study designed to compare efficacy and safety of melphalan, prednisone, and lenalidomide (MPR) alone or with maintenance lenalidomide (MPR-R) versus melphalan and prednisone in newly diagnosed, elderly multiple myeloma patients.[53] In this study, 402 patients received four 28-day cycles of lenalidomide (25 mg days 1–21) and low-dose dexamethasone (40 mg days 1, 8, 15, 22) as induction therapy. Cyclophosphamide (4 g/m^2) plus granulocyte-colony stimulating factor was used to mobilize stem cells. Patients were randomized for consolidation therapy to receive six 28-day cycles of melphalan (0.18 mg/kg, days 1–4), prednisone (2 mg/kg, days 1–4), and lenalidomide (10 mg, days 1–21), or melphalan 200 mg/m^2 with stem-cell support. The primary endpoint of the study was PFS, and all data were analyzed on an intent-to-treat basis. Dr. Palumbo reported that continuous treatment with the lenalidomide-containing regimen was associated with prolonged response when compared to melphalan and prednisone alone in this patient population. Among patients in the MPR-R arm, 60% attained a partial response in the first 3 months of treatment, with a 1-year overall survival

Table 6. Response Outcomes From a Prospective, Multicenter, Phase III Randomized Trial of VMP Versus VTP as Induction Therapy Followed by Maintenance Treatment With VT Versus VP in Elderly Untreated Patients With Multiple Myeloma

Outcome Following Induction, %	VMP (n=130)	VTP (n=130)
ORR	80	81
CR (if negative)	20	27
CR (if positive)	12	10
PR	48	46
MR	10	6
SD	8	11

Outcome Following Maintenance Therapy (%)	VT (n=91)	VP (n=87)
CR/nCR		
CR (if negative)	44	39
CR (if positive	15	16
PR	39	44

Data from Mateos MV et al.[50]

CR=complete response; IF=immunofixation; MR=minimal response; nCR=nodular complete response; ORR=overall response rate; PR=partial response; SD=stable disease; VMP=bortezomib, melphalan, and prednisone; VP=bortezomib; VT=thalidomide; VTP=bortezomib, thalidomide, and prednisone.

Table 7. Response to MPR-R or MPR and Autologous Transplant (Mel200) in a Prospective Phase III Study in Newly Diagnosed Patients With Multiple Myeloma

Regimen	ORR	CR	PR of Very Good or Better	PR	PD	Median Time to Initial Response (Months)
MPR-R (n=152), %	77	18	32	45	0	1.9
MPR (n=153), %	67	13	33	34	1	1.9
MP (n=154), %	49	5	11	37	0	2.8
P value	<.001	<.001	<.001			

Data from Palumbo A et al.[53]

CR=complete response; MP=melphalan and prednisone; MPR=melphalan, prednisone, and lenalidomide; MPR-R=melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance; ORR=overall response rate; PD=progressive disease; PR=partial response.

rate of 92% (Table 7). A 47% improvement in the rate of PFS was reported when comparing the MPR-R arm with the MPR arm in patients who switched from lenalidomide to placebo. The median PFS had not been achieved in the MPR-R arm, whereas a median value of 132 months had been reached with the MPR arm (HR, 0.530; 95% confidence interval [CI], 0.350–0.802). With MPR-R, there was a 63% decrease in time to the next treatment (HR, 0.369, 95% CI, 0.243–0.559). Overall, the MPR-R regimen was well-tolerated, with few toxicity-related treatment discontinuations. Overall, these authors concluded that patients receiving MPR-R achieved the optimal response versus patients receiving melphalan and prednisone as assessed by the European Group for Blood and Marrow Transplant criteria.[54]

Richardson and colleagues from the Dana-Farber Cancer Institute presented data on pomalidomide,[55] a new immunomodulatory molecule that has structural similarity to thalidomide and lenalidomide, but with a distinctly different activity profile.[56] A prior phase II study has shown that pomalidomide is efficacious in combination with low-dose dexamethasone in relapsed myeloma patients.[57] Dr. Richardson presented early data from a phase I/II study in 32 patients with relapsed/refractory multiple myeloma who had received 2–5 mg pomalidomide once daily for 21 days in a 28-day cycle for up to 4 cycles.[55] All patients had previously received lenalidomide, bortezomib, and dexamethasone. Seventy-eight percent had prior thalidomide therapy, and 59% had undergone stem-cell transplantation. The median number of prior regimens was in the range of 6–8 for individual dose groups, with the range of prior therapy across all dose groups being 2–18. The study is designed to progress to a phase II efficacy evaluation once the maximum tolerated dose has been established. Dr. Richardson reported that the maximum tolerated dose had been determined as 4 mg/day; 4 dose-limiting adverse events (neutropenia) were associated with 5-mg/day dose.[55] The most frequently reported pomalidomide-associated adverse events (all grades), with or without low-dose dexamethasone, were neutropenia (31%), fatigue (31%), anemia (19%), and rash (16%). A similar incidence of adverse events was observed in all dosing groups; the median time to neutropenia (all grades) was 44 days, and 80% of cases occurred approximately 90 days following the start of pomalidomide treatment. Twenty-five patients were evaluable for response; partial response or greater was observed in 7 patients (28%), and minimal response or greater was seen in 13 (52%; Table 8).

Table 8. Efficacy of Pomalidomide in a Phase I/II Dose-Ranging Study in Patients With Relapsed and Refractory Multiple Myeloma Who Have Failed Prior Therapy With Lenalidomide and Bortezomib

Response (n)	Pomalidomide Dose*			
	2 mg (n=6)	3 mg (n=8)	4 mg (n=8)	5 mg (n=10)
CR		1		
PR	1		2	3
Minimal response		1	3	2
SD	1	5	1	3
PD	1			1
Not evaluable	3	1	2	1

Data from Richardson P et al.[55]
CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

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Commentary

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Of the many interesting papers presented at the ASH 2009 symposium, some established new standards of care, while others already challenged these new standards. As other therapies appeared to be losing their place in the treatment paradigms, new and exciting agents provided hope for future advances in patient outcomes.

Chronic Lymphocytic Leukemia

Fludarabine has been the standard agent for the treatment of CLL for 2 decades.[1] At ASH, Rai and coworkers presented the long-term follow-up of a comparative study of this drug versus chlorambucil, demonstrating a survival advantage for fludarabine.[2] Although randomized trials suggested modest improvement on its single-agent activity with the addition of cyclophosphamide, there was greater toxicity and no survival advantage.[3] The treatment of CLL radically changed with the availability of monoclonal antibodies, especially rituximab, a chimeric anti-CD20 monoclonal antibody. Rituximab induces only 15% partial remissions as a single agent in patients with relapsed or refractory disease, which improves to 50–70% in previously untreated patients. However, its role is clearly in combination with chemotherapy. Phase II trials with rituximab combined with either fludarabine alone or in combination with cyclophosphamide achieve response rates of 90% or greater, with most patients experiencing a complete remission. In addition, a survival benefit was suggested using historical controls.[4,5] The GCLLSG recently reported on a large phase III trial that demonstrated not only a significant prolongation of PFS but an apparent survival advantage for FCR over FC as well.[6]

Nevertheless, all patients with CLL eventually relapse and require additional therapy. One of the most active drugs in this setting is bendamustine, an alkylating agent/antimetabolite hybrid developed in Germany in the 1960s.[7] It was approved by the FDA for CLL based largely on a randomized trial demonstrating a higher complete and overall response rate compared with chlorambucil, as well as a longer PFS, without a major difference in adverse effects.[8] Based on its impressive single-agent activity, the

GCLLSG combined it with rituximab in 48 patients with relapsed and refractory disease and achieved an overall response rate of 77% with 15% CRs, and, notably, 78% of fludarabine-refractory patients responded.[9] These encouraging results led to the CLL8 trial, in which a 91% response rate with 33% CRs was achieved in 117 previously untreated patients. The ongoing CLL-10 trial of FCR versus bendamustine and rituximab could redefine the initial treatment of this disease.

Based on the clinical success of rituximab, a number of other anti-CD20s are now in development. Ofatumumab, a human anti-CD20 that binds to a different epitope on CD20 than rituximab, was first reported on in a phase I study presented by Coiffier and colleagues.[10] It induced a response rate of over 40% in previously treated patients, although its activity in rituximab-resistant patients was not provided. In 59 patients whose disease was refractory to both fludarabine and alemtuzumab, it induced a response rate of 58%, leading to its recent approval by the FDA for this indication.[11] Similar results were achieved in patients who were fludarabine-refractory and had bulky disease, making them unsuitable for alemtuzumab. At ASH, Wierda and associates[12] reported results of the combination of fludarabine/cyclophosphamide plus ofatumumab in 61 previously untreated patients with active CLL. The overall response rates were comparable (77% group A, 73% group B) with 32% and 50% CRs, respectively. The response data did not compare favorably to published results with fludarabine-rituximab or FCR,[2,5] which was explained by the patients' high risk (primarily determined by an elevated ß$_2$ microglobulin).

The first monoclonal antibody approved by the FDA for CLL was the anti-CD52 alemtuzumab based on a 30% response rate in patients who were refractory to fludarabine and alkylating agents. However, its activity in those who have also failed rituximab is not known and is likely lower. One issue with alemtuzumab in CLL is the increased likelihood of opportunistic infections requiring antimicrobial prophylaxis and weekly PCR assays for cytomegalovirus because of the high risk of reactivation. Data on a number of alemtuzumab-based combinations were presented at ASH. Engert and coworkers[13] compared fludarabine versus fludarabine and alemtuzumab (FluCAM) in patients in first relapse. The data showed greater activity for the combination (ORR/CR 85%/30% vs 68%/16%, respectively) without additional toxicities, presumably related to the lower dose of fludarabine in the combination (90 mg/m^2 vs 125 mg/m^2 per cycle). However, alemtuzumab did not fare well in other studies. Lepretre and associates[14] compared FCR with fludarabine, cyclophosphamide, and alemtuzumab in 178 previously untreated patients. FCR was not only more effective, but it was significantly less toxic. CALGB investigators[15] consolidated FR responses to FR using alemtuzumab and encountered an unacceptably high risk of fatal opportunistic infections and aggressive transformation. Thus, despite the increased number of patients rendered free of minimal residual disease, the toxicity of this approach is prohibitive, and it should be discouraged.

Lenalidomide has also demonstrated promise in CLL with responses in 35–50% of relapsed and refractory patients, including those with unfavorable cytogenetics. At ASH, Ferrajoli and coworkers[16] presented data on the combination of lenalidomide and rituximab in 60 patients in the relapsed setting. The response rate was 68%—although there were no CRs—and the incidence of complications such as lenalidomide-associated tumor flare was reduced. This combination warrants further study.

CLL, rather than being a lymphoproliferative disorder, is more often characterized by a defect in apoptosis. A number of small molecules are being actively studied that may overcome defects in the apoptotic pathways. ABT-263 is not only active as a single agent, but it is now being combined with other drugs, including rituximab. The major side effect of this drug is transient thrombocytopenia.[17]

Non-Hodgkin Lymphoma

Rituximab has increased not only the complete and overall response rate to most chemotherapy regimens, but it has also prolonged PFS and overall survival in patients with advanced follicular NHL.[18-20] As a result, R-CHOP has become the most widely used regimen for these patients.[21] Studies from Germany and the United States have demonstrated that single-agent bendamustine has been associated with responses in 70–80% of relapsed and refractory patients.[7] In addition, when combined with rituximab, response rates in follicular and mantle cell lymphoma are more than 90%, the majority being CRs.[22,23] As a result of these data, Rummel and coworkers compared R-CHOP with rituximab plus bendamustine,[24] in what was perhaps one of the most important studies in lymphoma presented at the 2009 ASH symposium. The final results of their study included 513 evaluable patients with follicular lymphoma, mantle cell lymphoma, lymphoplasmacytoid lymphoma, and other indolent histologies. Although the overall response rates (~93%) were comparable between the arms, the CR rate was higher with bendamustine and rituximab (40.1% vs 30.8%, P=.0323). More importantly, at a median follow-up of 34 months, there was a significant prolongation of PFS (54.8 vs 34.8 months; P=.002) with less alopecia, neutropenia, infections, and neuropathy. Thus, rituximab plus bendamustine is a reasonable alternative for R-CHOP in frontline follicular lymphoma. Data presented at ASH demonstrated that stem cells can

be successfully harvested after bendamustine and rituximab, permitting autologous stem cell transplantation,[24] and there is no apparent increase in secondary malignancies with this regimen. Building upon these promising results have been several studies combining bendamustine and rituximab with other agents, particularly bortezomib. The phase I portion of the VERTICAL trial reported at ASCO[25] identified 90 mg/m^2 on days 1 and 2 as the dose of bendamustine for phase II studies. At ASH, Fowler and colleagues[26] presented the phase II data with this combination in 49 patients with relapsed and refractory follicular lymphoma, giving 5 cycles of bendamustine 90 mg/m^2 on days 1 and 2 with rituximab 375 mg/m^2 on days 1, 8, 15, and 22 of the first cycle and day 1 of each subsequent cycle, and bortezomib 1.6 mg/m^2 for 4 weeks' combination delivered at 5-week intervals. The overall response rate was 80%, with 47% CR. Friedberg and colleagues[27] also presented a similar combination, but with bortezomib at a dose of 1.3 mg/m^2 and cycles given every 4 weeks for 6 cycles. Their overall response rate was 84%, with 52% CR. Determination of whether either of these regimens is superior to bendamustine and rituximab alone will require a randomized trial.

Radioimmunotherapy is the most effective/least used therapy for NHL. At the ASH meeting, Kaminski and colleagues[28] reported an update of their data on single-agent I-131 tositumomab as the initial treatment of 76 patients with follicular lymphoma, and 1 patient with mantle cell lymphoma. The overall response rate in this relatively young (median age, 49 years) group of patients was 97%, with 75% CRs. At a median follow-up of 10 years, the median duration of response was 6%. For the CRs, the median duration of response was 10.9 years. The 10-year overall survival was 82%. There were 11 secondary malignancies, including a single case of myelodysplastic syndrome.

Radioimmunotherapy has also been used to consolidate an initial response. In the First-line Indolent Trial (FIT), patients received chemotherapy, generally without rituximab, and responders were randomized to y90-ibritumumab tiuxetan or observation with a significant advantage in PFS with the radioimmunoconjugate.[29] Results from a North American trial of R-CHOP followed by 1-131 tositumomab versus observation are pending. Other approaches for the initial management of follicular lymphoma include doublets of monoclonal antibodies and other biological agents. The CALGB has pioneered this approach, first with rituximab plus the anti-CD80 galiximab[30] and, most recently, rituximab plus the anti-CD22 epratuzumab. At ASH, Fowler and colleagues[31] presented data on 30 patients treated with rituximab and lenalidomide, with an 84% overall response rate and 79% CR/CRu. A confirmatory trial is being planned by the CALGB.

New anti-CD20 monoclonal antibodies have also been explored in NHL. Hagenbeek and colleagues[32] were the first to conduct a phase I trial of ofatumumab in NHL with a response rate of 43% and with no dose-limiting toxicity identified. The question remained regarding its activity in rituximab-resistant patients until ASH. Hagenbeek and associates[33] presented 116 patients with grade 1 or 2 follicular NHL resistant to at least 4 doses of rituximab either because of failure to respond to a rituximab-based regimen or progression within 6 months of such therapy. Ofatumumab was administered at 300 mg for the first dose, followed by 500 mg or 1,000 mg for weekly doses 2–8. The overall response rate at the 1,000 mg dose was 10%; this rate was 22% in patients resistant to rituximab monotherapy and only 9% in those refractory to chemoimmunotherapy. The median PFS was 6 months. Which, if any, of these antibodies will replace rituximab remains to be determined, as they appear to have comparable activity in patients with follicular lymphoma.

Another new agent being widely studied in lymphoma is lenalidomide, a second-generation immunomodulatory drug. Single-agent data in indolent and aggressive NHL suggest response rates of 20–30%.[34,35] More impressive is the 53% response rate reported in mantle cell lymphoma.[36] This oral agent is being combined with other active drugs, including rituximab and bendamustine.

Other drugs under investigation target a number of signaling pathways. BCR signaling is important during B-cell ontogenesis and is key to the survival of malignant B-cells. The survival of most B-cell lymphomas, most notably diffuse large B-cell lymphoma, may depend on the signals from the BCR. These effects are amplified by spleen tyrosine kinase (Syk), a cytoplasmic tyrosine kinase that is important in mediating immunoreceptor signaling in B cells, as well as macrophages, neutrophils, and mast cells. In vitro inhibition of Syk induces apoptosis of a number of lymphoma cell lines. Based on the importance of BCR in B-cell survival in normal B cells and lymphoma cells, Syk appears to be a reasonable therapeutic target.[37]

Fostamatinib disodium is an oral pro-drug that is rapidly converted to R406, a potent inhibitor of Syk. Friedberg and colleagues[38] reported that fostamatinib was well-tolerated; the most serious adverse effects included myelosuppression, fatigue, and diarrhea, which were rarely severe. Although responses occurred in a quarter of patients, the response rate in patients with CLL/small lymphocytic lymphoma was 54.5% and 23.5% for diffuse large B-cell lymphoma, but only 9.5% in follicular lymphoma and 11.1% in mantle cell lymphoma. The median PFS was 4.1 months for all patients.

The mTOR and PI3 kinase pathways are important in the regulation of a number of cellular functions, including oncogenesis, cellular metabolism, proliferation, and survival. Temsirolimus is an inhibitor of mTOR

recently approved for the treatment of relapsed or refractory mantle cell lymphoma. RAD-001, or everolimus, has shown some activity in lymphoma as well.[39] CAL-101 is a potent inhibitor of PI3K 100d and has demonstrated in vitro activity in CLL cells. Flinn and colleagues[40] reported the first phase I trial with this agent in 43 patients with CLL, indolent or aggressive NHL, and acute myeloid leukemia. Despite a median of 5 prior therapies, the response rate with this oral agent in NHL was 56%, and it was well tolerated. Additional studies are planned.

Diffuse Large B-Cell Non-Hodgkin Lymphoma and Mantle Cell Lymphoma

CHOP had been the standard therapy for diffuse large B-cell lymphoma for decades, until several studies showed that the addition of rituximab was beneficial. R-CHOP has become the international standard. Data had suggested an advantage for delivering the regimens on an every 14-day cycle (CHOP-14) rather than the standard 21-day cycle (CHOP-21).[41] At ASCO 2009, however, Cunningham and colleagues reported on an interim analysis that found no evidence of a difference in patient outcome between R-CHOP-14 and R-CHOP-21, although the follow-up was relatively short.[42] Also at ASH, the GELA group reported on data suggesting a lack of benefit from the more intensive treatment.[43] Final analyses of these 2 studies are needed; however, for now, R-CHOP-21 remains the standard for these patients. The next question will be how to improve on R-CHOP-21. Promising data with etoposide, prednisone, vincristine, and doxorubicin plus rituximab (R-EPOCH) from the National Cancer Institute and CALGB[44] have led to CALGB 50303, which is directly comparing dose-adjusted R-EPOCH with R-CHOP for the initial treatment of patients with diffuse large B-cell non-Hodgkin lymphoma. It is more than half way to completion. Other drugs have also been added to R-CHOP to enhance its efficacy, including epratuzumab, bortezomib, enzastaurin, and avastin. The data are not sufficiently mature to adopt any of the new combinations.

Mantle cell lymphoma is one of the more clinically challenging of the NHLs. Although it is highly responsive to conventional chemotherapy, it is considered an aggressive NHL that is incurable, with a median survival of about 6 years.[44] Unlike diffuse large B-cell lymphoma, there is little consensus on the initial treatment for mantle cell lymphoma. Although R-CHOP has become a standard, older studies do not support a role for the anthracycline, and the median PFS is only 18–22 months. For younger patients, HyperCVAD has been recommended[45]; however, a recent Southwest Oncology Group study failed to corroborate the previously published single institution results.[46] A number of other regimens, several of which include autologous stem cell transplantation, have provided encouraging results. However, whether they are an actual improvement requires a randomized trial. In CALGB 59909, Damon and colleagues used an aggressive chemotherapy regimen, with stem cell transplant and rituximab, which achieved a 2-year PFS of 76%, a 5-year PFS of 56%, and a 5-year survival of 64%.[47]

A number of new agents have demonstrated impressive activity in mantle cell lymphoma. At ASH, Rummel and colleagues presented the final results of a direct comparison of R-CHOP with R-bendamustine in follicular lymphoma, mantle cell lymphoma, and other indolent histologies.[24] As already noted, bendamustine and rituximab therapy was more effective and less toxic not only in the follicular and indolent subsets, but in the mantle cell lymphoma patients as well. Other new drugs with promise include bortezomib, which is approved for relapsed and refractory mantle cell lymphoma with a response rate of about 30%,[48] temsirolimus, which has a response rate of 22%,[49] and lenalidomide, which has a 50% response rate[36] and which does not appear to be enhanced by the addition of rituximab.[50] Several groups are proposing studies of bortezomib, bendamustine, and rituximab as the initial therapy for mantle cell lymphoma. Whether such strategies will improve patient outcome remains to be seen.

Myelodysplasia and Acute Myeloid Leukemia

Considerably less progress has been made in the treatment of MDS and AML compared with lymphomas and CLL. Few new agents have demonstrated promise. An anthracycline and cytarabine remain the standard of care, with only an increase in the dose of daunomycin providing an improvement in outcome in recent years. Clearly, new drugs are needed, yet few effective ones are available. Agents that have now become part of standard therapy for MDS include the hypomethylating agents, decitabine and 5-azacytidine, and the immunomodulatory drug lenalidomide. However, the optimal dose and schedule have yet to be defined. Garcia-Manero and colleagues, using decitabine, and Sekeres and associates,[51] with 5-azacytidine, failed to demonstrate an efficacy advantage for any schedule over another.

Lenalidomide is approved for MDS with chromosome 5q deletion, and it has also demonstrated some activity in other subtypes. At ASH, Fenaux and colleagues[52] confirmed the ability of low doses of this drug to achieve red blood cell transfusion independence while Mollgård and associates used doses of 10–30 mg. Two studies also demonstrated single-agent activity in high-risk MDS and AML as well.[53,54] Future trials may focus on integrating this agent into combinations.

Chronic Myelogenous Leukemia

Imatinib completely altered the approach to patients with CML. For example, no longer are younger patients immediately referred for allogeneic stem cell transplantation. In recent years, a number of other tyrosine kinase inhibitors and other agents have demonstrated activity in this disease as well. Studies at ASH confirmed the efficacy of dasatinib in the initial treatment of the disease. Importantly, also presented at ASH were data suggesting that nilotinib might actually be more effective than imatinib in previously untreated patients with chronic phase disease, and it thus may become the new standard of care.

Multiple Myeloma

In recent years, a plethora of new agents and combinations has not only increased the overall and complete response rates of patients with multiple myeloma but also challenged the role of stem cell transplantation early in the course of the disease. Drugs including thalidomide, lenalidomide, bortezomib, and doxil are being used in various combinations and permutations, with reported response rates exceeding 90%, which include many CRs. However, which of these regimens is superior and for which patient populations remain to be determined by randomized clinical trials. Several studies at ASH emphasized the way these drugs have altered our approach to this disease.[55,56]

Conclusion

In order to develop new therapies, patients and their physicians must be encouraged to participate in clinical research trials. The eventual goal is to individualize therapy, thus enhancing efficacy while minimizing toxicity. To reach this end, correlative studies are an essential component of all clinical research trials.

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Recent Advances in the Management of Hematologic Malignancies

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

1. In the study presented at ASH by Hallek of patients with active, previously untreated CLL who were randomized to receive either FC or FCR, ORR for patients treated with FCR was _____ versus _____ for those receiving FC.

   a. 88.4%, 73.1%
   b. 85.1%, 76.9%
   c. 90.9%, 32.7%
   d. 95.1%, 88.4%

2. Fischer presented data from a multicenter phase II trial designed to assess the efficacy and toxicity of bendamustine in combination with rituximab in patients with previously untreated CLL, which showed that the ORR was _____ , with _____ clinical CRs.

   a. 88.4%, 73.1%
   b. 85.1%, 76.9%
   c. 90.9%, 32.7%
   d. 95.1%, 88.4%

3. In a study by Engert examining the second-line treatment of patients with relapsed or refractory CLL, the combination of fludarabine and alemtuzumab was superior to fludarabine alone in which patients?

   a. patients with Rai stage 0-I disease
   b. patients with Rai stage I disease
   c. patients with Rai stage II disease
   d. patients with Rai stage III-IV disease

4. In a study by Cortes-Franco in CML patients with the T3151 mutation who had previously failed imatinib therapy, treatment with omacetaxine achieved a _____ rate of complete hematologic response and a _____ rate of major cytogenetic response in the chronic-phase disease cohort.

   a. 73%, 45%
   b. 86%, 27%
   c. 91%, 68%
   d. 94%, 72%

5. Vij presented a study showing that lenalidomide achieved CR/incomplete response in _____ of AML patients in an intent-to-treat population.

   a. 25%
   b. 30%
   c. 35%
   d. 40%

6. In Garcia-Manero's study of patients with MDS, PFS was more than ____ days for the daily regimen versus ____ days for the weekly regimen.

   a. 276, 189
   b. 313, 208
   c. 345, 298
   d. 451, 358

7. In an ASH study from Rummel of patients with follicular lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, and other indolent histologies, bendamustine-rituximab was _____ to R-CHOP for PFS in the overall population.

   a. equal
   b. inferior
   c. superior

8. In Cunningham's study of patients with diffuse large B-cell lymphoma, data showed a benefit from treatment with R-CHOP-21 over R-CHOP-14.

   a. true
   b. false

9. Study data from Mateos of elderly patients with newly diagnosed multiple myeloma suggest the potential of which agent for maintenance therapy?

   a. bortezomib
   b. pomalidomide
   c. prednisone
   d. thalidomide

10. In a study by Richardson of pomalidomide in patients with multiple myeloma, 4 dose-limiting adverse events (neutropenia) were associated with which dose?

    a. 2 mg/day
    b. 4 mg/day
    c. 5 mg/day
    d. 6 mg/day

Evaluation Form Recent Advances in the Management of Hematologic Malignancies

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)

1. Extent to Which Program Activities Met the Identified Objectives

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

1. Integrate prognostic factors into treatment decisions for patients with hematologic malignancies, including lymphoma, leukemia, myelodysplastic syndromes, and multiple myeloma	1 2 3 4 5
2. Identify factors influencing the choice of treatment for patients with myelodysplastic syndromes and leukemia	1 2 3 4 5
3. Describe the most recent data on treatment options for both newly diagnosed and recurrent multiple myeloma	1 2 3 4 5

2. 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

3. 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: _____

_____

4. Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

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