September 2008 www.clinicaladvances.com Volume 6, Issue 9, Supplement 17

Highlights in Hematologic Malignancies

A Review of Selected Presentations from the 2008 Annual Meeting of the American Society of Clinical Oncology and the 10th International Conference on Malignant Lymphoma

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A CME Activity
Approved for 1.25
AMA PRA
Category 1 Credit(s)™

Release Date: September 1, 2008
Expiration Date: September 30, 2009
Estimated time to complete activity: 1 hour

Sponsored by Postgraduate Institute for Medicine

Supported through an educational grant from
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Clinical Advances in HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

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Target Audience

This activity has been designed to meet the educational needs of hematologist and oncologists involved in the management of patients with lymphoma, leukemia, multiple myeloma, and myelodysplastic syndromes.

Statement of Need/Program Overview

Data are emerging on novel agents as well as new combination regimens for the treatment of hematologic malignancies. This monograph reviews some of the salient new data recently presented at international meetings of hematologists/oncologists.

Educational Objectives

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

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of hematologic malignancies
- Explain the results of these new study findings including current clinical trials evaluating therapy in the treatment of hematologic malignancies
- Explain how to integrate into clinical practice the latest knowledge and methods for treating patients with hematologic malignances in an effort to improve current prognosis statistics
- Identify future research directions for all therapies in hematologic malignancies.

Faculty

Edward Stadtmauer, MD

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Overview of Hematologic Malignancies

Hematopoietic stem cells give rise to all the cell types in the human blood. These cells can be divided into two distinct subsets based on the cell lineage from which they are derived: myeloid (macrophages, erythrocytes, platelets, etc.) and lymphoid (T and B cells). Hematologic malignancies include an array of cancer types that originate in the blood cells of the bone marrow or lymph system. Hematologic cancers are primarily classified according to the cell lineage from which the cancerous cell type is derived. The myeloid cancers include acute myeloid leukemia (AML) and chronic myeloid disorders such as chronic myelogenous leukemia (CML) and the myelodysplastic syndromes (MDS). The lymphoid cancers include acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma, and both Hodgkin lymphomas and non-Hodgkin lymphomas (NHLs).

Myeloid Leukemias

It is estimated that more than 46,000 new cases of leukemia (3% of all new cancers) and more than 21,000 leukemia-related deaths (3% of all cancer-related deaths) will occur in the United States in 2008.[1]

CML is a myeloproliferative disorder of hematopoietic stem cell origin characterized by increased proliferation of mature granulocytes (eosinophils, basophils, and neutrophils) that also demonstrate a decreased capacity for apoptosis. The Philadelphia chromosome is the defining cytogenetic feature of this disease and is present in nearly all patients with CML. This chromosomal rearrangement results in the *BCR-ABL* fusion gene, which encodes a constitutively active protein tyrosine kinase. CML accounts for up to 15% of all adult leukemias.[2] Patients with CML typically demonstrate gradual clinical progression and consequently live for many years. Allogeneic stem cell transplantation (SCT) can be curative but is associated with significant morbidity and mortality and many individuals are not eligible for this procedure. Imatinib, with its high response rate, low toxicity, and demonstrated long-term survival is currently the frontline agent of choice for CML, and second-line treatments include dose escalation of imatinib and the second-generation tyrosine kinase inhibitors dasatinib and nilotinib.[3]

AML is characterized by the proliferation of myeloid precursor cells that demonstrate a reduced capacity to differentiate into more mature cell types. The rapid proliferation and accumulation of these leukemic cells in the bone marrow and peripheral blood is characterized by rapid clinical progression. The increased production of these malignant precursor cells results in reduced levels of red blood cells, platelets, and neutrophils, leading to anemia and an increased risk of bleeding and infection. Treatment regimens for AML are usually chosen based on the patient's age at the time of treatment (younger or older than 60 years) because of the higher incidence of unfavorable cytogenetics, comorbidities, and other factors in older patients. Typically, regimens are based on a combination of cytarabine and an anthracycline (eg, daunorubicin, idarubicin) or an anthracenedione.[4]

Myelodysplastic Syndromes

MDS comprise a spectrum of hematopoietic stem cell malignancies characterized by a limited maturation capacity and rapid proliferation in at least one myeloid lineage. Thirty percent of patients with MDS progress to AML, which is often refractory to standard treatments, and a majority of the remaining patients die from infections or bleeding. For patients who have lower-risk disease, the goals of therapy are to improve blood counts, decrease infection rates, and decrease the requirement for blood transfusions. For patients with higher-risk disease, optimal therapy aims to prolong survival and delay progression to AML.[5] Three drugs have been approved by the US Food and Drug Administration for the treatment of MDS: lenalidomide for patients with the del(5q) chromosomal abnormality, azacitidine, and decitabine for high-risk or nonresponsive patients.[6]

Lymphomas

Lymphomas constitute an array of hematologic malignancies presenting as defects in mature lymphoid cells. As one of the major types of cancer, more than 70,000 new

cases of lymphoma are diagnosed each year.[7] Lymphomas are classified as either Hodgkin lymphoma or NHL, with NHL being significantly more prevalent than Hodgkin lymphoma. It is estimated that more than 66,000 new NHL cases (4.5% of all new cancers) will be diagnosed and more than 19,000 NHL-related deaths (3% of all cancer-related deaths) will occur in the United States in 2008.[1] NHL can be divided into either B- or T-cell subtypes. Whereas the majority of Hodgkin lymphomas arise from B cells, approximately 85% of NHL cases arise from B cells and approximately 15% arise from T cells.[8] The most common B-cell NHL subtypes include diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, with less common subtypes including CLL, mantle cell lymphoma (MCL), peripheral T-cell lymphoma, and small lymphocytic lymphoma.

Treatment of NHL is challenging due to variability in patient presentation and prognosis and ultimately depends on the stage and type of disease. Additionally, the aggressiveness of the cancer must also be considered when developing a therapeutic strategy. The addition of the monoclonal anti-CD20 antibody rituximab to cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP; R-CHOP) is the standard frontline treatment approach used for patients with NHLs.

Chronic Lymphocytic Leukemia

CLL is diagnosed by the presence of lymphocytosis in the blood. CLL is the most common leukemia in the United States, with an estimated 4,500 deaths occurring in 2007.[9] Typically, this syndrome demonstrates a gradual clinical progression. Early-stage CLL is associated with a low tumor burden and normal marrow function. The tumor burden increases as the disease progresses and bone marrow function becomes increasingly impaired. The overall 5-year survival rate for newly diagnosed patients is approximately 60%,[10] with a significantly lower survival rate in patients with aggressive CLL (<2–3 years).[11] Patients are typically treated with chemoimmunotherapy or chemotherapies including chlorambucil or cyclophosphamide (with or without prednisone), purine analog regimens, or alkylating agent–based combination regimens such as CHOP.[12]

Multiple Myeloma

Multiple myeloma is the second most common hematologic malignancy and is characterized by defects in plasma cells (mature B cells) that typically form localized tumors in the bone marrow. This cancer interferes with the normal blood-forming functions of the bone marrow, leading to a shortage of red blood cells, platelets, and infection-fighting white blood cells. More importantly, multiple myeloma is associated with multisystem dysfunction most commonly painful lytic bone lesions, renal insufficiency, neuropathy, and susceptibility to infection. Multiple myeloma has an estimated yearly incidence of 19,000 new cases in North America, with a median predicted survival of less than 5 years.[13] Patients with early-stage disease are often asymptomatic. The current standard of care for patients younger than 60 years of age with good organ function includes high-dose chemotherapy and autologous SCT.[14] Multiple myeloma is not considered curable with current treatment regimens. However, the development of new drugs including bortezomib, thalidomide, and lenalidomide has shown considerable promise in this setting.[15]

Treatment of Hematologic Malignancies

Traditional treatments directed against hematologic malignancies typically target rapidly dividing cells but are often nonspecific. Corticosteroids have a destructive (ie, lytic) effect on certain blood cells, particularly lymphocytes. Chemotherapeutic agents may kill rapidly dividing cells, although the narrow therapeutic line between the killing of cancer cells and normal cells is difficult to ascertain. Interferon alfa is an immunomodulator that affects cellular proliferation. Radiation therapy also kills rapidly dividing cells and is effective against localized hematologic malignancies, such as Hodgkin lymphoma.

Aside from these traditional treatment modalities, newer therapies are being developed that more selectively target cancer cells by honing in on characteristic molecular features of such cells. Such targeted therapies include drugs that can inhibit cancer cell proliferation by interfering with specifically targeted proteins required for tumor growth, as opposed to simply interfering with any rapidly dividing cell. These types of therapies can be as effective as traditional treatments and are typically less detrimental to healthy cells. Such targeted therapies fall into one of several categories including monoclonal antibodies (eg, rituximab, lumiliximab), small molecule inhibitors (eg, imatinib, dasatinib, temsirolimus, bortezomib, vorinostat), antisense oligonucleotide compounds (eg, oblimersen), cytadine analogs (eg, azacitidine), and immunomodulatory agents (eg, lenalidomide). All of these agents are now under clinical investigation in various hematologic malignancies. The results of several of these and other related studies are summarized in the following abstract reviews.

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May 30–June 3, 2008
Chicago, Ill.

June 4–7, 2008
Lugano, Switzerland

Myeloid Leukemia

7009 Dasatinib 2-year Efficacy in Patients With Chronic-phase Chronic Myelogenous Leukemia With Resistance or Intolerance to Imatinib (START-C)[1]

MJ Mauro, M Baccarani, F Cervantes, JH Lipton, Y Matloub, R Sinha, RM Stone

Dasatinib is a tyrosine kinase inhibitor that is significantly more potent than other pharmacologic inhibitors (ie, imatinib or nilotinib) developed for the treatment of CML. A phase II study is currently being conducted to evaluate the efficacy of dasatinib in 387 patients with chronic-phase CML resistant or intolerant to imatinib. Among these patients, previous treatment with imatinib resulted in complete hematologic response for 82%, complete cytogenetic response for 19%, and major cytogenetic response for 37%. After a 2-year follow-up, twice-daily dasatinib (70 mg; with dose escalations to 90 mg BID or reductions to 50 or 40 mg BID allowed for lack of response or toxicity) resulted in complete hematologic response in 91% of patients, complete cytogenetic response in 53%, major cytogenetic response in 62%, and a major molecular response in 47%. Furthermore, the major cytogenetic response rates were durable, with 88% of patients maintaining their response at 24 months. Progression-free survival at 2 years' follow-up was 80%, and overall survival was 94%. Importantly, responses were seen across all CML genotypes except those with the T315I mutation. Grade 3/4 toxicities were common, including thrombocytopenia (49%), neutropenia (50%), pleural effusion (9%), dyspnea (6%), bleeding (4%), diarrhea (3%), and fatigue (3%). However, the appearance of higher-grade toxicities was uncommon, indicating that dasatinib was generally well tolerated in these patients.

7051 A Double Blind Placebo-controlled Randomized Phase III Study of High Dose Continuous Infusion Cytosine Arabinoside With or Without VNP40101M in Patients With First Relapse of Acute Myeloid Leukemia[2]

D DeAngelo, SM O'Brien, N Vey, K Seiter, W Stock, A Cahill, A Pigneux, D Claxton, R Stuart, FJ Giles

VNP40101M is a novel alkylating agent that has been evaluated in several clinical trials and has demonstrated significant antileukemic activity.[3,4,5] The current analysis assayed the safety and efficacy of cytarabine (ara-C)

treatment with or without the addition of VNP40101M. The 210 patients with AML in this study were all 18 years of age or older, had a performance status in the range of 0–2, and were in relapse after their first complete response (range, 3–24 months). Treatment consisted of ara-C 1.5 g/m^2 on days 1–3 in combination with VNP40101M 600 mg/m^2 or a placebo control. The treatment (n=140) and control (n=70) groups were comparable in age (median, 59 years), performance status, the duration of first complete response (median, 290 days), and risk factors (ie, age and duration of first complete response). Patients who demonstrated significant bone marrow improvement were eligible to receive a second induction cycle. Following data safety monitoring board review, the study was placed on hold due to disproportionate death rates between the treatment and control groups. At this point, the overall response rate was 37% and 19% (*P*=.004) and the median overall survival duration was 128 and 182 days (*P*=.039) for the treatment and control groups, respectively. However, the death rate from all causes was 39% in the treatment group and 8.6% in the control group. In the treatment group, 67% of deaths were due to infection, sepsis, or pneumonia, and 18% were due to pulmonary events. In the control group, 30% of deaths were due to sepsis or pneumonia, 30% were due to AML, and 30% were due to multiple organ failure. Although a higher overall response rate was achieved with VNP40101M in combination with ara-C, this finding was countered by a significantly higher mortality rate among relapsed AML patients.

Myelodysplastic Syndromes

7000 A Phase I/II Study of Vorinostat, an Oral Histone Deacetylase inhibitor, in Patients With the Myelodysplastic Syndrome and Acute Results of the Phase I Trial: A New York Cancer Consortium[6]

LR Silverman, A Verma, R Odchimar-Reissig, A Cozza, V Najfeld, JD Licht, JA Zwiebel

Vorinostat is a histone deacetylase inhibitor with a broad spectrum of epigenetic activity that has demonstrated efficacy for the treatment of MDS and AML.[7] Silverman and colleagues presented data from a phase I trial that assayed the benefits of vorinostat in combination with ara-C for the treatment of MDS or AML. Twenty patients (median age, 68 years) were enrolled. Fourteen patients had MDS, and 6 patients had AML. Patients received a combination of vorinostat and ara-C in a 3+3 dose-escalating/de-escalating design, with a mean of 4.7 cycles administered (range, 1–11). At the time of the report, 3 patients had discontinued due to progression, comorbidities, or consent withdrawal. Among the 11 evaluable patients, 5 patients had a complete response, 1 had a complete response with incomplete blood count recovery, 3 had hematologic improvements, and had 2 stable disease (Table 1). The median time to response was 2 cycles. Grade 1/2 anorexia and fatigue were common, but no grade 3/4 nonhematologic toxicities were observed. These data indicate that this combination of vorinostat and ara-C is safe and also demonstrates an improved overall response rate, complete response rate, and time to response compared to ara-C alone. This trial is ongoing.

7006 Effect of Azacitidine on Overall Survival in Higher-risk Myelodysplastic Syndromes Without Complete Remission[8]

AF List, P Fenaux, GJ Mufti, E Hellström-Lindberg, S Gore, JM Bennett, LR Silverman, J Backstrom, AR Allen, CL Beach

Azacitidine is an inhibitor of DNA methylation that has significant effects on epigenetic gene silencing. This agent has been shown to extend the overall survival of patients with MDS when compared to conventional-care regimens.[9] The analysis presented by List and colleagues evaluated the effects of azacitidine relative to conventional-care regimens on the 1-year survival of patients with MDS. Patients with MDS including refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia, as well as an International Prognostic Scoring System score of intermediate-2– or high-risk, were included. A total of 358 patients were randomized to receive azacitidine 75 mg/m^2/day subcutaneously for 7 days every 28 days (n=179) and best supportive care or conventional-care regimens, which included low-dose ara-C (20 mg/m^2/day for 14 days every 28 days), standard chemotherapy (7+3 regimen), or best supportive care only (n=179). Erythropoietin was not included in any regimen. One-year survival rates were determined for all patients as well as for azacitidine subsets accord-

ing to International Working Group 2000–defined best response: complete response, partial remission, stable disease, hematologic improvement, or disease progression. The data indicate that the patients who received azacitidine had significantly higher 1-year survival rates than those who received conventional-care regimens: 68.2% versus 55.6%, respectively (*P*=.015). When subsets based on best response to azacitidine were analyzed, all responses showed a survival benefit with azacitidine treatment: complete response (96.7%), partial remission (85.5%), hematologic improvement (96.0%), or stable disease (73.3%). By contrast, only 28.6% of azacitidine recipients with disease progression were alive at 1 year. These data indicate that treatment with azacitidine improves the 1-year survival rate in patients with MDS, regardless of best response.

7032 A Multicenter Phase II Trial of the Decitabine Alternative 5-day Dosing Regimen: Analysis of Efficacy in Various Subgroups of Patients With Myelodysplastic Syndromes[10]

DP Steensma, MR Baer, JL Slack, R Buckstein, LA Godley, JS Larsen, S Arora, MT Cullen, HM Kantarjian

Decitabine is a demethylating agent that has seen wide use in the treatment of MDS. A previous single-center, phase II trial assayed the efficacy of decitabine in patients with MDS when administered intravenously once daily at 20 mg/m^2 over 1 hour for 5 days every 4 weeks. This dosing regimen demonstrated an overall improvement rate (International Working Group 2006–defined response: complete response, marrow complete response, partial response, and hematologic improvement) of 72%.[11] Steensma and associates presented data that addressed the efficacy and safety of decitabine in patients with MDS utilizing this same dosing regimen but in a multicenter setting. Patients enrolled in this study had a median age of 72 years, presented with all French-American-British MDS classifications, had International Prognostic Scoring System scores greater than 0.5, and had Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. In addition, 11% had secondary MDS, 27% had received prior MDS disease-modifying therapy, and 29% had poor-risk cytogenetics. The overall improvement rate was 50% for those patients in the intermediate-1–risk group, 61% for intermediate-2–risk patients, and 43% for high-risk patients. Overall improvement rates were 51% for patients with de novo MDS, 45% for patients with secondary MDS, and 44% for patients who had received prior disease-modifying agents. Furthermore, 82% of patients who experienced clinical improvement did so by cycle 2. The overall safety profile was in agreement with previous studies. This trial confirmed that a 5-day decitabine dosing schedule is safe and effective across a spectrum of patients with MDS.

7033 Treatment of High-risk MDS Patients With -7/del(7q) With Azacitidine Versus Conventional Care Regimens: Effects on Overall Survival[12]

GJ Mufti, P Fenaux, E Hellstrom-Lindberg, V Santini, AF List, S Gore, JF Seymour, LR Silverman, J Backstrom, CL Beach

Mufti and coauthors assessed the effects of azacitidine on overall survival in a subgroup of high-risk MDS patients that had the -7/del(7q) genotype. A total of 57 patients with the -7/del(7q) genotype were enrolled: 35% had -7/del(7q) alone and 65% had -7del(7q) as part of a complex karyotype. The median age of patients was 69 years, and 70% were male. Thirty patients were randomly assigned to receive azacitidine 75 mg/m^2/day for 7 days every 28 days, and 27 patients were assigned to conventional-care regimens consisting of one of three treatments: best supportive care only (transfusions, antibiotics, and granulocyte colony-stimulating factor [G-CSF] for neutropenic infection), low-dose ara-C (20 mg/m^2/day for 14 days every 28 days), or induction chemotherapy (7+3 regimen). None of the treatment regimens included erythropoietin. An 8.4-month difference (3-fold improvement) in overall survival was observed for those patients receiving azacitidine compared with those receiving conventional care. The risk of death was reduced by 67% for patients receiving azacitidine (hazard ratio, 0.33). Moreover, at 2 years, a 4-fold overall survival advantage was observed for these patients (33% of patients receiving azacitidine were alive vs 8% of the patients receiving conventional care). Significantly better response rates (International Working Group 2000 criteria) were also observed for patients receiving azacitidine versus conventional-care regimens with regard to complete and partial responses (43% vs 4%; *P*=.0005), complete responses (27% vs 4%; *P*=.03), red blood cell-transfusion independence

(57% vs 0%; *P*<.0001), hematologic improvement of the erythroid lineage (50% vs 0%; *P*<.0001), and hematologic improvement of the platelet lineage (50% vs 8%; *P*=.002). Significantly higher response rates were seen in azacitidine versus control patients with -7/del(7q) alone (64% vs 11%; *P*=.03) or with -7/del(7q) as part of a complex karyotype (21% vs 0; *P*=.02). Azacitidine was also reported to be well tolerated in these patients.

Lymphoma

057 Results of a Phase III Trial Evaluating Safety and Efficacy of Specific Immunotherapy, Recombinant Idiotype Conjugated to KLH with GM-CSF, Compared to Non-specific Immunotherapy, KLH With GM-CSF, in Patients With Follicular non-Hodgkin's Lymphoma[13]

R Levy, M Robertson, J Leonard, J Vose, and D Denney

MyVax is a patient-specific or personalized cancer vaccine that is composed of a tumor-specific idiotype protein attached to a carrier (ie, keyhole limpet hemocyanin [KLH]). This chimeric protein is administered in combination with an adjuvant (ie, granulocyte-macrophage colony-stimulating factor [GM-CSF]) to enhance the immune response. In this report, at the 10th International Conference on Malignant Lymphoma, in Lugano, Switzerland, Levy and colleagues presented data from a multicenter trial that examined the safety and efficacy of MyVax compared to a control immunotherapy, KLH alone, in patients with previously untreated follicular NHL. Patients received a series of 7 immunizations over a 24-week period. All patients received eight cycles of cyclophosphamide, vincristine, and prednisone (CVP), and those who maintained at least a partial response over the following 6 months were randomly assigned in a 2:1 fashion to the MyVax group or the control group. All patients also received GM-CSF at each immunization and over the following 3 days. Specific humoral immune responses were assayed before, during, and at 1 year following immunizations. Overall, progression-free survival rates and the time to subsequent antilymphoma therapy were not statistically different between the patients who received MyVax compared to those who received the control immunotherapy. However, for those patients who demonstrated a specific immune response to the tumor-specific idiotype protein (41% of evaluable patients), a greater than 2-fold improvement in progression-free survival (*P*=.0017) was observed compared to control patients.

213 Phase III Randomized Trial Comparing R-CHOP vs R-miniCEOP in Elderly Patients With Diffuse Large B-cell Lymphoma Prospectively Selected by a Multidimensional Evaluation Scale[14]

F Merli, S Luminari, A Tucci, P Pregno, M Musso, M Martelli, C Stelitano, L Baldini, P Massa, D Vallisa, F Salvi, E Barbolini, AM Liberati, C Bottelli, F Liariucci, M Federico

In Lugano, Switzerland, Merli and colleagues presented data from a phase III study that compared 21-day schedules of the R-CHOP and R-miniCEOP (rituximab, cyclophospharnide, epirubicin, vincristine, and prednisolone) regimens for the initial treatment of elderly patients with DLBCL. Furthermore, this study also assessed the usefulness of a Multidimensional Evaluation Scale (MES) to aid in the identification of elderly patients eligible for full-dose chemotherapy. The MES questionnaire included comorbidity, activities of daily living, instrumental activities of daily living, and geriatric syndrome scales. A total of 234 patients were randomized to the R-CHOP-21 (n=114) and R-miniCEOP-21 (n=120) arms. All patients had stage II–IV DLBCL (stage III–IV, 69%), were categorized as nonfrail, and were a median of 71 years old. The ratio of men to women ratio was 1:1, 27% had disease in extranodal sites, and 47% had an age-adjusted International Prognostic Index of 2–3. Patients received six courses of R-CHOP-21 or R-miniCEOP-21 (vinblastine 5 mg/m^2 instead of vincristine; epidoxorubicin 50 mg/m^2 instead of doxorubicin). The complete response rate was 74% for the R-CHOP-21 group versus 65% for the R-miniCEOP-21 group (*P*=.233). Like the response rate, toxicity was also reported to be similar between the two groups. The 2-year event-free and overall survival rates were 52% and 70%, respectively, with no differences between treatment groups. The median follow-up was 18 months. An analysis of the MES data did not identify any comorbidi-

Table 1. Reported Outcomes Among Evaluable Patients Receiving Vorinostat Plus Cytarabine

Cohort	Pts, n	Cytarabine, mg/m^2 Subcutaneously on Days 1–7	Vorinostat, mg/day for 14 Days	Total Dose of Cytarabine/Vorinostat	Response
1	3	55	200 BID	385/5,600	CR;CR;CR
2	3	55	200 TID	385/8,400	CR;SD;CRi
3	3	75	200 TID	525/8,400	SD;CR;HI
4	3*	75	200 BID	525/5,600	HI;HI

* One patient was inevaluable in this cohort.

CR=complete response; CRi=complete response with incomplete blood count recovery; HI=hematologic improvement; SD=stable disease.
Adapted from J Clin Oncol. 2008;26(pt15S):Abstract 7000

ties, activities-of-daily-living scores, or instrumental-activities-of-daily-living scores of prognostic relevance.

8509 International Study of Lenalidomide in Relapsed/Refractory Aggressive non-Hodgkin's Lymphoma[15]

MS Czuczman, CB Reeder, J Polikoff, NM Chowhan, I Esseessee, R Greenberg, A Ervin-Haynes, D Pietronigro, JB Zeldis, TE Witzig

Lenalidomide is an immunomodulatory agent with an unknown mechanism of action, although its efficacy for the treatment of NHL has been well demonstrated. It is a more potent derivative of thalidomide that is associated with fewer adverse effects. At the annual meeting of American Society of Clinical Oncology, Czuczman and colleagues presented data from a study that determined the activity and safety of lenalidomide in patients with relapsed/refractory aggressive NHL. Patients with detectable neoplasm (>2 cm) following more than one prior treatment regimen were enrolled. A total of 46 patients were eligible for response assessment and 79 for safety evaluation. The median age of all patients was 65 years (range, 21–84) and 74% were men. The median time from diagnosis was 2 years (range, 0.2–12) and the median number of prior treatment regimens was 3.5 (range, 1–13), with 96% of patients having received prior treatment that included rituximab. In this study, patients were administered lenalidomide 25 mg orally once daily on days 1–21 of every 28 days. A positive response was observed in 28% of patients assessed. Univariate analyses indicated that a positive response to lenalidomide was associated with two predictive factors: a low tumor burden (<50 cm^2) and greater than 230 days from the last rituximab dose to the start of lenalidomide treatment. The response rate in patients with favorable values for these predictive factors (n=20) was 50%, whereas the response rate for patients with unfavorable values (n=26) was 12% (P=.007). Among the grade 3/4 adverse events, the most common were neutropenia (24%), thrombocytopenia (16%), leukopenia (9%), anemia (6%), dehydration (5%), and fatigue (5%). Overall, this study confirmed that lenalidomide is effective and safe for the treatment of relapsed/refractory aggressive NHL.

8513 Phase III Study of Patients With Relapsed, Refractory Mantle Cell Lymphoma Treated With Temsirolimus Compared With Investigator's Choice Therapy[16]

G Hess, JE Romaguera, G Verhoef, R Herbrecht, M Crump, A Strahs, J Clancy, B Hewes, B Coiffier

Temsirolimus is an analog of rapamycin that functions as a discriminating blocker of the cyclin D1 translation regulator mammalian target of rapamycin (mTOR). MCL is a type of B-cell lymphoma characterized by translocation (11;14) that puts the cyclin D1 gene

Table 2. Survival and Objective Response Rate for Patients With Mantle Cell Lymphoma Administered Temsirolimus or Investigator's Choice Therapy

Parameter	Temsirolimus 175/75 mg (Arm 1)	Temsirolimus 175/25 mg (Arm 2)	Investigator's Choice (Arm 3)
n	54	54	54
Progression-free survival, independent assessment			
Median, months (97.5% CI)	4.8 (3.1–8.1)	3.4 (1.9–5.5)	1.9 (1.6–2.5)
Increase in median*	153%	79%	
Hazard ratio (97.5% CI)*	0.44 (0.25–0.78)	0.65 (0.39–1.10)	
P value*	.0009	.0618	
Overall survival			
Median, months (95% CI)	10.9 (8.1–14.1)	8.5 (5.8–14.0)	5.8 (4.8–12.4)
Increase in median*	88%	47%	
Hazard ratio (95% CI)*	0.62 (0.37–1.05)	0.80 (0.48–1.33)	
P value*	.0714	.3876	
Objective response rate (95% CI)	22% (11–33)	6% (0–12)	2% (0–5)
P value*	.0019	.6179	

CI=confidence interval.

*Arm 1 or arm 2 versus arm 3.

Adapted from *J Clin Oncol.* 2008;26(15S pt1): Abstract 8513.

adjacent to the heavy chain promoter, which results in the overexpression of cyclin D1 messenger RNA. In this report, Hess and coworkers presented data from a phase III trial that compared the efficacy of temsirolimus against an investigator's choice of therapy in patients with relapsed/refractory MCL. The authors reported the results for 162 patients following 105 progression-free survival events. Patients' median age was 67 years, 81% were men, 32% had undergone prior SCT, and 50% received more than three prior regimens (range, 2–7), all of which included an alkylating agent, an anthracycline, and rituximab. Patients were assigned to one of two schedules of temsirolimus: 175 mg three times a week followed by either 75 mg (Arm 1) or 25 mg (Arm 2) weekly. The control regimen, consisting of the investigator's choice of therapy (Arm 3), included gemcitabine (42%), fludarabine (26%), chlorambucil (6%), cladribine (6%), etoposide (6%), cyclophosphamide (4%), thalidomide (4%), vinblastine (4%), alemtuzumab (2%), or lenalidomide (2%). Among the three groups (Arm 1; Arm 2; Arm 3), the median progression-free survival duration (4.8; 3.4; 1.9 months), objective response rate (22%; 6%; 2%), and median overall survival duration (10.9; 8.5; 5.8 months) were all significantly improved for those patients receiving temsirolimus at 175/75 mg (Arm 1) compared with those receiving an investigator's choice of therapy (Arm 3). All groups demonstrated an acceptable safety profile and exhibited similar rates of adverse events greater than grade 3: thrombocytopenia (59%; 52%; 36%), anemia (20%; 11%; 17%), neutropenia (15%; 22%; 26%), and asthenia (13%; 19%; 8%).

Chronic Lymphocytic Leukemia

7003 Lumiliximab in Combination With FCR for the Treatment of Relapsed Chronic Lymphocytic Leukemia: Results From a Phase I/II Multicenter Study[17]

JC Byrd, JE Castro, IW Flinn, A Forero-Torres, TJ Kipps, NA Heerema, TS Lin, H Mu, S Tangri, S O'Brien

Lumiliximab is a monoclonal antibody that targets CD23, a cell surface receptor expressed on a large majority of CLL cells. At the 2008 annual meeting of the American Society of Clinical Oncology, in Chicago, Ill., and at the 10th International Conference on Malignant Lymphoma, in Lugano, Switzerland, Byrd and colleagues presented data from a phase I/II, multicenter study that evaluated the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide, and rituximab (FCR) in 31 patients with relapsed B-cell CLL and positive CD23 expression. Patients (mean age, 58 years) had received a median of 2 prior regimens (range, 1–20), and the majority had Rai stage I/II disease (71%). All patients completed the treatment, which consisted of lumiliximab 375 mg/m^2 (n=3) or 500 mg/m^2 (n=28) in combination with FCR for up to six 28-day cycles. The overall response rate was 65% based on National Cancer Institute–Working Group criteria; of these, 52% achieved complete response and 13% demonstrated partial response. Five of eight patients harboring the del(11q22.3) abnormality attained complete response. The projected median progression-free survival duration for all patients was 19.3 months based on a median follow-up of 16.8 months. Furthermore, the median progression-free survival for patients with any response and complete response was 23.4 and 30.4 months, respectively. Importantly, this study also confirmed that lumiliximab plus FCR had a comparable safety profile to that of FCR alone, with no additional toxicity. This acceptable safety profile, as well as the positive response, indicates that lumiliximab is potentially efficacious in treating patients with relapsed B-cell CLL.

7008 Effect of the Addition of Oblimersen (Bcl-2 antisense) to Fludarabine/Cyclophosphamide for Relapsed/Refractory Chronic lymphocytic Leukemia on Survival in Patients Who Achieve CR/nPR: Five-year Follow-up From a Randomized Phase III Study.[18]

KR Rai, J Moore, J Wu, SC Novick, SM O'Brien

Oblimersen is an antisense oligonucleotide that targets the apoptotic inhibitor Bcl-2. Oblimersen significantly enhances the efficacy of standard cytotoxic chemotherapeutics employed against CLL. A randomized phase III trial is currently being conducted in 241 patients with CLL to evaluate the efficacy of fludarabine and cyclophosphamide (FC) with or without the addition of oblimersen. A previous report from this trial indicated that patients who received oblimersen and FC demonstrated a significantly increased and more durable complete response rate compared with patients who received FC alone.[19] In the current report, Rai and colleagues determined whether survival times were also increased for the complete responders who received combination treatment with oblimersen and FC. Importantly, among the patients who achieved a complete response, the median survival time of the 12 patients receiving oblimersen and FC was significantly longer than that of the 3 patients in the FC group, at more than 55 versus 45 months. This increased survival time, as well as the increased rates and duration of complete response, suggests that oblimersen is a beneficial addition to FC treatment.

Multiple Myeloma

295 Bendamustine and Prednisone in Combination With Bortezomib in the Treatment of Patients With Advanced Multiple Myeloma[20]

W Pönisch, M Bourgeois, S Wang, N Jäkel, S Heyn, L Braunert, R Rohrberg, H Hyrtz, F Hoffmann, A Schwarzer, C Becker, H Al Ali, D Niederwieser

Bortezomib is a proteasome inhibitor that has shown significant efficacy for the treatment of patients with multiple myeloma. Pönisch and coworkers presented data at the 10th International Conference on Malignant Lymphoma assessing the efficacy and toxicity of combined bortezomib, bendamustine (a bifunctional molecule with an alkylating agent moiety plus an antimetabolite or purine analog–like component), and prednisone regimens in patients with advanced multiple myeloma. A total of 46 patients with a median age of 63 years (range, 31–77) and relapsed or refractory multiple myeloma (stage IIIa/b) were enrolled. The median time from first diagnosis was 36 months (range, 1–183), the duration of their last remission was 6 months (range, 0–36), and each patient had received a median of two previous therapies (range, 1–6), including thalidomide, autologous peripheral blood SCT, and autologous/allogeneic peripheral blood SCT, to which 16 patients were refractory. Furthermore, 22 patients had pre-existing thrombocytopenia, leukocytopenia, or anemia. Patients received bendamustine 60–80 mg/m^2 on day 1 and 2; bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; and prednisone 100 mg on days 1, 2, 4, 8, and 11. This regimen cycle was repeated every 21 days until reaching a maximum response or progressive disease. The median number of cycles that patients received was two (range, 1–7). The overall response rate was 78% following at least one cycle of chemotherapy and included 4% complete remission, 11% near complete remission, 13% very good partial remission, 33% partial remission, and 17% minor remission. Of the remaining patients, 9% demonstrated stable disease, and 13% had progressive disease. The outcome for patients without severe hematologic toxicities (n=24) was significantly better than those patients with severe hematologic toxicities (ie, grade 3/4; n=22). At 12 months, event-free and overall survival rates for patients without severe hematologic toxicities were 46% and 79%, respectively, as compared with 10% and 22%, respectively, for those patients with severe hematologic toxicities (P<.01). This regimen was reported to be well tolerated, with new cytopenias occurring infrequently.

8504 Randomized Trial of Lenalidomide Plus High-dose Dexamethasone Versus Lenalidomide Plus Low-dose Dexamethasone in Newly Diagnosed Myeloma (E4A03), a Trial Coordinated by the Eastern Cooperative Oncology Group: Analysis of Response, Survival, and Outcome[21]

SV Rajkumar, S Jacobus, N Callander, R Fonseca, D Vesole, MV Williams, R Abonour, DS Siegel, M Katz, PR Greipp

Lenalidomide has demonstrated clinical activity in the treatment of multiple myeloma and has been used in combination with dexamethasone. Rajkumar and colleagues presented a new analysis of data from the E4A03 trial, which assessed the outcome of patients with newly diagnosed myeloma treated with lenalidomide (25 mg/day orally on days 1–21 every 28 days) plus standard, high-dose dexamethasone (40 mg orally on days 1–4, 9–12, and 17–20 every 28 days; Arm 1) versus lenalidomide plus low-dose dexamethasone (40 mg orally on days 1, 8, 15, and 22 every 28 days; Arm 2). A total of 445 patients with untreated, symptomatic multiple myeloma and a median age of 65 years were enrolled. A total of 149 patients reported a stem cell harvest attempt, 97% of which were successful. Within the first four cycles, toxicities greater than grade 3 occurred in 50% of Arm 1 patients versus 30% of Arm 2 patients (P<.001). Partial responses or higher were seen in 82% of patients in Arm 1 versus 70% of patients in Arm 2 (P=.007), and very good partial response rates or better were observed in 52% of patients in Arm 1 versus 42% of patients in Arm 2 (P=.06). The overall survival rate was significantly superior in Arm 2 (P=.006), as 1-year survival was 96% in Arm 2 versus 88% in Arm 1, and 2-year survival was 87% in Arm 2 versus 75% in Arm 1. Of the 421 patients alive at the 4-month landmark analysis, 210 had gone off study, and 211 continued on their primary therapies. The overall 1- and 2-year survival rates among these patients were 96% and 80% for Arm 1 (n=91) and 99% and 91% for Arm 2 (n=120), respectively. This study demonstrated superior

overall survival rates for patients receiving lenalidomide plus low-dose dexamethasone compared to lenalidomide plus high-dose dexamethasone.

8521 A Randomized Southwest Oncology Group Study Comparing Dexamethasone to Lenalidomide Plus Dexamethasone (LD) as Treatment of Newly-diagnosed Multiple Myeloma: Impact of Cytogenetic Abnormalities on Efficacy of LD, and Updated Overall Study Results[22]

JA Zonder, JJ Crowley, V Bolejack, MA Hussein, DF Moore, BF Whittenberger, MH Abidi, BG Durie, B Barlogie

The Southwest Oncology Group (SWOG) recently reported superior 1-year progression-free survival for patients with newly diagnosed multiple myeloma when treated with lenalidomide in combination with dexamethasone compared with dexamethasone alone. In this analysis, Zonder and colleagues presented the 1-year progression-free and overall survival rates for a subset of these patients: those with abnormal karyotypes and high-risk cytogenetic abnormalities. The original study included 198 patients with newly diagnosed multiple myeloma who received lenalidomide 25 mg/day (28 of 35 days for 3 cycles, then 21 of 28 days as maintenance) and dexamethasone (40 mg on days 1–4, 9–12, and 17–20 as induction; 40 mg on days 1–4 and 15–18 as maintenance) or dexamethasone (same induction and maintenance schedules) and a placebo control. All patients received aspirin 325 mg/day. Abnormal karyotypes were seen in 10 of 52 samples from patients on dexamethasone and in 11 of 51 samples from patients on lenalidomide and dexamethasone. For patients with abnormal karyotypes on dexamethasone alone, the 1-year progression-free survival and overall survival rates were 33% and 77%, respectively. For patients with abnormal karyotypes on lenalidomide and dexamethasone, the 1-year progression-free and overall survival rates were 55% and 82%, respectively, compared with 86% (P=.13) and 97% (P=.02), respectively, for patients without an abnormal karyotype. Therefore, patients with abnormal karyotypes treated with lenalidomide and dexamethasone had higher progression-free and overall survival rates when compared to those on dexamethasone alone and showed lower progression-free and overall survival rates compared to those patients without abnormal karyotypes. High-risk cytogenetic abnormalities were seen in 11 of 45 samples from patients on dexamethasone and in 8 of 35 samples from patients on lenalidomide and dexamethasone. For these patients on lenalidomide and dexamethasone, the 1-year progression-free and overall survival rates were both 100% compared to 73% (P=.13) and 92% (P=.02), respectively, for patients without high-risk cytogenetic abnormalities. Therefore, patients with high-risk cytogenetic abnormalities did not show any difference in progression-free and overall survival rates compared to those patients without abnormal high-risk cytogenetic abnormalities.

8524 Final Analysis of MM-014: Single-agent Lenalidomide in Patients With Relapsed and Refractory Multiple Myeloma[23]

MA Hussein, PG Richardson, S Jagannath, S Singhal, W Bensinger, R Knight, JB Zeldis, Z Yu, M Olesnyckyj, KC Anderson

In this study, Hussein and coworkers evaluated the efficacy and safety of lenalidomide monotherapy (30 mg on days 1–21 every 28 days) in 222 patients with relapsed/refractory multiple myeloma. Patients did not receive dexamethasone, nor was anticoagulation prophylaxis recommended. This treatment was continued, as tolerated, until disease progression. At the time when the database was locked, 29% of patients had received treatment for more than 9 months. Patients had a mean time from diagnosis of 4 years, and all had previously received more than two prior multiple myeloma therapies (45% received >4 prior regimens), including bortezomib (43%), thalidomide (80%), and SCT (45%). Response was assessed using modified European Group for Blood and Marrow Transplantation criteria, and toxicity was assayed using National Cancer Institute–Common Toxicity Criteria, version 3. The overall response rate was 26%, and the stable disease rate was 66%. Of the 184 patients in the efficacy-evaluable population, the overall response rate was 32%, and the stable disease rate was 68%. At the end of the study 69% of patients had progressed, with a median time to progression of 5.4 months and a median progression-free survival duration of 4.7 months. The median duration of overall survival

was 1.9 years, with 41% of patients alive after 3 years. The median duration of response was 13 months, with a median follow-up of 14 months. Furthermore, no patients demonstrated grade 3/4 peripheral neuropathy, and only 4% developed febrile neutropenia or deep vein thrombosis. Grade 3/4 toxicities commonly experienced included neutropenia (60%), thrombocytopenia (39%), and anemia (20%). This study demonstrated that lenalidomide monotherapy is effective, well tolerated in patients with relapsed/refractory multiple myeloma, and responses were durable.

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Commentary

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Chronic Myelogenous Leukemia

Imatinib has revolutionized the therapy of CML. Six-year follow-up data from the IRIS study were published earlier this year, showing that imatinib remains an outstanding first-line therapy for the disease.[1] Approximately 88% of patients are alive, and 93% have not progressed to accelerated-phase disease or blast crisis. Approximately 84% of patients demonstrated progression-free survival. This agent remains the primary therapy for chronic-phase CML. In addition to imatinib, 2 agents have been approved by the US Food and Drug Administration (FDA) as second-line tyrosine kinase inhibitors in this setting for CML, nilotinib and dasatinib. Preclinical evidence predicted significant activity against BCR-ABL kinase for both these agents, and, in particular, the 2 most common mechanisms of resistance to imatinib.[2] At the 2008 ASCO annual meeting, data were presented from the START-C trial, which assessed dasatinib in the setting of imatinib resistance or intolerance.[3] This trial showed a high response rate and a high progression-free survival rate (80%) at 2 years in patients treated with dasatinib. The agent was generally well-tolerated, although there were episodes of neutropenia, thrombocytopenia, and pleural effusion occurring at a higher rate than is seen with imatinib.

Acute Leukemia

The combination of an anthracycline (eg, idarubicin or daunorubicin) or mitoxantrone with infusional ara-C remains the standard of care for initial treatment of patients with AML. Furthermore, consolidation with either cycles of high-dose ara-C or autologous or allogeneic stem cell transplantation remains the norm based on a risk-adapted strategy. Unfortunately, despite the success of these therapies, the majority of adult patients will relapse. Approaches for reinduction of remission remain to be improved. A new approach for remission induction, presented by DeAngelo and colleagues,[4] included the addition of a novel alkylating agent to high-dose ara-C to increase the response rate and potentially allow patients to proceed to stem cell transplantation or maintenance therapy at a higher rate. This trial randomly assigned patients to the novel alkylating agent VNP40101M versus placebo along with a continuous infusion of high-dose ara-C over 3 days. The results were encouraging; the patients receiving the alkylating agent plus ara-C demonstrated a higher response rate and improved survival over the control group. However, the results were cautionary because the treatment-related mortality rate was higher among patients who received the experimental therapy, particularly due to an increased rate of infection. The control group experienced more delayed mortality, primarily due to disease relapse. Further investigation of different doses, schedules, and combinations of this promising approach appear reasonable.

It should be noted that DeAngelo and colleagues administered VNP40101M to patients in a relatively early setting (ie, first relapse), and, currently, patients in this setting are expected to have response rates up to 50% with conventional combinations such as mitoxantrone and VP16, less toxic agents such as decitabine or azacitidine, or with the same regimen with which patients had achieved their first remission (eg, ara-C plus daunorubicin). Moreover, a patient with leukemia in first relapse usually undergoes therapy that is intended to reinduce remission, to be followed by a consolidation treatment of this remission with autologous or allogeneic stem cell transplantation. Therefore, the most important aspect of induction therapy is to achieve remission with low morbidity and mortality. The combination used by DeAngelo and colleagues induced remission at a relatively high rate, but it did so with more toxicity than the control group, and therefore

the percentage of patients ultimately able to proceed to stem cell transplantation remained limited.

Myelodysplastic Syndromes

Drugs targeting epigenetic mechanisms to induce expression of previously silenced genes have now been shown to be very effective in the treatment of patients with higher-risk myelodysplasia. Both azacitidine and decitabine have now been demonstrated to significantly alter the natural history of MDS, as in the study by List and associates presented at the 2008 ASCO meeting,[6] among others. The research by List and associates and Mufti and coworkers,[7] as well as Fenaux and coworkers presented in 2007,[8] lends further support to the use of azacitidine in patients with MDS regardless of cytogenetic subtype. Interestingly, even if the patients do not achieve complete remission, there is continued evidence of improved survival. It is remarkable that an agent such as azacitidine, which has been the subject of clinical research for almost 20 years due to persistent investigation of various schedules and dosages, is continuing to improve the clinical status of patients with MDS. Survival has been improved, even in patients with a substantial percentage of blasts, despite the majority of patients not entering complete remission.

In regard to decitabine, Steensma and colleagues produced reassuring results in their phase II study of an alternative regimen based on this demethylating agent given at 20 mg/m^2 over 1 hour for 5 days every 4 weeks in a very easy-to-administer outpatient regimen for physicians and patients.[9] This dose and schedule have been shown to be at least as efficacious, and perhaps even more so, in comparison to more cumbersome doses and schedules. None of these studies directly addresses the issue of whether one demethylating agent is superior to another. The data suggest that both azacitidine and decitabine are effective and are of reasonable toxicity, and can be administered safely and effectively in the outpatient setting. These agents for high-risk MDS, along with lenalidomide for low-risk MDS of either normal cytogenetics or characterized by the 5q-syndrome, have become standard treatments.

MDS remains a disease that has limited survival, and the potential for evolution to acute leukemia still exists. Additional agents are needed. For example, vorinostat, a histone deacetylase inhibitor, with epigenetic activity, has demonstrated efficacy in lymphoid malignancies.[10] The inhibition of histone deacetylase is a promising treatment for MDS and AML. The phase I trial by Silverman and colleagues presented at the 2008 ASCO meeting demonstrated that patients with MDS or AML could tolerate this agent very well when it was combined with ara-C.[11] This trial included a small number of patients, and so the results need to be interpreted cautiously; however, the fact that approximately 50% of patients entered complete or virtually complete response is very encouraging. It is appropriate that more patients be considered for this therapy.

Myeloid stimulating factors such as G-CSF and GM-CSF as well as erythropoietin-stimulating agents have substantially improved the anemia and neutropenia associated with hematologic malignancies. Thrombocytopenia, however, remains a significant problem. AMG 531 (romiplostim), a novel Fc peptide fusion protein, stimulates platelet production through the same mechanism as endogenous thrombopoietin; this agent has been investigated previously in the setting of chronic immune thrombocytopenia purpura.[12] In a recent study by Kantarjian and colleagues, patients who had MDS with severe thrombocytopenia received weekly subcutaneous injections of this agent.[13] Patients with baseline platelet counts below 20,000/µL had a 55% response rate, and patients with platelet counts greater than 20,000/µL had a 54% response rate. These encouraging data suggest that a stimulating agent for platelets may be successful in patients with hematologic malignancies.

Lymphoma

Follicular lymphoma is the second most common NHL, and though patients have a very long natural history, the likelihood of eliminating this disease is low. Ultimately, patients experience progressive disease or transformation to more aggressive lymphomas, leading to morbidity and mortality. Conventional chemotherapies (eg, CVP, CHOP) confer a high response rate, but residual disease remains. Several investigations raised to reduce minimal residual disease have been undertaken with, in particular, immunotherapeutic approaches including vaccines. The patient-specific vaccine investigated by Levy and coauthors was composed of a tumor-specific idiotype protein attached to KLH, administered to patients who had responded to initial CVP.[14] The group receiving the vaccine was compared to a control group. Though there was no difference in progression-free survival between the two groups, approximately 40% of the patients receiving the vaccine developed a specific immune response. When the in vitro immune-response patients were compared to the control, a significant improvement in progression-free survival was identified. This trial is one of the first to demonstrate a potential survival improvement with this form of vaccine therapy. The results are encouraging, but more investigation is required. Notably, these patients

did not receive rituximab, and numerous trials have now suggested that the combination of R-CVP or R-CHOP are superior to either chemotherapy regimens without rituximab. As such, a comparison of a rituximab-based immunotherapeutic approach with a vaccine-based immunotherapeutic approach is warranted.

Large-cell lymphoma remains a disease with a median age of diagnosis of 57 years, with a large proportion of patients over 70 years of age. This age group has frequent comorbid conditions that may preclude the use of, or reduce the ability of patients to receive, R-CHOP administered every 3 weeks. The best approach to treating older patients with large-cell lymphoma remains to be determined. It is reasonable to investigate reduced-intensity therapies in this older patient population. The reduced-intensity therapy proposed by Merli and colleagues was a combination of rituximab, cyclophosphamide, epirubicin, vincristine, and prednisolone (R-miniCEOP).[15] In this study, which enrolled patients at least 65 years of age (median age, 71 years), the response rates were similar among those receiving R-CHOP and R-miniCEOP. The latter regimen appeared well-tolerated, but it was not clearly superior to R-CHOP. Therefore, R-CHOP remains the standard against which other regimens should be compared.

Despite the available therapies for NHL, a subset of patients refractory to first- and second-line regimens exists. Therefore, the development of new therapies continues to be important. Lenalidomide has previously been shown to be active against lymphoid malignancies such as multiple myeloma and CLL; Czuczman and associates investigated the efficacy of single-agent lenalidomide in patients with relapsed and refractory NHL.[16] Approximately 28% of these heavily pretreated patients responded to the standard dose of lenalidomide. This agent was generally well-tolerated, with toxicities that were expected based on previous investigations of the agent. The activity of lenalidomide in this group of patients suggests clinical trials or combinations with other agents should be pursued in the future.

Temsirolimus, an inhibitor of mTOR, blocks cyclin D1 activity, and therefore is a reasonable agent for the treatment of mantle cell lymphoma (MCL). Results of a study comparing temsirolimus versus investigator's choice of therapy were presented by Hess and colleagues.[17] The study randomly assigned patients to doses and schedules of temsirolimus or the investigator's choice of therapy. Temsirolimus demonstrated superiority in terms of response rate and progression-free and overall survival. These data are promising and rationalize further studies of this agent in patients with MCL. However, this study's design cannot definitively identify this agent as superior to other approaches given the heterogeneity of the treatments and the potential for selection bias in patients chosen to receive chemotherapy versus the investigational therapy.

Chronic Lymphocytic Leukemia

The combination of fludarabine, cyclophosphamide, and rituximab (FCR) has become a standard therapy in the treatment of patients with CLL, given the demonstrated high response rates and improved survival duration. Nevertheless, the vast majority of patients who receive FCR will progress and have residual disease. Lumiliximab is an anti-CD23 monoclonal antibody (CD23 is expressed on CLL cells) that was administered with each dose of FCR (ie, L-FCR) in the study by Byrd and coworkers.[18] This study demonstrated that it was feasible to administer this agent along with FCR without a substantial increase in toxicities, particularly infectious toxicities, which is notable given that lumiliximab is a lympholytic agent. A high complete response rate of 52% was obtained. The degree of additive benefit of lumiliximab to FCR, however, will require further prospective studies.

Long-term follow-up of a trial assessing the efficacy of oblimersen, a Bcl-2 antisense plus FC, conducted by Rai and colleagues, showed that the addition of this agent was not associated with long-term toxicities in patients with CLL.[19] Some patients treated with this regimen achieved long-term survival, but the numbers remain low. The incremental benefit of this agent to FC remains difficult to discern from this trial.

Multiple Myeloma

Over the last 5 years, the treatment paradigms for multiple myeloma have undergone a substantial evolution. Novel therapies, such as the immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib, first demonstrated high response rates and improved survival in relapsed and refractory myeloma. These agents have now been adopted with dexamethasone as first-line therapies for multiple myeloma. Rajkumar and associates further updated data from the ECOG E4A03 trial that evaluated lenalidomide plus high- or low-dose dexamethasone as initial therapy for patients with myeloma.[20] These researchers have demonstrated that despite a higher response when lenalidomide is administered with high-dose dexamethasone, the combination of lenalidomide plus lower-dose dexamethasone leads to decreased toxicity and a superior 1- and 2-year survival. Lenalidomide plus low-dose dexamethasone is thus now considered the preferable regimen for patients with newly

diagnosed disease. The investigators also demonstrated that patients treated with this initial therapy were able to successfully undergo autologous stem cell collection and then high-dose melphalan and stem cell transplantation. The subgroup of patients who underwent stem cell transplantation on this trial had a 1-year survival rate of 96%.

SWOG also presented follow-up data of a study of lenalidomide plus high-dose dexamethasone versus high-dose dexamethasone alone in newly diagnosed patients with multiple myeloma.[21] The investigators showed superior response rates when lenalidomide was added to high-dose dexamethasone. However, toxicities and 1-year mortality reported in this study were substantially higher than those seen in E4A03, suggesting that the approach of low-dose dexamethasone is superior.

In the relapsed/refractory setting of myeloma, Hussein and coworkers once again demonstrated the activity of lenalidomide as monotherapy.[22] More importantly, the ability to continue this agent for a long period of time with acceptable toxicities was demonstrated. In particular, the likelihood of experiencing significant peripheral neuropathy, febrile neutropenia, or deep-vein thrombosis was 4% or less. These long-term data suggest that a maintenance program of single-agent lenalidomide in patients with responding relapsed/refractory myeloma is well-tolerated and efficacious.

Furthermore, single-agent bortezomib was shown to be superior to single-agent dexamethasone in this setting by Richardson and colleagues in 2005.[23] Despite the demonstrated activity of bortezomib alone, response rates remain less than 50%. Attempts to potentiate the effectiveness of bortezomib constitute a very important area of current investigation. Pönisch and colleagues reported the results of a study of the combination of a newly available chemotherapeutic agent, bendamustine, with bortezomib and corticosteroid in patients with advanced myeloma.[24] They found a very high response rate (78%), with reasonable toxicities. A proportion of patients demonstrated long-term survival.

Conclusion

In summary, a plethora of new agents and new approaches for the treatment of patients with hematologic malignancies are under clinical investigation that show very promising response rates as well as survival advantages to a subset of patients. The future research will focus on comparing the novel agents and combinations to each other, as well as biologic and risk adapted strategies to predict which subset of patients will respond to a given therapy. Gene-expression analysis and other molecular techniques may play a significant, though as yet undefined, role in this future research.

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Notes

Highlights in Hematologic Malignancies

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

1. In a multicenter study reported by Byrd and colleagues, the combination of _____ with fludarabine, cyclophosphamide, and rituximab (FCR) produced an overall response rate of 65%.

   a. oblimersen
   b. vorinostat
   c. lumiliximab
   d. lenalidomide

2. In a study presented by Mauro and colleagues it was determined that _____ of patients with chronic-phase CML, following treatment with dasatinib, demonstrated progression-free survival at the two-year follow-up.

   a. 80%
   b. 19%
   c. 91%
   d. 94%

3. Lenalidomide monotherapy was shown to be efficacious in patients with relapsed/refractory aggressive NHL, producing a positive response rate of _____ in a study presented by Czuczman and fellow investigators.

   a. 25%
   b. 33%
   c. 44%
   d. 28%

4. In a phase III study conducted by DeAngelo and colleagues, the overall response rate following ara-C treatment with and without the addition of VNP40101M was _____ and _____ in patients with relapsed acute myeloid leukemia.

   a. 37%, 19%
   b. 39%, 86%
   c. 30%, 30%
   d. 91%, 73%

5. Merli and fellow investigators report data from a phase III study that compared R-CHOP-21 and R-miniCEOP-21 in elderly patients with diffuse large b-cell lymphoma, which indicated a statistically _____ difference in complete response rates between these regimens.

   a. significant
   b. insignificant

6. In a study reported by List and colleagues, a 68.2% 1-year survival rate in response to _____ was observed in patients with MDS.

   a. decitabine
   b. vorinostat
   c. azacitidine
   d. rituximab

7. Data presented by Hess and colleagues indicate that patients with relapsed/refractory mantle cell lymphoma treated with temsirolimus (175 mg) demonstrated a median overall survival duration of _____ months.

   a. 10.9
   b. 3.4
   c. 1.9
   d. 4.2

8. Mufti and colleagues observed a _____ overall survival advantage for patients in a subgroup with high-risk MDS receiving azacitidine compared to those receiving conventional-care regimens.

   a. 43%
   b. 4-fold
   c. 33%
   d. 3-fold

9. A subset analysis performed by Zonder and colleagues found that lenalidomide in combination with _____ resulted in a statistically significant increase (P=.02) in overall survival rates for those patients with newly diagnosed multiple myeloma and abnormal karyotypes.

   a. prednisone
   b. bendamustine
   c. thalidomide
   d. dexamethasone

10. True or false: in patients demonstrating relapsed/refractory multiple myeloma, results presented by Hussein and colleagues indicate that lenalidomide monotherapy results in an overall response rate (complete response and partial response) of 26%.

    a. True
    b. False

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Evaluation Form Highlights in 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:

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of hematologic malignancies 1 2 3 4 5
- Review the results of these new study findings including current clinical trials evaluating therapy in the treatment of hematologic malignancies 1 2 3 4 5
- Explain how to integrate into clinical practice the latest knowledge and methods for treating patients with hematologic malignances in an effort to improve current prognosis 1 2 3 4 5
- Identify future research directions for all therapies in hematologic malignancies 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: _____

_____

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