EMERGING TARGETED THERAPIES
FOR HEMATOLOGIC MALIGNANCIES:
LEAVING A GENETIC AND EPIGENETIC IMPRINT FOR BETTER OUTCOMES

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EMERGING TARGETED THERAPIES FOR HEMATOLOGIC MALIGNANCIES:
LEAVING A GENETIC AND EPIGENETIC IMPRINT FOR BETTER OUTCOMES

The content of the supplement was drawn in part from sessions presented in 2009 at the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO) and the 14th Congress of the European Hematology Association (EHA). However, this independent continuing medical education activity is neither sponsored nor sanctioned by ASCO or EHA.

NEEDS ASSESSMENT
The introduction of monoclonal antibodies has led to new therapeutic options for the management of hematologic malignancies. The use of these “targeted” agents against specific cell-surface receptors, enzymes, and proteins has become an important strategy in the treatment of hematologic disorders, including myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and multiple myeloma (MM).

Allogeneic bone-marrow transplantation is the only curative option for MDS, but older patients are not appropriate candidates for this approach. As MDS affects hematopoietic stem cells (leading to ineffective hematopoiesis), treatment may result in infection, transfusion-related anemia, and progression to AML. The exploration of novel targets with relevance in myelopoesis has stimulated the development of an array of agents that show promise in the treatment of MDS, providing an opportunity for improvements in quality of life and, possibly, prolonged survival.

An increased understanding of the role that signaling pathways play in the pathogenesis of AML has also led to treatments that target known genetic markers and altered signaling pathways. Many of these approaches are designed to interfere with molecular genetic or epigenetic mechanisms. Other targeted approaches currently under development may have therapeutic potential to complement high-dose chemotherapy and bone-marrow transplantation, but the major challenge remains to identify targets of critical pathophysiologic importance. These targets may be helpful in developing appropriate treatment for older patients with AML, particularly those aged ≥65 years who are intrinsically resistant to chemotherapy.

Novel therapies also have changed the standard approach to induction therapy for patients with newly diagnosed MM who are eligible for autologous stem cell transplantation (SCT). For patients who are not eligible for autologous SCT, novel treatment has shown efficacy for newly diagnosed MM, and a steroid-independent salvage regimen has shown benefit for relapsed/refractory MM.

The use of novel agents, alone and in combination, has emphasized the importance of the role of the target in defining response. This supplement will focus on the development of targeted treatment approaches that will expand the therapeutic options for patients with hematologic malignancies.

REFERENCES

EDUCATIONAL OBJECTIVES
After taking part in this educational activity, participants should be able to:
• Assess the risk factors and current standards of care for patients with hematologic malignancies
• Describe the latest management approaches for hematologic malignancies, including leukemia, multiple myeloma, and myelodysplastic syndromes
• Identify appropriate management options based on emerging data on novel agents that are being developed for the treatment of hematologic malignancies

TARGET AUDIENCE
Oncologists, hematologist-oncologists, hematologists, and other clinicians involved in the care of patients with cancer

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Novel Hypomethylating Agents Treat High-Risk Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) is a collection of hematologic malignancies that share an insufficient production of normal bone marrow or myeloid cells. With progressing bone marrow failure, patients gradually display worsening cytopenias. The prognosis and treatment of MDS vary depending on the patient’s International Prognostic Scoring System (IPSS) score. Patients with a low/intermediate-1 risk score may live with their disease for a number of years and may be treated with biologic, targeted therapies. Patients with an intermediate-2 or higher score are at increased risk for transformation to acute myeloid leukemia (AML), which may justify the use of more intensive therapies and novel chemotherapeutic agents.

Hypomethylating agents have been a major focus of clinical research over the last few years, particularly for patients with high-risk MDS. The two best-studied hypomethylating agents are the structurally similar nucleoside analogs azacitidine and decitabine. Azacitidine appears to improve overall survival, but MDS remains an incurable disease if not cured through allogeneic stem cell transplantation (SCT). However, most patients with MDS are older, with a median age of 70 years at the time of diagnosis, and, therefore, are not appropriate candidates for allogeneic SCT.

MDS is relatively common, with an incidence estimated as high as 50 cases per 100,000 people per year. Mortality in patients with MDS is high, and most patients require transfusions, emergency department visits, and hospitalizations. In higher-risk patients, progress has been seen with the use of reduced-intensity conditioning allogeneic SCT in elderly patients and in studies of the hypomethylating agents azacitidine and decitabine, leading to their approval for the treatment of symptomatic MDS by the FDA. The results of a landmark phase III study showed a significant survival benefit for azacitidine over conventional treatments in patients with higher-risk MDS. Azacitidine and decitabine both inhibit DNA methyltransferases, the enzymes responsible for maintenance of the cell’s specific pattern of cytosine methylation.

Two dosing regimens of decitabine have demonstrated efficacy in MDS: 15 mg/m² intravenously over 3 hours every 8 hours for 3 days every 6 weeks and 20 mg/m² intravenously over 1 hour once daily for 5 consecutive days every 4 weeks. At the American Society of Clinical Oncology annual meeting in Orlando, Florida, David Steensma, MD, of the Mayo Clinic, Rochester, Minnesota, reviewed the results of two randomized phase III studies comparing the 3-day dosing regimen of decitabine to conventional treatments.

### TABLE. RESPONSE TO TREATMENT WITH DECITABINE

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<th>Median no. of cycles</th>
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<th>Overall improvement (%)</th>
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<td>15.2</td>
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<td>20.3</td>
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</table>

*As measured by IWG 2000 criteria; aPatients who became RBC transfusion independent while on-study.
AML=acute myeloid leukemia; CR=complete response; IWG=International Working Group; RBC=red blood cell.
schedule of decitabine with supportive care and two phase II studies of the 5-day dosing schedule. The patients with MDS in these studies had IPSS classification scores of intermediate-2 or high-risk and de novo MDS. The duration of overall improvement, defined as complete response plus partial response plus hematologic improvement, ranged between 9.2 months and 11.3 months across all studies. The researchers observed a trend toward improved outcomes with an increased number of decitabine treatment cycles. The best response was seen among the 93 patients who received the 5-day dosing schedule for 7 cycles, including an overall complete response rate of 37%, overall improvement rate of 65%, and overall survival of 20.3 months (see table). Dr. Steensma stated that increasing the number of decitabine treatment cycles that are administered to patients with MDS may provide additional benefit. A meta-analysis and systematic review of randomized, controlled trials by Gurion and colleagues at the Rabin Medical Center in Petach Tikva, Israel, yielded 4 trials comparing treatment with 5-azacitidine and decitabine to conventional care (best supportive care or chemotherapy) in 952 patients with MDS. The results were presented at the European Hematology Association annual meeting in Berlin, Germany. Time to AML transformation or death, overall response, and toxicity were assessed for all patients. Data for analysis of overall survival were available for 782 patients in 3 of the 4 trials. There was an overall survival advantage with treatment with 5-azacitidine compared with conventional care, but not with decitabine treatment, reported Dr. Gurion. Both hypomethylating agents showed a significant advantage in time to AML or death and in overall response. As expected, a higher rate of grade 3/4 adverse events was observed with the use of the drugs compared with conventional care.

Developing higher hematologic responses, improving quality of life, and prolonging survival remain important treatment goals for patients with MDS. Azacitidine has become the new gold standard for monotherapy against which newer upfront regimens for MDS must be tested. It may also serve as the backbone for newer or combination regimens in the treatment of high-risk MDS.

Predicting Outcomes of Allogeneic Stem Cell Transplantation

Younger patients with myelodysplastic syndrome (MDS) who have high-risk disease with multiple cytogenetic abnormalities are the most likely candidates for allogeneic stem cell transplantation (SCT), the only known cure for the disease. Researchers are now attempting to predict which pretransplant patient characteristics may lead to better overall survival and whether azacitidine induction prior to transplantation affects outcome.

The World Health Organization (WHO) classification, along with the state of disease at transplantation, are two of the most powerful predictors for post-transplant survival, according to new research presented at the 2009 European Hematology Association annual meeting in Berlin, Germany. The WHO classification of MDS incorporated data on the importance of unilineage versus multiligneage dysplasia. Studies have shown that multilineage dysplasia is associated with a worse outcome. Olga Lopez-Villar, MD, Hospital University of Salamanca, Salamanca, Spain, and colleagues reviewed patient characteristics and outcomes for 190 patients with MDS who received allogeneic SCT at 11 centers in Spain between 1987 and 2008. The median age of patients was 49 years. They had a range of WHO classifications, including refractory anemia with without ringed sideroblasts (6.9%), refractory cytopenia with multilineage dysplasia (7.6%), refractory anemia with excess of blasts (RAEB)-1 (15.2%), RAEB-2 (23.4%), 5q-syndrome (1.4%), MDS unclassifiable (2.1%), myelodysplastic/myeloproliferative disease (13.1%), secondary acute myeloid leukemia (27%), and other MDS (2.8%). Patients with chronic myelomonocytic leukemia were also included in the analysis.
About half (42%) of the patients were treated with chemotherapy before transplantation. At transplant, 25.7% of these patients were in complete remission (CR) and 7.3% had a partial response. The rest of the patients received allogeneic SCT without previous chemotherapy (53.2%) or underwent allogeneic SCT in progression without previous chemotherapy (3.7%). Myeloablative conditioning was used in 72.3% of patients; 27.7% of patients were significantly older and received reduced-intensity conditioning. At 10-year follow-up, the overall survival rate was 51% and the event-free survival rate was 48% (see figure). WHO classification was predictive for survival, reported Dr. Lopez-Villar. Disease status at transplant significantly influenced the outcome only for high-risk patients; better results were seen for patients in CR at transplant and those who did not receive pretransplant chemotherapy.

Although patients with MDS receive no clear benefit from cytotoxic induction chemotherapy after allogeneic SCT, they may benefit from azacitidine therapy prior to transplantation. Christopher R. Cogle, MD, of the University of Florida, Gainesville, and colleagues analyzed posttransplant outcomes in 43 patients with MDS, including 9 patients who received azacitidine before transplant and 34 patients who did not. The patients who received azacitidine were significantly older (P < .01), more immunosuppressed at transplant (P < .05), and less likely to receive myeloablative conditioning (P < .05). The azacitidine group also was marginally more likely to have higher disease burden and more likely to have received a graft from an unrelated donor. These patient characteristics reflect the current clinical use of azacitidine as a bridge to transplant for older patients who have no readily available, matched, related donors.

Dr. Cogle reported at the American Society of Clinical Oncology annual meeting in Orlando, Florida, that after a median follow-up of 7 months, the group that received azacitidine before allogeneic SCT demonstrated significantly higher donor chimerism at days 30, 60, and 100 (P < .01). There was no difference in the rates of acute and chronic graft-versus-host disease or median overall survival between the two groups. However, those who received azacitidine pretransplant had a trend toward higher relapses.

Induction with azacitidine results in higher short-term donor chimerism posttransplant, said Dr. Cogle. This effect is probably due to increased immunosuppression in an older population. The increased rate of relapse in the azacitidine group likely reflects the progressive nature of chemotherapy-insensitive disease at transplant. He said these results support administration of azacitidine prior to transplant for patients with MDS, although the data need to be confirmed by a randomized, controlled trial.

REFERENCES

**FIGURE.** Overall and event-free survival following allogeneic stem cell transplantation.2
Lenalidomide Treatments in Myelodysplastic Syndrome for Higher-Risk and Young Patients

The advent of lenalidomide, an analog of thalidomide, has provided a breakthrough therapy for patients with transfusion-dependent anemia due to low- or intermediate-risk myelodysplastic syndrome (MDS) associated with a deletion of chromosome 5q, with or without additional cytogenetic abnormalities. The drug reduces transfusion requirements and reverses cytologic and cytogenetic abnormalities in patients who have MDS with the chromosome 5q deletion.1 Patients with the 5q deletion syndrome, those with an isolated 5q deletion, and those with lower International Prognostic Scoring System (IPSS) scores or lower transfusion requirements at baseline are more likely to experience a longer duration of transfusion independence with lenalidomide treatments.2

One out of 6 patients with MDS carries the chromosome 5q deletion, and about two-thirds of these patients have low or intermediate-1 IPSS scores and relatively favorable prognoses. The other one-third have intermediate-2 or higher IPSS scores because of an increase in marrow blasts and/or other chromosomal abnormalities.3 Lenalidomide is a potentially interesting treatment in higher-risk MDS with del 5q because of the sensitivity of del 5q clones to the drug. In the pivotal study of lenalidomide in MDS with del 5q, 3 of 8 patients found to have high or intermediate-2 IPSS scores had significant hematologic improvement.4

The Groupe Francophone des Myélodysplasies, a French research group, conducted the first clinical trial to assess the therapeutic efficacy of lenalidomide in higher-risk MDS patients with del 5q.1 The phase II study included 47 patients, median age 69 years, with higher-risk MDS, including 60% with high IPSS scores and 40% with intermediate-2 risk scores. Chromosome 5q deletion was isolated in 19% of the patients; 23% of the patients had one additional abnormality and 58% of the patients had more than one additional abnormality. The patients received 10-mg doses of lenalidomide once daily for 21 days every 4 weeks and completed a median of 2 cycles.

The overall response rate was 27% according to the International Working Group 2006 criteria or 41% according to the World Health Organization definition of MDS in which patients who had refractory anemia with excess blasts in transformation were excluded. Seven patients achieved hematologic complete remission (CR), 2 patients achieved marrow CR, 4 patients had hematologic improvement–erythroid, and 12 patients became red blood cell transfusion-independent for a median duration of 6.5 months. The median hematologic response was 6.5 months, and the median CR duration was 11.5 months.

There was a close correlation between cytogenetic and hematologic improvement, the researchers reported. Six of the 9 patients with isolated del 5q achieved CR compared with only 1 of the 11 patients with one additional abnormality and none of the 27 patients with more than one additional abnormality (see table). Another significant predictor of CR was pretreatment platelet counts of more than 100,000/mm³. A little more than one-third of patients with initial platelet counts of more than 100,000/mm³ obtained CR compared with none of the patients with platelet counts <100,000/mm³.

In this trial, lenalidomide showed little efficacy in patients with higher-risk MDS with chromosomal abnormalities in addition to del 5q. The researchers are testing a combination of lenalidomide with chemotherapeutic drugs or hypomethylating agents for these patients with a poor prognosis.1

The immunomodulatory, antiangiogenic, and antiproliferative effects of lenalidomide also make it a potential

<table>
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<tr>
<th>TABLE. PROGNOSTIC FACTORS OF COMPLETE REMISSION</th>
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<td>Factor Category</td>
<td>n</td>
<td>No. of CRs</td>
<td>CR (%)</td>
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<td>&gt;1 additional abnormality</td>
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<td>&lt;20%</td>
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<td>&lt;100</td>
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CR=complete remission.
therapy for pediatric patients with MDS.\textsuperscript{4} Stacey L. Berg, MD, Texas Children’s Cancer Center, Houston, reported on the results of a phase I and pharmacokinetics study of lenalidomide in 46 children with recurrent or refractory solid tumors and 3 children with MDS at the American Society of Clinical Oncology annual meeting in Orlando, Florida.

Lenalidomide was administered orally once daily for 21 of 28 days in escalating doses of 15, 25, 40, 55, and 70 mg/m\textsuperscript{2} per day for children with solid tumors and in a fixed dose of 5 mg/m\textsuperscript{2} per day for children with MDS. After a median of 1 cycle, none of the patients with MDS had a dose-limiting toxicity. The pharmacokinetic parameters were similar to those seen in adults.\textsuperscript{4} No objective responses were seen, but Dr. Berg reported that lenalidomide enhanced IL-2 and IL-15 concentrations in children with recurrent or refractory solid tumor and was well-tolerated.\textsuperscript{4}

REFERENCES

HDAC Inhibitors and Myelodysplastic Syndrome: Ongoing Epigenetic Research

A n understanding of epigenetic changes in myelodysplastic syndrome (MDS) led to the development of the widely used hypomethylating agents azacitidine and decitabine. The importance of epigenetic therapy in the treatment of MDS motivated researchers to look for alternative therapeutic strategies targeting other mechanisms that may contribute to aberrant gene transcription and dysregulated cell growth.\textsuperscript{1}

Among the newer therapies introduced for refractory, relapsed, and resistant disease are histone deacetylase (HDAC) inhibitors. HDAC inhibitors block deacetylation function, causing cell cycle arrest, differentiation, and/or apoptosis of many tumors.\textsuperscript{2} Histone deacetylases are inhibited by various compounds, including phenylbutyrate and valproic acid (short-chain fatty acids), SNDX–275 (formerly MS–275) and MGCD0103 (benzamides), romidepsin (a cyclic peptide), and vorinostat and trichostatin A (hydroxamic acids).\textsuperscript{3}

In some early-phase clinical trials, HDAC inhibitors have exhibited potent antitumor activity in myeloid malignancy, suggesting their usefulness as novel cancer therapeutic agents. Preclinical data show marked synergy between DNA methyltransferase inhibitors and HDAC inhibitors, which indicates that HDAC inhibitors may be more effective when used in combination with other drugs for the treatment of MDS. At least a dozen ongoing phase I and II trials in MDS are investigating combination therapy with DNA methyltransferase inhibitors and HDAC inhibitors.\textsuperscript{4}

As a class, HDAC inhibitors are limited by toxicity due to myelosuppression, fatigue, and gastrointestinal symptoms. Patients with MDS commonly develop thrombocytopenia, which is currently limited to treatment with platelet transfusions. An international study reported at the American Society of Clinical Oncology annual meeting in Orlando, Florida, investigated the subcutaneous or intravenous administration of romiplostim in thrombocytopenic patients with MDS.\textsuperscript{5} Romiplostim is an Fc-peptide fusion protein (peptibody) that stimulates platelet production by the same mechanism as thrombopoietin, said Mikkael Sekeres, MD, of the Cleveland Clinic, Cleveland, Ohio.

The phase II, multicenter, single-arm, open-label study included 28 patients, mean age 71 years, who had International Prognostic Scoring System (IPSS)}
Targeted Therapies Treat Relapsed/Refractory Multiple Myeloma

Multiple myeloma is the second most common hematologic cancer. Although hematopoietic stem cell transplantation has improved the response rate and duration of overall survival, the disease remains incurable. Research aimed at the molecular basis of multiple myeloma has led to a number of new treatment strategies. Clinical-trial results show remarkable efficacy with thalidomide, lenalidomide, or bortezomib in combination with dexamethasone. In addition, these novel drugs can be incorporated into regimens used to treat transplant-ineligible patients or those with relapsing disease. Mounting evidence points to the need for reevaluation of the role of stem cell transplantation in multiple myeloma.

Development of these drugs has transformed the therapeutic management of multiple myeloma and catalyzed a renewed interest in other classes of agents. New agents such as second-generation proteasome inhibitors, immunomodulators, histone deacetylase inhibitors, heat shock protein 90 inhibitors, and alkylphospholipid Akt inhibitor perifosine, have shown promising preclinical results, encouraging safety profiles, and
early evidence of antmyeloma activity as monotherapy or in combination with other conventional or novel treatments.

The combination of bortezomib and pegylated liposomal doxorubicin is an important addition to the therapeutic armamentarium for the management of relapsed/refractory multiple myeloma. Bortezomib was the first proteasome inhibitor to receive regulatory approval for this indication. Modulation of proteasome function, however, is also a rational strategy for chemosensitization. A variety of agents, such as anthracyclines, have shown synergistic activity with bortezomib preclinically. This synergy led to the evaluation of a regimen of bortezomib with pegylated liposomal doxorubicin, which has induced a predictable and manageable toxicity profile and has shown encouraging antmyeloma activity.

In an international, randomized, phase III trial, pegylated liposomal doxorubicin plus bortezomib compared to bortezomib monotherapy demonstrated a longer time to progression, duration of response, progression-free survival, and overall survival. Benefits were also seen in almost all clinically relevant patient subgroups, including those considered to have high-risk disease.

The pegylated liposomal doxorubicin plus bortezomib regimen has become one of the standards of care for patients with relapsed/refractory myeloma. Addition of other active antmyeloma agents to this combination is being studied as well.

Although novel agents have demonstrated enhanced efficacy when combined with other antmyeloma agents, especially dexamethasone, the steroid doses employed in multiple myeloma regimens were often poorly tolerated. Asher Chanan-Khan, MD, of the University of Buffalo, Buffalo, New York, and colleagues investigated the efficacy of a steroid-free combination, including bortezomib, pegylated liposomal doxorubicin, and thalidomide (VDT regimen) in a phase II clinical trial of 23 patients with relapsed/refractory myeloma or other plasma cell cancers. Patients had a median of five prior therapies, and two-thirds of them were refractory to their last regimen.

The overall response rate was 55.5%, median progression-free survival was 10.9 months, and median overall survival was 15.7 months. The most common adverse effects were fatigue and sensory neuropathy.

Dr. Chanan-Khan noted that this three-drug combination is an effective steroid-free salvage regimen with the ability to induce durable remission, even in patients with refractory multiple myeloma.

**REFERENCES**


**LENALIDOMIDE MONOTHERAPY SAFE, EFFECTIVE FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA**

Heavily pretreated, relapsed/refractory multiple myeloma patients can achieve a 2-year median overall survival with lenalidomide monotherapy.

Lenalidomide plus dexamethasone is effective for the treatment of relapsed/refractory multiple myeloma, but dexamethasone can lead to dose-limiting toxicities, noted Paul Richardson, MD, of the Dana-Farber Cancer Institute, Boston, Massachusetts. Richardson and colleagues conducted a study of 222 patients with relapsed and refractory multiple myeloma who received lenalidomide 30 mg/day once daily on days 1-21 every 28 days until disease progression or intolerance. Two-thirds of the patients had received at least 3 previous treatment regimens.

Partial response or better was reported in 26% of patients, and minimal response was reported in 18%. Response rate was similar for patients who had received 2 or fewer prior treatments (45%) and those who had received 3 or more prior treatments (44%). Median time to progression was 5.2 months, median progression-free survival was 4.9 months, and median overall survival was 23.2 months.

The most common grade 3 or 4 adverse events were neutropenia (60%), thrombocytopenia (39%), and anemia (20%), which proved manageable with dose reduction and supportive care. Grade 3 or 4 febrile neutropenia was noted in 4% of patients.

Dr. Richardson noted that acceptable toxicities and activity support the use of single-agent lenalidomide in patients with relapsed/refractory multiple myeloma, as well as the use of lenalidomide in steroid-sparing combinations. This study shows that patients who are frail or who have very indolent relapse can be salvaged with just a single agent, with minimal adverse events.

New Hematopoietic Stem Cell Transplantation Strategies in Multiple Myeloma

A key therapeutic advance in the treatment of multiple myeloma was the introduction of high-dose melphalan therapy supported by autologous hematopoietic stem cell transplantation (SCT). Studies have shown a significant increase in the rate of complete remission or very good partial remission with autologous SCT compared with conventional chemotherapy, and these results have led to significantly prolonged progression-free survival and overall survival.1 Multiple myeloma survival beyond 10 years has become more common. Recent studies show superior 10-year event-free survival estimates of 50% and overall survival estimates of 35%, which demonstrate that a cure requires long-term follow-up.2

Despite a better outcome with high-dose therapy than with conventional-dose treatment, almost all patients with multiple myeloma ultimately relapse. Several newer autologous SCT strategies, including double (or tandem) autologous SCT and nonmyeloablative regimens, have been proposed to further increase complete remission rates. The International Myeloma Foundation is now addressing issues regarding stem cell mobilization and autologous SCT in myeloma in the context of new therapies.3 A tandem transplant procedure involves the administration of a second cycle of high-dose melphalan and a second stem cell infusion within a few months after the first procedure.4 However, appropriate timing for the use of tandem transplantation or nonmyeloablative regimens remains a question.3

Leyla Shune, MD, of the University of Minnesota, Minneapolis, Minnesota, and colleagues examined the outcomes in 51 patients with multiple myeloma who received autologous SCT either as salvage therapy (after failing a prior autologous SCT; 15 patients) or as planned therapy (36 patients). Patients in the salvage-therapy group were significantly older (median age 58 years) than those in the planned-therapy group (median age 49 years) and had a longer interval from diagnosis to transplant (median 47 months versus 10 months), Dr. Shune reported at the American Society of Clinical Oncology (ASCO) annual meeting in Orlando, Florida.

Of the 51 patients, 44 received an autologous SCT from an HLA-identical sibling, 5 received umbilical cord blood (4 in the salvage-therapy group; 1 in the planned-therapy group), and 2 received unrelated donor SCT (1 in each group). Of the 36 patients in the planned-therapy group, 13 underwent a tandem transplant, ie, a planned autologous SCT followed by nonmyeloablative SCT from a sibling donor. All patients in the salvage-therapy group and half of those in the planned-therapy group received nonmyeloablative autologous SCT. Patients in the salvage-therapy group had been more heavily pretreated.

A complete response was observed in 34% of patients in the salvage-therapy group and in 47% of patients in the planned-therapy group. After a median follow-up of 24 months and 41 months, relapse rates were similar. Two-year relapse rates were 28% in the salvage-therapy group compared with 37% in the planned-therapy group (P = .7). The salvage-therapy group had significantly lower rates of 2-year disease-free survival than the planned-therapy group (16% vs 32%, P = .05).

Dr. Shune noted that patients who received planned autologous SCT had good overall survival and low transplant-related mortality (see table). Although there was a lower relapse rate in the heavily pretreated salvage therapy patients, a significantly higher rate of transplant-related mortality at 1 year (47% in the salvage-therapy group vs 22% in the planned-therapy group, P = .02) led to a lower rate of 2-year survival (16% versus 57%, P = .003).

For patients with advanced multiple myeloma, their baseline immune status can contribute to inconsistencies in donor engraftment and may also impede a maximal graft-versus-myeloma effect after reduced-intensity autologous SCT.5 No specific salvage regimen has been designed for patients with multiple myeloma who may be candidates for reduced-intensity autologous SCT.

TABLE. TREATMENT OUTCOMES

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Salvage Therapy</th>
<th>Planned Therapy</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>TRM at 1 year</td>
<td>47%</td>
<td>22%</td>
<td>.02</td>
</tr>
<tr>
<td>Relapse/progression at 2 years</td>
<td>28%</td>
<td>37%</td>
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<tr>
<td>Survival at 2 years</td>
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<tr>
<td>DFS at 2 years</td>
<td>16%</td>
<td>32%</td>
<td>.05</td>
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</table>

DFS = disease-free survival; TRM = treatment-related mortality.

HDAC Inhibitors and Emerging Therapies for Multiple Myeloma

With a greater understanding of the biology of multiple myeloma, researchers have begun to identify novel treatment strategies. These include a combination of the potent histone deacetylase (HDAC) inhibitor vorinostat with two standard therapies for multiple myeloma, lenalidomide and dexamethasone, or an immunoproteasome-specific inhibitor that may provide antiamyeloma activity with greater specificity and less toxicity than current inhibitors.

Treatment of patients with relapsed/refractory multiple myeloma remains extremely challenging and represents a specific unmet medical need. Vorinostat, an oral inhibitor of Class I and II histone deacetylase enzymes, enhances the antiamyeloma activity of other proapoptotic agents and provides potential synergistic activity in combination with lenalidomide and dexamethasone. Antiamyeloma activity of other proapoptotic agents and provides potential synergistic activity in combination with lenalidomide and dexamethasone.1,2

Acute graft-versus-host disease (GvHD) grade II-IV was observed in 9 of 19 patients (47%), and chronic GvHD grade III-IV was observed in 9 of 17 patients (52%). Treatment-related mortality at 100 days was 5% and at 60 months was 30%.

Dr. Jamshed reported that this chemotherapeutic combination is an active regimen that allows for consistent engraftment of allogeneic progenitor cells from donors in patients with multiple myeloma.

REFERENCES
conducted a phase I, multicenter, open-label, nonrandomized, dose-escalation study to evaluate vorinostat plus lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. Dr. Siegel reported the results of this trial at the European Hematology Association annual meeting in Berlin, Germany. Of 18 patients assessed to date for safety, 16 (89%) experienced ≥1 adverse events (AEs) and 13 patients (72%) experienced a total of 32 drug-related AEs, which were mostly mild or moderate in severity. The most frequently reported drug-related AEs were diarrhea in 8 patients (44%), fatigue in 6 patients (33%), neutropenia in 6 patients (33%), and thrombocytopenia in 5 patients (28%). Serious AEs were reported in 3 patients, with only 1 (diarrhea) considered drug related; no patients discontinued treatment because of AEs.

The maximum tolerated dose has not yet been established. Dose-limiting evaluation is ongoing at dose level 5 (see table), which consists of vorinostat 400 mg on days 1-7 and 15-21 in combination with lenalidomide 25 mg on days 1-21 and dexamethasone 40 mg on days 1, 8, 15, and 22 in each 28-day cycle. No dose-limiting toxicity was observed. Dose escalation continues to determine the maximal tolerated dose.

Of 15 patients evaluable for efficacy, 11 (73%) experienced a clinical benefit with the combination therapy. Complete response was achieved in 1 patient, partial response in 4 patients, minimal response in 1 patient, stable disease in 5 patients, and progressive disease in 4 patients. The overall response rate was 40%. Two patients who had received prior lenalidomide therapy had a partial response, and 3 had stable disease. Twelve patients remained on treatment, and 6 patients discontinued treatment due to disease progression.

Dr. Siegel said these preliminary results suggest the combination of vorinostat with lenalidomide and dexamethasone may represent an effective and convenient oral combination therapy that is active and generally well-tolerated in the treatment of relapsed/refractory multiple myeloma.

The combination of vorinostat plus the proteasome inhibitor bortezomib in patients with multiple myeloma has also been found to be well-tolerated and active in two phase I trials, even among some patients with prior exposure to bortezomib.

The proteasome has emerged as an important target for cancer therapy with the approval of bortezomib, the first proteasome inhibitor approved for relapsed/refractory multiple myeloma. However, many patients with multiple myeloma do not respond to bortezomib, and others develop resistance. Also, nonspecific proteasome inhibitors such as bortezomib induce peripheral neuropathy and other toxicities that may prevent administration of full doses. The immunoproteasome is a variant of the proteasome and is found predominantly in hematopoietic cells. It differs from the constitutive proteasome found in most other cells and is being investigated as a target for specific inhibition in multiple myeloma.

Deborah J. Kuhn, MD, of the University of Texas MD Anderson Cancer Center, Houston, Texas, and colleagues conducted a study in which they identified IPSI-001 as a specific inhibitor of immunoproteasome.

IPS1-001-induced accumulation of ubiquitin-protein conjugates, proapoptotic proteins, and activated caspase-mediated apoptosis. It potently inhibited proliferation in myeloma patient samples and other hematologic malignancies and was able to overcome conventional and novel drug resistance, including resistance to bortezomib. Dr. Kuhn noted that these findings provide a rationale for the translation of this emerging therapy into clinical testing.

### REFERENCES


Targeted Therapy for Acute Myeloid Leukemia With Farnesyltransferase Inhibitor Tipifarnib

Acute myeloid leukemia (AML) is mainly a disease of the elderly, with a median age of 67 years at diagnosis among all Americans. In general, patients with AML who are >60 years of age and receive conventional therapy have a poor outcome, with less than half of these patients with good performance status achieving a complete response. The median survival of patients with AML who are aged >60 years ranges from 7 to 14 months. Inferior outcomes often can be attributed to a higher frequency of complex cytogenetic abnormalities, which are identified in more than half of all adult patients with AML, and an inability to tolerate aggressive chemotherapy.

The aim of therapy in elderly patients with AML is remission, even if the remission is short-lived. Standard intensive treatment for patients with AML <80 years of age can reduce the chances of early death and improve quality of life longer than palliation alone.

The integration of cytogenetic aberrations and molecular mutations into treatment decisions can help clinicians categorize most patients with AML into prognostically relevant subgroups. This information is the basis for the development of treatment strategies to target genetic mutations or epigenetic pathways. As researchers have learned more about the development of leukemia, they have identified new targets for therapy, including FLT3-kinase signaling, the KIT receptor kinase, farnesyltransferase inhibitors, hypermethylation, and histone deacetylases. The goal of targeted therapy is to maximize the treatment of leukemia with fewer adverse effects.

A number of trials have been undertaken with farnesyltransferase inhibitors. Monotherapy with the farnesyltransferase inhibitor tipifarnib exhibits modest activity against AML. Jeffrey E. Lancet, MD, of H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, and colleagues conducted a multicenter phase II study of tipifarnib in 158 patients, median age 74 years, with previously untreated, “poor-risk” AML. Poor risk was defined as any of the following: ≥65 years of age, adverse cytogenetic profile (eg, −5/5q, −7/7q, +8, abn 11q, complex ≥3 unrelated abnormalities), AML arising from antecedent hematologic disorder, and therapy-related AML. Complete remission was achieved in 22 patients (14%). Another 15 patients achieved partial remission or hematologic improvement for an overall response rate of 23%. The duration of complete remission was a median of 7.3 months. Complete responders survived for a median of 18 months.

A multivariate analysis found a negative correlation with survival for adverse karyotype, age ≥75 years, and poor performance status. Early death was rare in the absence of progressive disease, and drug-related nonhematologic serious adverse events were observed in about half of the patients.

In addition to its clinical activity as monotherapy, tipifarnib has shown additive or synergistic in vitro effects when combined with several antileukemia drugs. Preclinical studies showed that tipifarnib acts synergistically with the topoisomerase II poison etoposide. This finding led to a multicenter phase I trial of tipifarnib plus etoposide in 84 elderly patients with AML, median age 77, who were not candidates for conventional therapy, which had as principal investigator Judith E. Karp, MD, of Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, Maryland.

The patients received 224 cycles of oral tipifarnib 300-600 mg twice daily for 14 or 21 days plus oral etoposide 100-200 mg daily on days 1-3 and 8-10. Dr. Karp noted that the 14-day regimen of tipifarnib was better tolerated. Dose-limiting toxicities of grade 4 mucositis, grade 3 hyperbilirubinemia, and multorgan failure occurred with the 21-day regimen of tipifarnib.

In the group receiving 14-day tipifarnib, complete remissions were

| TABLE. COMPARISON OF 14-DAY VERSUS 21-DAY TIPIFARNIB ADMINISTRATION |
|-----------------|-----------------|-------|
|                 | 14 days (A)     | 21 days (B) | P    |
| **Toxicity, no. (%) of patients** |                 |       |     |
| Grade 3 mucositis | 2/54 (4)        | 4/30 (13) | .18  |
| Induction death   | 3/54 (6)        | 6/30 (20)| .06  |
| **Efficacy, day to begin cycle 2, median (range)** |                 |       |     |
| Complete remission, no. (%) of patients | 16/54 (30)      | 5/30 (17)| .29  |

EMERGING TARGETED THERAPIES FOR HEMATOLOGIC MALIGNANCIES: LEAVING A GENETIC AND EPIGENETIC IMPRINT FOR BETTER OUTCOMES

achieved in 16 of 54 patients (30%) compared to 5 of 30 patients (17%) in the group receiving 21-day tipifarnib (see table). Complete remissions occurred in 50% of two 14-day tipifarnib cohorts, including patients who received tipifarnib 600 mg and etoposide 100 mg and those who received tipifarnib 400 mg and etoposide 200 mg. These two dosage schedules will be tested in a randomized phase II trial. In addition, the tipifarnib plus etoposide combination induced complete remissions in 9 of 43 patients (21%) with adverse cytogenetics.

Dr. Karp noted that tipifarnib plus etoposide is a promising orally bioavailable regimen that yielded encouraging clinical results and warrants further evaluation in elderly patients with AML who are not candidates for conventional induction chemotherapy owing to advanced age, poor-risk biologic disease features, and/or the presence of significant non-hematologic comorbidities. Future studies will need to compare these two-drug combinations, as well as single-agent oral etoposide, to low-dose cytarabine and oral clofarabine, which also show activity in elderly patients with AML.

REFERENCES

Targeted-Therapy Regimens Highly Active in Acute Myeloid Leukemia

Two new targeted-therapy regimens, one a novel schedule of the methylating agent decitabine and the other an FLT3-kinase inhibitor combined with standard chemotherapy, appear to be highly active in patients with acute myeloid leukemia (AML).

Decitabine, which was described elsewhere in this supplement, is a pyrimidine analog that leads to hypomethylation, which, in turn, promotes tumor suppressor genes and differentiation in AML. William Blum, MD, Ohio State University, Columbus, and colleagues had previously established an optimal dose of 20 mg/m$^2$/day of decitabine for the treatment of AML, with promising clinical activity seen in poor-risk older patients. In the current phase II study, this dose of decitabine was given to 33 previously untreated patients with AML aged ≥70 years, median age 74 years, who were not candidates for intensive chemotherapy or who had refused it.

Induction therapy with intravenous decitabine 20 mg/m$^2$/day was administered on days 1-10 of 4-week cycles. If AML persisted, individuals received a repeat of the 10-day course. Patients who responded were given maintenance therapy with 3-5-day courses, depending on the degree and duration of neutropenia.

Of the 33 patients, 15 had either secondary AML or treatment-related AML. Cytogenetic testing showed that 14 of these patients had complex karyotype, defined as ≥3 abnormalities, 13 had normal karyotype, and 1 had t(8;21) chromosomal translocation. Nearly all of the patients (31 of 33) had at least two poor-risk factors, including age ≥70 years, a prior hematologic disorder, unfavorable karyotype, or ECOG 2 performance status.

As shown at the American Society of Clinical Oncology annual meeting in Orlando, Florida, 14 of 33 patients (42%) achieved complete remission (CR) and 19 of 33 patients (58%) achieved either CR or complete remission with insufficient hematologic recovery (CRi). CR was observed in all subsets of disease and cytogenetic risk groups, and the duration of CR to the meeting date ranged from 2 to >14 months. For 6 patients who relapsed after CR, the median time from initial response to relapse was 6.5 months. The median follow-up is 8 months for the 19 surviving patients. Median overall survival has not been reached.

Patients received a median number of 5 cycles. Most (9 of 14 patients) who achieved CR required only 1 cycle before achieving an initial response. Those patients who had CRi as initial response needed 1 to 3 (median 1) more cycles to achieve full CR.

Nonhematologic toxicities were infrequent, but 24 of 33 patients (73%) had infection and/or febrile neutropenia. Within 8 weeks, 15% of patients died as a result of infection.

Dr. Blum noted that this novel schedule of induction decitabine therapy, along with modified maintenance therapy based on outcome, was highly active in this poor-risk group of patients with AML. The promising survival data suggest that a comparative study with intensive therapy is warranted.

PATIENTS WITH FLT3 MUTATIONS

The high incidence of FLT3 mutations (35%–40%) found in patients with AML has led to the development and studies of specific FLT3-tyrosine kinase inhibitors.
A handful of unspecific inhibitors of FLT3 kinase signaling, including sorafenib, have also been investigated for treatment of this disease. Sorafenib, an orally active multikinase inhibitor with potent activity against FLT3 kinase, has been shown to induce apoptosis in FLT3-mutant human AML cell lines. In a phase I study of patients with AML, monotherapy with sorafenib in escalating doses was well-tolerated with no myelosuppression and with significant clinical activity predominantly in patients with FLT3 mutations. Farhad Ravandi, MD, University of Texas MD Anderson Cancer Center in Houston, reported the results of a phase I/II study at the European Hematology Association annual meeting in Berlin, Germany. The objective of the study was to determine the clinical activity and tolerability of a combination of sorafenib and standard AML chemotherapy.

In the phase I portion of the study, 10 patients, median age 34 years, with relapsed AML were treated with cytarabine 1.5 g/m² over 24 hours daily for 4 days (3 days for patients aged >60 years) and idarubicin 12 mg/m² daily for 3 days along with escalating doses of sorafenib 400 mg every other day, 400 mg daily, and 400 mg twice daily for 7 days during induction. Patients who achieved CR received up to 5 courses of consolidation with idarubicin 8 mg/m² daily for 2 days and cytarabine 0.75 g/m² daily for 3 days plus continuous sorafenib 400 mg twice daily for up to 28 days per cycle. The treatment cycles were repeated every 4 to 6 weeks.

The patients had a median of 2 prior therapies. Seven patients were FLT3-ITD positive, and 4 achieved CR. Sorafenib 400 mg twice daily was established as a safe induction dose, noted Dr. Ravandi.

In the phase II portion of the study, 48 patients, median age 53 years, were treated, including 12 patients with FLT3-ITD and 2 with FLT3-TKD. Cyto genetic studies showed that 20 patients were diploid, 5 were +8, 5 were -5/-7, 3 were t(9;11), and 11 were miscellaneous; cytogenetic information was unavailable for 4 patients. The FLT3-mutation burden was low in blasts from 4 patients and high in 10. Seven patients were FLT3-ITD+/NPM1- and 1 was FLT3 D835+/NPM1-.

A total of 45 patients were evaluable for response, of whom 38 patients (84%) achieved CR (34 patients) or complete remission with incomplete platelet recovery (CRp; 4 patients), including all 14 patients with FLT3 mutations. Four patients were resistant to therapy. Dr. Ravandi noted that the regimen was well-tolerated with some grade 3 and higher adverse events possibly related to the addition of sorafenib during induction. These included hyperbilirubinemia (6 patients), elevation of transaminases (3 patients), diarrhea and colitis (4 patients), rash (3 patients), pancreatitis (1 patient), pericarditis (1 patient), elevated creatinine (1 patient), and cardiac/hypertension (3 patients). During induction, 3 patients died from pneumonia.

With a median follow-up of 28 weeks, the probability of survival at 6 months in this study is 85%. Nine patients have relapsed with a median CR duration of 8 months. Among the patients with FLT3 mutation, 6 have relapsed and 8 remain in CR.

The researchers also performed correlative blood studies that confirmed potent activity of sorafenib against ERK and FLT3 signaling. Dr. Ravandi observed that sorafenib can be safely combined with idarubicin and cytarabine to induce a high CR rate, particularly in patients with FLT3 mutations.

REFERENCES

**CYTARABINE DERIVATIVE SAFE IN PATIENTS WITH SECOND SALVAGE ACUTE MYELOID LEUKEMIA**

A novel derivative of cytarabine administered as second salvage therapy has manageable toxicity in AML patients.

A multicenter phase II study led by Francis J. Giles, MD, University of Texas Health Sciences Center, San Antonio, assessed cytarabine 5’-elaidic acid ester (CP-4055) when given as second salvage therapy in 40 patients with AML, median age 48 years, who were refractory/relapsed to two previous chemotherapeutic regimens. The patients received CP-4055 2,000 mg/m²/day over 24 hours on days 1-5 every 3 weeks. The majority of the patients had previous ara-C-based therapy.

In the first 20-patient cohort, the most frequently reported adverse events of grade 3 or higher were myelosuppression, abdominal pain, colitis, diarrhea, nausea, fatigue, and elevated liver function tests (LFTs), Dr. Giles reported at the American Society of Clinical Oncology annual meeting in Orlando, Florida. Clinical activity was observed in 3 patients, 2 who achieved CR and 1 who had complete remission with incomplete platelet recovery. Dr. Giles noted that toxicity was manageable, and drug continuation was recommended.

Of all 40 patients, 7 (18%) had LFT elevations of grade 3 or more and 4 (10%) had LFT elevations of grade 2. Clinical activity has also been reported among the second 20-patient cohort in this ongoing trial.

Novel Compounds Successfully Treat Acute Myeloid Leukemia in Elderly Patients

S everal novel compounds currently in clinical trials show preliminary promise as therapies for traditionally difficult-to-treat elderly patients with acute myeloid leukemia (AML).

Most patients with AML who are aged ≥65 years are intrinsically resistant to intensive chemotherapy because of known poor-risk factors. Typically, older patients have been treated either with best supportive care (typically hydroxyurea) or with low-dose Ara-C. However, many targeted approaches are currently under development that may be of use for elderly patients with AML. A major challenge remains to identify targets of critical importance. Some of those targets attempt to inhibit tyrosine kinases and farnesyltransferases, promote apoptosis, inhibit hypomethylation of DNA by using DNA methyltransferase inhibitors or histone deacetylase inhibitors, or induce angiogenesis.

Often, elderly patients with AML are discouraged about receiving treatment owing to high treatment-related mortality and low response rates. The novel chemotherapy drug temozolomide, an oral alkylating agent, has been shown to be effective in patients with AML who lack expression of O6-alkylguanine-DNA alkyltransferase (AGAT) in leukemic blasts. Studies show that long-term exposure to temozolomide in low doses can significantly inhibit AGAT activity.3

Interim results of an ongoing phase II clinical trial were reported by the lead investigator, Bruno Medeiros, MD, Stanford University, Stanford, California, at the American Society of Clinical Oncology (ASCO) annual meeting in Orlando, Florida. In this study, temozolomide therapy is being tailored to high-risk patients with no AGAT activity receive protracted doses of temozolomide 100 mg/m² orally for 14 days followed by conventional doses of temozolomide.

The first 15 patients, median age 78 years, have completed treatment, including 8 patients with de novo AML and 5 with secondary AML. Nine patients had a normal karyotype, and 3 had a complex karyotype. Two patients had only an NPM1 mutation, and 1 had an NPM1/FLT3-ITD mutation.

Complete remission (CR) was achieved in 6 of 13 patients after 1 cycle of therapy, and 3 patients remained in remission for a median duration of 22 weeks. With a median follow-up of 38 weeks, the median overall survival for all patients is 12 weeks and for responders is 26.5 weeks.

Nonhematologic toxicities were minimal. Hematologic toxicities associated with treatment were difficult to distinguish from disease-related cytopenias. Disease progression led to the death of 7 patients, and 2 patients died of neutropenic sepsis.

Dr. Medeiros noted that the preliminary data suggest that temozolomide therapy may be individualized according to AGAT activity for elderly patients with AML.

OTHER EMERGING THERAPIES

Results of a multicenter phase II study with the topoisomerase II inhibitor voreloxin were reported at ASCO by Michael Maris, MD, Rocky Mountain Blood and Marrow Transplant Program, Denver, Colorado. Clinical activity was shown with 2 dosing schedules in previously untreated elderly patients with de novo or secondary AML who were unlikely to benefit from standard chemotherapy.4 Eleven of 29 patients (38%) achieved a CR or a complete remission with incomplete platelet recovery (CRp) with 3 weekly voreloxin doses. Interim results showed CR or CRp for 6 of 21 evaluable patients (29%) with 2 weekly voreloxin doses, with 2 patients in heme recovery.

In an international, retrospective phase II study, the novel sulfonyl hydrazine alkylating agent laromustine induced CR or CRp in about one-quarter of elderly patients with AML and adverse cytogenetics. Laromustine also led to a 12% 1-year overall survival compared with no response in patients who received low-dose Ara-C or best supportive care.1

In a multicenter, European phase I/II study, the aminopeptidase inhibitor tosedostat elicited a bone marrow response in 11 of 35 elderly patients (31.4%) with relapsed/refractory AML, including 6 CRs and 5 partial responses.3 In addition, 4 patients achieved complete hematologic recovery and 1 reached a cytogenetic response, reported Gert Ossenkoppele, MD, VU University Medical Center, Amsterdam, the Netherlands, at EHA. Median overall survival was 131.5 days. Tosedostat was well-tolerated over exposures up to 12 months in these patients with a poor prognosis and will be tested in a pivotal trial in relapsed AML.

REFERENCES
1. In patients with myelodysplastic syndrome (MDS), both a 3-day and a 5-day dosing schedule of decitabine have demonstrated efficacy in clinical trials.
   a. True
   b. False

2. In a study of patients with MDS who received allogeneic stem cell transplantation, what was the 10-year overall survival rate?
   a. 25%
   b. 48%
   c. 51%
   d. 65%

3. Which of the following drugs approved for the treatment of hematologic malignancies has immunomodulatory, antiangiogenic, and antiproliferative effects?
   a. Lenalidomide
   b. Azacitidine
   c. Decitabine
   d. Bortezomib

4. Histone deacetylase inhibitors may be more effective when used in combination with other drugs for the treatment of MDS.
   a. True
   b. False

5. In patients with relapsed/refractory multiple myeloma, which drug combination is an effective steroid-free salvage regimen?
   a. Bortezomib plus pegylated liposomal doxorubicin and thalidomide
   b. Thalidomide plus lenalidomide and bortezomib
   c. Bortezomib plus lenalidomide and rituximab
   d. Melphalan plus doxorubicin and vincristine

6. In patients with advanced multiple myeloma, a six-drug infusional chemotherapy regimen failed to facilitate donor engraftment.
   a. True
   b. False

7. In a study of relapsed/refractory multiple myeloma, which combination of oral agents resulted in a 73% clinical benefit?
   a. Thalidomide, melphalan, prednisone
   b. Vorinostat, lenalidomide, dexamethasone
   c. Bortezomib, melphalan, prednisone
   d. Bortezomib, melphalan, lenalidomide

8. In a study of elderly patients with acute myeloid leukemia, which combination of agents led to complete remissions in 21% of patients with adverse cytogenetics?
   a. Cytarabine and oral clofarabine
   b. Cytarabine and daunorubicin
   c. Tipifarnib and etoposide
   d. Cytarabine and idarubicin

9. In a study of patients with relapsed AML, which agent was added to standard chemotherapy and induced an 84% complete remission rate?
   a. Sorafenib
   b. Decitabine
   c. Azacitidine
   d. Gemtuzumab

10. Targeted therapies currently under investigation in clinical trials for elderly patients with AML include which of the following agents?
    a. Tosedostat
    b. Laromustine
    c. Voreloxin
    d. Temozolomide
    e. All of the above
EMERGING TARGETED THERAPIES FOR HEMATOLOGIC MALIGNANCIES:
LEAVING A GENETIC AND EPIGENETIC IMPRINT FOR BETTER OUTCOMES

PROGRAM EVALUATION AND ANSWER SHEET

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The amount of time I spent on this activity was ___________ (max of 1.5 hours).

Exam Answer Form Darken the circle with the correct answer to each question in the CME activity.

1. A B
2. A B C D
3. ABCD
4. AB
5. A B C D
6. A B
7. A B C D
8. A B C D
9. A B C D
10. A B C D E

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1. How would you rate this activity overall? (5 = excellent, 1 = poor; please circle one)
   5 4 3 2 1

2. Do you feel each of the educational objectives listed on page 2 was met?
   Objective 1 Yes Partially No N/A
   Objective 2 Yes Partially No N/A
   Objective 3 Yes Partially No N/A

3. In your opinion, did you perceive any commercial bias?
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6. Do you intend to make changes in your practice as a result of this activity? Yes No
   If yes, please explain: ___________________________________________________________________

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