

Novel Therapeutic Agents for the Treatment of Myelodysplastic Syndromes

Bruce D. Cheson, James A. Zwiebel, Janet Dancy, and Anthony Murgo

Few chemotherapy agents have demonstrated activity in patients with myelodysplastic syndromes (MDS) and supportive management remains the standard of care. An increasing number of new drugs in development are being directed at specific molecular or biological targets of these diseases. Topotecan, a topoisomerase I inhibitor, has shown single-agent activity and is now being combined with other agents, including cytarabine. The aminothiol amifostine induces responses in about 30% of patients; however, its role is still being clarified. Agents that inhibit histone deacetylase and target DNA hypermethylation, thus permitting derepression of normal genes, include 5-azacytidine, decitabine, phenylbutyrate, and depsipeptide. Arsenic trioxide has demonstrated impressive activity in acute promyelocytic leukemia and preclinical data suggest the potential for activity in MDS. UCN-01 is a novel agent that inhibits protein kinase C and other protein kinases important for progression through the G₁ and G₂ phases of the cell cycle. Dolastatin-10 has extremely potent in vitro activity against a variety of tumor cell lines. Since its dose-limiting toxicities include myelosuppression, it is being studied in acute myelogenous leukemia (AML) and MDS. *Ras* may play a role in MDS, and activation of this gene and its signaling pathways may require farnesylation. Several farnesyl transferase inhibitors are now available for study in patients with MDS. An increasing body of data suggests a possible role for angiogenesis in MDS, and several antiangiogenesis agents are in clinical trials, including thalidomide, SU5416, and anti-vascular endothelial growth factor (VEGF) antibodies. Development of new drugs and regimens will be facilitated by recently developed standardized response criteria. Future clinical trials should focus on rational combinations of these agents and others with the goal of curing patients with MDS.

Semin Oncol 27:560-577. This is a US government work. There are no restrictions on its use.

THE MYELODYSPLASTIC syndromes (MDS) are a heterogeneous group of hematopoietic disorders characterized by pancytopenia, generally in the setting of a hypercellular bone marrow. MDS

From the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD.

Address reprint requests to Bruce D. Cheson, MD, National Cancer Institute, Executive Plaza North—Room 741, Bethesda, MD 20892.

This is a US government work. There are no restrictions on its use.

have historically been referred to as oligoblastic leukemia, refractory anemia, smoldering acute leukemia, or preleukemia. In 1982, the French-American-British (FAB) group presented a classification, modified in 1985, which currently is the most widely used.^{1,2} The FAB group separated MDS into five categories: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), and RAEB in transformation (RAEB-T). The distinction between RAEB-T and acute myelogenous leukemia (AML) is based on histopathology, not clinical features. As a result, patients with MDS may exhibit a clinical picture consistent with AML with rapidly increasing numbers of blasts, but without the requisite number to fulfill the criteria for the diagnosis of AML.³ Recently, a World Health Organization (WHO) steering committee proposed changes to the MDS subtypes with the major modifications including reclassifying chronic myelomonocytic leukemia (CMML) as a myeloproliferative disorder and decreasing the threshold for diagnosing AML from 30% blasts to 20%.⁴ This system may eventually replace the FAB.

The likelihood of transformation to AML varies by FAB subtype⁵⁻⁸: approximately 10% to 20% for RA or RARS, 20% to 30% for CMML, 40% to 50% for RAEB, and 60% to 75% for RAEB-T. Nevertheless, the MDS are uniformly fatal, even without progression to AML, because of infection and bleeding.^{9,10}

Over the years, a number of scoring and prognostic systems have been published to facilitate comparisons among reports of various treatments for MDS. Recently, the International Prognostic Scoring System (IPSS) has been widely adopted.¹¹ Factors taken into consideration included bone marrow blasts, cytogenetics, and cytopenias. Groups were identified with relative risks for transformation to AML and overall survival. Patients in the good cytogenetics group were those with a normal karyotype; poor risk included patients with complex abnormalities or with an involved chromosome 7; intermediate-risk patients consisted of all others (Table 1).

There are no curative therapies other than stem cell transplantation, which is an option for only a subset of patients. Therefore, numerous therapies

Table 1. International Prognostic Scoring System for the Myelodysplastic Syndromes

Prognostic Variable	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5-10		11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias (no. of lineages)	0/1	2/3			

NOTE. The total of the values for each prognostic variable is used to place patients in 1 of 4 risk groups: low, intermediate-1, intermediate-2, and high. These risk groups have significantly different outcomes.

have been and are being investigated to improve the outlook for these patients. Drugs selected for study in MDS have typically been those with significant activity in AML. Thus, cytarabine has been most widely evaluated, dating back more than 30 years when Ellison et al¹² first reported complete remissions with doses of cytarabine as low as 10 mg/m²/d. Response rates were clearly dose-dependent, which encouraged the development of higher dose regimens. Subsequently, anecdotal reports and small series were published in which cytarabine at 10% to 20% of the standard dose administered either subcutaneously or by continuous intravenous infusion appeared to be effective in the treatment of AML and MDS.¹³⁻²² Additional studies and a randomized phase III trial failed to support a major role for this therapy.²³⁻²⁵

Anthracyclines and related compounds have had been studied as single agents only to a limited extent.^{26,27} In a study in which hydroxyurea and etoposide were compared in patients with CMML, response rates and survival were not impressive with either agent, but favored the former.²⁸ Other drugs that have been evaluated include 6-thioguanine and homoharringtonine, but both showed limited activity.^{29,30}

NEW AGENTS

Several agents with unique mechanisms of activity are currently or will soon be evaluated in clinical trials for patients with MDS.

Topoisomerase I Inhibitors

Topotecan is a topoisomerase I inhibitor whose activity in acute leukemia led to its testing in MDS. The initial report included 47 patients with RAEB, RAEB-T, or CMML.³¹ They were a poor-risk group, as demonstrated by the fact that the median age was 66 years, 70% exhibited cytogenetic abnormalities, and more than half were

thrombocytopenic before topotecan therapy. Topotecan was delivered at a dose of 2 mg/m² as a continuous 24-hour infusion for 5 days. Treatment resulted in 28% complete remissions and an additional 13% of patients who experienced significant hematologic improvement. All eight patients with cytogenetic abnormalities before treatment and who achieved a complete remission became cytogenetically normal once in complete remission. The median remission duration was 7.5 months with 38% of patients still alive 1 year following treatment. Whether chronic oral topotecan is effective is undergoing evaluation.

The same investigators have shown that combination of topotecan and cytarabine is extremely active in patients with MDS. Beran et al³² reported on 86 patients with MDS and CMML, most of whom (66%) were previously untreated, but who were considered high risk based on age or cytogenetic abnormalities. Topotecan was administered at a dose of 1.25 mg/m² by continuous infusion daily for 5 days, and cytarabine at 1 g/m² by a 2-hour infusion daily for 5 days. A complete remission was attained in 56% of patients, with 7% treatment-related deaths and a median survival of 60 weeks.³² Preliminary results have been published of aggressive combination of topotecan, fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF); there were 50% complete remissions and 40% partial remissions, and the regimen appeared to be well tolerated.³³

Amifostine

Amifostine (Ethylol; Alza Pharmaceuticals, Palo Alto, CA) is a phosphorylated aminothiol that protects bone marrow progenitors and other normal tissues from the toxicities associated with chemotherapy or radiation therapy. It was developed by the Walter Reed Army Medical Institute

(thus, the military code name WR-2721) during the Cold War as part of a classified research project to identify an agent that would protect military personnel from radiation in the event of nuclear war. Amifostine was found to afford greater protection against radiation than more than 4,000 other compounds screened. Nevertheless, the Army terminated development of this compound in 1988 because of its poor oral bioavailability and the prohibitive nausea, vomiting, diarrhea, and abdominal cramps with the oral formulation.

Further research was encouraged by the observation that amifostine stimulates hematopoiesis in both animal models and in vitro studies, and that it enhances the formation of hematopoietic progenitors from MDS bone marrow. In the initial phase I/II study,³⁴ the drug was administered at doses of 100, 200, or 400 mg/m² three times per week or 740 mg/m² weekly for 3 weeks. These investigators treated 18 patients at a median age of 73 years. FAB types included RA (seven patients), RARS (n = 5), RAEB (n = 4), and RAEB-T (n = 2). Seventeen patients were anemic, 15 of whom were transfusion-dependent; 12 had an absolute neutrophil count less than 1,000/ μ L and 14 were thrombocytopenic. Hematologic improvement was observed in 83% with the three-times-a-week schedules, including either an increase in neutrophils or a reduction in red blood cell transfusion requirements. More than 40% of patients had a rise in their platelet counts. However, there was acceleration to AML in several patients with RAEB-T. Although 61% of patients had clonal cytogenetic abnormalities before therapy, the abnormalities persisted even in patients with a hematologic response. No data regarding duration of response were provided, although responses were reported to persist during continuation therapy.

List et al³⁵ reported the results of a subsequent multicenter trial of amifostine in 117 patients, 104 of whom were evaluable at the time of presentation. A neutrophil response occurred in 10 (33%) of 30 patients, and was considered major in nine and minor in the other. A red blood cell response was evaluable in 66 patients, and a major response occurred in seven, with three experiencing a minor response. A major improvement in platelet count was seen in seven of 27 patients, with a minor response in three others, and 21% of patients had an increase in the reticulocyte count. A decrease in myeloblasts and sideroblasts occurred in 28% and

31%, respectively. The overall response rate was 30%, which is significantly lower than in the previous trial. Adverse events that were moderate or severe included fatigue (14%, 18%), nausea (19%, 36%), and vomiting (14%, 27%). In a smaller series,³⁶ a single or multilineage response was noted in five of 12 patients (58%). The absolute neutrophil count increased in 25% (by 102 to 1,560/ μ L), platelets in 50% (by 24,000 to 49,000/ μ L), reticulocytes in 25% (1.9% to 20%), and hemoglobin in 16% (5.3 to 5.6 g/dL).

In other reports, results with this agent were disappointing.^{37,38} Hofmann et al³⁸ described 32 patients with RA/RARS (n = 26) and RAEB/RAEB-T (n = 15) treated at a dose of 200 mg/m² three times per week followed by a 2-week interval, for four courses. Limited benefit was observed even in patients with low- or intermediate-risk disease by the IPSS.

The role of amifostine in MDS is still being clarified. Nevertheless, combinations of amifostine with other agents such as 5-azacytidine are being evaluated.

Agents That Target Transcription

Recent developments in understanding the molecular basis for transcriptional repression and activation have presented new possibilities for cancer therapy. Two mechanisms of gene silencing, promoter hypermethylation and histone deacetylation, appear to be interrelated. The utility of targeting DNA hypermethylation and histone deacetylation is being explored clinically. Agents shown to inhibit histone deacetylase in vitro include sodium phenylbutyrate, depsipeptide, hybrid polar compounds,³⁹ and MS-27-275.⁴⁰ Hypomethylating agents include 5-azacytidine and 5-aza-2-deoxycytidine. The exploration of these agents in the clinic, either alone or in combination with retinoids, demethylation agents, and chemotherapeutic agents, is a novel and promising area of cancer therapeutics.

Hypomethylating agents. 5-Azacytidine and 5-aza-2'-deoxycytidine are pyrimidine analogs that have been extensively evaluated in patients with MDS. These compounds are metabolized intracellularly to triphosphates and subsequently incorporated into newly synthesized DNA, where they directly inhibit DNA synthesis and inhibit the activity of DNA methyltransferase, the enzyme required for 5'-cytosine methylation of cytosine-

guanosine (CpG) dinucleotides.⁴¹⁻⁴⁵ As a result, cytosine methylation is blocked in newly replicated DNA, but not in the DNA of resting or nondividing cells. Inhibition of methylation by 5-azacytidine and decitabine is associated with transcription of genes previously silenced by methylation of promoter region CpG-rich islands, and with cellular phenotypic changes; these effects can occur at concentrations that are too low to inhibit DNA synthesis directly or to cause substantial cytotoxicity.^{41,43-45} The potential application of 5-azacytidine and decitabine as inhibitors of DNA methylation and inducers of cell differentiation of normal and neoplastic hematopoietic progenitor cells is an area of active investigation.^{43,45-48}

5-Azacytidine initially demonstrated activity in AML,⁴⁹⁻⁵³ but with considerable toxicity at doses required for response. Since the drug also induces in vitro cellular differentiation in association with hypomethylation of DNA, it was of interest for study in MDS. Chitambar et al⁵⁴ used a relatively low dose (10 to 35 mg/m²/d for 14 days) to treat 13 patients, three of whom achieved a partial response. Cancer and Leukemia Group B (CALGB) investigators⁵⁵ conducted a phase II trial of 5-azacytidine at 75 mg/m²/d by continuous infusion for 7 days every 28 days in 48 patients with MDS and noted 11% complete remissions and 25% partial remissions. Major toxicities included nausea and vomiting; one patient died of neutropenic sepsis. Subcutaneous administration resulted in slightly lower response rates—7% complete remissions, 17% partial remissions, and 14% with trilineage improvement, but less than a partial response.⁵⁶ These findings are similar to those achieved with low-dose cytarabine.

The CALGB recently reported the preliminary results of a phase III randomized trial of 5-azacytidine versus observation in 191 patients with MDS.⁵⁷ The patients were stratified by FAB subtype (19% RA, 4% RARS, 42% RAEB, 21% RAEB-T, 6% CMML); patients with RA or RARS had, in addition, symptomatic cytopenias. 5-Azacytidine was administered subcutaneously at a dose of 75 mg/m²/d for 7 days every 4 weeks for four cycles. Patients on the observation arm could receive 5-azacytidine upon progression. Hematologic responses were significantly higher in patients randomized to receive 5-azacytidine compared with observation ($P < .0001$): 63% (6% complete response, 10% partial response, and 47% improve-

ment) versus 7% (all improvement, no complete or partial responses). The median time to leukemic transformation or death was 22 months for patients on the treatment arm, compared with 12 months for the patients randomized to observation ($P = .0034$). The 12- and 24-month overall survival rate was higher in patients randomized to receive azacytidine (70% and 41% versus 62% and 25%, respectively), as was the median survival time (18 versus 14 months), but the differences were not yet significant. Treatment with 5-azacytidine was associated with subjective improvement in quality of life as measured by fatigue, dyspnea, physical functioning, positive affect, and psychological distress.⁵⁸ Whether 5-azacytidine improves overall survival or reduces transformation to leukemia will require additional follow-up evaluation.

5-Aza-2'-deoxycytidine (decitabine) is another hypomethylating agent with potent in vitro activity. In earlier studies, decitabine administered as an intermittent intravenous infusion achieved brief responses in a small series of patients with MDS; however, the majority experienced life-threatening neutropenia and/or thrombocytopenia.⁵⁹ Wijermans et al⁶⁰ reviewed the experience with this agent in MDS and found a 54% response rate of 29 elderly patients, although there were 17% toxic deaths. This drug is under development for MDS both in Europe and the United States.^{46,60}

Histone deacetylation and DNA hypermethylation. Retinoids, other hormone receptors, and the Myc/Mad/Max network of growth regulators exert their effects on gene expression by interacting with nuclear corepressor complexes that are present on the DNA of promoter regions.^{61,62} Gene silencing occurs with the recruitment of histone deacetylases and the formation of a nuclear corepressor-histone deacetylase complex (NCHDC). Histone deacetylase catalyzes the removal of acetyl groups from histone proteins, inducing a conformational change that results in an environment unfavorable to gene transcription. A NCHDC has been found to play an important role in acute promyelocytic leukemia (APL), where the NCHDC is recruited by both the PML-RAR α and PLZF-RAR α fusion proteins, which form as a consequence of chromosomal translocations t(15;17) and t(11;17), respectively.⁶³⁻⁶⁷ A NCHDC is also recruited by ETO, a component of the fusion product resulting from the t(8;21) chromosomal translocation in AML.^{68,69} Moreover, inhibitors of histone deacetylase have

been found to overcome transcriptional repression and to potentiate retinoid-induced differentiation of APL and AML cells.^{63-66,69} A clinical test of this observation was performed in a patient with APL who had become refractory to both chemotherapy and all-*trans* retinoic acid (ATRA). Administration of both ATRA and a histone deacetylase inhibitor, sodium phenylbutyrate (see below), resulted in a complete remission. The clinical response was associated with acetylation of histone proteins in the leukemic cells.⁷⁰

While methylation of CpG islands in gene promoter regions has long been known to be associated with gene silencing, it was not known how such DNA hypermethylation exerts its effect on gene transcription. Recent studies have shed light on both the role of DNA hypermethylation in the inactivation of tumor suppressor genes, as well as the mechanism of transcriptional repression. Examples of genes associated with CpG hypermethylation include, among others, *RB* in retinoblastoma, *VHL* (the von Hippel-Lindau gene) in renal carcinoma, *p16INK4A* and *p15INK4A* (cyclin-dependent kinase inhibitors) in solid tumors and in hematologic malignancies, and *hMLH1* (a DNA mismatch repair gene) in colon cancer.⁷¹ The mechanism of gene silencing by DNA hypermethylation now appears to involve the recruitment of a NCHDC by the methyl-CpG-binding protein, MeCP2.^{72,73} In fact, the combined administration of a demethylating agent and a histone deacetylase inhibitor has been shown to synergize in reactivating genes that were silenced in cancer cells.⁷⁴ This finding not only links the processes of DNA hypermethylation and histone deacetylation, but also presents therapeutic targets for agents that are relatively nontoxic, or used at nontoxic doses.

Phenylbutyrate

Phenylbutyrate (PB) is a low-molecular-weight phenyl-fatty acid that been used clinically to treat hyperammonemia in children with inborn errors of urea synthesis.⁷⁵ It also been shown to enhance fetal hemoglobin production in some patients with hemoglobinopathies.⁷⁶ A number of mechanisms have been proposed for the antitumor effect of PB, including (1) elimination of glutamine necessary for nucleic acid and protein synthesis in rapidly growing normal and tumor cells^{77,78}; (2) inhibition of the mevalonate pathway of cholesterol synthesis

leading to interference of post-translational processing of proteins, modification of lipid metabolism, inhibition of protein isoprenylation, and regulation of gene expression through DNA hypomethylation^{79,80}; (3) activation of a peroxisome proliferator-activated receptor by PB, a transcriptional factor regulating lipid metabolism and cell growth⁸¹; and (4) regulation of gene expression through histone hyperacetylation via inhibition of nuclear histone deacetylases.⁸²⁻⁸⁴

PB has been shown to induce differentiation, tumor cytostasis, and reversion of malignant phenotype in several in vitro models.^{80,85-89} PB, as a histone deacetylase inhibitor, may have synergistic activity with ATRA in the treatment of APL.^{65,67,90} The PML-RAR fusion protein was shown to recruit a transcriptional corepressor complex that includes a histone deacetylase. ATRA alone could partially dissociate the complex, allowing increased transcription, but butyrate (or other inhibitors of histone deacetylases) in combination with ATRA was able to completely abrogate the inhibition of transcription. In light of these observations, an APL patient who experienced multiple relapses after ATRA treatment was treated with PB in combination with ATRA under compassionate release, and achieved a complete remission.⁷⁰

Depsipeptide

Depsipeptide (NSC 630176) is a bicyclic peptide originally isolated from *Chromobacterium violaceum*, strain 968, by Fujisawa Pharmaceutical Co (Osaka, Japan). In the original observations, depsipeptide selectively decreased the mRNA expression of the *c-myc* oncogene and inhibited the growth of the Ha-*ras*-transformed NIH3T3 clonal cell line, Ras-1, but had no effect on Ha-*ras* mRNA expression.⁹¹ It did not affect DNA synthesis, but caused cell cycle arrest at G₀/G₁. Recently, it has been shown to be a histone deacetylase inhibitor.⁹²

Byrd et al demonstrated that incubation of chronic lymphocytic leukemia cells with depsipeptide resulted in an alteration in apoptosis-associated proteins: an increase in *Bax* with no change in *Bcl-2*, and a decrease in *p27* expression.⁹³

In collaboration with Fujisawa Pharmaceutical Co, the National Cancer Institute (NCI) is currently sponsoring two phase I trials of depsipeptide administered as a 4-hour intravenous infusion. In one trial, a once-weekly infusion schedule (days 1,

8, and 15 every 28 days) is used, while the other trial evaluates a twice-weekly (days 1 and 5 every 21 days) schedule.

MS-27-275

MS-27-275 is a benzamide derivative that was synthesized by Mitsui Pharmaceuticals (Tokyo, Japan) in a search for novel antitumor agents.⁴⁰ The compound was found to have histone deacetylase activity *in vitro* at micromolar concentrations. In addition, when administered orally, MS-27-275 inhibited the growth of a number of tumor xenografts. The NCI, in collaboration with Mitsui Pharmaceuticals, plans to sponsor phase I trials of this agent in the near future.

Hybrid Polar Compounds

Hexamethylene bisacetamide (HMBA) was the first of the class of hybrid polar compounds to be evaluated as an antitumor agent in MDS and AML. The limited clinical activity that was observed was attributed to the inability to achieve the plasma concentrations that were required to induce differentiation in cells *in vitro* and to dose-limiting thrombocytopenia.⁹⁴ Subsequently, Richon et al³⁹ described compounds structurally related to HMBA, but which exhibited 3-log greater potency in inducing terminal differentiation and apoptosis in transformed cell lines. In addition, these compounds possess histone deacetylase inhibitory activity at micromolar concentrations. Recently, one such compound, M-carboxycinnamic acid bishydroxamide (CBHA), was found to induce apoptosis in human neuroblastoma, and the effect was associated with CD95/CD95 ligand expression by the tumor cells.⁹⁵ These agents should be entering into early clinical trials in the near future.

Arsenic Trioxide

Arsenic was used as a medicinal 2,400 years ago in the time of the ancient Greeks and Romans. Paul Ehrlich used organic arsenicals for the treatment of syphilis. Arsenicals are still included as ingredients in folk remedies of some cultures, particularly in China and other parts of Asia. Arsenic was widely used to treat syphilis before the advent of penicillin, and the organic arsenical melarsoprol is a recognized treatment for the meningoencephalitic stage of African trypanosomiasis.⁹⁶ Fowler's solution (1% arsenic trioxide in

potassium bicarbonate), formulated in the 18th century to treat a variety of infectious and neoplastic disorders, was reported by US physicians in the 1930s to be useful in the treatment of chronic myelogenous leukemia (CML), and more recently by hematologists in China to treat various forms of leukemia, including CML.⁹⁷

Recent interest in the development of arsenic trioxide as an anticancer agent emanates from reports by Chinese investigators^{98,99} of its efficacy in the treatment of APL. These favorable results in APL were confirmed in the United States by investigators at Memorial Sloan-Kettering Cancer Center (MSKCC).¹⁰⁰

Preclinical studies have shown that human APL cells are very sensitive to the growth-inhibitory and cytotoxic effects of arsenic trioxide.^{101,102} Sensitivity to arsenic trioxide *in vitro* has also been demonstrated against a variety of other tumor types, including those derived from myeloid leukemias other than PML,¹⁰¹ myeloma,¹⁰³ lymphoid leukemia and lymphoma,¹⁰⁴⁻¹⁰⁷ prostate cancer,¹⁰⁸ and a various other solid tumors.¹⁰⁹

The mechanism of antitumor activity of arsenic trioxide is not understood, but it appears to depend to some degree on dose and tumor type. The principal target in APL cells is the promyelocytic leukemia gene-retinoic acid receptor- α fusion transcript (PML/RAR- α).^{102,110} Arsenic trioxide causes the degradation of the PML/RAR- α and wild-type PML proteins, thus inhibiting their effect on growth and differentiation.^{102,111,112} Unlike ATRA, arsenic trioxide does not downregulate wild-type RAR- α .¹⁰² In NB4 cells, a human APL cell line with t(15;17) and the PML/RAR- α fusion protein, the effects of arsenic trioxide treatment are dose-dependent¹⁰²: induction of partial (nonterminal) differentiation at relatively low concentrations (0.1 to 0.5 $\mu\text{mol/L}$) with predominantly apoptosis at higher concentrations (0.5 to 2 $\mu\text{mol/L}$). However, induction of apoptosis by arsenic trioxide involves mechanisms other than modulation of PML or PML/RAR- α .¹⁰¹ For example, growth inhibition and apoptosis induced by arsenic trioxide has been associated with downregulation of *bcl-2* expression in APL and other myeloid cell lines.^{101,102} Arsenic trioxide is known to react with sulfhydryl (SH) groups and thus alter many different enzyme systems, including those that affect protein tyrosine phosphorylation.^{113,114} The antitumor properties of arsenic trioxide have been attrib-

uted, at least in part, to effects on mitochondria.^{105,115,116} Studies with isolated systems suggest that arsenic trioxide induces apoptosis by directly influencing the mitochondrial permeability transition pore, which can be inhibited by *Bcl-2*, an endogenous antagonist of permeability transition pore function.¹¹⁶ Mitochondrial transmembrane potential collapse has been demonstrated in malignant lymphocytic cells undergoing arsenic trioxide-induced apoptosis.¹⁰⁵ Cells become more sensitive to arsenic trioxide when combined with inhibitors of glutathione (GSH) synthesis, including ascorbic acid.^{105,117} Additional data suggest that induction of mitotic arrest and apoptosis by arsenic trioxide is related to the binding of this trivalent arsenical to two cysteine residues in tubulin, thus blocking the guanosine triphosphate (GTP) binding site and leading to disruption of microtubule formation during mitosis.¹¹⁸

Most clinical experience with arsenic trioxide comes from trials conducted in China and the United States in patients with refractory or relapsed APL.^{98-100,119,120} In a study by Shen et al,⁹⁹ arsenic trioxide was administered intravenously at a fixed dose of 10 mg/d, either alone or in combination with other chemotherapy. Nine of 10 patients treated with arsenic alone and all five of the remaining patients treated with a combination regimen achieved complete hematologic remissions. Niu et al¹²⁰ recently reported the results of arsenic trioxide treatment in 58 patients with APL. Clinical complete remission was obtained in eight of 11 patients (72.7%) with newly diagnosed APL and 40 of 47 patients (85.1%) with relapsed disease. In a pilot study conducted at MSKCC in the United States,¹⁰⁰ arsenic trioxide was administered intravenously over 2 to 4 hours at doses ranging from 0.06 to 0.2 mg/kg/d; the initial course of treatment was continued until the bone marrow was morphologically clear of leukemia. The median duration of induction therapy was 33 days (range, 12 to 39 days), with one to five courses administered to responding patients. A complete hematologic remission was achieved in 11 of the 12 patients. The median duration of remission was 5 months (range, 1 to >9 months). In eight patients, the bone marrow tested negative by reverse-transcription polymerase chain reaction (RT-PCR) for PML/RAR- α after two courses of therapy. The three patients whose bone marrow remained RT-PCR-positive relapsed during the

second course of treatment. None of the patients whose bone marrows were RT-PCR-negative relapsed at the time of the report. The results of this single-institution study are being confirmed in a multicenter trial.¹²¹ A dose-finding phase I study of arsenic trioxide is being conducted by investigators at MSKCC to determine the recommended phase II dose in hematologic malignancies other than APL.¹²¹

Major toxicities attributed to arsenic trioxide involve a variety of organ systems. Skin changes are common, including dryness, hyperkeratosis, pruritus, rash, erythema, and hyperpigmentation. Gastrointestinal toxicity includes nausea, vomiting, abdominal pain, anorexia, and stomatitis. Renal and hepatic toxicity and hyperglycemia are also observed. Patients can experience a variety of constitutional symptoms and muscular skeletal complaints, such as lassitude, fatigue, weight gain, arthralgia, bone pain, myalgia, toothache, and headache. Cardiovascular and neurologic complications may be a particular concern in patients who receive more than a few courses of therapy.¹¹⁹ Neurotoxicity includes peripheral motor or sensory neuropathy and seizures. Some patients experience lightheadedness, dizziness, and hypotension during the 1- or 2-hour infusion, but this is usually alleviated by extending the infusion to 4 hours. Other cardiac effects that have been reported include second-degree heart block, prolongation of the QT interval, and torsades des pointes; patients exposed to amphotericin B, or those with hypokalemia or hypomagnesemia for any reason, may be at higher risk for these cardiac abnormalities.¹⁰⁰

Of interest is that patients with APL treated with arsenic trioxide can develop fluid retention and a syndrome similar to the "retinoic acid syndrome,"^{122,123} with fever, fluid retention, weight gain, dyspnea, pneumonitis, and leukocytosis. Signs or symptoms of the syndrome are usually manifested within 1 to 3 weeks of initiating therapy.¹²² The syndrome can be effectively treated with high doses of dexamethasone without the need to interrupt arsenic administration.

Based on the favorable clinical results in APL and promising preclinical data suggesting a broader range of activity, the NCI will further develop arsenic trioxide as an anticancer agent in patients with variety of hematologic malignancies, including MDS.

Protein Kinase C Inhibitors

UCN-01 (NSC 638850). UCN-01 or (3 α ,9 β ,10 α ,11 α ,13 β)-(+) -2,3,10,11,12,13-hexahydro-3-hydroxy-10- methoxy-9-methyl-11-(methylamino)-9,13-epoxy-1H,9H-diindolo[1,2,3- gh: 3',2'1'-im]-pyrrolo[3,4- j] [1,7]benzodiazonin-1-one, is the 7-hydroxy analog of staurosporine. It is a fermentation product isolated from the culture broth of a *Streptomyces* species. UCN-01 was originally identified as a selective inhibitor of calcium and phospholipid-dependent protein kinase C (PKC).¹²⁴⁻¹²⁷ Subsequently, it has been found to inhibit a number of serine/threonine kinases in a concentration dependent manner that results in arrest of cells in G₁ and abrogation of the G₂/M checkpoint. It was selected for clinical development because of its potent in vitro and in vivo antiproliferative activity, as well as for its novel mechanism of action.

UCN-01 directly inhibits of a number of other protein kinases important for orderly progression through the G₁ and G₂ phases of the cell cycle. UCN-01-induced G₁ arrest is associated with the accumulation of the dephosphorylated pRb, reduction in expression of cyclin A, and the induction of the CDK-inhibiting proteins p21 and p27.¹²⁸ The G₂/M transition is regulated by Cdc2, which is activated by the phosphorylation of threonine residue 161¹²⁹ and inactivated by phosphorylations of threonine-14 and tyrosine-15.^{130,131} UCN-01 abrogates G₂ checkpoint by inhibiting Chk-1 kinase. The downstream effect of inhibiting Chk-1 is loss of inhibitory phosphorylation of Cdc-2. Persistent activation of Cdc-2 results in progression through G₂ to M.¹³²

UCN-01 demonstrated cytotoxic effects in vitro and against a variety of murine and human malignant cell lines in vivo. Initial screening studies in the NCI human tumor cell line screen suggested preferential inhibition of renal, CNS, lung, and leukemia cell lines. In vitro, UCN-01 at low micromolar concentrations can induce apoptosis K562 and HL60 leukemia cells lacking functional p53 and resistant to apoptosis induced by DNA-damaging agents.¹³³ Experiments assessing treatment schedule suggested extended durations of exposure to UCN-01 resulted in a more prolonged antitumor response.¹³⁴ UCN-01 has also been shown to enhance antitumor effects of several chemotherapeutic cancer agents, including cytarabine and fludarabine, as well as 5-fluorouracil,

gemcitabine, the camptothecins, and cisplatin, in vitro and in vivo.^{133,135-138} UCN-01 can circumvent resistance of *bcl-2*-overexpressing leukemic cells to cytarabine-induced apoptosis.¹³⁹ These results suggested that UCN-01-induced abrogation of G₂ checkpoint prevents repair of DNA damage induced by standard therapies.

Phase I studies evaluating schedules of 72 hours and 3-hour intravenous infusions were initiated in the United States and in Japan, respectively. Although drug accumulation was not noted in the animal studies, pharmacokinetic data from the first patients administered UCN-01 revealed a very long half-life of several weeks, extremely small volume of distribution at steady-state, and a very low systemic clearance, in contrast to the large distribution volume and rapid systemic clearance in animal models.¹⁴⁰⁻¹⁴² Subsequent studies showed that UCN-01 binds tightly to human α -acid glycoprotein (hAGP); this tight binding alters the clearance of UCN-01, producing prolonged exposures after a single dose.¹⁴³ To prevent drug accumulation, doses after the first cycle were reduced by half in both phase I studies.

To date, only the NCI study has been completed. The highest dose reached was 53 mg/m²/24 h \times 72 hours (\times 36 hours for cycles \geq 2) every 4 weeks.¹⁴⁴ Dose-limiting toxicities were transient and usually asymptomatic hypoxia, self-limited hyperglycemia, lactic acidosis with hyperglycemia, nausea/vomiting, and transient elevation of liver transaminases. Other frequently observed toxicities were transient, asymptomatic hypotension, headache, fatigue, anemia, fever, myalgia, and anorexia. With a two-compartment model fitted to the observed plasma concentrations, the median value for apparent volume of the central compartment (V_c) was 2.6 L (range, 0.1 to 9.1 L), clearance was 0.01406 L/h (range, 0.001 to 0.04 L/h), and the terminal half-life was 574 hours (range, 199 to 4,099 hours). Because of extensive plasma protein binding, salivary drug concentrations were measured as a surrogate for free plasma concentrations. The median salivary "free" UCN-01 concentration at the maximum tolerated dose was 45 nmol/L (range, 29 to 182 nmol/L), which is associated with G₂ checkpoint abrogation.

Given the prolonged half-life, phase I studies of UCN-01 on 1- and 3-hour infusions every 3 to 4 weeks have been initiated. Preclinical studies sug-

gest that the potential benefit is greatest when UCN-01 is combined with DNA damaging and S-phase-specific agents. Given the evidence of activity as a single agent and in combination with antimetabolites and nucleoside analogs, studies assessing the activity of UCN-01 in combination with cytarabine in RAEB/RAEB-T and AML and fludarabine in lymphoproliferative disorders are planned.

Dolastatin-10. Dolastatin-10 is a naturally occurring peptide isolated from the marine mollusk *Dolabella auricularia*. It is a linear pentapeptide (molecular weight 785) with four of its five subunits derived from modified amino acids.¹⁴⁵ This antimitotic agent has potent cytotoxic activity and causes cells to accumulate in metaphase arrest. Dolastatin-10 binds tubulin and inhibits microtubule assembly and tubulin-dependent GTP binding, and noncompetitively interferes with vincristine and vinblastine binding to tubulin.^{146,147} Examination of configurational isomers and peptide segments of dolastatin-10 indicated that the middle amino acid residue, dolaisoleucine, was most critical for interaction with tubulin and cytotoxic effect.¹⁴⁸ Studies with radiolabeled dolastatin-10 established tight binding of the peptide to tubulin and substantial accumulation of dolastatin-10, in comparison to vinca alkaloids. The level of intracellular accumulation correlated with cytotoxic potency.¹⁴⁹ The drug is modulated by the multidrug resistance (*MDR*) gene product.¹⁴⁹

Dolastatin-10 is one of the most potent *in vitro* cytotoxic anticancer compounds, with a 50% inhibitory concentration (IC_{50}) for P388 murine leukemia cells of 5×10^{-11} mol/L. Complete synthesis of the natural product permitted extensive preclinical assessment. Total growth inhibition of sensitive cell lines in the NCI cell line screen was noted at 0.1 to 1.0 nmol/L of drug. The compound's antitumor activity has been established against human leukemia and lymphoma cell lines and against solid tumors, including melanoma, prostate cancer, and small cell lung cancer cells, in a variety of *in vitro* assays.¹⁵⁰⁻¹⁵⁵ Maximal cytotoxic effect was time-dependent up to 8 hours of exposure. The growth inhibitory activity of dolastatin-10 for a lymphoma cell line could be potentiated by pretreatment with bryostatin 1, a PKC inhibitor.¹⁵⁶ Dolastatin-10 associated growth inhibition also occurs at drug levels that are inadequate for microtubule disruption; like other

tubulin-binding compounds, cytotoxic effects of the compound may be related to modulation of apoptosis-associated proteins. Tumor cells exposed to dolastatin-10 undergo apoptosis and the compound induces phosphorylation of the antiapoptotic *bcl-2* protein.^{157,158} Expression of *bcl-2* and other antiapoptotic proteins (eg, *Bcl-XL*, *Bag-1* and *XIAP*) decreased in 30% to 60% of cells from AML patients being treated with dolastatin-10, while comparable increases in proapoptotic family members *Bcl-XS* and *Bax* were measured.¹⁵⁸

In vivo studies of dolastatin-10 administered by several routes (intraperitoneally, intravenously, and orally) in the treatment of early- and late-stage human xenograft models established that dolastatin-10 produced growth delays and complete regressions of subcutaneously implanted LOX melanomas and NCI-H522 non-small cell lung cancers cell lines and the intraperitoneally administered promyelocytic leukemia cell line HL-60. Single-dose bolus scheduling was most effective when compared with multiple-dosing administration.¹⁵⁹ Because of extensive protein binding and rapid metabolism of the compound, a critical threshold level of free drug was necessary for maximal antitumor efficacy. The maximal antitumor effect was achieved when plasma levels between 1 and 10 ng/mL could be maintained for 5 to 8 hours. Pharmacokinetic studies in CD2F1 mice indicated that the drug had a half-life of approximately 5.6 hours.¹⁶⁰ Preclinical toxicology studies established that myelosuppression was the dose-limiting toxicity following single-dose administration in CD2F1 mice, Fischer-341 rats, and beagle dogs. Mice were the least sensitive species. The cytotoxic effects of dolastatin-10 were examined in cultures of hematopoietic progenitor cells and these studies confirmed that mouse cells were almost 1,000-fold less sensitive than canine and human marrow progenitor cells.¹⁶¹

Dolastatin-10 phase I studies of patients with solid tumors have been conducted at M.D. Anderson Cancer Center (MDACC) and the Mayo Clinic to assess an intravenous bolus administration every-3-week schedule. Maximal tolerated doses of 300 and 400 $\mu\text{g}/\text{m}^2$, respectively, were identified and appeared to correlate with the extent of prior cytotoxic therapy. Reversible myelosuppression was the dose-limiting toxicity. A median time to granulocyte nadir of 19 days was noted, with recovery usually within 3 to 8 days.

Extramedullary toxicities, including phlebitis, fatigue, diarrhea, and neurosensory changes, were infrequent and relatively mild. No objective responses were noted.^{162,163} Three compartment pharmacokinetic modeling established a γ half-life of 16 to 19 hours and plasma clearance rates that were relatively slow (range, 0.82 to 12.63 L/h/m) and characterized by high inpatient and outpatient variability. Pharmacodynamic assessment identified a correlation between dolastatin-10 area under the curve (AUC) and decline in neutrophil count.¹⁶⁴ The MDACC phase I trial also evaluated the potential for dolastatin-10 dose escalation with cytokine support, with the objective of maximizing the duration that plasma levels exceeded 1 ng/mL. Patients managed with prophylactic G-CSF received dose escalations starting at 300 $\mu\text{g}/\text{m}^2$ and were able to receive up to 660 $\mu\text{g}/\text{m}^2$ of dolastatin. Higher doses were associated with development of dose-limiting thrombocytopenia and granulocytopenia, but there were no significant nonhematologic toxicities observed during the trial. Objective responses were not observed in any of the 19 patients treated. Pharmacokinetic analysis from this trial confirmed that plasma levels of dolastatin-10 above the targeted 1 ng/mL could be maintained for greater than 30 hours in these patients.¹⁶⁵

Since myelosuppression remained the dose-limiting toxicity, a phase I trial of dolastatin-10 was initiated at MDACC to establish a dose of dolastatin-10 for treatment of patients with acute leukemia. More than 16 patients with acute myeloid leukemia and two patients with acute lymphoblastic leukemia have been treated with doses ranging from 400 $\mu\text{g}/\text{m}^2$ to 1,200 $\mu\text{g}/\text{m}^2$. Patients were refractory to prior therapy or had relapsed after a median first complete response duration of 33 weeks. One patient achieved a partial remission with decrease in bone marrow blasts to 9% and platelet recovery; 60% of patients with circulating blasts (>20%) had a significant decrease in blast counts with an increase in neutrophils, and 17 of 18 patients developed at least a transient decrease in white blood cell counts. The response to dolastatin-10 appeared to correlate with *MDR* expression. Nonhematologic toxicities were minimal even at doses threefold higher than administered to solid tumor patients; drug-related toxicities reported included grade 1 hypokalemia and grade 2 nausea.¹⁶⁶ Continued dose escalation of dolastatin

10 is planned for this trial. The promising indications of activity may lead to further assessment of dolastatin-10 on a more frequent dosing schedule.

Farnesyl Transferase Inhibitors

The family of *Ras* genes encode 21-kd proteins that function as molecular switches that regulate diverse signaling pathways involved in cell growth, differentiation, and apoptosis. *Ras* is synthesized as an inactive cytosolic precursor molecule that achieves functional localization by integrating into the plasma membrane. The first step in the processing involves the enzyme farnesyl transferase. Therefore, farnesyl transferase inhibitors are of interest in MDS because they inhibit an enzyme required for *RAS* activation of a number of signaling pathways.¹⁶⁷ Several agents in this class are entering clinical development, including R115777 (Janssen Pharmaceuticals, Titusville, NJ), BMS-214662 (Bristol-Meyers-Squibb, Wallingford, CT), and LB-42908 (LG Chem, Taejon, Korea).^{168,169} However, these agents may act at sites other than farnesyl transferase, such as those involving geranylgeranyl protein transferase.¹⁶⁷

R115777

R115777 (NSC 702818) is a potent nonpeptidomimetic inhibitor of farnesyl protein transferase (FPTase).¹⁷⁰ The antitumor activity of R115777 is possibly related to blocking the post-translational farnesylation of *Ras* proteins (H-, N-, and K-) that are frequently mutated in a variety of cancers. This farnesylation is a critical step in the process of membrane anchorage of these proteins and is an essential requirement for the activation of the *Ras* signaling pathway.¹⁷¹

Preclinical studies demonstrated that R115777 inhibits the growth of H-*ras*-, K-*ras*-, and N-*ras*-transformed cell lines and tumor xenografts. In vitro, R115777 inhibited the proliferation of NIH 3T3 cells transfected with the T24 H-*ras* oncogene and two human colon tumor cell lines bearing K-*ras* mutations. In vivo, R115777 significantly reduced the growth of the T24 H-*ras*-transfected 3T3 cells and the LoVo human colon and the CAPAN-2 human pancreatic tumor xenografts after oral administration.¹⁷⁰

One phase I trial at the NCI using 5-day twice-daily dosing every 2 weeks revealed no dose-limiting toxicity up to the highest dose of 1,300 mg twice daily.¹⁷² Nausea, vomiting, and

fatigue were the most common adverse events, but no ophthalmologic or hematologic toxicities were noted. Two other regimens, 21-day twice daily every 4 weeks and continuous administration for 4 weeks, are being investigated in three other ongoing phase I studies. In another ongoing phase I study of chronic twice-daily dosing, one instance of dose-limiting febrile neutropenia and thrombocytopenia was observed at the 500-mg twice-daily dose level; other adverse events included one instance of grade 3 skin hypersensitivity and one of grade 2 leukopenia.¹⁷³

In collaboration with Janssen Pharmaceuticals, the Cancer Therapy Evaluation Program (CTEP) is planning a development program of R115777, including phase II studies in colorectal, pancreas and prostate adenocarcinoma, non-small cell lung cancer, glioblastoma, melanoma, and MDS. Phase I studies will include combination trials with topotecan, as well as trials in patients with hematologic malignancies with a leukemic phase, in which tumor cells can be easily sampled for drug effects.

Angiogenesis Inhibitors

An increasing body of data suggests that there may be a role for angiogenesis in multiple myeloma, non-Hodgkin's lymphomas, acute leukemias, and MDS.¹⁷⁴⁻¹⁸¹ Angiogenesis and tumor-associated neovascularization have been implicated in the pathogenesis of a number of human tumors by leading to tumor growth, invasion, and metastasis. These complex processes involve multiple steps and pathways that depend on a balance between positive and negative regulatory factors, as well as interactions among the tumor, its vasculature, and the surrounding extracellular tissue matrix. Tumors appear to remain dormant for an indefinite period of time, with their growth being controlled by apoptosis. Eventually they acquire an angiogenic phenotype, at which time progression occurs with increased tumor growth and metastasis.

Several lines of evidence suggest a potential role for antiangiogenesis agents in MDS. MDS may result from a defect in apoptosis. In other leukemia systems, angiogenesis factors such as basic fibroblast growth factor (bFGF) upregulate *bcl-2*, delaying programmed cell death.¹⁸⁰ Several new antiangiogenesis agents are available for clinical trials, including thalidomide and SU5416.¹⁸²⁻¹⁸⁴ Deliliers et al¹⁸⁵ evaluated bone marrow angiogenesis in 81

patients with various subtypes of MDS, and the results were compared with 10 normal controls. They used immunostaining with anti-CD31, anti-CD34, and anti-vascular endothelial growth factor (VEGF), and examined microvessel density (MVD). MVD was significantly higher in patients than controls, but lower than in patients with AML or myeloproliferative disorders. There was a correlation between MVD and cytologic subtypes, with higher levels detected in patients with RAEB-T and CMML. Based on these data, Raza et al¹⁸⁴ studied thalidomide in patients with RA. They reported on 33 patients with a median age of 69 years; 20 had RA or RARS, 12 RAEB, and two CMML. Of these 20 evaluable patients, eight had either a greater than 50% reduction in red blood cell requirements or a rise in hemoglobin of ≥ 2 g/dL; four showed greater than 30,000/ μ L increase in platelets, and one had a neutrophil response greater than 500/ μ L.

Angiogenesis inhibitors have a number of potentially attractive features. They have a unique mechanism of action and are relatively without toxicity, which makes them of interest for combination regimens. Angiogenesis agents also differ from traditional chemotherapy, since they may be more cytostatic than cytotoxic.

Immunosuppressive Therapy

Several lines of evidence have suggested an immunologic contribution to the pathogenesis of MDS. As a result, drugs such as azathioprine, cyclosporine, and antithymocyte globulin (ATG) have been studied and anecdotal responses reported.¹⁸⁶⁻¹⁹⁰ Mollidrem et al¹⁸⁷ described 25 transfusion-dependent patients with MDS and less than 20% blasts who were successfully treated with a single course of ATG at a dose of 40 mg/kg for 4 days. Barrett et al^{187,191} updated this experience with 60 MDS patients, showing that they were able to render one third independent of red blood cell transfusions, with 87% of responders free of progression at 2.5 years. Further study of this approach is warranted.

SUMMARY AND CONCLUSIONS

We have clearly moved beyond the empiric study of new chemotherapy drugs and biologic agents for treating patients with MDS. This strategy is no longer appropriate given our increasing knowledge of the molecular and immunologic

abnormalities associated with this diverse group of disorders. We have a large number of new agents that are either currently or will soon be in clinical trials that target biologic or molecular pathways. It is important to rapidly accrue patients to these studies. Unfortunately, patients often receive new investigational drugs after failing extensive prior therapy, when they are least likely to respond. Patients with MDS who are not suitable transplant candidates can be considered for treatment with a new agent as part of their initial therapy, until an effective treatment for this disease becomes available.

To identify new effective agents, standardized response criteria are needed to ensure comparable patient groups among studies and collection of complete prognostic factor information; the availability of uniform response criteria would facilitate the interpretation of data and the ability to compare results among various studies. Therefore, standardization would help us to identify new agents with promising activity. In addition, criteria provide a framework upon which to test scientific correlative studies of new biologic and immunologic insights into MDS. Recently, an international group of researchers with expertise in MDS developed a series of recommended guidelines to achieve these goals.¹⁹²

Also critical for evaluating and clarifying outcomes of treatments and for designing trials is to effectively and prospectively stratify patient selection. Studies in MDS should provide risk-based criteria for patient entry and evaluation (ie, FAB group, or IPSS category¹¹). Such stratification could include age, performance status, and prognostic risk category, such as the IPSS.

It is unlikely any of the single agents will make a major impact on patient outcome. However, failure of a single agent to induce significant benefit may not be the fault of the drug, but rather the manner in which it was tested: clinical trials evaluating a suboptimal dose or schedule may lead to an erroneous impression that a compound is inactive. Negative results in preliminary trials may lead to the premature discarding of potentially valuable agents. For example, antiangiogenic drugs are likely to be cytostatic and, therefore, may not induce traditional responses in phase II studies. Future strategies must identify the appropriate therapeutic targets and to design rational drug

combinations to attack those targets with the goal of eventually curing patients with MDS.

REFERENCES

1. Bennett JM, Catovsky D, Daniel M-T, et al: Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 51:189-199, 1982
2. Bennett JM, Catovsky D, Daniel MT, et al: Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British group. *Ann Intern Med* 103:626-629, 1985
3. Cheson BD, Cassileth PA, Head DR, et al: Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. *J Clin Oncol* 8:813-819, 1990
4. Harris NL, Jaffe ES, Diebold J, et al: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: Report of the clinical advisory committee meeting—Airlie House, Virginia. *J Clin Oncol* 17:3835-3849, 1999
5. Tricot G, Vlietinck R, Boogaerts MA, et al: Prognostic factors in the myelodysplastic syndromes: Importance of initial data on peripheral blood counts, bone marrow cytology, trephine biopsy and chromosome analysis. *Br J Haematol* 60:19-32, 1985
6. Todd WM, Pierre RV: Preleukaemia: A long-term prospective study of 326 patients. *Scand J Haematol* 36:114-120, 1986
7. Vallespi T, Torrabadella M, Julia A, et al: Myelodysplastic syndromes: A study of 101 cases according to the FAB classification. *Br J Haematol* 61:81-92, 1985
8. Kerkhofs H, Hermans J, Maak HL, et al: Utility of the FAB classification for myelodysplastic syndromes: Investigation of prognostic factors in 237 cases. *Br J Haematol* 65:83-92, 1987
9. Weisdorf DJ, Oken MM, Johnson GJ, et al: Chronic myelodysplastic syndrome: short survival with or without evolution to acute leukaemia. *Br J Haematol* 55:691-700, 1983
10. Kantarjian HM, Keating MJ, Walters RS, et al: Therapy-related leukemia and myelodysplastic syndrome: Clinical, cytogenetic, and prognostic features. *J Clin Oncol* 4:1748-1757, 1986
11. Greenberg P, Cox C, LeBeau M, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 89:2079-2088, 1997
12. Ellison RR, Holland JF, Weil M, et al: Arabinosyl cytosine: A useful agent in the treatment of acute leukemia in adults. *Blood* 32:507-523, 1968
13. Baccarani M, Tura S: Differentiation of myeloid leukaemic cells: new possibilities for therapy. *Br J Haematol* 42:485-490, 1979
14. Baccarani M, Zaccaria A, Bandini G, et al: Low dose arabinosyl cytosine for treatment of myelodysplastic syndromes and subacute myeloid leukemia. *Leuk Res* 7:539-545, 1983
15. Griffin JD, Spriggs D, Wisch JS, et al: Treatment of preleukemic syndromes with continuous intravenous infusion of low-dose cytosine arabinoside. *J Clin Oncol* 3:982-991, 1985
16. Hoelzer D, Ganser A, Schneider W, et al: Low-dose cytosine arabinoside in the treatment of acute nonlymphoblastic leukemia and myelodysplastic syndromes. *Semin Oncol* 12:208-211, 1985
17. Powell BL, Capizzi RL, Jackson DV, et al: Low dose ara-C

for patients with myelodysplastic syndromes. *Leukemia* 2:153-156, 1988

18. Roberts JD, Ershler WB, Tindle BH, et al: Low-dose cytosine arabinoside in the myelodysplastic syndromes and acute myelogenous leukemia. *Cancer* 56:1001-1005, 1985

19. Tricot G, De Bock R, Dekker AW, et al: Low dose cytosine arabinoside (ara-C) in myelodysplastic syndromes. *Br J Haematol* 58:231-340, 1984

20. Winter JN, Variakojis D, Gaynor ER, et al: Low-dose cytosine arabinoside (ara-C) therapy in the myelodysplastic syndromes and acute leukemia. *Cancer* 56:443-449, 1985

21. Wisch JS, Griffin JD, Kufe DW: Response of preleukemic syndromes to continuous infusion of low-dose cytarabine. *N Engl J Med* 309:1599-1602, 1983

22. Degos L, Castaigne S, Tilly H, et al: Treatment of leukemia with low-dose ara-C: A study of 160 cases. *Semin Oncol* 12:196-199, 1985

23. Cheson BD, Jaspense DM, Simon R, et al: A critical appraisal of low-dose cytosine arabinoside in patients with acute non-lymphocytic leukemia and myelodysplastic syndromes. *J Clin Oncol* 4:1857-1864, 1986

24. Cheson BD, Simon R: Low-dose ara-C in acute nonlymphocytic leukemia and myelodysplastic syndromes: A review of 20 years' experience. *Semin Oncol* 14:126-133, 1987

25. Miller KB, Kyungmann K, Morrison FS, et al: The evaluation of low-dose cytarabine in the treatment of myelodysplastic syndromes: A phase-III intergroup study. *Ann Hematol* 65:162-168, 1992

26. De Bock R, Van Hoof A, Van Hove W, et al: Oral idarubicin (IDA) for RAEB, RAEBt, and acute leukemia (AL) post myelodysplastic syndrome (MDS). A phase II open study. *Proc Am Soc Clin Oncol* 8:204, 1989 (abstr 794)

27. Shibuya T, Teshima T, Harada M, et al: Treatment of myelodysplastic syndrome and atypical leukemia with low-dose aclarubicin. *Leuk Res* 14:161-167, 1990

28. Wattel E, Guerci A, Hecquest B, et al: A randomized trial of hydroxyurea versus VP16 in adult chronic myelomonocytic leukemia. *Blood* 88:2480-2487, 1996

29. Spitzer TR, Lazarus HM, Crum ED, et al: Treatment of myelodysplastic syndromes with low-dose oral 6-thioguanine. *Med Pediatr Oncol* 16:17-20, 1988

30. Feldman E, Sullivan P, Ahmed T, et al: Phase II trial of homoharringtonine (HHT) in patients with myelodysplastic syndromes (MDS). *Blood* 72:198a, 1988 (suppl 1, abstr 701)

31. Beran M, Kantarjian H, O'Brien S, et al: Topotecan, a topoisomerase I inhibitor is active in the treatment of myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood* 88:2473-2479, 1996

32. Beran M, Estey E, O'Brien S, et al: Topotecan and cytarabine is an active combination regimen in myelodysplastic syndromes and chronic myelomonocytic leukemia. *J Clin Oncol* 17:2819-2830, 1999

33. Besa EC: A new combination chemotherapy using topotecan, fludarabine, ara-C and G-CSF for aggressive myelodysplastic syndromes and acute myelogenous leukemia in the elderly: Dose finding for topotecan study. *Blood* 94:307a, 1999 (suppl 1, abstr 1375)

34. List AF, Brasfield F, Heaton R, et al: Stimulation of hematopoiesis by amifostine in patients with myelodysplastic syndrome. *Blood* 90:3364-3369, 1997

35. List AF, Holmes H, Vempaty H, et al: Phase II study of

amifostine in patients with myelodysplastic syndromes (MDS): Impact on hematopoiesis. *Proc Am Soc Clin Oncol* 18:51a, 1999 (abstr 190)

36. Galanopoulos A, Kritikou-Griva E, Gligori J, et al: Treatment of myelodysplastic syndrome with amifostine and its effect on hematopoiesis. *Blood* 94:306a, 1999 (suppl 1, abstr 1367)

37. Bowen DT, Denzlinger C, Brugger W, et al: Poor response rate to a continuous schedule of Amifostine therapy for "low/intermediate risk" myelodysplastic patients. *Br J Haematol* 103:785-787, 1998

38. Hofmann WK, Seipelt G, Kalina U, et al: Effect of treatment with amifostine used as single agent in patients with refractory anemia on clinical outcome and serum TNF α levels. *Blood* 94:305a, 1999 (suppl 1, abstr 1363)

39. Richon VM, Emiliani S, Verdin E, et al: A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases. *Proc Natl Acad Sci USA* 95:3003-3007, 1998

40. Saito A, Yamashita T, Mariko Y, et al: A synthetic inhibitor of histone deacetylase, MS-27-275, with marked in vivo antitumor activity against human tumors. *Proc Natl Acad Sci USA* 96:4592-4597, 1999

41. Glover AB, Leyland-Jones B: Biochemistry of azacitidine: A review. *Cancer Treat Rep* 71:959-64, 1987

42. Momparler RL, D'Erse D: Kinetics of phosphorylation of 5-aza-2'-deoxycytidine by deoxycytidine kinase. *Biochem Pharmacol* 28:1443-1444, 1979

43. Creusot F, Acs G, Christman JK: Inhibition of DNA methyltransferase and induction of Friend erythroleukemia cell differentiation by 5-azacytidine and 5-aza-2'-deoxycytidine. *J Biol Chem* 257:2041-2048, 1982

44. Taylor SM, Constantinides PA, Jones PA: 5-Azacytidine, DNA methylation, and differentiation. *Curr Top Microbiol Immunol* 108:115-27, 1984

45. Christman JK, et al: Effect of 5-azacytidine on differentiation and DNA methylation in human promyelocytic leukemia cells (HL-60). *Cancer Res* 43:763-769, 1983

46. Pinto A, Zagonel V: 5-aza-2'-deoxycytidine (decitabine) and 5-azacytidine in the treatment of acute myeloid leukemias and myelodysplastic syndromes: Past, present and future trends. *Leukemia* 7:51-60, 1993

47. Issa JP, Baylin SB, Herman JG: DNA methylation changes in hematologic malignancies: Biologic and clinical implications. *Leukemia* 11:S7-11, 1997 (suppl 1)

48. Singal R, Ginder GD: DNA methylation. *Blood* 93:4059-4070, 1999

49. Vogler WR, Miller DS, Keller JW: 5-Azacytidine (NSC 102816): A new drug for the treatment of myeloblastic leukemia. *Blood* 48:331-337, 1976

50. Saiki JH, Bodey GP, Hewlett JS, et al: Effect of schedule on activity and toxicity of 5-azacytidine in acute leukemia. A Southwest Oncology Group study. *Cancer* 47:1739-1742, 1981

51. Glover AB, Leyland-Jones BR, Chun HG, et al: Azacitidine: 10 years later. *Cancer Treat Rep* 71:737-746, 1987

52. Larson RA, Sweet DL, Golomb HM, et al: Response to 5-azacytidine in patients with refractory acute nonlymphocytic leukemia and association with chromosome findings. *Cancer* 49:2222-2225, 1982

53. Saiki JH, McCredie KB, Vietti TJ, et al: 5-Azacytidine in acute leukemia. *Cancer* 42:2111-2114, 1978

54. Chitambar CR, Libnoch JA, Matthaeus WG, et al: Evaluation of continuous infusion low-dose 5-azacytidine in the treatment of myelodysplastic syndromes. *Am J Hematol* 37:100-104, 1991
55. Silverman LR, Davis RB, Holland JF, et al: 5-Azacytidine (AZ) as a low dose continuous infusion is an effective therapy for patients with myelodysplastic syndromes (MDS). *Proc Am Soc Clin Oncol* 8:198, 1989 (abstr 768)
56. Silverman LR, Holland JF, Nelson D, et al: Trilineage (TLR) response of myelodysplastic syndromes (MDS) to subcutaneous (SQ) azacytidine (Aza C). *Proc Am Soc Clin Oncol* 10:222, 1991 (abstr 747)
57. Silverman LR, Demakos EP, Peterson B, et al: A randomized controlled trial of subcutaneous azacytidine (AZA C) in patients with the myelodysplastic syndrome (MDS): A study of the Cancer and Leukemia Group B (CALGB). *Proc Am Soc Clin Oncol* 17:14a, 1998 (abstr 53)
58. Kornblith A, Herndon II J, Silverman LR, et al: The impact of 5-azacytidine on the quality of life of patients with the myelodysplastic syndrome (MDS) treated in a randomized phase III trial of the Cancer and Leukemia Group B (CALGB). *Proc Am Soc Clin Oncol* 17:49a, 1998 (abstr)
59. Zagonel V, Pinto A, Attadia V, et al: Phase I-II clinical-biological study of 5-aza-2'-deoxycytidine (5azaCdR) as a differentiation inducer in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) of the elderly. *Proc Am Soc Clin Oncol* 8:197, 1989 (abstr 767)
60. Wijermans PW, Krulder JWM, Huijgens PC, et al: Continuous infusion of low-dose 5-aza-2'-deoxycytidine in elderly patients with high-risk myelodysplastic syndrome. *Leukemia* 11:19-23, 1997
61. Nagy L, Kao HY, Chakravarti D, et al: Nuclear receptor repression mediated by a complex containing SMRT, mSin3A, and histone deacetylase. *Cell* 89:373-380, 1997
62. Sommer A, Hilfenhaus S, Menkel A, et al: Cell growth inhibition by the Mad/Max complex through recruitment of histone deacetylase activity. *Curr Biol* 7:357-365, 1997
63. Lin RJ, Nagy L, Inoue S, et al: Role of the histone deacetylase complex in acute promyelocytic leukaemia. *Nature* 391:811-814, 1998
64. Grignani F, De Matteis S, Nervi C, et al: Fusion proteins of the retinoic acid receptor- α recruit histone deacetylase in promyelocytic leukaemia. *Nature* 391:815-818, 1998
65. He LZ, Guidez F, Tribioli C, et al: Distinct interactions of PML-RAR α and PLZF-RAR α with co-repressors determine differential responses to RA in APL. *Nat Genet* 18:126-135, 1998
66. David G, Alland L, Hong SH, et al: Histone deacetylase associated with mSin3A mediates repression by the acute promyelocytic leukemia-associated PLZF protein. *Oncogene* 16:2549-2556, 1998
67. Guidez F, Ivins S, Zhu J, et al: Reduced retinoic acid-sensitivities of nuclear receptor corepressor binding to PML- and PLZF-RAR α underlie molecular pathogenesis and treatment of acute promyelocytic leukemia. *Blood* 91:2634-2642, 1998
68. Gelmetti V, Zhang J, Fanelli M, et al: Aberrant recruitment of the nuclear receptor corepressor-histone deacetylase complex by the acute myeloid leukemia fusion partner ETO. *Mol Cell Biol* 18:7185-7191, 1998
69. Lutterbach B, Westendorf JJ, Linggi B, et al: ETO, a target of t(8;21) in acute leukemia, interacts with the N-CoR and mSin3 corepressors. *Mol Cell Biol* 18:7176-7184, 1998
70. Warrell RP Jr, He LZ, Richon V, et al: Therapeutic targeting of transcription in acute promyelocytic leukemia by use of an inhibitor of histone deacetylase. *J Natl Cancer Inst* 90:1621-1625, 1998
71. Baylin SB, Herman JG, Graff JR, et al: Alterations in DNA methylation: A fundamental aspect of neoplasia. *Adv Cancer Res* 72:141-196, 1998
72. Nan X, Ng HH, Johnson CA, et al: Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature* 393:386-389, 1998
73. Jones PL, Veenstra GJ, Wade PA, et al: Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. *Nat Genet* 19:187-191, 1998
74. Cameron EE, Bachman KE, Myohanen S, et al: Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer. *Nat Genet* 21:103-107, 1999
75. Brusilow SW, Danney M, Waber LJ, et al: Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis. *N Engl J Med* 310:1630-1634, 1984
76. Collins AF, Pearson HA, Giardina P, et al: Oral sodium phenylbutyrate therapy in homozygous beta thalassemia: A clinical trial. *Blood* 85:43-49, 1995
77. Rosenfeld H, Roberts J: Enhancement of antitumor activity of glutamine antagonists 6-diazo-5-oxo-L-norleucine and acivicin in cell culture by glutaminase-asparaginase. *Cancer Res* 41:1324-1328, 1981
78. Weber G: Biochemical strategy of cancer cells and the design of chemotherapy: G.H.A. Clowes Memorial Lecture. *Cancer Res* 43:3466-3492, 1983
79. Prasanna P, Shack S, Wilson VL, et al: Phenylacetate and derivatives as novel, nontoxic chemopreventive agents. *Proc Am Assoc Cancer Res* 35:325, 1994 (abstr 1935)
80. Samid D, Hudgins WR, Shack S, et al: Phenylacetate and derivatives: simple compounds with complex antitumor activities. *Journal* 35:#2435, 1994
81. Pineau T, Hudgins WR, Liu L, et al: Activation of a human peroxisome proliferator-activated receptor by the antitumor agent phenylacetate and its analogs. *Biochem Pharmacol* 52:659-667, 1996
82. Boffa LC, Vidali G, Mann RS, et al: Suppression of histone deacetylase in vivo and in vitro by sodium butyrate. *J Biol Chem* 253:3364-3366, 1978
83. Candido EP, Reeves R, Davie JR: Sodium butyrate inhibits histone deacetylation in cultured cells. *Cell* 14:105-113, 1978
84. Sealy L, Chalkley R: The effect of sodium butyrate on histone modification. *Cell* 14:115-121, 1978
85. Samid D, Ram Z, Hudgins WR, et al: Selective activity of phenylacetate against malignant gliomas: Resemblance to fetal brain damage in phenylketonuria. *Cancer Res* 54:891-895, 1994
86. Liu L, Bar-Ner M, Weber J, et al: Enhancement of tumor immunogenicity by phenylacetate and derivatives: Changes in surface antigens and tumor-derived immunosuppressive factors. *Proc Am Assoc Cancer Res* 35:A2866, 1994 (abstr)
87. Liu L, Shack S, Stetler-Stevenson WG, et al: Differentiation of cultured human melanoma cells induced by the aromatic

fatty acids phenylacetate and phenylbutyrate. *J Invest Dermatol* 103:335-340, 1994

88. Wood CG, Lee C, Grayhack JT, et al: Phenylacetate and phenylbutyrate promote cellular differentiation in human prostate cancer systems. *Proc Am Assoc Cancer Res* 35:403, 1994 (abstr 2404)

89. Engelhard HH, Homer RJ, Duncan HA, et al: Inhibitory effects of phenylbutyrate on the proliferation, morphology, migration and invasiveness of malignant glioma cells. *J Neurooncol* 37:97-108, 1998

90. Yu KH, Weng LJ, Fu S, et al: Augmentation of phenylbutyrate-induced differentiation of myeloid leukemia cells using all-trans retinoic acid. *Leukemia* 13:1258-1265, 1999

91. Ueda H, Nakajima H, Hori Y, et al: Action of FR901228, a Novel Antitumor Bicyclic Depsipeptide Produced by *Chromobacterium violaceum* no. 968, on Ha-ras Transformed NIH3T3 Cells. *Biosci Biotech Biochem* 58:1579-1583, 1994

92. Nakajima H, Kim YB, Terano H, et al: FR901228, a potent antitumor antibiotic, is a novel histone deacetylase inhibitor. *Exp Cell Res* 241:126-133, 1998

93. Byrd JC, Shinn C, Ravi R, et al: Depsipeptide (FR901228): A novel therapeutic agent with selective, in vitro activity against human B-cell chronic lymphocytic leukemia cells. *Blood* 94:1401-1408, 1999

94. Andreeff M, Stone R, Michaeli J, et al: Hexamethylene bisacetamide in myelodysplastic syndrome and acute myelogenous leukemia: A phase II clinical trial with a differentiation-inducing agent. *Blood* 80:2604-2609, 1992

95. Zhou X, Richon VM, Ngo L, et al: Cloning of the cDNA encoding phenylalanyl tRNA synthetase regulatory alpha-subunit-like protein whose expression is down-regulated during differentiation. *Gene* 233:13-19, 1999

96. Webster LT: Drugs used in the chemotherapy of protozoan infections, in Gilman AG, Rau TW, Nies AS, et al (eds): Goodman and Gilman's The Pharmacologic Basis of Therapeutics. New York, NY, Pergamon, 1990, pp 1008-1018

97. Kwong YL, Todd D: Delicious poison: Arsenic trioxide for the treatment of leukemia. *Blood* 89:3487-3488, 1997 (letter)

98. Zhang P, Wang ZY, Hu XH, et al: Arsenic trioxide treated 72 cases of acute promyelocytic leukaemia. *Chin J Haematol* 17:58-60, 1996

99. Shen ZX, Chen GQ, Ni JH, et al: Use of arsenic trioxide (As₂O₃) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. *Blood* 89:3354-3360, 1997

100. Soignet SL, Maslak P, Wang ZG, et al: Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. *N Engl J Med* 339:1341-1348, 1998

101. Wang ZG, Rivi R, Delva L, et al: Arsenic trioxide and melarsoprol induce programmed cell death in myeloid leukemia cell lines and function in a PML and PML-RARalpha independent manner. *Blood* 92:1497-1504, 1998

102. Chen GQ, Shi XG, Tang W, et al: Use of arsenic trioxide (As₂O₃) in the treatment of acute promyelocytic leukemia (APL): I. As₂O₃ exerts dose-dependent dual effects on APL cells. *Blood* 89:3345-3353, 1997

103. Rousselot P, Labaume S, Marolleau JP, et al: Arsenic trioxide and melarsoprol induce apoptosis in plasma cell lines and in plasma cells from myeloma patients. *Cancer Res* 59:1041-1048, 1999

104. Ishitsuka K, Hanada S, Suzuki S, et al: Arsenic trioxide inhibits growth of human T-cell leukaemia virus type I infected T-cell lines more effectively than retinoic acids. *Br J Haematol* 103:721-728, 1998

105. Zhu XH, Shen YL, Jing YK, et al: Apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide at clinically achievable concentrations. *J Natl Cancer Inst* 91:772-778, 1999

106. Zhang W, Ohnishi K, Shigeno K, et al: The induction of apoptosis and cell cycle arrest by arsenic trioxide in lymphoid neoplasms. *Leukemia* 12:1383-1391, 1998

107. Bazarbachi A, El-Sabban ME, Nasr R, et al: Arsenic trioxide and interferon-alpha synergize to induce cell cycle arrest and apoptosis in human T-cell lymphotropic virus type I-transformed cells. *Blood* 93:278-283, 1999

108. Zhou DC, Gao M, Ferrari AC, et al: Arsenic trioxide is an equipotent inducer of apoptosis in androgen-dependent and androgen-independent LNCaP prostate cancer cell sublines. *Proc Am Assoc Cancer Res* 39:588, 1998 (abstr)

109. Yang CH, Wang TY, Chen YC: Cytotoxicity of arsenic trioxide in cancer cell lines. *Proc Am Assoc Cancer Res* 39:227, 1998 (abstr)

110. Chen GQ, Zhu J, Shi XG, et al: In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As₂O₃) in the treatment of acute promyelocytic leukemia: As₂O₃ induces NB4 cell apoptosis with downregulation of Bcl-2 expression and modulation of PML-RAR alpha/PML proteins. *Blood* 88:1052-1061, 1996

111. Shao W, Fanelli M, Ferrara FF, et al: Arsenic trioxide as an inducer of apoptosis and loss of PML/RAR alpha protein in acute promyelocytic leukemia cells. *J Natl Cancer Inst* 90:124-133, 1998

112. Zhu J, Koken MH, Quignon F, et al: Arsenic-induced PML targeting onto nuclear bodies: Implications for the treatment of acute promyelocytic leukemia. *Proc Natl Acad Sci USA* 94:3978-3983, 1997

113. Goyer RA: Toxic effects of metals, in Klaassen CD (ed): Casarett and Doull's Toxicology: The Basic Science of Poisons. New York, NY, McGraw-Hill, 1996, pp 691-698

114. Klaassen CD: Heavy metals and heavy-metal antagonists. *Journal* 1649-1671, 1996

115. Kroemer G, de Th H: Arsenic trioxide, a novel mitochondriotoxic anticancer agent? *J Natl Cancer Inst* 91:743-745, 1999 (editorial)

116. Larochette N, Decaudin D, Jacotot E, et al: Arsenite induces apoptosis via a direct effect on the mitochondrial permeability transition pore. *Exp Cell Res* 249:413-421, 1999

117. Dai J, Weinberg RS, Waxman S, et al: Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system. *Blood* 93:268-277, 1999

118. Li YM, Broome JD: Arsenic targets tubulins to induce apoptosis in myeloid leukemia cells. *Cancer Res* 59:776-780, 1999

119. Huang SY, Chang CS, Tang JL, et al: Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. *Br J Haematol* 103:1092-1095, 1998

120. Niu C, Yan H, Yu T, et al: Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: Remission induction, follow-up, and molecular monitoring in 11 newly diag-

nosed and 47 relapsed acute promyelocytic leukemia patients. *Blood* 94:3315-3324, 1999

121. Soignet S, Frankel S, Tallman M, et al: U.S. multicenter trial of arsenic trioxide (AT) in acute promyelocytic leukemia (APL). *Blood* 94:698a, 1999 (suppl 1, abstr)

122. Camacho L, Soignet S, Heller G, et al: Leukocytosis and the "retinoic acid syndrome" during induction treatment of acute promyelocytic leukemia with arsenic trioxide. *Blood* 94:595a, 1999 (suppl 1, abstr)

123. Frankel SR, Eardley A, Lauwers G, et al: The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 117:292-296, 1992

124. Takahashi I, Kobayashi E, Asano K, et al: UCN-01, a selective inhibitor of protein kinase C from *Streptomyces*. *J Antibiot* 40:1782-1784, 1987

125. Takahashi I, Saitoh Y, Yoshida M, et al: UCN-01 and UCN-02, new selective inhibitors of protein kinase C. II Purification, physico-chemical properties, structural determination and biological activities. *J Antibiot* 42:571-576, 1989

126. Tamaoki T, Nakano H: Potent and specific inhibitors of protein kinase C of microbial origin. *Biotechnology* 8:732-735, 1990

127. Tamaoki T: Use and specificity of staurosporine, UCN-01, and calphostin C as protein kinase inhibitors. *Methods Enzymol* 201:340-347, 1991

128. Akiyama T, Yoshida T, Tsujita T, et al: G1 phase accumulation induced by UCN-01 is associated with dephosphorylation of Rb and CDK2 proteins as well as induction of CDK inhibitor p21/Cip1/WAF1/Sdi1 in p53-mutated human epidermoid carcinoma A431 cells. *Cancer Res* 57:1495-1501, 1997

129. Morgan DO: Principles of CDK regulation. *Nature* 374:131-134, 1995

130. Jin P, Gu Y, Morgan DO: Role of inhibitory CDC2 phosphorylation in radiation-induced G2 arrest in human cells. *J Cell Biol* 134:963-970, 1996

131. McGowan CH, Russell P: Cell cycle regulation of human Wee1. *EMBO J* 14:2166-2175, 1995

132. Yu L, Graves P, Tempczyk A, et al: Chk1 is a target of the anticancer agent UCN-01. *Proc Am Assoc Cancer Res* 40:304, 1999 (abstr 2019)

133. Shao RG, Shimizu T, Pommier Y: 7-Hydroxystaurosporine (UCN-01) induces apoptosis in human colon carcinoma and leukemia cells independently of p53. *Exp Cell Res* 234:388-397, 1997

134. Seynaeve CM, Stetler-Stevenson M, Severs S, et al: Cell cycle arrest and growth inhibition by the protein kinase antagonist UCN-01 in human breast carcinoma cells. *Cancer Res* 53:2081-2086, 1993

135. Monks A, Harris E, Connelly J, et al: Enhancement of fludarabine and gemcitabine toxicity by UCN-01 in a variety of tumor cell lines. *Proc Am Assoc Cancer Res* 40:7, 1999 (abstr 45)

136. Akinaga S, Nomura K, Gomi K, et al: Enhancement of antitumor activity of mitomycin C in vitro and in vivo by UCN-01, a selective inhibitor of protein kinase C. *Cancer Chemother Pharmacol* 32:183-189, 1993

137. Wang Q, Fan S, Eastman A, et al: UCN-01: A potent abrogator of G2 checkpoint function in cancer cells with disrupted p53. *J Natl Cancer Inst* 17:956-965, 1996

138. Pollack IF, Kawecki S, Lazo JS: Blocking of glioma

proliferation in vitro and in vivo and potentiating the effects of BCNU and cisplatin: UCN-01, a selective protein kinase inhibitor. *J Neurosurg* 84:1024-1032, 1996

139. Wang S, Vrana JA, Bartimole TM, et al: Agents that down-regulate or inhibit protein kinase C circumvent resistance to 1-beta-D-arabinofuranosylcytosine-induced apoptosis in human leukemia cells that overexpress Bcl-2. *Mol Pharmacol* 52:1000-1009, 1997

140. Sausville EA, Lush RD, Headlee D, et al: Clinical pharmacology of UCN-01: Initial observations and comparison to preclinical models. *Cancer Chemother Pharmacol* 42:S54-S58, 1998

141. Fuse E, Tani H, Kurata N, et al: Unpredicted clinical pharmacology of UCN-01 caused by specific binding to human alpha-1-acid glycoprotein. *Cancer Res* 58:3248-3253, 1998

142. Fuse E, Tani H, Takai K, et al: Altered pharmacokinetics of a novel anticancer drug, UCN-01, caused by specific high affinity binding to alpha-1-acid glycoprotein in human. *Cancer Res* 59:1054-1060, 1999

143. Hill DL, Tillery KF, Rose LM, et al: Disposition in mice of 7-hydroxystaurosporine, a protein kinase inhibitor with antitumor activity. *Cancer Chemother Pharmacol* 35:89-92, 1994

144. Senderowicz A, Headlee D, Lush R, et al: Phase I trial of infusional UCN-01, a novel protein kinase inhibitor, in patients with refractory neoplasms. *Proc Am Soc Clin Oncol* 18:159a, 1999 (abstr 612)

145. Pettit GR, Kamano Y, Herald CL, et al: The isolation and structure of a remarkable marine animal antineoplastic constituent: Dolastatin 10. *J Am Chem Soc* 109:6883-6885, 1987

146. Bai R, Pettit GR, Hamel E: Dolastatin 10, a powerful cytostatic peptide derived from a marine animal. Inhibition of tubulin polymerization mediated through the vinca alkaloid binding domain. *Biochem Pharmacol* 39:1941-1949, 1990

147. Bai RL, Pettit GR, Hamel E: Binding of dolastatin 10 to tubulin at a distinct site for peptide antimetabolic agents near the exchangeable nucleotide and vinca alkaloid sites. *J Biol Chem* 265:17141-17149, 1990

148. Bai R, Roach MC, Jayaram SK, et al: Differential effects of active isomers, segments, and analogs of dolastatin 10 on ligand interactions with tubulin. Correlation with cytotoxicity. *Biochem Pharmacol* 45:1503-1515, 1993

149. Verdier-Pinard P, Kepler JA, Pettit GR, et al: Sustained intracellular retention of dolastatin 10 causes its potent antimetabolic activity. *Mol Pharmacol* 57:180-187, 2000

150. Jacobsen SEW, Ruscetti FW, Longo DL, et al: Antineoplastic dolastatins: Potent inhibitors of hematopoietic progenitor cells. *J Natl Cancer Inst* 83:1672-1677, 1991

151. Beckwith M, Urba WJ, Longo DL: Growth inhibition of human lymphoma cell lines by the marine products, dolastatins 10 and 15. *J Natl Cancer Inst* 85:483-488, 1993

152. Maki A, Mohammed R, Raza S, et al: Effect of dolastatin 10 on human non-Hodgkin's lymphoma cell lines. *Anticancer Drugs* 7:344-350, 1996

153. Steube KG, Grunicke D, Pietsch T, et al: Dolastatin 10 and dolastatin 15: effects of two natural peptides on growth and differentiation of leukemia cells. *Leukemia* 6:1048-1053, 1992

154. Turner T, Jackson WH, Pettit GR, et al: Treatment of human prostate cancer cells with dolastatin 10, a peptide

isolated from a marine shell-less mollusc. *Prostate* 34:175-181, 1998

155. Kalemkerian GP, Ou X, Adil MR, et al: Activity of dolastatin 10 against small-cell lung cancer in vitro and in vivo: Induction of apoptosis and bcl-2 modification. *Cancer Chemother Pharmacol* 43:507-515, 1999

156. Mohammed RM, Varterasian ML, Almatchy VP, et al: Successful treatment of human chronic lymphocytic leukemia xenografts with combination biological agents auristatin PE and bryostatins 1. *Clin Cancer Res* 4:1337-1343, 1998

157. Haldar S, Basu A, Croce C: Serine-70 is one of the critical sites for drug-induced bcl-2 phosphorylation in cancer cells. *Cancer Res* 58:1609-1615, 1998

158. Maki A, Diwakaran H, Redman B, et al: The bcl-2 and -53 oncoproteins can be modulated by bryostatin 1 and dolastatins in human diffuse large cell lymphoma. *Anticancer Drugs* 6:392-397, 1995

159. Aherne GW, Hardcastle A, Valenti M, et al: Antitumor evaluation of dolastatins 10 and 15 and their measurement in plasma by radioimmunoassay. *Cancer Chemother Pharmacol* 38:225-232

160. Newman RA, Fuentes A, Covey JM, et al: Preclinical pharmacology of the natural marine product dolastatin 10 (NSC 376128). *Drug Metab Dispos* 22:428-432, 1994

161. Mirsalis JC, Schindler-Horvat J, Hill JR, et al: Toxicity of dolastatin 10 in mice, rats and dogs and its clinical relevance. *Cancer Chemother Pharmacol* 44:395-402, 1999

162. Pitor HC, McElroy EA, Reid JM, et al: Phase I trial of dolastatin-10 (NSC 376128) in patients with advanced solid tumors. *Clin Cancer Res* 5:525-531, 1999

163. Tran HT, Newman RA, Beck DE, et al: A phase I, pharmacokinetic/pharmacodynamic study of dolastatin-10 in adult patients with advanced solid tumors. *Proc Am Assoc Cancer Res* 38:306-307, 1997 (abstr 2056)

164. Garteiz DA, Madden T, Beck DE, et al: Quantitation of dolastatin-10 using HPLC/electrospray ionization mass spectrometry: Application in a phase I clinical trial. *Cancer Chemother Pharmacol* 41:299-306, 1998

165. Madden T, Tran HT, Felix E, et al: Dolastatin 10 (dola 10) administered with G-CSF allows substantial escalation of the maximum tolerated dose (MTD) in patients (pts) with advanced solid tumors. *Proc AACR-NCI-EORTC Int Conf* 61:61, 1999 (abstr 300)

166. Cortes JE, Wright J, Giles FJ, et al: Phase I study of dolastatin-10 in refractory or relapsed acute leukemia. *Blood* 94:508a, 1999 (suppl 1, abstr 2274)

167. Cox AD, Der CJ: Farnesyltransferase inhibitors and cancer treatment: Targeting simply Ras? *Biochim Biophys Acta* 1333:F51-F71, 1997

168. Yang W, Del Villar K, Urbano J, et al: Advances in the development of farnesyltransferase inhibitors: Substrate recognition by protein farnesyltransferase. *J Cell Biochem* 27:12-19, 1997 (suppl)

169. Wright J, Blatner GL, Cheson BD: Clinical trials referral resource. Clinical trials with the farnesyl transferase inhibitor R115777. *Oncology (Huntington)* 13:1527-1533, 1999

170. Skrzat S, Angibaud P, Venet M, et al: R115777, a novel imidazole farnesyl protein transferase inhibitor (FTI) with potent oral antitumor activity. *Proc Am Assoc Cancer Res* 39:317-318, 1998 (abstr 216a)

171. Gibbs JB, Oliff A: The potential of farnesyltransferase inhibitors as cancer therapeutics. *Annu Rev Pharmacol Toxicol* 37:143-166, 1997

172. Zujewski J, Horak ID, Woestenborghs R, et al: Phase I trial of farnesyl-transferase inhibitor, R115777, in advanced cancer. *Proc Am Assoc Cancer Res* 39:270, 1998 (abstr 1848)

173. Schellens JHM, de Klerk G, Swart M, et al: Phase I and pharmacologic study with the novel farnesyltransferase inhibitor (FTI) R115777. *Proc Am Assoc Cancer Res* 40:724, 1999 (abstr A4780)

174. Christiansen I, Gidlöf C, Wallgren A, et al: Serum levels of soluble intercellular adhesion molecule 1 are increased in chronic B-lymphocytic leukemia and correlate with clinical stage and prognostic markers. *Blood* 84:3010-3016, 1994

175. Gu XF, Bikfalvi A, Chen YZ, et al: Constitutive and selective expression of basic fibroblast growth factor in human leukemia cell lines. *Eur J Haematol* 55:189-194, 1995

176. Nara N, Kurokawa H, Tohda S, et al: The effect of basic and acidic fibroblast growth factors (bFGF and aFGF) on the growth of leukemic blast progenitors in acute myelogenous leukemia. *Exp Hematol* 23:1030-1034, 1995

177. Menzel T, Rahman Z, Calleja E, et al: Elevated intracellular level of basic fibroblast growth factor correlates with stage of chronic lymphocytic leukemia and is associated with resistance to fludarabine. *Blood* 87:1056-1063, 1996

178. Salven P, Teerenhovi L, Joensuu H: A high pretreatment serum vascular endothelial growth factor concentration is associated with poor outcome in non-Hodgkin's lymphoma. *Blood* 90:3167-3172, 1997

179. Perez-Atayde AR, Sallan SE, Tedrow U, et al: Spectrum of tumor angiogenesis in the bone marrow of children with acute lymphoblastic leukemia. *Am J Clin Pathol* 150:815-821, 1997

180. König A, Menzel T, Lynen S, et al: Basic fibroblast growth factor (bFGF) upregulates the expression of bcl-2 in B cell chronic lymphocytic leukemia cell lines resulting in delaying apoptosis. *Leukemia* 11:258-265, 1997

181. Singhal S, Mehta J, Desikan R, et al: Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 341:1565-1571, 1999

182. Singhal S, Mehta J, Eddlemon P, et al: Marked antitumor effect from anti-angiogenesis (AA) therapy with thalidomide (T) in high risk refractory multiple myeloma (MM). *Blood* 92:318a, 1998 (suppl 1, abstr 1306)

183. Rosen L, Mulay M, Mayers A, et al: Phase I dose-escalating trial of SU5416, a novel angiogenesis inhibitor in patients with advanced malignancies. *Proc Am Soc Clin Oncol* 18:161a, 1999 (abstr 618)

184. Raza A, Lisak L, Andrews C, et al: Thalidomide produces transfusion independence in patients with long-standing refractory anemias and myelodysplastic syndromes (MDS). *Blood* 94:661a, 1999 (suppl 1, abstr 2935)

185. Deliliers GL, Prunerri GC, Corteleszi A, et al: Angiogenesis in myelodysplastic syndromes. *Leuk Res* 23:S24, 1999

186. Zervas J, Geary CG, Olesky S: Sideroblastic anemia treated with immunosuppressive therapy. *Blood* 44:117-123, 1974

187. Molldrem JJ, Caples M, Mavroudis D, et al: Antithymocyte globulin for patients with myelodysplastic syndrome. *Br J Haematol* 99:699-705, 1997

188. Okada M, Okamoto T, Yamada S, et al: Good response

to cyclosporine therapy in patients with myelodysplastic syndromes having the HLA-DRB1*1501 allele. *Blood* 94:306a, 1999 (suppl 1, abstr 1370)

189. Samuelsson J, Larfars G: Unusual clinical presentation in a patient with myelodysplastic syndrome, with subsequent hematological remission and suppression of the malignant clone following treatment with cyclosporine A, erythropoietin and granulocyte colony-stimulating factor. *Leuk Res* 23:513-517, 1999

190. Berer A, Ohler L, Simunitsch I, et al: Long-term improvement of hematopoiesis following cyclosporine treat-

ment in a patients with myelodysplastic syndrome. *Wien Klin Wochenschr* 111:815-818, 1999

191. Barrett AJ, Molldrem JJ, Saunthrajarian Y, et al: Prolonged transfusion independence and disease stability in patients with myelodysplastic syndrome (MDS) responding to antithymocyte globulin (ATG). *Blood* 92:713a, 1998 (suppl 1, abstr 2932)

192. Cheson BD, Bennett JM, Kantarjian H, et al: Response criteria for clinical trials in the myelodysplastic syndromes: Recommendations from and international working group. *Blood* (in press)

Seminars in Oncology

October 23, 2000

HEALTH SCIENCES
LIBRARIES

Editors John W. Yarbrow, MD, PhD • Michael J. Mastrangelo, MD

Novel Therapeutic Approaches for Hematologic Malignancies in the 21st Century

John C. Byrd, MD, Michael A. Caligiuri, MD,
and Michael R. Grever, MD, *Guest Editors*

Contributors

Kenneth C. Anderson • Karen K. Ballen • Pamela S. Becker
Ivan Borello • John C. Byrd • Michael A. Caligiuri • Bruce D. Cheson
Janet Dancey • Stefan Faderl • Ian W. Flinn • N. Gökbuget
Michael R. Grever • D. Hoelzer • Raymond P. Warrell Jr
Hagop M. Kantarjian • Michael Keating • Thomas J. Kipps
Jeff Margolis • Dana C. Matthews • Anthony Murgu
Steven C. Novick • Susan O'Brien • Peter J. Quesenberry
Kanti Rai • Noopur Raje • Katherine L. Ruffner
F. Marc Stewart • Moshe Talpaz • Steven P. Treon
Jamie K. Waselenko • William G. Wierda • James A. Zweibel

W.B. SAUNDERS COMPANY

A Harcourt Health Sciences Company

Seminars in Oncology

EDITORS

John W. Yarbro, MD, PhD
Michael J. Mastrangelo, MD

Seminars in Oncology (ISSN 0093-7754) is published bimonthly by W.B. Saunders Company, Corporate and Editorial Offices: The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399. Accounting and Circulation Offices: W.B. Saunders Company, 6277 Sea Harbor Dr, Orlando, FL 32887-4800. Months of issue are February, April, June, August, October, and December. Periodicals postage paid at Orlando, FL 32862, and at additional mailing offices.

POSTMASTER: Send change of address to *Seminars in Oncology*, W.B. Saunders Company, Periodicals Department, 6277 Sea Harbor Dr, Orlando, FL 32887-4800.

Editorial correspondence should be addressed to John W. Yarbro, MD, PhD, 2604 Luan Court, Columbia, MO 65203.

Business correspondence (subscriptions, change of address) should be addressed to the Publisher, W.B. Saunders Company, Periodicals Department, 6277 Sea Harbor Dr, Orlando, FL 32887-4800.

Change of address notices, including both the old and new addresses of the subscriber, should be sent at least one month in advance.

Customer Service: 1-800-654-2452; outside the United States and Canada, (407) 345-4000.

Yearly subscription rates: United States and possessions: individual, \$168.00; institution, \$243.00; single issue, \$52.00. All other countries: individual, \$265.00; institution, \$310.00; single issue, \$52.00. For all areas outside the United States and possessions, there is no additional charge for surface delivery. For air mail delivery, add \$24.00. Student/resident: United States and possessions: \$92.00; all other countries: \$265.00. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the signature of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Current prices are in effect for back volumes and back issues. Back issues sold in conjunction with a subscription are on a prorated basis. Current and back single issues exist in limited quantities and are offered for sale subject to availability. 1999 bound volume price: \$85.00; customers outside USA, please add \$15.00 for postage. To purchase a 1999 bound volume, customer must be a subscriber for 1999. *Cumulative Index (1980-1989) price:* \$95.00; customers outside USA, please add \$2.25 for surface delivery, or \$8.00 for air mail delivery. Prices are subject to change without notice. Checks should be made payable to W.B. Saunders Company and sent to *Seminars in Oncology*, W.B. Saunders Company, Periodicals Department, PO Box 628239, Orlando, FL 32862-8239.

Copyright © 2000 by W.B. Saunders Company. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means now or hereafter known, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system,

without permission in writing from the publisher. Printed in the United States of America.

Correspondence regarding permission to reprint all or part of any article published in this journal should be addressed to W.B. Saunders Company, Periodicals Department, Orlando, FL 32887. Telephone number 1-407-345-2500.

Other correspondence (copyediting, production) should be addressed to W.B. Saunders Company, The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399.

The appearance of the code at the bottom of the first page of an article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients, for those registered with the Copyright Clearance Center, Inc. (222 Rosewood Drive, Danvers, MA 01923; (508) 750-8400; www.copyright.com). This consent is given on the condition that the copier pay the stated per-copy fee for that article through the Copyright Clearance Center, Inc. for copying beyond that permitted by Sections 107 or 108 of the US Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. Absence of the code indicates that the material may not be processed through the Copyright Clearance Center, Inc.

Advertising representative: Cunningham Associates, 180 Old Tappan Rd, Old Tappan, NJ 07675, telephone 1-201-767-4170; fax 1-201-767-8065.

The ideas and opinions expressed in *Seminars in Oncology* do not necessarily reflect those of the Editor or the Publisher. Publication of an advertisement or other product mention in *Seminars in Oncology* should not be construed as an endorsement of the product or the manufacturer's claims. Readers are encouraged to contact the manufacturer with any questions about the features or limitations of the products mentioned. The Publisher does not assume any responsibility for any injury and/or damage to persons or property arising out of or related to any use of the material contained in this periodical. The reader is advised to check the appropriate medical literature and the product information currently provided by the manufacturer of each drug to be administered to verify the dosage, the method and duration of administration, or contraindications. It is the responsibility of the treating physician or other health care professional, relying on independent experience and knowledge of the patient, to determine drug dosages and the best treatment for the patient.

The contents of *Seminars in Oncology* are included in *Index Medicus*/MEDLINE, Current Contents, *Excerpta Medica*/EMBASE, and BIOSIS.

W.B. Saunders Company



Philadelphia, PA

A Harcourt Health Sciences Company

Seminars in Oncology

EDITORS

JOHN W. YARBRO, MD, PhD
Professor Emeritus
University of Missouri
Columbia, MO

MICHAEL J. MASTRANGELO, MD
Associate Clinical Director
Kimmel Cancer Center
Jefferson Medical College
Philadelphia, PA

EDITORIAL BOARD

Clara D. Bloomfield, MD, *Columbus, OH*
Gianni Bonadonna, MD, *Milan, Italy*
John C. Byrd, MD, *Bethesda, MD*
Charles Coltman, Jr, MD, *San Antonio, TX*
Robert Comis, MD, *Philadelphia, PA*
Donald C. Doll, MD, *Columbia, MO*
Bernard Fisher, MD, *Pittsburgh, PA*
Harvey M. Golomb, MD, *Chicago, IL*
David T. Harris, MD, *Philadelphia, PA*
David P. Kelsen, MD, *New York, NY*

Hillard M. Lazarus, MD, *Cleveland, OH*
Michele Maio, MD, *Aviano, Italy*
Michael C. Perry, MD, *Columbia, MO*
Stojan Plesnicar, MD, *Ljubljana, Slovenia*
Spyros Retsas, MD, *London, England*
Richard L. Schilsky, MD, *Chicago, IL*
Yan Sun, MD, *Beijing, China*
Nicholas J. Vogelzang, MD, *Chicago, IL*
Norman Wolmark, MD, *Pittsburgh, PA*

Associate Editor
Current Clinical Practice

Raymond B. Weiss, MD
Lombardi Cancer Center
Georgetown University, Washington, DC

Past Editor

Richard S. Bornstein, MD
1974-1999 (Deceased)

Seminars in Oncology

Novel Therapeutic Approaches for Hematologic Malignancies in the 21st Century

John C. Byrd, MD, Michael A. Caligiuri, MD, and Michael R. Grever, MD, *Guest Editors*

VOL 27, NO 5

OCTOBER 2000

Contents

Novel Therapeutic Approaches for Hematologic Malignancies in the 21st Century: Introduction <i>John C. Byrd, Michael A. Caligiuri, and Michael R. Grever</i>	493
Arсенicals in Hematologic Cancers <i>Steven C. Novick and Raymond P. Warrell Jr</i>	495
Gene Therapy of Hematologic Malignancies <i>William G. Wierda and Thomas J. Kipps</i>	502
Manipulation of the Stem Cell as a Target for Hematologic Malignancies <i>Karen K. Ballen, Pamela S. Becker, F. Marc Stewart, and Peter J. Quesenberry</i>	512
New Approaches to Treating Malignancies With Stem Cell Transplantation <i>Jeff Margolis, Ivan Borrello, and Ian W. Flinn</i>	524
Current Uses of Monoclonal Antibodies in the Treatment of Acute Leukemia <i>Katherine L. Ruffner and Dana C. Matthews</i>	531
New Approaches to Acute Lymphoblastic Leukemia in Adults: Where Do We Go? <i>D. Hoelzer and N. Gökbuget</i>	540
Novel Therapeutic Agents for the Treatment of Myelodysplastic Syndromes <i>Bruce D. Cheson, James A. Zweibel, Janet Dancey, and Anthony Murgu</i>	560
New Treatment Approaches for Chronic Myelogenous Leukemia <i>Stefan Faderl, Hagop M. Kantarjian, Moshe Talpaz, and Susan O'Brien</i>	578
Novel Therapies for Chronic Lymphocytic Leukemia in the 21st Century <i>John C. Byrd, Jamie K. Waselenko, Michael Keating, Kanti Rai, and Michael R. Grever</i>	587
Immunotherapeutic Strategies for the Treatment of Plasma Cell Malignancies <i>Steven P. Treon, Noopur Raje, and Kenneth C. Anderson</i>	598
Subject Index	614