VOL 27, NO 5 OCTOBER 2000

Seminars in Oncology

Editors John W. Yarbro, 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 Murgo
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

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.

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

Novel Therapeutic Agents for the Treatment of Myelodysplastic Syndromes

Bruce D. Cheson, James A. Zwiebel, Janet Dancey, 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 G_1 and G_2 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 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 subtype[5-8]: 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

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.

0093-7754/00/2704-0001$0.00/0
doi:10.1053/sonc.2000.9691

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 al[12] first reported complete remissions with doses of cytarabine as low as 10 mg/m^2/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/m^2 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 al[32] 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/m^2 by continuous infusion daily for 5 days, and cytarabine at 1 g/m^2 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 (Ethyol; 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/m^2 three times per week or 740 mg/m^2 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/μL 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 al[35] 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/μL), platelets in 50% (by 24,000 to 49,000/μL), 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 al[38] described 32 patients with RA/RARS (n = 26) and RAEB/RAEB-T (n = 15) treated at a dose of 200 mg/m^2 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-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.