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SPECIAL REPORT Critical Issues in Blood Disorders and Cancer

A Continuing Education Program

Letter From the Editors

Welcome to the 2004 Pharmacy Edition of **Frontiers in HematOncology**, a report designed to address concerns of the health-system pharmacist. This issue contains a Continuing Education (CE) Program reviewing 2 important symposia—"Prognosis and Treatment of Myelodysplastic Syndromes (MDS)," held at the 2004 Making a Difference in Oncology (MADONC) conference in St Petersburg, Fla, and "Challenges in Anticoagulation Therapy: A Case-Based Approach," held at the 2003 Midyear Clinical Meeting of the American Society of Health-System Pharmacists (ASHP) in New Orleans, La.

At MADONC, Alan List reviewed MDS prognosis and the status of novel therapies. At ASHP, Edith Nutescu, Henry Bussey, Jr., and David Frame discussed newer anticoagulant agents and the emerging role of low-molecular-weight heparins (LMWHs) in cancer. These symposia provided the content for this CE Program, accredited by the University of Illinois at Chicago College of Pharmacy. This issue also includes news from the 2003 Annual Meeting of the American Society of Hematology (ASH) in San Diego, Calif.

Your comments on this issue or suggestions for future issues will be appreciated. Please write to the Editors at **Frontiers in HematOncology**, BioScience Communications, 1500 Broadway, New York, NY 10036, USA, or fax us at +1-212-704-0120. ■

Prognosis and Treatment of Myelodysplastic Syndromes: Novel Therapeutic Strategies

BASED ON A PRESENTATION BY ALAN F. LIST, MD

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This article summarizes a symposium held in St Petersburg, Fla, during the April 2004 sessions of Making a Difference in Oncology (MADONC).

The myelodysplastic syndromes (MDS) show striking hematologic, pathologic, and biologic heterogeneity, creating an obstacle to the development of new treatment strategies. The recent recognition that the morphologic features characterizing this malignant phenotype arise from mechanistically diverse biologic processes has raised awareness that treatment strategies must be tailored to the pathobiology of the disease. This finding has shifted traditional perceptions about the disease and generated a new paradigm for therapeutic development, which has yielded treatments with the prospect to alter the natural history of the disease.

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MADONC Symposium

Prognostic Modeling

The heterogeneity of MDS demands the careful assessment of key features of the disease in order to determine a patient's likely clinical course. Morphologic classification using the French-American-British (FAB) system alone is insufficient. Many factors other than leukemia burden affect survival—including lineage penetrance and severity of the maturation defect, genetic and molecular abnormalities, and clinical and pathologic features. Variables with independent prognostic power can be identified by prognostic modeling, which offers the potential to predict the outcome of clinical management decisions.

The International Prognostic Scoring System (IPSS) uses a score based on 3 prognostic features: bone marrow blast cell percentage, cytogenetic pattern, and the number of cytopenias. Patients are divided into 4 risk groups—low, intermediate-1, intermediate-2, and high—in accordance with expectations for survival and risk of and interval to acute myeloid leukemia progression. Coupled with the newly developed World Health Organization classifications for leukemias and lymphomas, the IPSS provides the foundation for much needed universal criteria for response assessment.

As with other malignancies, management decisions should be guided by the risks imposed by the disease, the patient's age and performance status, the expectation for treatment tolerance, and quality of life. Generally,

patients with low or intermediate-1 IPSS risk survive longer. Consequently, their primary treatment goal should be the amelioration of hematologic deficits for at least an 8-week duration. For those with intermediate-2 or high IPSS risk, the most important objective should be to extend survival. A host of new therapies and approaches bring these objectives within reach.

Thalidomide and CC5013

The first of the antiangiogenic agents to be investigated in MDS is thalidomide. A recent phase II study reported that 18% of assessable patients experienced either transfusion independence or a more than 50% decrease in transfusion burden, while improvement in nonerythroid lineages was less common.¹ The median time to erythroid response was 16 weeks, with 29% of the 51 patients who completed a minimum of 3 months of treatment experiencing clinical benefit. Prolonged drug treatment appears necessary to maximize benefit, and therefore, doses below 200 mg qd appear optimal to minimize the risk of cumulative neurologic toxicity. Because of the need for extended treatment, thalidomide appears best suited for treatment of patients with lower-risk disease.

CC5013 (lenalidomide; Revlimid™) is a more potent analogue of thalidomide with an improved safety profile. List and colleagues reported that 67% of the 36 patients with symptomatic or trans-

Critical Issues in Blood Disorders and Cancer

A Continuing Education Program based on symposia conducted at the 8th Annual Making a Difference in Oncology (MADONC) meeting in St Petersburg, Fla (April 2004) and the 38th American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting in New Orleans, La (December 2003).

Sponsored by an unrestricted educational grant from Pharmion Corporation

Learning Objectives

Upon completion of this program, participants should be able to:

- Review current approaches for the classification of myelodysplastic syndromes (MDS), and summarize current knowledge of MDS biology
- Discuss the use of emerging treatment options for MDS
- Describe the dosing and administration issues concerning the use of anticoagulants in special populations, such as obese, renal-impaired, and pregnant patients
- Provide an overview of the controversies in monitoring newer anticoagulant agents, including low-molecular-weight heparins (LMWHs), factor Xa-inhibitors, and direct thrombin inhibitors
- Discuss the relationship between coagulation and cancer, and describe the use of traditional anticoagulants and LMWHs in cancer patients

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This publication may contain some discussion of off-label medication uses. Dosages, indications, and methods for drug use and procedures referred to in this newsletter reflect data presented at meetings of recognized oncology and hematology associations or drawn from the clinical experience of the authors. Physicians should consult complete prescribing information before administering any of the drugs discussed herein and should follow their clinical judgment in weighing the benefits of treatment against the risks.

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The University of Illinois at Chicago College of Pharmacy is approved by the Accreditation Council for Pharmacy Education as a provider of continuing pharmaceutical education. The program is approved for 2 contact hours (0.2 CEUs). A statement of credit will be awarded and sent within 6 weeks upon successful completion of assessment questions (70% or better) and completion of the program evaluation. If a score of 70% or better is not achieved, no credit will be awarded and the registrant will be notified. This program has been assigned ACPE Program Number 016-999-04-006-H01.

MADONC Symposium

fusion-dependent anemia who completed 8 or more weeks of CC5013 treatment experienced an erythroid response according to IWG (International Working Group) criteria.² Twenty patients achieved sustained transfusion independence or a 2 g/dL or greater rise in hemoglobin. Time to response varied by dose and schedule assignment, ranging from 8 weeks at the 25 mg/d dosage to more than 13 weeks at 10 mg/d for 21 days. Sixty-five percent of patients had either complete or partial (>50%) reduction in the proportion of abnormal metaphases, improvement in primitive progenitor cell outgrowth, and diminished cytologic dysplasia. However, dose-limiting myeloid and platelet toxicity occurred at all dose levels, requiring either dose reduction or treatment interruption in approximately 60% of patients.

Farnesyl Transferase Inhibitors

The proto-oncogene *Ras* encodes a number of guanosine triphosphate hydrolases (GTPase) that serve as critical regulatory elements in signal transduction, cellular proliferation, and maintenance of the malignant phenotype in MDS and chronic myelomonocytic leukemia (CMML). In a phase II study, Karp and colleagues demonstrated that tipifarnib, an inhibitor of farnesyl transferase—the enzyme that catalyzes the attachment of a farnesyl residue to *Ras* proteins to activate transforming activity—produced responses in 12 of 30 patients and disease stabilization in 12 patients with poor-prognosis acute myeloid leukemia (AML) or MDS.³ Lancet and colleagues also showed in a larger phase II trial that tipifarnib yielded an overall response rate of 33% in a similar population of patients.⁴ The median overall survival for all patients was 8 months; among responders, more than 60% were still alive at 15 months. Grade 4 toxicity—largely infection and gastrointestinal events—occurred in only 13% (12 of 96) of evaluable patients.

Similar results have been reported with the farnesyl transferase inhibitor lonafarnib. In an expanded phase II study of 67 patients with MDS or CMML, Feldman and colleagues showed that this agent produced

erythroid responses in 35% of patients, platelet responses in 22% of patients with thrombocytopenia, and a 50% or greater reduction in percentage of bone marrow blast cells in 43% of patients with excess blasts.⁵ Two patients with CMML experienced rapid and sustained leukocytosis, which appears to be analogous to the leukemia differentiation syndrome seen with retinoid therapy of acute promyelocytic leukemia.⁶

Although the farnesyl transferase inhibitors were initially developed to interrupt mutant *Ras*-induced cell signaling, the trials show that the clinical benefit of tipifarnib and lonafarnib occurs independent of mutation status. This finding means that blockade of wild-type *Ras* or other farnesylated molecules may be more relevant to the activity of these drugs in the treatment of MDS and CMML.

DNA Methyltransferase Inhibitors

Some genetic modifications of DNA, which disrupt normal gene expression, are potentially reversible. One such regulatory process involves a universal feature of the neoplastic phenotype, the methylation of cytosine residues by DNA methyltransferases (DMT) within gene promoters. Two investigational DMT inhibitors, decitabine and 5-azacitidine, are now in advanced clinical testing and may become the first agents to receive a Federal Drug Administration indication for MDS. (*Editor's note:* 5-azacitidine received approval in May 2004.)

Recently announced results of a phase III study of 170 MDS patients showed that those receiving decitabine plus supportive care had a significantly increased time to progression to AML or death, compared with patients who were given supportive care alone. The overall response rate in the decitabine group was 22% (9 complete responses and 11 partial responses), compared with 0% in the supportive care arm.

The greatest impact from decitabine was in patients with high-risk IPPS scores, the target population. Patients with lower-risk disease received no benefit in terms of survival extension.

In a trial performed by the Cancer and Leukemia Group B (CALGB), 194 patients

with MDS were randomized to receive subcutaneous 5-azacitidine (75 mg/m²/d for 7 consecutive days every 28 days) or supportive care alone for 16 weeks.⁷ Those in the latter group whose disease progressed were able to transfer to treatment before the end of the 16-week period of observation if they experienced disease progression. The investigators reported that 60% of patients who were given 5-azacitidine showed hematologic benefit, including 7% with complete response, 16% with partial response, and 37% with single or multilineage hematologic improvement. Only 5% of those receiving supportive care showed any improvement. 5-Azacitidine also extended the median time to leukemic transformation, compared with supportive care (21 months vs 13 months).

The impact of 5-azacitidine on disease progression was impressive in this trial. Transformation to acute myelogenous leukemia occurred in 15% of patients on the 5-azacitidine arm and in 38% receiving supportive care. ■

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Challenges in Anticoagulation Therapy: A Case-Based Approach

The following pages summarize a symposium held in New Orleans, La, at the December 2003 Midyear Clinical Meeting of the American Society of Health-System Pharmacists (ASHP).

Clinical Applications of Novel Anticoagulants in High-Risk Patient Populations: Obesity, Renal Insufficiency, and Pregnancy

BASED ON A PRESENTATION BY EDITH NUTESCU, PHARMD

University of Illinois at Chicago Medical Center, Chicago, Ill

The Obese Patient

Weight extremes are a particular concern in the dosing of anticoagulants, especially in obese patients (body mass index >30%). The pharmacokinetic characteristics of low-molecular-weight heparins (LMWHs) suggest that ideal body weight may be a better dosing predictor than total body weight. However, pharmacokinetic studies of dalteparin, enoxaparin, and tinzaparin¹⁻³ show that the actual body weight correlates best with anticoagulant response to LMWHs as measured by anti-Xa levels in patients up to a weight of 190 kg (see **Figure 1**). Therefore, dose adjustment for excess body weight would not appear to be necessary.

In fact, not giving enough medication to these patients may be of higher concern than

giving too much medication. This was demonstrated in a study comparing 2 different doses of enoxaparin (1.5 mg/kg qd or 1.0 mg/kg bid) with heparin in patients with venous thromboembolism (VTE), where a subgroup analysis of obese patients showed that the rate of thrombosis was twice as high in the once-daily enoxaparin group than in the twice-daily enoxaparin and heparin groups.⁴ In high-risk situations, such as obesity, dose capping—a maximum allowable dose for a given drug in 24 hours—may not be appropriate. Actual body weight may be a better way to prevent underdosing in these patients.

Therefore, LMWH dosing in obese patients should be based on total body weight, up to a maximum of 190 kg. The

package insert for dalteparin recommends dose capping, but that question has not yet been definitively answered. For enoxaparin, twice-daily dosing is recommended until further efficacy data on once-daily dosing are available and dose capping is unnecessary. Tinzaparin should be administered once a day, and neither weight-based dose adjustments nor capping is required. Monitoring anti-Xa levels is not recommended up to 160 kg. In patients weighing more than 160 kg, clinical data from large trials are lacking; therefore, periodic monitoring might be prudent above this weight. This will depend on whether the indication for LMWH is acute or longer-term. Moreover, the intensity of monitoring may be different among the various LMWHs, since the rate of accumulation differs.

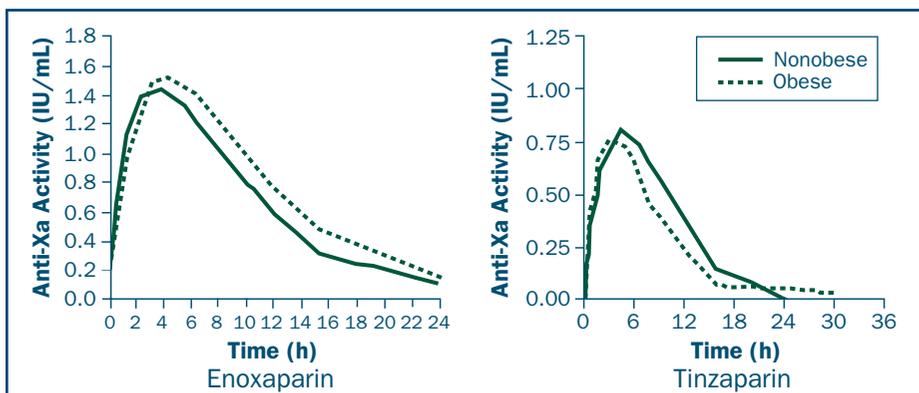


Figure 1. Pharmacokinetic studies of enoxaparin, tinzaparin, and dalteparin (data not shown) demonstrate that body weight does not affect the response to LMWHs as measured by anti-Xa levels in patients up to a weight of 190 kg. Adapted with permission from Sanderink *et al.* *Clin Pharmacol Ther.* 2002;72:308-318²; Hainer *et al.* *Thromb Haemost.* 2002;87:817-823.³

Renal Insufficiency

Dosing and monitoring of LMWHs are especially important considerations in patients with renal insufficiency. Pharmacokinetic studies have shown that anti-Xa activity is prolonged in patients with severe renal impairment (creatinine clearance <30 mL/min) and, to a lesser extent, in patients with moderate dysfunction (30 to 50 mL/min). Drug clearance dropped by about 40% in the most severely impaired patients.⁵ These results were confirmed in a study by Becker and colleagues, who analyzed a subgroup of patients in the TIMI IIA trial, which compared enoxaparin with heparin in acute coronary syndromes.⁶ The investigators found that as

renal function declines, drug accumulation increases, as measured by anti-Xa activity (see **Figure 2**). Although the number of patients with creatinine clearance <40 mL/min was small (n = 7), the trend suggests that the dose of enoxaparin should be reduced to about 0.5 to 0.75 mg/kg. If the dose is not adjusted, periodic anti-Xa monitoring may be used to ensure that safe drug levels are maintained.

Tinzaparin pharmacokinetic studies reveal a slightly different profile.^{7,8} The degree of accumulation in patients with renal dysfunction was found to be about 20% to 25%, compared with healthy individuals. The investigators concluded that the pharmacodynamic effects of the drug were similar in both groups. Therefore, initial dose adjustments appeared to be unnecessary. Comparable results were reported by Pautas and colleagues in a trial of 200 elderly patients with age-related renal impairment (mean creatinine clearance = 51.2 mL/min) requiring full anticoagulation with tinzaparin.⁹ On the basis of these initial kinetic studies, it appears that initial dose decrease may not be necessary with tinzaparin; however, periodic monitoring of anti-Xa activity with long-term use is recommended. It is

important to note that there are differences in the kinetic profiles of LMWHs in patients with renal impairment, and dose adjustments for one agent may not apply to the other agents of the class.

Clinicians have raised concerns about bleeding complications in patients with kidney failure. Gerlach and colleagues found that patients with renal insufficiency receiving unadjusted doses of enoxaparin in either prophylactic or treatment doses had significantly higher rates of total and major bleeding events, as well as higher mortality rates.¹⁰ Higher and similar rates of major bleeding in the renally impaired patients also were seen for unadjusted enoxaparin as well as for monitored, dose-adjusted unfractionated heparin in the ESSENCE and TIMI IIB trials (about 1% in healthy patients vs 7.5% in enoxaparin patients with renal impairment and 6% in heparin patients with renal impairment).¹¹ Other LMWHs have reported differences in bleeding complication patterns in patients with VTE.

For example, Strauss and colleagues found that bleeding rates of patients receiving tinzaparin for VTE ranged from 6.1% in healthy individuals (creatinine clearance >80 mL/min) to 6.7% in those with renal

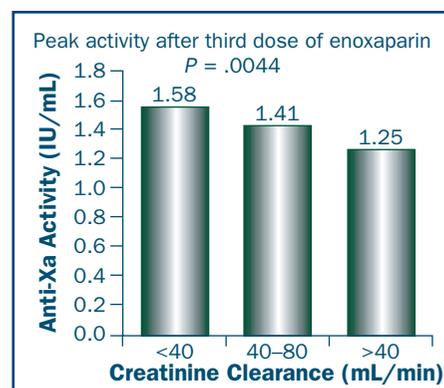


Figure 2. A study by Becker and colleagues comparing enoxaparin with heparin in acute coronary syndromes found that as renal function declines, drug accumulation increases, as measured by anti-Xa activity. Adapted with permission from Becker et al. *Am Heart J.* 2002;143:753-759.⁶

impairment (creatinine clearance <30 mL/min)—whereas in the heparin group major bleeding complications increased from 6.4% in normal patients to 13.8% in those with kidney dysfunction.¹²

Guidelines for dosing adjustment will vary for each LMWH and its reported accumulation rates in the kinetic studies. For enoxaparin, dosage reductions are recommended in patients with creatinine clearance <30 mL/min. A subcutaneous dose of 1 mg/kg qd is recommended for treatment of VTE, and a subcutaneous dose of 40 mg qd is recommended for prophylaxis. Patients with moderate renal impairment do not require initial dose adjustment; however, periodic monitoring of anti-Xa activity may be considered if the agent is used for a prolonged period of time and accumulation may occur.

Pregnancy

Which are the best anticoagulants to use in pregnancy? A consensus statement issued in 1998 by the American College of Obstetricians and Gynecologists advised: “Patients with venous thrombosis, pulmonary embolism, or thrombophilic disorders may be treated at least as effectively with LMWH as with unfractionated heparin.” The American College of Chest Physicians also lists LMWHs as alternative anticoagulants to unfractionated heparin for all indications in pregnancy, including heart valves, although the evidence is not robust. LMWHs do not cross the placenta, there is no anti-Xa activity in fetal or cord blood, and no evidence of

CASE REPORT

Presentation

A 39-year-old woman presents to the ER with severe shortness of breath lasting for almost 2 days. She claims that her symptoms began a week earlier with left-lower-extremity pain. A ventilation-perfusion scan reveals a moderate to high probability of pulmonary embolism. The woman's medical history is nonsignificant, although her mother had 2 strokes and a previous deep vein thrombosis (DVT). She weighs 288 pounds (131 kg), is 5'2" tall, began oral contraceptives within the past 6 months, and takes a multivitamin daily and a nonsteroidal agent as needed.

Therapeutic Recommendations

Heparin would not be the best option in a 39-year-old obese woman who is positive for pulmonary embolism. An LMWH would be recommended for the acute phase. Only tinzaparin has been studied in acute pulmonary embolism, although both dalteparin and enoxaparin have been used in DVT trials, in which more than one third of patients also had acute symptomatic pulmonary embolism. A once-daily treatment schedule would be preferable in this patient. If, however, the safety and efficacy data on pulmonary embolism are limited, it may be better to use a more established agent with a twice-daily regimen. Monitoring of anti-Xa activity would not be necessary, since the patient weighs less than 180 kg. Actual body weight could be used for dosing if either tinzaparin or enoxaparin is chosen. If dalteparin is used, current clinical studies indicate that dose capping at 18,000 IU/d would be suggested; however, that would bring into question whether this morbidly obese patient receives enough anticoagulant up-front. Fondaparinux is also a treatment option, and it can be used in fixed doses, without monitoring or further adjustment in obese patients.

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the drugs has been found in breast milk.¹³

Nevertheless, kinetic changes with these agents do occur over the course of pregnancy, particularly during the third trimester. Mean anti-Xa activity tends to decrease as pregnancy progresses, especially in the third trimester.¹⁴ This means that LMWHs are cleared more quickly and completely toward the end of pregnancy. Therefore, dose adjustments guided by anti-Xa activity may be required as drug levels diminish.

Factor X-a Inhibitors and Direct Thrombin Inhibitors

Fondaparinux has been shown to reduce the risk of VTE by 55% in orthopedic surgery, compared with enoxaparin,¹⁵ and this benefit has been maintained in obese patients as well. Dosing adjustments were not required. A recent trial¹⁶ also suggested that once-daily, weight-based dosing of fondaparinux without monitoring was at least as safe and effective as adjusted-dose heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism. Thus, fondaparinux is a viable option for some patients requiring anticoagulation therapy. As with other anticoagulants, the incidence of major bleeding with unadjusted doses of fondaparinux increases with decreasing renal function, and fondaparinux is contraindicated in patients with a creatinine clearance <30 mL/min. The direct thrombin inhibitor ximelagatran also appears to accumulate as creatinine clearance decreases.¹⁷ Therefore, patients with renal impairment (<30 mL/min) will require some dosing adjustment. ■

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Controversies in Monitoring Newer Anticoagulation Agents

BASED ON A PRESENTATION BY HENRY BUSSEY, JR., PHARM D

University of Texas Health Science Center, San Antonio, and ClotCare Online Resource (www.clotcare.com)

Low-molecular-weight heparins (LMWHs) have become the treatment of choice in patients requiring anticoagulant prophylaxis or treatment. The 3 approved compounds offer predictable pharmacokinetics and pharmacodynamics; blood levels typically peak about 4 hours following administration and reach therapeutic anti-factor Xa levels of approximately 0.6 to 1.1 IU/mL with dosages recommended for treating acute events. The consistent kinetics of the LMWHs ensure consistent effects and obviate the need to

monitor coagulation tests in most uncomplicated adult patients.

Monitoring therapeutic drug levels in more complex situations, however, is absolutely essential. In particular, pregnancy, renal failure, weight extremes, high risk of thrombosis or bleeding, or very long-term therapy may warrant periodic monitoring, according to consensus recommendations by groups such as the College of American Pathologists (CAP) and the American College of Chest Physicians (ACCP).

Because an unfractionated heparin dosage is usually adjusted on the basis of the activated partial thromboplastin time (aPTT), many clinicians feel that unfractionated heparin may be a better choice than LMWH in complicated patients. This approach, however, may not fully take into account the limitations of the aPTT test. Current ACCP guidelines recommend that every laboratory should define its therapeutic aPTT range on the basis of heparin serum concentrations—either by measurement of

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anti-Xa levels or by protamine titration. The difficulty is that the correlation between the different reagents and the therapeutic target is not exact. A recent study by Raschke and Hirsh showed that contemporary thromboplastins produce a higher aPTT than do older reagents (see **Table**).¹ This means that if clinicians are using traditional aPTT targets of 1.5 to 2.5, they are likely to be underdosing the majority of their patients.

Warfarin complicates matters further. Kearon and colleagues have shown that the addition of warfarin can affect the aPTT substantially but not predictably in patients already receiving heparin.² Therefore, decreasing the heparin dose in response to the elevated aPTT frequently results in subtherapeutic heparin levels in these patients. The fact that the current ACCP guidelines call for laboratories to define their therapeutic aPTT range on the basis of heparin concentrations should correct for differences in reagent sensitivity, but no such method of correction has been recommended to adjust for the effect of warfarin on the aPTT.

High-Risk Pregnancy

Venous thromboembolism is a major cause of morbidity and mortality in high-risk pregnancy. The LMWHs have become a preferred option in these women because they do not cross the placenta and have

TABLE. aPTT RANGES VS MODERN THROMBOPLASTINS

Reagent (Manufacturer)	aPTT Seconds	aPTT Ratio	Year
Actin (Dade)	49-92 to 49-109	1.9-3.7 to 2.1-4.6	2001
Actin FS (Dade)	60-85	1.8-2.5	1989
	79-105	2.3-3.0	1991
	72-119 to 98-165	2.6-4.3 to 3.7-6.2	2001
Actin FSL (Dade)	57-98 to 84-124	2.1-3.5 to 2.6-3.8	2001
IL Test (Fisher)	49-109 to 63-101	1.7-3.8 to 1.9-3.3	2001
Thrombosil (Ortho)	44-75 to 58-112	1.6-2.7 to 2.4-4.5	2001

Reprinted with permission from Raschke et al. *Ann Intern Med.* 2003;138:720-723.¹

a more favorable side effect profile than unfractionated heparin. Monitoring anti-Xa in these patients is strongly recommended, because changes in hemodynamics can increase drug clearance throughout the course of pregnancy. The current ACCP recommendations suggest that peak anti-Xa levels should be maintained at a minimum of 1.0 IU/mL for pregnant women with mechanical heart valves, which is slightly higher than for nonpregnant women.

Two papers have indicated that dose adjustments based on changes in weight during pregnancy may be an acceptable alterna-

tive to anti-Xa monitoring.^{3,4} Bombeli and colleagues also have proposed the use of D-dimer or thrombin-antithrombin (TAT) complex, indicators of clotting activation, measured every 2 to 3 weeks, as a barometer of the optimal LMWH dose.⁵ They found that in nearly 85% of pregnancies, either D-dimer or TAT values increased above the normal range, requiring at least 1 LMWH dose adjustment. While further studies will be necessary to determine whether elevated D-dimer and TAT are truly reflective of a prothrombotic state, the data support the need for close monitoring of anti-Xa blood levels in high-risk pregnancy.

One final point: pregnancy in itself is a hypercoagulable state, and pregnant women with lupus anticoagulant have an even greater risk of thrombosis. For these patients, it is essential to ensure effective thromboprophylaxis while protecting against the possibility of hemorrhage. This can be achieved through regular anti-Xa monitoring.

Weight

Weight extremes are another clinical situation in which anti-Xa levels should be followed carefully. Obese patients have a decreased blood volume-to-body weight ratio; for small or frail patients, the ratio is increased. Therefore, it might be expected that if LMWH dosing regimens are based on body weight, obese patients would be overdosed and underweight patients underdosed. In fact, however, the most recent data suggest that in the obese, basing LMWH dosing on total body weight (up to 160 to 190 kg) may be appropriate. Dose capping with dalteparin is recommended (at 20,000 IU/d in acute coronary syn-

CASE REPORT

Presentation

The patient is a 32-year-old woman who had a stroke in 1993. At that time, she was found to be positive for lupus anticoagulant and was started on warfarin. Five years later, she had a mitral valve replacement (St Jude) and continued to take warfarin, maintaining an international normalized ratio of 3.2. The patient, who wanted to become pregnant, weighs 220 pounds (100 kg), is 5'5" tall, and has a serum creatinine of 1.8 mg/dL. How should this patient have been managed and monitored?

Therapeutic Recommendations

Although many Europeans might leave this patient on warfarin because they consider the risk of fetal abnormalities to be low after week 12 of pregnancy (but high at weeks 6 to 12), in our litigious society no prudent clinician would keep this woman on warfarin. Unfractionated heparin also would not be a good choice of therapy. The patient has lupus anticoagulant and wants to become pregnant; both conditions are hypercoagulable states, and unfractionated heparin is not a fully reliable treatment in such circumstances. An LMWH would be the drug of choice for this patient, with the variations in pharmacokinetics associated with pregnancy, obesity, and renal insufficiency carefully noted. Peak blood levels should be kept above 1 IU/mL—which will require periodic anti-Xa testing. Published recommendations do not specify a frequency of monitoring, and it would be reasonable to vary the frequency depending on prior values, dosage changes, and clinical findings.

dromes, per the package insert), as is twice-daily dosing with enoxaparin and once-daily dosing with tinzaparin. Few published studies have addressed the small and frail patient, however. As a consequence, the perception that body-weight dosing might lead to underdosing remains theoretical and speculative.

New Factor Xa and Thrombin Inhibitors

The first of the factor Xa inhibitors, fondaparinux, is now available. It is administered subcutaneously, is eliminated renally, and has a half-life of approximately 17 hours, which could be a concern in patients with renal impairment. The half-life is even longer in patients with renal insufficiency. Idraparinux, another factor Xa inhibitor in development, has an even longer half-life of

several days. Once-a-week dosing with idraparinux also could result in drug accumulation in patients with normal renal function. Both of these compounds require careful monitoring and dose adjustment in patients with complicated conditions such as renal impairment.

The first oral direct thrombin inhibitor likely to reach the market is ximelagatran. This compound, which is eliminated renally, has a half-life of 3 to 5 hours and a bioavailability of 20%. This relatively low bioavailability raises concerns about factors that may either enhance or further reduce absorption. Ximelagatran has a more predictable dose response that may obviate the need for dosing adjustments based on laboratory monitoring. With this drug, monitoring standards for adequate anticoagulant effect remain to be developed. ■

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Prophylaxis and Treatment of Venous Thromboembolism in Cancer Patients

BASED ON A PRESENTATION BY DAVID FRAME, PHARM D

Rush University Medical Center, Chicago, Ill

Approximately 15% of cancer patients have clinically relevant thrombosis. However, this figure underestimates the true prevalence, as postmortem examinations show that from 20% to 50% of patients with metastatic cancers have anatomical thrombosis. More importantly, thrombosis is the second most common cause of death in hospitalized cancer patients.¹ Compared with noncancer patients, those with cancer have higher rates of first venous thromboembolism (VTE) and 3 to 5 times higher rates of VTE following surgery.²

Risk Factors

The primary risk factors for thrombosis in cancer patients include type of cancer, disease stage, use of an indwelling central catheter, inherited or situational risk factors such as family history of cancer or prolonged immobility, and chemotherapies such as tamoxifen and the aromatase inhibitors.³ These risk factors contribute to the etiology of thrombosis, which, as Vir-

chow first noted more than a century ago, stems from abnormalities in blood constituents (especially tumor-cell initiators such as tissue factor and the cancer procoagulant) that induce a hypercoagulable state, endothelial injury secondary to direct tumor invasion, and circulatory stasis.

Angiogenesis and Cancer

Not only does tissue factor play a major role in causing thrombosis in cancer patients, it also is essential to the process of angiogenesis, the induction of new blood vessel growth into solid tumors.⁴ Recent approaches to modulating the effects of tissue factor in cancer have looked at tissue factor pathway inhibitor (TFPI), which inhibits not only tissue factor but also factors VIIa and Xa.⁴ A preclinical study using a chick embryo model of human colon cancer demonstrated that the administration of tinzaparin, which stimulated production of endothelial TFPI, helped return the angiogenesis index to levels comparable to untreated controls as soon as 24 hours fol-

lowing stimulation of angiogenesis by vascular endothelial growth factor (VEGF).⁴ Tinzaparin has also been shown to inhibit colon and lung carcinoma-induced angiogenesis (see the **Figure**), and to retard tumor growth and metastasis by upregulating the production of endothelial TFPI.⁴

LMWHs and Cancer

There is a growing body of evidence suggesting that adjunctive therapy with LMWHs may improve survival rates in cancer patients. One analysis evaluated the relative effects of LMWH and unfractionated heparin on total and cancer-related mortality in patients with proximal deep vein thrombosis (DVT), compared with a group of patients without cancer. Hull and colleagues found that the rate of cancer-related mortality was significantly reduced with LMWH, compared with heparin (12.6% vs 27%, respectively; $P = .041$), whereas there was no significant difference between the agents in noncancer patients.^{5,6}

What makes this study interesting is that

ASHP Symposium

patients received only 7 to 10 days of LMWH or heparin and then were switched to long-term warfarin. The survival curves began to separate right from the beginning and increased as time went on. However, we do not know whether this is a treatment effect or whether the LMWH is actually changing the disease process.

Lee and colleagues compared once-daily dalteparin and warfarin in the prevention of recurrent VTE in patients with malignancies and found that dalteparin reduced the risk of recurrence by almost 50%.⁷ Again, LMWHs appear to be more beneficial than traditional anticoagulants. One potential confounding factor: in this trial, the investigators lowered the international normalized ratio (INR) of patients in the warfarin group to 2.0 (range, 1.5 to 2.5) when their platelet count was between 50,000 and 99,000 per cubic millimeter. Previous studies have shown that the risk of VTE increases markedly when the INR falls below 2.0, and in this trial many of the warfarin patients who experienced a second VTE had INRs below 2.0.

Although the once-daily dose appears beneficial, since most of the recurrent VTE in this study occurred in patients receiving

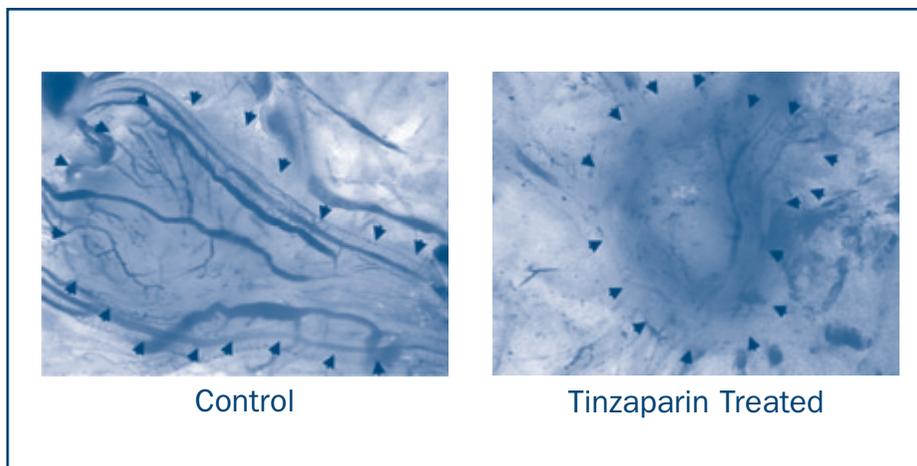


Figure. In a study by Mousa and colleagues using a chick embryo model of human colon cancer, administration of tinzaparin was shown to significantly inhibit colon carcinoma–induced angiogenesis. Reprinted with permission from Mousa et al. *Semin Thromb Hemost.* 2002;28:45-52.⁴

warfarin with INRs below 2.0, it is difficult to say definitively that once-daily dalteparin is the correct dose to choose.

This problem of dose is even more apparent in a study conducted by Merli and colleagues.⁸ They compared the rate of VTE recurrence in cancer patients receiving once-

daily enoxaparin, twice-daily enoxaparin, and unfractionated heparin. The once-a-day enoxaparin group had a twofold increase in the risk of a second VTE, compared with the other 2 treatment arms. Dr. Frame's personal choice when using enoxaparin is the twice-daily dose. ■

CASE REPORT

Presentation

The patient is a 46-year-old woman with breast cancer that has metastasized to the brain and the bone. She is currently completing her second cycle of chemotherapy with doxorubicin and docetaxel and has been receiving tamoxifen as well. Her tumor is estrogen receptor–positive. She presents with left-lower-leg edema and swelling, as well as redness and warmth in her calf that extends from below the calf almost up to the knee. A Doppler exam revealed a proximal DVT. What is the patient's risk of VTE, and what are the best treatment options for her?

Therapeutic Recommendations

There are 2 potential treatment options for this patient: she could be admitted to the hospital and given unfractionated heparin for about 1 week, followed by long-term warfarin, or she could be given long-term LMWH. This patient is very stable, so there was no reason to admit her for a week's stay in the hospital. For this and other reasons, tinzaparin was chosen. Tinzaparin produces significantly higher levels of TFPI than other LMWHs and is the least costly. Warfarin therapy would be extremely difficult, if not contraindicated, in this patient. The patient has brain metastases, increasing the risk of intracranial bleeding. In addition, she is early in the process of receiving chemotherapy, and different types of chemotherapy can produce dramatic shifts in the INR. This instability would require the patient to return to the anticoagulation clinic several times a week to check her INR during chemotherapy. Moreover, doxorubicin and docetaxel chemotherapy is associated with neutropenia, which could require the use of adjunctive antibiotics that may interact with warfarin. The potential for reducing the risk of cancer mortality in this patient was another factor in favor of LMWH therapy.

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ASH News

The 45th Annual Meeting of the American Society of Hematology (ASH) was held in San Diego, Calif, in December 2003. The following pages contain news coverage of selected highlights of scientific sessions from that meeting.

Novel Therapies Show Promise in Acute Leukemias

Chemotherapy, the current treatment of choice for most forms of acute leukemia, is associated with serious side effects, including infection, anemia, and bleeding. Fortunately, recent data presented at the 45th Annual Meeting of the American Society of Hematology (ASH) suggest that investigators are gaining ground in developing novel therapeutic approaches that are less broadly destructive than chemotherapy.

Combining Forces Against Acute Promyelocytic Leukemia

Arsenic trioxide and all-*trans* retinoic acid (ATRA) have both been shown to be effective treatments for acute promyelocytic leukemia (APL). Now, a study from the Shanghai Institute of Hematology in China has demonstrated that combination therapy with these 2 compounds is superior to monotherapy in producing clinical remission (CR) and disease-free survival (DFS) in newly diagnosed patients.

In this study, 61 patients were randomized to ATRA, arsenic trioxide, or combination therapy for remission induction and maintenance therapy, reported Sai-Juan Chen, MD. Chemotherapy was also used when the peripheral white blood cell count was over 30 to $40 \times 10^9/L$. Although CR rates were high in all 3 groups ($\geq 90\%$), the time to achieve CR was significantly shorter for patients treated with combination therapy.

All 20 patients treated with combination therapy remained in CR after a follow-up of 8 to 30 months, compared with only

7 of 37 monotherapy patients. According to the study investigators, the superior efficacy of the combination approach may be due to a synergistic effect of ATRA and arsenic trioxide on cell apoptosis and degradation of the promyelocytic leukemia-retinoic acid receptor alpha (PML-RAR α) oncoprotein. "This new approach may make APL a curable disease in most cases," said Dr. Chen.

Differentiation and Apoptosis: A 2-Pronged Approach to Treatment

ATRA and arsenic trioxide appear to work in APL by selectively inducing differentiation and apoptosis of leukemic cells. However, there is little evidence to date suggesting that these agents are effective in other forms of acute leukemia, according to Zhen-yi Wang, MD, of the Shanghai Institute of Hematology. One reason for this may be that ATRA and arsenic trioxide are mechanism-based treatments that primarily target the PML-RAR α oncogene, which plays a unique and critical role in the pathogenesis of APL.

Nevertheless, the success of ATRA and arsenic trioxide in APL has stimulated the search for other compounds that selectively induce differentiation and/or apoptosis. The key problem, said Dr. Wang, is finding the oncogenes, or the genes and related proteins, involved in the genesis of leukemia, and elucidating the mechanisms by which leukemia develops.

One promising candidate for targeted therapy, Dr. Wang said, is M2 acute myeloid leukemia (AML), a subtype of AML that

occurs in up to 25% of patients. Dr. Wang and colleagues at the Shanghai Institute have isolated a compound from a Chinese medicinal herb that may be effective in M2 AML. The compound, SIH-10, has been shown to induce apoptosis in a mouse cell line of M2 AML and to prolong survival by 44% in an animal model of the disease.

Combining Rituximab and CHOP in Non-Hodgkin's Lymphoma

In one of the most anticipated—and controversial—presentations at ASH, Thomas Habermann, MD, of the Eastern Cooperative Oncology Group in Boston, Mass, reported that the addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) does not significantly improve response rate, time to treatment failure (TTF), or overall survival in older patients with diffuse large B-cell lymphoma.

According to Dr. Habermann, patients who received rituximab plus CHOP (R-CHOP) had an overall response rate of 78%, compared with 77% for patients who received CHOP alone. This is in marked contrast to a previously published study of 399 older patients with diffuse large B-cell lymphoma, in which response rates were 76% for R-CHOP and 63% for CHOP alone (Coiffier et al).

In the study by Dr. Habermann and colleagues, 632 patients were randomized to R-CHOP (n = 318) or CHOP (n = 314) for induction therapy. Patients who achieved

continued on back cover

CE POSTTEST

- Which of the following comorbid conditions would not require periodic anti-factor Xa monitoring when using a low-molecular-weight heparin in venous thromboembolism prophylaxis?
 - Kidney dialysis
 - Pregnancy
 - Lupus anticoagulant-positive
 - Hypertension
- Peak anti-Xa levels in a pregnant woman who weighs 205 pounds and has a mechanical heart valve should be maintained at a minimum of _____ IU/mL.
 - 0.25
 - 3.0
 - 1.0
 - 0.6
- Enoxaparin patients with renal dysfunction may need a dose adjustment to _____ mg/kg.
 - 0.5 to 0.75
 - 1.0 to 1.5
 - 2.0 to 2.5
 - 0.0 to 0.25
- In pregnant women, mean anti-factor Xa activity tends to _____.
 - Rise slowly over time
 - Decrease as pregnancy progresses
 - Remain constant
 - Rise early, diminish, then rise again postpartum
- In an animal model of lung metastasis, the addition of tinzaparin _____.
 - Stimulated proangiogenic factors
 - Increased the rate of hemorrhage
 - Severely reduced platelet levels
 - Reduced tumor growth
- Postmortem exams have found anatomical thrombosis in _____ of patients with metastatic cancer.
 - 20% to 50%
 - 1% to 5%
 - 5% to 15%
 - 50% to 75%
- Which of the following is *not* a prognostic feature of the International Prognostic Scoring System?
 - Percentage of bone marrow blast cells
 - Cytopenias
 - Median time to acute myeloid leukemia
 - Karyotype
- In patients taking 5-azacitidine, _____ progressed to AML.
 - 25%
 - 15%
 - 20%
 - 10%
- The farnesyl transferase inhibitors are believed to target which signaling pathway in neoplastic cells?
 - Phosphoinositol-3-kinase/*Akt*
 - Stress-activated protein kinases
 - Jun*-kinases
 - Ras*/mitogen-activated protein kinases
- Which of the following compounds has remarkable erythroid activity in patients with low to intermediate risk of myelodysplastic syndromes?
 - Decitabine
 - CC5013
 - 5-Azacitidine
 - Tipifarnib

POSTTEST INSTRUCTIONS

To receive credit, photocopy completed answer sheet and evaluation form and send by FAX to +1-312-413-0497 or by mail to:

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ANSWER FORM

Frontiers in HematOncology, Pharmacy Edition *Critical Issues in Blood Disorders and Cancer*

Please circle the letter that corresponds to your answer to each question. There is only one correct answer per question.

- | | | | | | | | | | |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | a | b | c | d | 6. | a | b | c | d |
| 2. | a | b | c | d | 7. | a | b | c | d |
| 3. | a | b | c | d | 8. | a | b | c | d |
| 4. | a | b | c | d | 9. | a | b | c | d |
| 5. | a | b | c | d | 10. | a | b | c | d |

PROGRAM EVALUATION

Please circle the appropriate number:

(1 = completely agree, 5 = strongly disagree)

- | | | | | | |
|--|------------------------------|-----------------------------|---|---|---|
| The program objectives were met (see page 2). | 1 | 2 | 3 | 4 | 5 |
| The program was clearly written. | 1 | 2 | 3 | 4 | 5 |
| The content of this program was relevant and useful to me. | 1 | 2 | 3 | 4 | 5 |
| Did you detect any bias in this presentation? | <input type="checkbox"/> Yes | <input type="checkbox"/> No | | | |
| How long did it take you to complete this material? | _____ | | | | |

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continued from page 10

either complete or partial response were then randomized to maintenance rituximab (n = 207) or observation (n = 208). After a median follow-up of 3.1 years, no statistically significant differences in response rates, overall survival, or TTF were seen between treatment groups in the induction phase, although R-CHOP was found to improve TTF in the maintenance phase.

Because of the potentially confounding

influence of rituximab maintenance on induction therapy, a weighted analysis was performed that removed the effects of subsequent maintenance therapy. This analysis found that R-CHOP produced significant improvements in TTF and overall survival in the induction phase. Another unplanned analysis demonstrated that rituximab conferred a TTF benefit during the maintenance phase, but only in those patients who

did not receive R-CHOP during the induction phase. However, it should be kept in mind that these results were derived from secondary, unplanned analyses, Dr. Habermann cautioned. ■

SUGGESTED READING

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346:235-242.

Presidential Symposium Honors Pioneers in Epigenetics

ASH President Ronald Hoffman, MD, paid tribute to 3 seminal leaders in epigenetic research at the presidential symposium concluding the 2003 ASH meeting. Honored were Arthur L. Beaudet, MD, of Baylor College of Medicine; Stephen Baylin, MD, of Johns Hopkins University; and Gary Felsenfeld, PhD, of the National Institutes of Health.

“Epigenetics is the study of mitotically heritable changes in gene expression—changes that are not caused by alterations in DNA sequence,” Dr. Hoffman said. “Epige-

netics concerns the inheritance of information on the basis of differential gene expression, whereas genetics focuses on information inherited through the gene sequence.

“During this post-genome project era, the influence of epigenetics on human disease will become increasingly apparent, leading to further insights into the biogenesis of a variety of diseases and to the development of novel therapeutic approaches.” Each of the symposium speakers had made “major contributions to our understanding of epigenetics,” Dr. Hoffman added.

Dr. Beaudet, in his discussion of genomic imprinting and complex disease traits, focused on noncancer aspects of epigenetics. Dr. Baylin discussed the “fundamental role of epigenetics in cancer” and the promise of molecularly targeted therapies in such disorders as myelodysplastic syndromes—considering whether epigenetics “defines cancer as a disease of chromatin alterations.” Dr. Felsenfeld outlined theoretical aspects and potential practical applications of chromatin structure, epigenetic signaling, and hemoglobin switching. ■

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