In selecting the articles for this Update, we found that the topics that generated the most attention in the past year were the newer concepts in anticoagulation, thrombosis, hemostasis, transfusion therapy, hemochromatosis, and novel therapies for hematologic malignancy. In each of these areas, new findings have provided better ways to treat patients.

Anticoagulation

Clinical research in anticoagulant therapy has left many questions unanswered. The articles we have chosen suggest answers to such questions as, What is the correct daily dose of warfarin? How long should a patient continue to receive anticoagulants? Which patients should undergo prophylactic anticoagulation? The answers help to make the practice of hematology more effective and predictable.

Warfarin Dose Requirement Is Influenced by the Genes


Variations in the rate of response to a given dose of warfarin have been problematic. Effective daily doses can range from as low as 0.5 mg to higher than 60 mg. In an effort to make sense of the puzzle, Aithal and colleagues conducted a case–control study to determine whether genetic differences in the cytochrome P450 system influence the individual variability in dose requirements for warfarin. An asymmetric carbon in warfarin (C9) produces the enantiomers R-warfarin and S-warfarin, which are metabolized by different enzymes. S-warfarin, which is three times more potent than R-warfarin, is metabolized by the cytochrome P450 CYP2C9. The authors used polymerase chain reaction to evaluate the two allelic forms of CYP2C9 that have only 5% and 12% of the activity of the wild-type enzyme in patients with low-dose warfarin requirements (≤1.5 mg/d; n = 36), those with normal dose requirements who were being treated in an anticoagulation clinic (clinic controls; n = 52), and normal persons (n = 100).

The odds ratio for having one or more of the two variant alleles in the low-dose warfarin group compared with the normal population was 6.21. Twenty percent of patients in the low-dose group and 2% of clinic controls had two variant alleles.

For the low-dose group compared with clinic controls, the odds ratio for excessive international normalized ratios at initiation of warfarin treatment was 5.97. The low-dose group was also at increased risk for bleeding complications (rate ratio, 3.68) compared with clinic controls. On the basis of these results, the researchers surmised that heterozygosity or homozygosity for the two allelic forms of CYP2C9 are associated with lower warfarin dose requirements.

From our point of view, this study provides strong evidence for the role of genetic variation in the cytochrome P450 system in influencing this variability. The genetic variability may also accentuate the response to drugs that are known to induce increased sensitivity to warfarin. This study further supports the initiation of warfarin therapy at a daily dose of 5 mg, as shown in an earlier article (1).

Thromboprophylaxis with Low-Molecular-Weight Heparin Was Evaluated in Hospitalized, Acutely Ill Medical Patients


Venous thromboembolism is commonly found at autopsy of patients who have died during hospitalization. Although evidence supports routine thromboprophylaxis for surgical patients, its value for other hospitalized medical patients is not as clear. To provide that type of information, Samama and colleagues conducted a randomized, double-blind controlled trial that compared routine enoxaparin with placebo for thromboprophylaxis. Patients were randomly assigned to receive enoxaparin subcutaneously at either 40 mg/d (n = 291) or
20 mg/d ($n = 287$) or to receive placebo ($n = 288$). Treatment was administered for 6 to 14 days, and patients were followed for a total of 30 days. All patients were screened for deep venous thrombosis between days 6 and 14, or earlier if thrombosis was suspected clinically. The inclusion criteria were highly selective; the investigators excluded patients with a history of stroke or major surgery in the past 3 months, those who were at increased risk for bleeding, and those who had underlying thrombophilia. Sponsored by Rhône-Poulenc Rorer, the study was conducted at 60 centers in nine countries (none in the United States) between 1996 and 1998 and enrolled 1102 patients.

The incidence of venous thromboembolism (detected by bilateral venography or duplex ultrasonography for thrombosis in the lower extremities and by lung scanning, pulmonary angiography, or helical computed tomography for pulmonary emboli) was 5.5% in the group receiving 40 mg of enoxaparin daily compared with 15% in the 20-mg/d group and 14.9% in the placebo group. The authors observed that 40 mg of enoxaparin per day reduced the risk for venous thromboembolism by 63% in medical patients at moderate risk for this complication; without prophylaxis, venous thromboembolism would be assumed to occur in 9% to 26% of the patients. We were disappointed that the study did not compare enoxaparin with unfractionated heparin, and found that because the study was highly selective in its inclusion and exclusion criteria, the results may not be generalizable.

After a First Episode of Idiopathic Venous Thromboembolism, Patients Should Receive Anticoagulation for More Than 3 Months

Kearon and colleagues conducted a double-blind prospective study to compare the effects of anticoagulation extended beyond 3 months on rates of symptomatic venous thromboembolism and bleeding in patients with a first episode of venous thromboembolism occurring spontaneously. All patients received 3 months of anticoagulation with warfarin and were then randomly assigned to receive continued warfarin ($n = 79$) or placebo ($n = 83$) for another 24 months. The investigators excluded patients who had transient risk factors, had known underlying hypercoagulable states (history of cancer within 5 years or inherited disorders), or required long-term treatment with drugs likely to promote a bleeding diathesis. Suspected recurrent thromboembolism was documented by comparing compression ultrasonography and impedance plethysmography findings with results of baseline studies and, if necessary, venography. Patients were also screened for factor V Leiden mutation, G20210A prothrombin mutation, anticardiolipin antibodies, and lupus anticoagulants.

After patients had been followed for an average of 10 months, the study was terminated because the rate of recurrence of venous thromboembolism was 27.4% per patient-year in the placebo group compared with 1.3% per patient-year in patients who continued to receive anticoagulation ($P < 0.001$), a 95% reduction in recurrence. The authors found no significantly greater risk for major bleeding in the group receiving extended warfarin compared with placebo recipients ($P = 0.09$).

The authors concluded that patients with a first episode of idiopathic venous thromboembolism should receive anticoagulation for more than 3 months, although the duration of the extension is still not defined and requires consideration of the risk for bleeding in a given patient. They also noted that only patients with a lupus anticoagulant or anticardiolipin antibody were identified as a subgroup at higher risk for recurrence after 3 months of warfarin treatment.

From the internist’s perspective, additional studies are needed to define the optimal duration and intensity of anticoagulant therapy that should be recommended after a first episode of thrombosis. Clinical trials should include patients with well-defined underlying hypercoagulable states associated with factor V Leiden mutation; the prothrombin gene mutation; and deficiencies of protein C, protein S, and antithrombin III.

Heparin-Induced Thrombocytopenia

Although thromboembolic complications of heparin-induced thrombocytopenia mandate the cessation of heparin therapy, many patients with this syndrome re-
quire continued anticoagulation for their primary underlying disease. Several other drugs have been used with varying degrees of success; the most reliable of these are the thrombin-specific inhibitors argatroban and recombinant hirudin (r-hirudin).

**Treatment of Heparin-Induced Thrombocytopenia with Recombinant Hirudin Results in Recovery of Platelet Count and Clinical Benefit**


Greinacher and colleagues evaluated the efficacy of the thrombin-specific inhibitor recombinant hirudin (r-hirudin) for the treatment of heparin-induced thrombocytopenia in a multicenter prospective phase II study that included four groups of patients: 1) patients with heparin-induced thrombocytopenia who had thrombosis \((n = 51); \) bolus dose, 0.4 mg/kg of body weight; subsequent dosage, 0.15 mg/kg per hour); 2) patients with heparin-induced thrombocytopenia who did not have thrombosis \((n = 18); \) dosage, 0.1 mg/kg per hour); 3) patients with heparin-induced thrombocytopenia who had thrombosis and were receiving thrombolysis \((n = 5); \) and 4) patients with heparin-induced thrombocytopenia undergoing cardiopulmonary bypass surgery \((n = 8). \) Different dosing regimens were used for each group. The degree of anticoagulation was measured by using the activated partial thromboplastin time, except in the bypass patients, for whom the ecarin clotting time was used. Efficacy in 71 hirudin-treated patients was compared with that in 120 historical controls.

Platelet counts increased rapidly in 89% of the patients. The incidence of the combined end point of death, amputation, and new thromboembolic events was significantly reduced in patients treated with r-hirudin compared with historical controls (hazard ratio, 0.508 [95% CI, 0.290 to 0.892]; \(P = 0.014).\)

Of the patients receiving r-hirudin, 30% experienced at least one bleeding event; in 13%, a major bleeding event developed. Bleeding complications were not correlated with plasma hirudin levels, and the incidence was similar to that seen in the historical controls.

The authors concluded that treatment of heparin-induced thrombocytopenia with r-hirudin results in prompt recovery of platelets and clinical benefit. This first prospective study of clinical experience with r-hirudin indicates that the drug is an effective and safe alternative anticoagulant for this life- and limb-threatening disorder. The authors did not describe the outcomes of patients undergoing bypass surgery who received r-hirudin; this area requires further exploration.

It should be recognized, however, that r-hirudin and argatroban also prolong the prothrombin time, thus making initiation of warfarin therapy more complex. In addition, renal function should be carefully established in patients who are to receive r-hirudin treatment because more than 90% of the drug is eliminated through the kidneys and appropriate dose adjustments must be made for renal insufficiency. Argatroban is not excreted by the kidneys but rather by the liver. Therefore, dose adjustments are not required for argatroban in patients with renal insufficiency. Argatroban and r-hirudin have no known antidote and must be used with caution in patients at risk for bleeding. The internist will want to balance this fact with the realization that patients with heparin-induced thrombocytopenia are at high risk for life-threatening thrombosis.

**Thrombotic Thrombocytopenic Purpura**

Widespread platelet thrombi in the microcirculation characterize thrombotic thrombocytopenic purpura (TTP). Therapeutic advances have greatly improved the prognosis for this once uniformly fatal disorder. However, relapse after initial successful treatment is common. Recent studies indicate that TTP is an autoimmune disorder. This new understanding of pathophysiology may well prompt improved treatment to prevent relapse.

**Antibodies to von Willebrand Factor–Cleaving Protease May Explain the Clinical Presentation of TTP**


Tsai and colleagues explored the hypothesis that the predisposition to platelet thrombi in patients with TTP is caused by a deficiency of the plasma protease that
cleaves the large multimers of von Willebrand factor. Plasma von Willebrand factor–cleaving protease activity was measured in 37 patients with TTP by incubating the plasma samples with purified von Willebrand factor and assaying the von Willebrand factor dimers generated on sodium dodecylsulfate gels. Inhibitors to the protease activity were measured by incubating patient plasma or purified IgG with normal plasma and then assaying these samples for protease activity.

All 37 patients had essentially no plasma protease activity in the acute phase but demonstrated normal activity in the remission period. Mean protease activity was approximately 100% in 74 plasma samples from normal study participants and from patients with other disorders, such as hemolytic anemia, thrombocytopenia, thrombosis, and heparin-induced thrombocytopenia. The researchers found that 67% of the patients with TTP had inhibitory activity against the plasma protease, which appeared to be due to IgG antibodies.

The authors concluded that antibodies to von Willebrand factor–cleaving protease found in the plasma of patients with TTP play a role in the formation of platelet thrombi. In the presence of high levels of intravascular shear stress, von Willebrand factor has increased platelet-binding sites; under normal circumstances, these would be reduced through degradation of the multimers by plasma protease. The authors postulate that because the protease activity is absent in patients with TTP, platelet thrombi may be formed more easily in the circulation.

The finding in this study of an IgG antibody to the enzyme suggests that TTP is an autoimmune disorder that may respond to corticosteroids in addition to plasma exchange for the acute phase. Perhaps recurrences, which occur in approximately 30% of adults, could be prevented or treated with immune suppression.

Nonfamilial TTP May Have an Immune-Mediated Basis

The prognosis and treatment of patients with TTP or the hemolytic uremic syndrome may be influenced by the severity and cause of the von Willebrand factor–cleaving protease deficiency. Furlan and colleagues conducted a multicenter study to determine the prevalence of von Willebrand factor–cleaving protease deficiency in familial and nonfamilial TTP and the hemolytic uremic syndrome. Plasma samples were obtained from patients classified on a clinical basis by their physicians as having familial or nonfamilial TTP or the hemolytic uremic syndrome; protease activity was measured by quantitating the extent of von Willebrand factor degradation that occurred after incubation of purified von Willebrand factor with patient plasma.

The results suggested that the patients with nonfamilial TTP (n = 24) had a moderate or severe decrease in protease activity during an acute event, which appeared to be due to an inhibitor (identified in a subgroup as IgG). Patients with familial TTP (n = 6) also had no protease activity, but no antibody was detected. Patients with nonfamilial (n = 13) or familial (n = 10) hemolytic uremic syndrome had normal or slightly decreased protease activity.

In light of these data, together with those reported by Tsai and Lian, the authors provide strong evidence for an immune basis for nonfamilial acute TTP. They conclude that familial TTP is associated with a deficiency of von Willebrand factor–cleaving protease that is not immune mediated and that the pathogenesis of clinically defined hemolytic uremic syndrome does not appear to be related to the von Willebrand factor–cleaving protease.

In our view, these two studies on TTP provide a very solid basis with which to understand the pathophysiology of TTP and on which to develop treatment strategies that go beyond plasma exchange for the acute phase. von Willebrand factor–cleaving protease is present in normal concentrations in fresh frozen plasma, probably accounting for the clinical responses to plasma infusion, and is not inactivated by solvent-detergent treatment of plasma. An important point for clinicians is that measurement of protease activity may be a way to differentiate the diagnosis of TTP from that of the hemolytic uremic syndrome. Additional prospective studies are needed to confirm the very clear distinction between these two disorders that was reported by Furlan and colleagues. The role of these assays (when they become commercially available) in guiding treatment remains to be determined.
Transfusion Therapy

When patients receive a transfusion, the intended result is improvement of oxygen delivery to the tissue. The questions that have arisen are, Does the transfusion really benefit the patient? Are we actually harming the patient?

A Conservative Policy of Red-Cell Transfusion Is Equal or Superior to a Liberal Transfusion Policy


Hebert and colleagues conducted a randomized, controlled clinical trial to compare the effect of a restricted transfusion strategy with that of a liberal strategy on mortality and severity of organ dysfunction in anemic critically ill patients. Normovolemic, anemic patients in an intensive care unit were randomly assigned to be maintained at a hemoglobin level of 70 to 90 g/L or 100 to 120 g/L. Of 2039 eligible patients, 838 consented to participate. The study was terminated before the intended recruitment goal of 1620 was met because of a slow rate of accrual. At baseline, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, multiple-organ dysfunction score, primary diagnoses, number of patients receiving mechanical ventilation, and hemoglobin levels at randomization did not significantly differ between the two groups.

The average daily hemoglobin level was 85 g/L in the restricted-strategy group and 107 g/L in the liberal-strategy group. In the restricted-strategy group, the number of red cell units transfused was decreased by 54% and the number of patients who were transfused was reduced by 33%. The primary outcome measure—all-cause mortality rate at 30 days—did not significantly differ between groups (18.7% in the restricted-strategy group vs. 23.3% in the liberal-strategy group; difference, 4.6 percentage points [CI, −0.84 to 10.2 percentage points]; P = 0.11). No difference was seen between the two groups with respect to the secondary outcome measures of mortality during the entire intensive care unit stay and mortality at 60 days. However, the mortality rate during hospitalization, another secondary outcome measure, was lower in the restricted-strategy group than in the liberal-strategy group (22.2% vs. 28.1%; P = 0.05). Kaplan–Meier survival curves were significantly improved by restricted-strategy transfusions compared with the liberal-strategy transfusions in the subgroup that was younger than 55 years of age (P = 0.02) and in the subgroup that had less severe disease (P = 0.02); the latter subgroup included patients with a score of 20 or less in the APACHE II scoring system (scores > 15 indicate more severe disease). Both subgroups were planned a priori. In addition, fewer cardiac events (myocardial infarction, pulmonary edema) occurred in the restricted-strategy group than in the liberal-strategy group during the stay in the intensive care unit (P < 0.01). No difference was noted in other complications between the two groups.

The authors concluded that a restricted transfusion policy was at least equal to if not superior to a liberal transfusion policy for critically ill patients. We accept the authors’ suitably conservative recommendation to use the lower hemoglobin level trigger for most patients, except possibly for those with active coronary syndromes. The authors noted a significant difference in the percentage of patients with cardiac disease who were enrolled in the study compared with those not enrolled. Possibly because of a lack of support by patients’ physicians for the study, this difference may affect the generalizability of the results to patients with severe cardiac disease. The reasons for a lack of benefit from a liberal transfusion policy are speculative, but deleterious immunosuppressive and microcirculatory effects of transfusion have been suggested, as have the consequences of volume overload.

Hemochromatosis

Greater realization that hereditary hemochromatosis is common and that the iron overload that can occur in this disorder is preventable has spurred interest in early diagnosis. The three articles chosen here describe current research in this area.

Routine Hemochromatosis Screening for Asymptomatic Persons of Northern European Ancestry Is Justified

Olynyk and colleagues sought to assess the prevalence and clinical expression of the mutated hemochromatosis gene (HFE) in a population of Anglo-Celtic ancestry. They studied 3011 blood samples obtained in 1994 from residents of a community in western Australia, which were then tested in 1998 for fasting serum transferrin saturation, ferritin levels, and for the HFE mutations C282Y (cysteine replaced by tyrosine at position 282) by polymerase chain reaction. Patients with transferrin saturation greater than 0.45 were also tested for the H63D (histidine replaced by aspartate) mutation, which is less clearly implicated in the hemochromatosis phenotype. All homozygotes for the C282Y mutation and all patients with persistently elevated transferrin saturation or ferritin levels (>300 ng/mL) when testing was repeated in 1998 were evaluated for evidence of iron overload.

Sixteen study participants (7 men and 9 women; 12 previously undiagnosed) were identified as homozygous (0.5%); 15 of the 16 had elevated transferrin saturation (>0.45). One homozygous participant had an elevated serum ferritin level and a normal transferrin saturation. The sensitivity (95%), specificity (94%), and positive predictive value (6%) of a single transferrin value greater than 0.45 to identify persons with homozygous hemochromatosis were greater than for an elevated ferritin level. Twenty-five percent of the homozygous participants maintained normal ferritin levels over a 4-year period.

The authors found that in this study sample, 1 in 200 participants were homozygous for the C282Y mutation of the HFE gene. Half of the homozygous participants were symptomatic, and 6 who had not previously received a diagnosis of hemochromatosis showed a progressive increase in ferritin levels. Twenty-five percent of the homozygous participants maintained normal ferritin levels over a 4-year period.

### Table. Distribution of HFE Genotypes according to Clinical Presentation

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients with Hereditary Hemochromatosis (n = 66)</th>
<th>Patients with Liver Disease (n = 132)</th>
<th>Referred for Evaluation of Iron Overload (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y/C282Y</td>
<td>60 (91)</td>
<td>6 (4.5)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>C282Y/H63D</td>
<td>2 (3)</td>
<td>8 (6.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other patterns*</td>
<td>3 (4.5)</td>
<td>31 (23.5)</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Homozygous wild type</td>
<td>1 (1.5)</td>
<td>87 (66)</td>
<td>7 (37)</td>
</tr>
</tbody>
</table>

* C282Y/wild type; H63D/wild type; H63D/H63D.

### Figure. Proposed algorithm for the evaluation of possible hereditary hemochromatosis in a person with a negative family history.

- Evaluation for Hereditary Hemochromatosis (in a person with a negative family history)
  - Fasting transferrin saturation
    - Normal (<45%)
      - No further evaluation
    - Elevated (≥45%)
      - Genetic testing

- C282Y/C282Y
  - Age < 40 years
    - Normal ALT/AST level
      - Evaluate for other causes of iron overload; liver biopsy may be considered
    - Elevated ALT/AST level
      - Proceed with therapeutic phlebotomy
  - Age ≥ 40 years
    - Normal ALT/AST level
      - Liver biopsy for further evaluation
    - Elevated ALT/AST level
      - Consider liver biopsy

ALT = alanine aminotransferase; AST = aspartate aminotransferase; wt = wild type.
Hereditary hemochromatosis is the most common genetic disorder in persons of northern European ancestry. This study shows that clinical penetrance may be low, particularly in women, but that most of the persons identified as homozygous for the C282Y mutation of the HFE gene will have increased hepatic iron. The authors recommended measurement of both fasting transferrin saturation and serum ferritin level as the initial tests for population-based screening, with the goal of identifying patients before hepatic iron overload results in fibrosis or cirrhosis. The fact that one of the homozygous participants in this study would not have been identified if only the transferrin saturation had been measured prompted this recommendation. Readers should note that the frequency of the HFE C282Y mutation in patients who appear to have hereditary hemochromatosis in other populations can be much lower. In Italy, for example, only 64% of patients with clinical findings of hemochromatosis have the HFE C282Y mutation.

Patients with Liver Disease and Suspected Iron Overload May Be Homozygous for C282Y

Bacon and colleagues conducted a cross-sectional study to determine the prevalence of HFE mutations in patients with a clinical diagnosis of hereditary hemochromatosis and in patients with chronic liver disease. The prevalence of HFE mutations (C282Y and H63D) was examined in 198 patients: 1) 66 patients identified as having hereditary hemochromatosis by previous standard criteria (hepatic iron index > 1.9 mmol/kg per year or HLA identity to a proband) and 2) 132 patients with liver disease (19 with suspected iron overload) and documented hepatic iron concentration levels.

The distribution of HFE genotypes found in this study is shown in the Table.

All of the C282Y homozygous patients had increased hepatic iron levels, although 15% had hepatic iron index levels less than the 1.9 mmol/kg per year criterion used previously for the clinical diagnosis of hemochromatosis. The authors found that patients with liver disease and suspected iron overload have a marked chance of being homozygous for C282Y. In view of two of their findings—namely, that the youngest homozygous C282Y patient to have substantial fibrosis or cirrhosis was 40 years of age and that 8 of 10 compound heterozygotes (C282Y/H63D) had increased hepatic iron content—the authors propose the algorithm shown in the Figure for evaluation of a patient with a negative family history.

The issue of genetic screening for hemochromatosis, however, is controversial. The editorialists commenting on this article (2) were concerned about using genotype information before independent assessment of whether patients are likely to benefit from diagnosis and treatment when they do not meet the previously defined criteria for case identification. They argue that widespread genetic testing and labeling of persons with a genetic disease are not justified when it is not clear how to predict which patients are likely to develop complications if they are left untreated.

Physicians Should Strive To Detect and Treat Hemochromatosis before Iron Loading Occurs

McDonnell and colleagues conducted an international survey of patients with hemochromatosis to determine the type and frequency of symptoms in patients with hemochromatosis before diagnosis and treatment. The survey was done through the auspices of several hemochromatosis patient advocacy and support organizations, the Centers for Disease Control and Prevention, and many academic institutions. Of the 2851 respondents, 35% received a diagnosis because of symptoms, 45% because of an abnormal laboratory test result, and 20% because of a diagnosis in a family member. For symptomatic patients (59%), the median delay between symptom onset and diagnosis was 7 years, and an average of 3.5 physicians were seen before a diagnosis was made. The major symptoms reported were extreme fatigue (45%), joint pain (44%), and impotence or loss of libido (26%). Severe complications were more likely in patients older than 40 years of age (84%) than in those younger than 40 years (16%).

Before hemochromatosis was diagnosed, 67% of the patients received a diagnosis (in order of frequency) of arthritis, liver or gall bladder disease, gastric disorder,
hormone deficiency, or psychiatric disorder. The survey revealed that 27% of patients had been treated for iron deficiency or had taken iron supplements. After phlebotomy therapy, 86% of patients reported alleviation of symptoms. Fatigue, skin bronzing, and depression frequently improved with therapy, whereas joint pain, loss of libido, heart fluttering, and abdominal pain were less likely to improve. Physicians had recommended phlebotomy (90%), testing for family members (75%), and avoiding iron supplements (65%) or alcohol (41%). Other dietary information was uncommon.

The authors concluded that the diagnosis of hemochromatosis was delayed in most of the surveyed patients, and they suggested that there is room for improvement in the detection and management of this disorder.

The delay in diagnosis in symptomatic patients is not surprising considering that the reported symptoms are ones commonly encountered in an internist’s patient population. Nevertheless, a heightened awareness of this disorder is warranted because of its high frequency (1 in 200) and the improvement in survival and morbidity that can result from iron removal by phlebotomy.

Novel Therapies for Hematologic Malignancy

The next two articles describe new approaches to the treatment of hematologic malignancies. The first article demonstrates the usefulness of thalidomide for treating refractory multiple myeloma, and the second details the effectiveness of a nonmyeloablative conditioning regimen for recipients of bone marrow from HLA-mismatched donors.

Thalidomide, an Antiangiogenic Drug, Is Active against Refractory Multiple Myeloma


Because multiple myeloma is essentially incurable with conventional chemotherapy, Singhal and colleagues sought to determine the efficacy of thalidomide, a drug with antiangiogenic properties, in patients with refractory multiple myeloma.

The study participants—84 patients, most previously treated with high-dose chemotherapy and autologous transplantation—received a thalidomide dosage that gradually increased from 200 mg/d to 800 mg/d. Fifty-five percent of the patients reached the maximum dosage. Because 11% of patients were intolerant of side effects, they withdrew from the study. Of those who continued in the study, 21 patients (24%) had a greater than 50% decrease in myeloma paraprotein level, including two complete remissions (disappearance of paraprotein and normal bone marrow findings and improvement in hemoglobin levels). Six other patients had a 25% decrease in the paraprotein level. Median duration of event-free survival was 3 months; 22% of the patients remained event-free and 58% were alive after a median follow-up of 14.5 months. The major adverse effects were constipation, weakness, fatigue, somnolence, and neuropathy. Fewer than 5% of the patients had any myelosuppression.

In light of these results, Singhal and colleagues concluded that thalidomide can induce clinically significant objective responses in refractory myeloma with generally tolerable side effects. This is the first clinical report of tumor response to a drug with antiangiogenic properties. Increased vascularity of bone marrow myeloma infiltrates has been shown to correlate with advanced disease and poor prognosis (3). However, whether the tumor responses resulted from thalidomide’s antiangiogenic effect is not clear.

Other possible mechanisms have been suggested. In vitro, thalidomide can alter expression of adhesion molecules, inhibit tumor necrosis factor-α, increase interleukin-10 levels, stimulate cytotoxic T cells, and induce type 2 helper T-cell (Th2) cytokines. The lack of myelotoxicity supports the use of thalidomide in combination with conventional chemotherapy for previously untreated patients.

Allogeneic Bone Marrow Transplantation without Myeloablative Conditioning May Have Immunotherapeutic Benefit


Sykes and colleagues tested whether graft-versus-lymphoma effects without excessive graft-versus-host disease
can result from a new approach in bone marrow transplantation. The approach uses nonmyeloablative conditioning (mainly immunosuppressive methods) to permit donor marrow engraftment and mixed chimerism (the coexistence of donor and recipient hematopoietic cells in the transplant recipient) to occur. For the study, five patients with chemoresistant non-Hodgkin lymphoma who had had multiple previous treatments received transplants from related donors who were mismatched at one or two of six HLA antigens. The conditioning regimen included cyclophosphamide, antithymocyte globulin, radiation to the thymus, and steroids.

All patients developed chimerism of the peripheral blood leukocytes (41% to 96% donor lymphocytes, 8% to 93% donor monocytes, and 2% to 100% donor granulocytes), and all developed graft-versus-host disease, which was generally controllable with steroids. Two patients sustained excellent tumor responses: One had complete remission lasting for more than 1 year, and the other had a partial response with no evidence of disease except for gallium positivity. One patient died of progressive disease, and two died of transplant-related complications (aspergillosis and pulmonary hemorrhage).

Mixed chimerism could be induced in all patients. The antilymphoma responses seem to suggest that the transplant exerted an immunotherapeutic effect without necessitating myeloablative therapy.

Nonmyeloablative allogeneic bone marrow transplantation, the so-called minitransplant, is an exciting approach to immunotherapy for lymphomas, leukemias, and certain solid tumors that is being explored in many transplantation centers. Less toxic, nonmyeloablative, immunosuppressive conditioning regimens allow bone marrow engraftment of donor lymphocytes, which can then mount a graft-versus-tumor reaction with tolerable or no graft-versus-host disease.

This early report indicates the promise of this approach for otherwise refractory patients. In a recent update of this study, antitumor responses and donor chimerism were reported in 70% of 20 chemoresistant patients with hematologic malignancies (4). Donor lymphocyte infusion was able to convert partial chimerism to complete donor chimerism.

However, graft-versus-host disease and transplant mortality remain a challenge. Tumor responses in refractory patients in this study and in others are encouraging. Other groups are exploring various immunosuppressive regimens, such as combinations containing fludarabine, Campath-1H (an investigational humanized rat antibody to CD52), or low-dose irradiation that can allow engraftment and graft-versus-tumor effect with little graft-versus-host disease. This approach has also been shown to be effective in the treatment of metastatic renal-cell cancer (5).

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References