CURRENT THERAPY IN HEMATOLOGY-ONCOLOGY 1983-1984

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B.C. DECKER INC • Philadelphia • Toronto
The C.V. MOSBY COMPANY • Saint Louis • Toronto • London

Publisher: **B.C. Decker Inc.**
3228 South Service Road
Burlington, Ontario L7N 3H8

North American and worldwide sales and distribution:
The C.V. Mosby Company
11830 Westline Industrial Drive
Saint Louis, Missouri 63141

In Canada: **The C.V. Mosby Company, Ltd**
120 Melford Drive
Toronto, Ontario M1B 2X5

Current Therapy in Hematology-Oncology 1983–1984 ISBN 0-941158-05-5

Library of Congress catalog card number: 82-83696

10 9 8 7 6 5 4 3 2 1

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PREFACE

The most rewarding developments in medicine over the past decade or so have been the advances in treatment. Diseases which had been recognized for many years but for which no effective treatments were possible now respond to specific therapy. While this may be true for many fields of medicine advances in treatment in hematology and oncology have been particularly successful, the retention of the term "pernicious anemia" being a therapeutic anachronism. With improvements in diagnosis the challenge facing the physician is now often therapeutic. It may not only be a question of which is the most effective treatment, but how is it best given, and how may the complications that arise from treatment be best managed. The many excellent contributions to this book are evidence of these advances in treatment and patient care.

Hematology and oncology in particular have contributed to, and benefited from, the development and use of chemotherapeutic drugs in the treatment of malignant diseases. The use of these drugs initially often as single agents and more recently in various combinations has stimulated clinical and more basic research. It has resulted in the recognition that accurate staging is critical in the selection of the most appropriate form of treatment (chemotherapy, radiation therapy, surgery, or transplantation). The complications that accompany intensive treatment have been largely overcome by the improvements in antibiotics and by the availability of blood products. It is now widely accepted that the results of treatment can only be objectively assessed by properly controlled clinical trials. Advances in treatment have not diminished the care and consideration that have to be given to the patient and the patient's family during the whole course of an illness.

The shared background, experience and overlap in the practice of the hematologist and medical oncologist, led to the decision to include both topics in a single volume on current therapy. This has necessitated the editors being selective in the topics to be included. In oncology emphasis has been given to the more common tumors and to alternative approaches to their treatment rather than trying to provide comprehensive coverage of all malignant diseases.

The editors wish to express their sincere appreciation to the contributors; to their long-suffering wives; to Mrs. Audrey Moffett for excellent secretarial services; to our publisher Brian Decker and his staff for the many suggestions and actions taken in achieving the rapid publication of a volume of such high quality. The rapid advances in therapy will be met by seeking new contributors to future editions that it is intended will be published every two or three years.

Michael C. Brain
Peter B. McCulloch

December, 1982

CONTENTS

APLASTIC ANEMIA

RICHARD CHAMPLIN, M.D. and
ROBERT PETER GALE, M.D., Ph.D.

Aplastic anemia is a life-threatening hematologic disorder characterized by bone marrow failure with pancytopenia and a hypocellular bone marrow. This disease may result from a number of potential pathophysiologic mechanisms. Most cases are associated with absent or defective hematopoietic stem cells. A small number of cases may be attributable to defects in the bone marrow supportive stroma, or to abnormalities of regulatory cells or factors. Recently there has been considerable interest in the role of lymphoid cells and the immune system in the regulation of hematopoiesis and the potential role of immune suppression of hematopoiesis in the pathogenesis of aplastic anemia.

Aplastic anemia may result from exposure to a number of etiologic agents. The most common agents associated with this disease are listed in Table 1. A large number of drugs have been reported to produce bone marrow failure. This may occur as a predictable dose-related toxicity, as with cancer chemotherapeutic agents, or as an unpredictable idiosyncratic event, as with chloramphenicol or phenylbutazone. In addition, aplastic anemia may be caused by a number of toxins or infections and may rarely occur in association with a thymoma or with pregnancy. In 75% of patients with aplastic anemia, a likely etiologic agent cannot be identified and the disease is termed idiopathic.

The prognosis of aplastic anemia depends on a number of factors. The most important factor is the severity of pancytopenia, the reticulocyte count being the most meaningful prognostic indicator. In addition, patients with an indolent presentation—with an interval from first symptoms to diagnosis greater than 4 months—have a better prognosis than those with an abrupt onset of symptoms. In general, the etiology of the aplastic anemia has little prognostic importance. Patients with aplastic anemia related to non-A and non-B hepatitis, however, tend to have a fulminant disease with an extremely poor prognosis.

The treatment of aplastic anemia involves three major components: identification and withdrawal of potential etiologic factors, supportive care with blood product transfusions and management of infections, and therapy designed to restore normal hematopoiesis.

WITHDRAWAL OF POTENTIAL ETIOLOGIC AGENTS

The most direct approach to the treatment of aplastic anemia is to eliminate the causative factor(s). Aplasia is an uncommon complication following contact with any of the agents listed in Table 1 and may develop weeks to months after a brief exposure. In general, the etiology in a given case of aplastic anemia can only be suspected from the clinical history. Nonetheless, hematologic recovery may take place following withdrawal of the etiologic factor, and aplasia is likely to recur upon re-exposure to the offending agent. The aplastic anemia that occurs during pregnancy may improve after therapeutic abortion, and patients with aplastic anemia associated with a thymoma may recover following thymectomy. Unfortunately, a correcta-

TABLE 1 Common Etiologic Agents in Acquired Aplastic Anemia

Drugs
Antibiotics (chloramphenicol, penicillin, cephalosporins, sulfonamides)
Anti-inflammatory agents (phenylbutazone, indomethacin, gold, penicillamine)
Oral hypoglycemic drugs (chloropropamide, tolbutamide)
Antineoplastic cytotoxic drugs
Antithyroid drugs, phenothiazines, antimalarials (quinacrine), diuretics (thiazides), antiepileptic drugs
Toxins
Pesticides (gammabenzene hydrochloride, chlorphenothane [DDT])
Aromatic hychocarbon solvents and glues (benzene, toluene, xylene, napthaline)
Dyes, industrial toxins
Infections
Hepatitis, Epstein Barr virus, rubella, Venezuelan equine encephalitis, cytomegalovirus, brucellosis, tuberculosis, toxoplasmosis
Rheumatic and immunologic disorders
Systemic lupus erythematosus, cryoglubulinemia, graft-versus-host disease
Paroxysmal nocturnal hemoglobinuria
Radiation
Thymona
Pregnancy

ble etiologic factor can only rarely be identified, and other therapeutic approaches are required to restore normal bone marrow function in most patients.

SUPPORTIVE CARE

Aplastic anemia is characterized by failure of the bone marrow to produce adequate numbers of erythrocytes, platelets, and granulocytes. Each of the elements may be replaced, to an extent, by the transfusions of blood components.

It is generally possible to maintain adequate levels of hemoglobin for many years with transfusions of red blood cells. Erythrocytes should usually be administered as packed red cells, although whole blood or frozen red cells may be required in some circumstances. The major complications of red blood cell transfusions include transfusion reactions, circulatory volume expansion, iron overload, and transmission of infections such as hepatitis. Febrile transfusion reactions are frequently caused by contamination of the red cells by leukocytes and can be minimized by transfusion of washed or leukocyte-poor packed red cells.

An adequate number of circulating platelets can be initially attained in most patients by transfusions of platelets from unselected donors. Most patients become sensitized to HLA and other antigens present on the transfused platelets, leading to the development of antibodies that impair platelet function and shorten platelet survival. Ultimately the patient may become refractory and not achieve an increment in the platelet count following platelet transfusions. The time to develop antiplatelet antibodies is highly variable and does not correlate well with the number of platelet transfusions. Patients who become refractory to platelet transfusions from unselected donors may respond to platelets from HLA-matched donors. Sensitization may also occur to non-HLA antigens, and some patients become refractory to HLA-matched platelets as well. Splenectomy and immunosuppressive drugs, such as corticosteroids or cytotoxic agents, generally fail to improve the response of sensitized patients to platelet transfusions. Recently, several methods were proposed to detect antiplatelet antibodies and for cross-matching tests to allow selection of compatible donors for platelet transfusions. Unfortunately, these tests are not widely available, and contradictory data regarding their reproducibility and clinical utility have been reported.

Indications for the use of platelet transfusions must be individualized. Platelet survival is shortened by fever, infection, splenomegaly, disseminated intravascular coagulation, and active bleeding. The requirement for platelet transfusions is determined by the patient's platelet count, clinical status, bleeding tendency, and response to previous platelet transfusions. The risk of spontaneous hemorrhage is directly related to the degree of thrombocytopenia and increases substantially when the platelet count is less than 10×10^9/L. However, many patients with aplastic anemia tolerate very low platelet counts without symptomatic hemorrhage. Since the major limitation of long-term platelet transfusion support is sensitization and development of antiplatelet antibodies, it is generally prudent to reserve platelet transfusions until the first signs of symptomatic bleeding appear. Prophylactic weekly or biweekly platelet transfusions may be required in selected patients who have a demonstrated bleeding tendency, and these transfusions are generally advisable in patients with less than 20×10^9 platelets/L who have an unstable or rapidly falling platelet count.

Patients with aplastic anemia have reduced numbers of granulocytes and, under certain circumstances, may require granulocyte transfusions. Current techniques allow collection of 2 to 4×10^{10} granulocytes from normal donors under optimal conditions. This corresponds to approximately 10 percent of the average daily production of granulocytes, but is as little as 1 percent of the maximal production during periods of infection or stress. Patients with severe granulocytopenia and bacterial infections such as septicemia, pneumonia, perirectal abcess, and cellulitis generally respond favorably to broad-spectrum antibiotics alone. Patients with documented infections who fail to respond to a 48- to 72-hour trial of appropriate antibiotic treatment may benefit from daily granulocyte transfusions. In contrast, no benefit in survival has been demonstrated in patients receiving granulocytes for undocumented infections or for fever alone. The use of "prophylactic" granulocyte transfusions in an effort to prevent infections in granulocytopenic patients cannot be recommended.

Adverse reactions are common in patients receiving granulocyte transfusions. Hepatitis, cytomegalovirus, and other infections may be transmitted. Granulocyte transfusions may also sensitize the recipient to HLA and non-HLA antigens, and may compromise the subsequent response to platelet as well as granulocyte transfusions. Febrile transfusion reactions and chills are frequent. Leukoagglutination may occur leading to serious pulmonary

complications. Because of these adverse effects, as well as the limited clinical benefit, granulocyte transfusions should be reserved for documented infections in patients who fail to respond to appropriate antibiotics.

Another major consideration in transfusion support relates to the fact that many patients with aplastic anemia are candidates for bone marrow transplantation. Blood products may sensitize these patients to histocompatibility antigens of the donor and thereby predispose them to rejection of the transplant. Transfusions should be minimized in patients who are potential bone marrow transplant candidates and blood products from genetically related donors should be avoided.

The prevention and treatment of infections is of critical importance in the management of patients with aplastic anemia. Most infections in granulocytopenic patients are acquired from the endogenous microbial flora of the skin and gastrointestinal tract. A variety of measures have been proposed to decrease the incidence of these infections, ranging from oral nonabsorbable antibiotics and reverse isolation to more intensive attempts to achieve total decontamination in laminar air flow units. Selected patients with short-term myelosuppression following cytotoxic chemotherapy may benefit from these measures, but the efficacy of these measures in patients with aplastic anemia has not been established.

Granulocytopenic patients who develop fever or infections require an intensive diagnostic and therapeutic approach. Fever generally indicates a bacterial, fungal, or viral infection. Gram-negative sepsis is common and may be rapidly fatal. Granulocytopenic patients with unexplained fever or overt infections should be promptly hospitalized and treated for a presumed bacterial infection until a definitive diagnosis is established. A broad-spectrum combination of antibiotics, such as an aminoglycoside (gentamicin, tobramycin, or amikacin) and a semisynthetic penicillin (ticarcillin or piperacillin), should be initially employed and modified when the results of bacteriologic and fungal cultures are available. Patients responding to antibiotics should receive a full 10- to 14-day course of treatment. Systemic candidiasis, aspergillosis, and other fungal infections are also common in granulocytopenic patients and should be suspected in patients who either fail to respond to antibiotics or who respond but develop recurrent fever. A definitive diagnosis may be difficult, and a therapeutic trial of amphotericin B is often indicated. Surveillance cultures of the skin, nasopharynx, throat, and stool may identify patients at high risk to develop invasive fungal infections. Recently assays for circulating antigens from cryptococcus, aspergillus, and candida have been developed. These techniques may prove useful for the early diagnosis of invasive fungal infections.

TREATMENT DESIGNED TO RESTORE NORMAL HEMATOPOIESIS

The ultimate survival of patients with aplastic anemia depends on recovery of adequate bone marrow function. A number of therapeutic measures have been proposed to stimulate hematopoiesis.

Androgens have several well-defined effects on hematopoiesis and have been the most extensively studied treatment for aplastic anemia. Androgens increase erythropoietin production and enhance the erythroid end organ sensitivity to erythropoietin. Andorgens may also stimulate pluripotent stem cells and enhance both erythroid and granulocytic colony formation in vitro. The androgens most extensively studied in clinical trials have been oxymetholone and fluoxymesterone, which are taken orally, and nandrolone, which requires parenteral administration.

Androgens have been of limited efficacy in aplastic anemia. Patients with severe aplastic anemia rarely respond to androgen treatment, and overall survival has not been improved in several controlled clinical trials. A minority of patients with moderate pancytopenia may respond, but only after a 1- to 3-month therapeutic trial. Erythropoiesis is more likely to respond than granulocyte or platelet production. A small number of patients have shown an androgen-dependent response in which their peripheral blood counts improve while androgens are continued, but pancytopenia recurs when the drug is withdrawn. Prolonged treatment with androgens may be associated with substantial toxicity. Masculinization and fluid retention are common, and premature epiphyseal fusion may take place in children. The most serious complications of androgens is hepatoxicity. Cholestatic hepatitis frequently occurs in patients treated with the orally administered androgens. Peliosis hepatitis and hepatoma have been observed in patients receiving all classes of androgens.

Several conclusions may be drawn regarding the use of androgens. Patients with severe aplastic anemia are unlikely to benefit, and definitive treatment such as bone marrow transplantation should not be delayed to permit a trial of androgens. Adult patients with mild to moderate aplasia, however,