CURRENT THERAPY IN HEMATOLOGY-ONCOLOGY

1985 • 1986

BRAIN / CARBONE

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PREFACE

The second edition of *Current Therapy in Hematology-Oncology* is entirely new. We have expanded the oncology section to include seventeen new topics: principles of cancer management, esophageal, gastric, pancreatic, and colorectal cancers, uterine and cervical cancer, primary brain tumors, metastatic brain tumor, soft tissue sarcoma, pediatric solid tumors, CNS complications of cancer, renal complications of cancer, cancer prevention, pain control, and psychological distress in the cancer patient.

Contributors to the hematology section are new as well, providing a fresh perspective on the treatment of patients with hematologic disease.

In this expanded edition, the primary aim is again that of enabling practicing physicians to benefit from the experience of expert clinicians and investigators in managing patients with hematologic and malignant diseases. The authors are widely recognized clinical investigators active in the study and treatment of the diseases they discuss. We have asked them to focus on the precise therapeutic approach they use in the management of a disease, in the choice of treatment, and in assessing the benefits and risks of the treatment advocated.

We are grateful to the many colleagues who have contributed and who have presented their approach and recommendations in such a clear and concise way. We want to thank Brian Decker and his editorial and publishing staff, Mary Mansor, Anna Sonser, Dennis Boyes, and others for their expert editing and the rapid publication of the second edition. We would also like to express our appreciation to our personal secretaries, Audrey Moffett and Suzanne Parman, for their expeditious handling of the many communications with contributors and publishers. Last but not least, we would like to express our appreciation to our families who have adjusted so well to the pressures and distractions entailed in preparing the book. In order to keep abreast of the rapid advances in therapy we will be seeking new contributors for future editions which will be published every two years.

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Paul P. Carbone

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Oncology

HEMATOLOGY

APLASTIC ANEMIA AND ALLIED DISORDERS

EDWARD C. GORDON-SMITH, M.A., M.Sc., F.R.C.P.

In this chapter the treatment of a variety of disorders, loosely grouped under the heading of "aplastic anemia", is considered. The term "aplastic anemia" is used to mean idiosyncratic, acquired aplastic anemia which may follow exposure to certain drugs, chemicals, or viruses. Hereditary aplastic anemias include two well characterized disorders, Fanconi's anemia and dyskeratosis congenita, as well as some poorly characterized anomalies. Pure red cell aplasia may be acquired or congenital and refers to the erythroblastopenic anemias. The term "congenital hypoplastic anemia", usually used to describe the congenital form of this disorder (Diamond-Blackfan syndrome), is misleading, since the pathogenesis and natural history of the pure red cell aplasia is quite distinct from other types of true aplastic anemia.

ACQUIRED APLASTIC ANEMIA

Acquired aplastic anemia is a relatively rare disorder with an incidence of approximately 13 per million per annum in Europe and North America, though it may be higher in the Far East and in other countries where drugs such as chloramphenicol are widely used. Because it is so rare, treatment is difficult since management requires considerable patience and enthusiasm on the part of both the physician and the patient; the former may have little experience with it, and the latter has never heard of it. The first step in treatment is a careful explanation of the disease, its prolonged course, and its dangers. The usual first reaction of patients and relatives on hearing the diagnosis is relief that the disease is not acute leukemia, but the prognosis for aplastic anemia is certainly worse than for acute lymphoblastic leukemia, and probably worse than for acute myeloid leukemia. On the other hand, aplastic anemia is a deficiency disorder, brought about solely by the failure of hemopoietic stem-cell proliferation, so that the proliferative problems of the leukemias do not occur. Systemic symptoms directly caused by the disease are absent, and although the patient is pancytopenic with a hypoplastic marrow, he may feel completely well and thus not appreciate the dangers of the disease.

Treatment of the patient with aplastic anemia is considered in two distinct parts. The first part concerns replacement therapy or support in the form of blood product transfusion and prevention or treatment of infection; the second concerns ways in which recovery of bone marrow function is accelerated.

Spontaneous remission of aplastic anemia occurs in perhaps as many as 20 percent of patients, and it is not known whether all patients have the capacity to recover if they are kept alive long enough, or whether in some cases the damage to the marrow is irreversible. In any case, it is important to support the patient by careful attention to detail and by anticipating and preventing major problems.

Severe Aplastic Anemia

It is possible to differentiate a group of aplastic anemia patients with a particularly bad prognosis. Many attempts have been made to define the poor prognosis group precisely, but a simple definition seems to be most useful and workable. Severe aplastic anemia defines those patients with pancytopenia with less than $400/mm^3$ neutrophils, less than $20{,}000/mm^3$ platelets, less than 0.2 percent reticuloyctes, and a marrow with more than 80 percent of remaining cells nonmyeloid (or at least 3 of the 4 above). These patients have about a 1 in 10 chance of being alive at one year, even with major support. Experience would suggest that the most significant cell line is the granulocytic, and that patients who have even a few neutrophils $> 200/mm^3$ fare much better than those with none $< 100/mm^3$. This probably reflects the impossibility of providing granulocyte replacement, but also emphasizes the importance of infection as the main cause of death.

Support Therapy for Aplastic Anemia

It is essential to achieve a stable healthy state before commencing the chosen method of definitive treatment to induce remission of aplastic anemia. The various means to achieve this are considered separately, but in practice, all measures are instituted simultaneously.

Red Cell Transfusion

Most patients at presentation are anemic and require red cell transfusions. In the past, the hemoglobin of patients with aplastic anemia was kept low, $<$ 7 g/dl, in order to provide a large drive for hemopoiesis, but with no clinical evidence to prove this theory, patients are now transfused according to their clinical needs. Red cell transfusions do have special dangers however. Hemorrhage, including fatal cerebral hemorrhage, is more frequent during or just after red cell transfusions than during nontransfused pe-

riods in the thrombocytopenic patient. This is related to a fall in platelet count during transfusion of red cells that may be simply a dilutional effect or may be caused by minor degrees of immune complex formation. Whatever the cause it is important to give platelet transfusions at the same time as, or immediately after, red cell transfusions, especially if the platelet count is $< 20{,}000/m^3$ before starting.

Problems with iron overload are rare in aplastic anemia. If the patient runs into problems, it is usually after some years of tranfusion therapy and indicates a relatively good prognosis. Chelation therapy need not be started during the first year of treatment.

Transfusion reactions occur with the same frequency in aplastic anemia patients as in other chronically transfused patients, and it may be necessary to use white-cell-poor blood. There are two special features of aplastic anemia which may indicate its use. The first is the emergence of clones of red cells with the characteristics of paroxysmal nocturnal hemoglobinuria (PNH). About 15 percent of patients with aplasia who survive more than three months develop PNH clones at some time. White-cell-poor blood may be necessary to avoid hemolysis in these patients. The second indication for the use of white-cell-poor blood from the beginning is the development of antiplatelet antibodies. There is some indication that these antibodies may be avoided or delayed by giving white-cell-depleted blood products.

Platelet Transfusion

There is no consensus on how platelet transfusions should be used in aplastic anemia. The nature of the disease means that the patient will require such transfusions for a prolonged period of time (unless "cured" by bone marrow transplantation or immunosuppression). Antiplatelet antibodies, either anti-HLA or specifically antiplatelet, will develop in the majority (about 60%) of patients after a variable period of time, and support will become difficult. It would be ideal to give only HLA-matched, white-cell-free platelets when clinically indicated, but the availability of such platelets is limited. Furthermore, clinical indications for platelet transfusion are vague. Warning signs include the development of buccal and/or retinal hemorrhages, sudden spread of petechial hemorrhages, and the need for red cell transfusions. Infected patients are much more likely to bleed than uninfected patients. Unfortunately, fatal cerebal hemorrhage may occur without any of these prodromes.

At the opposite end of the therapeutic spectrum is the use of random donor platelets on a prophylactic basis with the introduction of HLA-compatible platelets when required. Several points indicate that this approach may be acceptable. A substantial minority of patients does not develop significant resistance to platelet transfusions. Even if some resistance does develop and platelet increments become poor, bleeding may be arrested by platelet transfusions. I use platelet transfusions routinely with red cell transfusions, give prophylatic transfusion two or three times weekly to out-patients whose platelet count is $<20{,}000/mm^3$, and modify this only when the patient is hospitalized and can be very closely observed. Death from cerebral hemorrhage has become rare, except in patients with uncontrollable sepsis.

Granulocyte Transfusions

Prophylactic granulocyte transfusions are not used in the treatment of aplastic anemia. Therapeutic transfusions are given in desperate situations, and certainly with localized infections they may have some beneficial effects. In general, if granuloycte transfusions are required in the support of patients with aplastic anemia, infections are out of control, and intensive granulocyte support for at least four days is required to achieve remission of infection.

Prevention of Infection

Patients with aplastic anemia present a special problem in the prevention of infection. Unlike leukemia, neutropenia is likely to be prolonged for months or even years. If the neutrophil count is very low ($< 100/mm^3$) it is doubtful that it is ever possible to eradicate an infection. Fungal infections are particularly intransigent. Sources of infection may be endogenous, from the gastrointestinal tract, skin, or upper respiratory passages, or may be exogenous. The exogenous infections are mainly Pseudomonas, Klebsiella or Aspergillus, but each hospital will have its own special problems.

Isolation

Patients with severe aplastic anemia should always be managed in isolation. Minimal requirements include an adequate isolation room and strict attention to details of reverse barrier nursing. Very strict regimes for hand-washing by all staff who enter the room, particularly if they are likely to touch intravenous lines, is essential. It is preferable to have some form of filtered air (laminar air flow is the most effective) to exclude Aspergillus and other fungal pathogens.

Decontamination

Both the patient and the environment should be rid of potential pathogens from the outset. Unfortunately, there is no way to achieve complete bacterial sterilization of the patient short of autoclaving, so a compromise has to be made. Potential pathogens of the gastrointestinal tract are mainly aerobic bacteria and *Candida*. Fatal anaerobic infections are rare. Nonabsorbable antibiotics are given from the outset. A suitable regime consists of nystatin suspension, 500,000 U *q6h*, amphotericin tablets 100 mg *q6h* amphotericin lozenges as much as tolerated, chlorhexidine mouth wash after food, framycetin 500 mg *q6h*, colistin 1.5×10^6 U *q6h* (doses for adults). Food should be freshly cooked and of low bacterial content (sterilized food is difficult to obtain and is unpalatable).

The major problem with this regime is patient compliance, and considerable tact and sympathy from nursing staff and relatives are necessary to obtain a satisfactory result. A similar result is achieved by using cotrimoxazole (Bactrim) instead of framycetin and colistin, but cotrimoxazole has a significant marrow suppressive effect and at least initially the nonabsorbable antibiotics are preferred. Cotrimoxazole does prevent *Pneumocystis carinii* infections, and if this is a particular local problem, cyotrimoxazole should be used. Chlorhexidine skin lotion, chlorhexidine baths and antibacterial creams are used for skin and orifice decontamination. Particular care must be taken during insertion of intravenous lines and major procedures (such as the insertion of Hickman catheters) should be accompanied by intravenous vancomycin (500 mg given slowly over 30 mins *q6h* for 24 hours) to prevent *Staphylococcus epidermidis* infection.

Such measures are readily introduced when the patient is hospitalized. The chronic nature of the disease and the psychologic stresses on the patient mean that considerable treatment has to be continued on an out-patient basis. If patient compliance is good, the oral regimes are continued and the patient is advised to keep to a diet of freshly cooked food, and to avoid high bacterial foods such as salads, cooked meats, and fruit. Help from a dietitian is always welcome. Close social contact with people and animals is discouraged, but pets should not be banished from a home, particularly when children are the sufferers. Although cats and dogs are potential transmitters of pathogens, such transfers seem to be very rare and the emotional support of a pet may be very great.

Treatment of Infection

Once an infection is identified, or presumed because of fever, treatment must be started promptly. As with other causes of neutropenia, rapidly fatal gram negative sepsis is most likely if the neutrophil count is less than $100/mm^3$. The antibiotic regime chosen should have a broad spectrum of effect, including antibacterial action against *Pseudomonas* and *Klebsiella*. The regimes most favoured are a β-lactam antibiotic with an aminoglycoside, or a third generation cephalosporin on its own. The antibiotics should be started as soon as the appropriate samples for identification of the pathogen have been taken. If a particular organism is isolated, the antibiotics are changed appropriately.

The main problems in the treatment of aplastic anemia are how long to continue with antibiotics, and what to do if the fever does not respond. With very low neutrophil counts it is difficult, if not impossible, to eradicate infection. Even if fever responds promptly and a sensitive organism is isolated, recurrence of infection is common after the antibiotics are stopped. The compromise is to treat the infection as for bacterial endocarditis and continue treatment for three weeks minimum, although this is not always possible in practice. The major toxicity is the nephrotoxicity of the aminoglycosides, and careful monitoring of antibiotic levels for therapeutic and toxic actions is needed. A degree of hypokalemia is usual, and potassium supplements may be required.

If the fever fails to respond to treatment, and no pathogen is isolated, fungal infection should be suspected. Aspergillus infections are the most lethal, and are relatively common in patients with aplastic anemia of some duration who have had multiple antibiotics. Aspergillus infection of the sinuses is particularly distressing and difficult to treat. Amphotericin still seems to be the most effective antifungal agent. It is given intravenously in high dosage (> 0.6 mg/kg) from the outset (after a test dose has been given). Major side effects are nephrotoxicity (which may be minimized by a high urine output) and hypokalemia. Fevers and rashes are common early in the course of treatment; they may resolve spontaneously or respond to hydrocortisone. Again there are major problems with duration of therapy. For proven fungal infections, at least six weeks treatment is needed.

Definitive Treatment for Aplastic Anemia

There are two main therapies which offer some hope of cure or remission in aplastic anemia: bone marrow transplantation or immunosuppressive therapy with antilymphocyte (antithymocyte) globulin. Anabolic steroids have a dubious role in the management of acquired aplastic anemia.

Bone marrow transplantation

For patients < 40 years of age who have severe aplastic anemia and an HLA-identical sibling willing to act as donor, bone marrow transplantation is the first treatment choice. At presentation, all patients are assessed on the basis of age and severity of disease as possible candidates, and HLA-typing is obtained on all family members as soon as possible. If a suitable donor is available, transplantation should be carried out as soon as possible, which usually means 1 to 2 months after diagnosis. Early transplantation minimizes the risk of rejection which is exacerbated by large numbers of transfusions, and the patient is usually in good clinical condition and uninfected at the time of transplantation. Although transfusions have been implicated in graft failure following bone marrow transplantation, it is more important to have a stable transfused patient than a sick, untransfused one.

The details of bone marrow transplantation are discussed elsewhere in this book (see chapter on *Bone Marrow Transplantation*). For patients with aplastic anemia, the main problem has been graft failure, but an immunosuppressive regime of cyclophosphamide 50 mg/kg per day for 4 days coupled with cyclosporin given for 12 months post transplant achieves a better than 95 percent engraftment and an overall survival of more than 75 percent. Cyclosporin is started the day before the donor bone marrow is infused.