Blood Component Therapy For Cancer

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During the last decade, significant advances have been made in the management of cancer. However, these very benefits can produce adverse secondary effects that may efface the success of therapy or result in sometimes life-threatening situations.

Control of complications through utilization of appropriate blood components may increase the survival of cancer patients following treatment. Studies conducted at M.D. Anderson Hospital and Tumor Institute clearly indicate that blood components are an important aspect of the comprehensive care of cancer patients, and should assume a definite place in the therapeutic armamentarium.¹

However, as with any other therapy, the unwise use of blood and its components can itself produce severe complications. Effective hemotherapy requires that the clinician select the appropriate blood component for a given clinical situation. It is critical, therefore, that the blood bank utilize the latest technical advances to prepare all of the essential components. (Table.)

Common Side-Effects of Antineoplastic Therapy

Myelosuppression, resulting in granulocytopenia, thrombocytopenia and anemia, is a common side-effect of a variety of antineoplastic treatments.¹ Granulocytopenia and thrombocytopenia place the patient at considerable risk of hemorrhage and infection. In spite of antibiotic therapy, infection associated with granulocytopenia remains the primary cause of death in the patient with acute leukemia and is responsible for 70 percent of all cancer deaths.²

Anemia is present in 90 percent of acute leukemia patients and 60 percent of those with disseminated cancer. The major causes of anemia in cancer patients are hemorrhage, hemolysis and inadequate compensatory erythropoiesis induced by the disease or its treatment. Autoimmune hemolytic anemia of both the “warm” and “cold” type occur especially in patients with hematologic neoplasms. Hemolysis may be due to a number of factors, the most important of which are changes in red blood cells, development of autoantibodies, in vivo activation of complements, splenomegaly and the effects of tumor metabolism.¹ Control of complications is now possible with hemotherapy.

Whole Blood

A unit of whole blood consists of 435
to 500 ml. of blood plus an anticoagulant solution, packaged in a plastic container. The National Institutes of Health has approved the use of three types of anticoagulants: acid citrate dextrose (ACD), citrate phosphate dextrose (CPD) and heparin. With proper collection and storage, ACD and CPD whole blood can be used within a 21-day period. This 21-day storage limit is based on the post-transfusion survival of erythrocytes in the recipient's circulation.

Most blood needs of the cancer patient can be met by preparations other than whole blood. While transfusion of whole blood may produce some hemo-therapeutic benefit, it may result in sensitization to platelets, granulocytes, lymphocytes, as well as different components of the plasma. This is a serious consequence as most cancer patients treated with modern antineoplastic modalities will sooner or later need the additional support of platelet and/or granulocyte transfusions.

These components will be of no benefit to the patient if he has been sensitized to them through prior transfusions of whole blood. In addition, patients so transfused are apt to develop antibodies to proteins in the plasma. The donor’s plasma may contain traces of some foreign substance whose corresponding antibody is present in the recipient’s plasma, resulting in an adverse allergic reaction. Therefore, the physician must make every effort to avoid the transfusion of whole blood. Although it is accepted practice to replace any significant blood loss during surgery with whole blood, many patients are treated just as effectively with packed cell transfusions and, if necessary, supplemental balanced salt solutions.

Fresh blood is variously defined. The term may refer to whole blood that is to be used within a few hours after collection or within five to seven days. The availability of specific blood components such as platelet concentrates, granulocytes, fresh frozen plasma and red cell preparations make the use of fresh blood in the treatment of cancer generally obsolete. At M.D. Anderson Hospital fresh whole blood has not been used for several years.

Packed Red Blood Cells
Packed red blood cells remain after most of the plasma has been removed from whole blood. The plasma may be separated following either centrifugation or undisturbed sedimentation at anytime before the expiration date of the blood. Since packed red blood cells have the same red cell mass as whole blood, this component provides the same oxygen carrying capacity, but in a smaller volume. The decrease in volume reduces the possibility of circulatory overload and cardiovascular failure. In addition, removal of the plasma decreases the total amount of electrolytes present in the unit of red cells due to a substantial reduction in the amount of citrate, sodium, potassium and ammonia. This is beneficial not only for patients with cardiac conditions but also for those with uremia and hepatic dysfunction. A further benefit is that the amount of Anti-A and Anti-B antibodies, normally present in the blood of individuals lacking the corresponding antigen, is substantially decreased. This has a real logistic value since it allows the use of blood for recipients with blood types other than group O during periods of shortage.

However, packed red blood cells, like whole blood, contain all of the platelets and white blood cells present in the original units of blood. Therefore, despite its advantages, packed red blood cells

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should not be used when long-term platelet and granulocyte transfusions are anticipated. These patients, like those transfused with whole blood, may become sensitized to platelets and white blood cell antigens and develop a refractoriness to subsequent administration of such elements.

**Leukocyte-Poor Packed Red Blood Cells**

Leukocyte-poor packed red blood cells is the component that remains after removal of most leukocytes and platelets from whole blood. Separation of the leukocytes and platelets from whole blood is accomplished by inverted centrifugation or serial batch washings using the IBM Cell Processor. Units prepared by the latter method result in residual white counts of 0.5-0.7 x 10^9, with a red blood cell recovery of 87 percent or better. 5

Leukocyte-poor units prepared by inverted centrifugation have one disadvantage: the loss of 20 to 25 percent of the red blood cells.

The primary purpose of leukocyte-poor red blood cells is to prevent or avoid febrile reactions caused by antibodies to white blood cells, as well as to platelets. It has been shown that some febrile reactions occurring one to three hours after transfusion of whole blood or packed red blood cells, may be the result of in vivo reaction of antibodies with incompatible antigens or transfused leukocytes. 5-9 A potential candidate for bone marrow transplantation should be given leukocyte-poor blood to prevent the development of multiple antibodies to leukocytes and platelets.

From a hemotherapeutic point of view, leukocyte-poor red blood cell preparations, obtained by serial batch washing, are far superior in respect to red blood cells than packed blood cells or whole blood. 5 This component gives the patient a red cell increment that contains only residual amounts of white blood cells and platelets. Therefore all efforts should be made to provide the cancer patient with this type of blood component whenever transfusions of red blood cells are required.

**Frozen-Thawed Red Blood Cells**

Techniques have been developed for freezing blood in the presence of cryoprotective compounds such as glycerol.

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Blood is frozen under controlled conditions and the glycerol subsequently removed by washing. The red blood cells are then reconstituted with saline for transfusion. Although frozen red cells have numerous advantages over conventionally stored blood, its major disadvantage is the greater expense incurred from processing. In fact, economic considerations have thus far prevented the wider use of frozen blood.

The extensive washing procedure used to remove the glycerol also removes blood group antibodies, microaggregates, other plasma proteins, plasma electrolytes and some, if not all, of the hepatitis virus. In addition, the freezing and thawing process eliminates the majority of platelets and leukocytes, reducing their number at least 10-fold and possibly destroying the viability of those few remaining. At M.D. Anderson Hospital, frozen blood is used in patients who require long-term platelet and white blood cell transfusions and when sensitization to these elements is undesirable.

Frozen red blood cells can easily be obtained from any blood bank with moderately sophisticated techniques. If not available, however, leukocyte-poor packed red blood cells, obtained by
| Blood Component                  | Advantages                                                                 | Disadvantages                                                                                      |
|---------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Packed red blood cells          | Provides the same O₂ content as whole blood but in a smaller volume, thus reducing the risk of circulatory overload and cardiovascular failure. | May cause sensitization to platelets and WBC antigens and should not be used when long-term platelet and granulocyte transfusions are anticipated. |
| Leukocyte-poor packed red blood cells | Indicated when transfusions of RBCs are required. | Loss of 20-25 percent of RBCs may occur when prepared by the inverted centrifugation technique. |
| Frozen-thawed red blood cells    | Recommended for patients requiring long-term platelet and WBC transfusions, since freezing-thawing process eliminates most platelets and WBCs. | More expensive than conventionally stored blood.                                                      |
| Platelets                       | Prevents bleeding in patients with thrombocytopenia, platelet function defects and tumor necrosis. | Excessive platelet transfusions may cause alloimmunization and refractoriness. Donor and recipient should be HLA-matched as closely as possible. |
| Granulocyte transfusions        | Primarily indicated for patients with hematologic neoplasms and life-threatening infections. | Generally available only in large treatment centers.                                                |
| Fresh frozen plasma             | Indicated for patients with clotting factor deficiencies when specific concentrates are not available. | Use as an expander is questionable. Fever, urticaria and erythema are not uncommon. Carries risk of hepatitis. |
serial batch washing, are recommended.

**Platelets**

In 1961, Gaydos, Freireich and Mantel showed that the likelihood of hemorrhage is proportionate to the platelet count, and that the lower the platelet count, the more severe the hemorrhage. Platelet transfusions are now administered to prevent bleeding as a result of thrombocytopenia or other conditions including disseminated intravascular coagulation, platelet function defects and tumor necrosis. It is important to recognize that there is a variable level at which bleeding may be anticipated with a slow onset of thrombocytopenia associated with bone marrow hypoplasia or leukemia. Since bleeding and infection are the major causes of death in patients with cancer, especially leukemia, the use of platelet concentrates was a major breakthrough in component therapy.

The indications for administering platelets to patients with thrombocytopenia have been a source of considerable controversy. The platelet count should not be used as the sole justification because of the hazard of developing platelet antibodies after a number of transfusions. At most large cancer centers, thrombocytopenic patients are transfused prophylactically to prevent hemorrhage, as well as during periods of active bleeding. Patients can expect longer hemorrhage-free intervals if the platelet count can be elevated to above 20,000/mm³. Although there is considerable variation in the platelet level at which patients develop bleeding problems, there appears to be an increased risk of serious spontaneous hemorrhage at counts below 20,000/mm³. Some patients, however, have had platelet counts of 5,000/mm³ for months without bleeding. Rapid falls in platelet count, infection, fever and clotting abnormalities further accentuate the tendency to hemorrhage, and should be kept in mind when deciding to administer platelets.

Since the early 1950s, when plastic equipment made available the safe manipulation of blood in sterile closed systems, platelets have been separated from other blood components and utilized as platelet-rich plasma (PRP) or platelet concentrate (PC). In this fashion, platelet concentrates can be obtained from every blood donation or by a more sophisticated process called plateletapheresis, in which platelets are...

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the recipient to the antigens carried by the platelets and make future much-needed transfusions devoid of clinical benefit. It must be remembered that there are times when a platelet transfusion is not indicated in spite of a very low platelet count. On the other hand, bleeding can be the result of inadequate platelet function, in the face of an adequate count.11

In 1969, Yankee and colleagues reported that the use of tissue-typed HLA compatible donors or HLA compatible platelets contributed immensely to the management of the patient sensitized to platelet transfusions.13 He concluded that both related and unrelated HLA-matched donors can be employed for long-term transfusion therapy.15 In cancer patients requiring platelet transfusions, donors and recipient should be HLA-matched as closely as possible.

**Granulocyte Transfusions**

It is not technically difficult to obtain adequate numbers of white cells by the process of leukopheresis from single donors.11 Vallejos and collaborators have, in addition, demonstrated that these cells are functional in vivo.16 In the past decade, leukocyte transfusions have been increasingly used at M.D. Anderson Hospital for the supportive care of patients, primarily those with hematologic neoplasms. The development of more efficient techniques for blood cell separation and harvesting have made granulocytes an important adjunct in the management of life-threatening infections. Although within reach of most physicians, granulocyte transfusion is still practiced primarily in large cancer centers only.

Myelosuppression in cancer patients is the most frequent indication for leukocyte transfusion. Those with severe granulocytopenia as a primary manifestation of disease, with or without myelosuppression, and those who are in danger of overwhelming infection are also candidates for granulocyte replacement.2

**Fresh Frozen Plasma**

Fresh frozen plasma is separated from whole blood within four hours of collection, and stored at −18°C or colder in order to totally preserve the coagulation factors. This component is generally indicated in the treatment of patients with clotting factor deficiencies when specific concentrates are not readily available. In some instances, fresh frozen plasma is used in conjunction with packed red blood cells in replacement transfusion of fresh blood. However, the use of plasma as an expander is somewhat questionable. The work of Hutchinson and co-workers suggests that it may be relatively ineffective for this purpose and, in fact, may have a histamine-releasing effect.17,18 Fever, urticaria and erythema are not uncommon after plasma transfusion, and are presumably due to an allergic reaction. In addition, fresh frozen plasma carries the same risk of hepatitis as does whole blood.

**Adverse Reactions to Transfusions**

Blood components are as potentially hazardous as drugs and should be used only when there is an unequivocal indication. In general, an adverse reaction can be considered a failure to achieve the objective of hemotherapy. Effective blood component therapy requires that the clinician choose the appropriate preparation for a given clinical situation, based on careful judgement and sound clinical justification.
Aside from the well-known risk of post-transfusion hepatitis, it has been estimated that about 0.5 percent of transfusions are accompanied by some type of side-effect.4 Hemolytic transfusion reactions may develop as a result of (1) intravascular hemolysis of red blood cells, most commonly from incompatibility in the ABO system, or (2) extravascular hemolysis, in which the red cells combine with antibody in the vascular space but destruction occurs extravascularly, for example, in the reticuloendothelial system of the spleen, liver and bone marrow. Other transfusion reactions include fever associated with the administration of blood, leukocytes, platelets or bacterial pyrogens; in many cases, however, there is no readily identifiable cause. In addition, transfusion may sometimes result in generalized pruritus and urticaria. The underlying cause of allergic reactions is believed to be sensitivity to plasma protein components in the transfused blood, and includes the passive transfer of antibodies to the recipient who may be subsequently exposed to the antigen in medication or food.5 The recipient may also develop a disease carried in the blood of the donor, such as serum hepatitis, malaria and syphilis. A careful donor history and appropriate tests can greatly reduce the risk of disease transfer. Some patients will develop delayed transfusion reactions. Delayed hemolytic reactions may occur anywhere from 72 hours to 14 days after the transfusion of a blood component.4

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