Problems in Crossmatching Blood from Cancer Patients

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ABSTRACT

The term "cancer" is an umbrella for a large number of malignant diseases which vary in severity and type. Therefore, many problems are associated with crossmatching a patient with this diagnosis. Blood use may vary greatly in amount and in the urgency of its need. The diseases themselves may cause cold reactive autoagglutinins to appear. The diseases and their treatments may cause red cell antigenic structure to be modified or antibodies to decrease in strength. Multiple transfusions may induce the formation of multiple antibodies. A few blood groups have been associated with a higher incidence of carcinoma in the patients possessing them. All of these possibilities must be considered by the blood bank when a transfusion request for a patient with "cancer" is received.

Introduction

The patient with a suspected or confirmed diagnosis of malignancy represents a series of unique and continuing challenges to the blood bank. The patient may need a biopsy or surgery, which may be either minor or major. Depending on the severity of this surgery, it may require differing amounts of blood and differing methods of handling the transfusion requests. The patient may have a presurgical anemia which will need to be corrected. The patient may develop anemia later in the course of the disease owing to continued bleeding. There may be destruction of the bone marrow owing to radiation or chemotherapy or actual destruction of the red cells owing to the same agents. Furthermore, some cancers may produce serological abnormalities as part of the disease or as sequelae which need to be resolved, or at least addressed, before the patient can be transfused at all. Therefore, the patient with cancer may present quantitative blood bank problems, which depend on the amount of blood needed and the urgency of its need, and qualitative serologic problems, which are found during the crossmatching procedures. For these reasons, it is a great mistake to lump all patients with cancer into one group. The patient with the small basal cell carcinoma, which is removed under local anesthesia, is a far different case than that of the patient with a sarcoma, who is to undergo a hemipelvectomy. Therefore, an attempt will be made to present in a general manner the utilization of the blood bank for a patient with carcinoma and will be illustrated with specific conditions.
Quantitative Differences in the Use of Blood

Presurgical Anemia

There are a number of causes for presurgical anemia in the patient with cancer. Often, the lesion has a bleeding surface which has caused a slow continuing blood loss or, in some cases, a massive hemorrhage owing to invasion of a blood vessel. If the anemia is slight, it should not be treated since the transfusion may produce more problems than it cures; however, if it is symptomatic and causes enough fear in the anesthesiologist that surgery is postponed, then it should be treated. In addition, if the patient is being treated by irradiation or chemotherapy, there may be bleeding caused by necrosis of the tumor or destruction of neighboring tissue or the bone marrow may be suppressed. All can produce a continually progressive anemia or an anemia found just prior to surgery.

The diagnosis of this anemia is essential. It should be born in mind that all anemias in the cancer patient are not due to blood loss alone. If the diagnosis is not made, but nevertheless transfusion therapy is initiated, the cause of the anemia may be masked and the subsequent diagnosis and treatment may be made more difficult. The presurgical patient should be studied for all other possible deficiencies. A patient with a low platelet count (<50,000) will usually bleed when subjected to surgery. This deficiency will have to be corrected. It is possible that the patient's coagulation factors may be decreased due either to a developing disseminated intravascular coagulation, by invasion of the liver and/or bone marrow by the tumor or by destruction of the bone marrow by X-rays or some of the drugs currently used. If the coagulation parameters are abnormal, then the determination must be made of which factors are deficient and why they are depressed. These deficiencies must be treated before surgery can be undertaken with relative safety.

Transfusion During Surgery

During surgery, the patient may require no blood at all; on the other hand, the patient may require a massive transfusion. Examples of this have already been given; the classic situation, however, is the breast biopsy. If the biopsy is benign, blood usually is not needed; however, if the mass is malignant, and if the patient has authorized the surgeon to go ahead with the surgery immediately, a considerable volume of blood may be used, depending on the type lesion found at surgery. For this reason, there may be a need to change transfusion strategies quickly. In this case, the type and screen procedure is uniquely fitted to handling these patients. This procedure has been the subject of considerable discussion recently1,2 and, therefore, will be outlined only briefly.

On request, and prior to surgery, the patient's blood group and Rh type are determined, after which there is screening for unexpected blood group antibodies (those other than anti A and B), using a well selected set of screening cells. If no antibodies are found, the patient's blood grouping studies are recorded, but no specific blood is crossmatched. Therefore, no blood is sequestered for the possibility that it might be used subsequently. If there is a need for blood, the donor's and patient's blood samples are then tested only with an immediate-spin crossmatch (to test the ABO compatibility), and the blood is released for transfusion. A traditional crossmatch is not performed.

The major advantage of this procedure is that a smaller amount of blood needs to
be retained on reserve to give safety to a larger number of patients, since a particular unit is not kept solely for a specific patient. Therefore, this procedure essentially replaces the old double and triple crossmatch technique where units of blood were crossmatched on several patients who probably would not use all the blood. Furthermore, if blood needs become greater than expected, more blood can be released with little extra time required and with great safety to the patient. Finally, the Type and Screen procedure decreases the workload on each technologist. This has several advantages. It decreases the cost of the crossmatch to the hospital, and it allows the technologist to do a better job on fewer tasks rather than to do a poorer job on many.

There is a small theoretical danger to the patient with this procedure. Many of the patients are transfused repeatedly to correct for the blood loss that has occurred. These individuals will have a higher incidence of blood group antibodies and will have more varied types owing to the repeated antigenic exposure. It is conceivable that the patient may have a rare antibody which is so uncommon that its corresponding antigen will not be on the screening cells. If the rare antigen for this antibody is found on the red cells of the unit to be transfused, this incompatibility will not be detected by the type and screen procedure. The possibility of this occurrence is felt to be <1 in 10,000\(^1,2\) and thus does not represent much of a threat. However, it has caused most blood bankers to feel that the Type and Screen procedure should be reserved primarily for those patients who are not expected to be transfused, and the blood kept only for safety. If there is a good chance that large amounts of blood are going to be used, it is safer to crossmatch the units. The units are then held in reserve for that patient alone, are immediately available, and a direct test for compatibility has already been made between the patient and the specific units of blood.

**Blood Bank Support for Chemotherapy**

If a tumor or its metastases continue to grow, blood loss similar to that described for presurgical anemia may occur and will have to be treated. At present, these complications constitute only a minor problem to the blood bank. The use of chemotherapy is now almost universal in metastatic and in some non-metastatic tumors. With its use, the blood bank is needed to provide more support than was previously needed. Many of the drugs cause necrosis of the tumor tissue and direct bleeding. In addition, some of the drugs have been shown to produce a direct hemolysis of the red cells.\(^{20}\) Furthermore, since some drugs are directly toxic to rapidly growing tissue, they often suppress the bone marrow, the immunologic defense mechanism, and other growing tissues. Many of the patients experience anemia, agranulocytosis, thrombocytopenia, and/or acquired immune deficiencies. All of these disorders must be treated if they become life threatening.

By far the easiest disorder to treat is anemia. Once a diagnosis of its cause has been made, the transfusion can be carried out with little difficulty. The next easiest disorder to treat is thrombocytopenia. Most patients on chemotherapy will experience this to a degree at some time or another. For this reason, the availability is essential at all times of adequate numbers of platelet concentrates. Preferably, these are group and type specific or at least group compatible. However, Goldfinger and McGinnis\(^8\) have demonstrated that in the thrombocytopenic patient who is Rh negative and im-
munosuppressed, only about 7.8 percent develop Rh antibodies if given platelet concentrates which are Rh positive. Although this method of therapy cannot be recommended as routine, it is comforting to know that if a patient is bleeding, and platelets are hard to find, there is a small way out.

Platelets should be given to raise the count to >25,000 in patients who are experiencing bleeding owing to petechiae, ecchymoses, oozing, or hemorrhage. If the platelet deficiency is not corrected, the bleeding will continue. If platelets are given to this type of patient, they should be reevaluated at least every other day.

A therapeutic mode which is becoming exceedingly popular (possibly too popular) is the use of granulocyte transfusions in the agranulocytic patient. There are a number of authors who feel that it is of very debatable help, and some articles have pointed out very specific dangers with this therapy. It appears that granulocyte transfusions are of most value in the granulocytopenic, septic patient who has been tried at least 48 hours on an adequate antibiotic regimen with no abatement of the infection. In these cases, the patient often responds dramatically to a course of granulocytes.

On the other hand, the use of granulocyte transfusions as prophylaxis to prevent infection has been very disappointing. The isolation of these granulocytes requires a trained team to run the machine and a good source of donors who are willing to put up with the discomfort and time involved in this procedure. Usually this requires a large, well equipped medical center with special oncology facilities. Furthermore, in these cases extra support facilities, including laminar flow rooms, reverse isolation facilities, and a trained nursing staff, are also needed. With all of these constraints, the response to granulocytes can be most dramatic. It is often disappointing, however, to find a patient who experienced a dramatic response, after which the bone marrow did not regenerate and the patient again became septic. At this time, the decision must be made to reinstitute the treatment again. Considering that one course of granulocytes (10 or more days) may cost upward of $5,000, this is not a decision to be made lightly, especially if the patient may not receive a long term benefit from it.

A final, debatable therapeutic mode should be considered in transfusing these carcinoma patients. Since most of the patients receiving chemotherapy are immunosuppressed to some degree, there is a danger of their developing Graft versus Host (GVH) disease. Several cases have been reported in patients who were congenitally immunosuppressed or who received chronic myelocytic leukemic (CML) cells for transfusion. However, there is at least one case of an adult with leukemia who was treated with granulocytes from his relatives and who did develop GVH. Most blood products, especially granulocyte and platelet concentrates, contain a significant number of lymphocytes. Two hundred to 400 lymphocytes have been found in units of fresh frozen plasma which have been stored for six months at −30°C. From these findings, a good argument can be made for irradiating all blood products before transfusion, thus destroying all viable cells which could invade the host and produce GVH. On the other hand, the incidence of GVH is very low, and there is no real knowledge of the danger to a patient when treating him with large quantities of irradiated products. It should be born in mind that each unit of blood products is exposed to 1500 rads of radiation or higher. Although one might feel that the danger is very small,
nevertheless, the widespread use of this treatment will require a long term study of its effects before it can be regarded as innocuous.

Qualitative Serological Abnormalities

By far the most common serological abnormality which is encountered with cancer patients is the presence of a cold reactive auto-agglutinin. This is seen most frequently with patients who have lymphomas of varying types and with genito-urinary carcinoma; however, it can be found with almost any condition at one time or another. Numerous studies have shown that a cold agglutinin by itself is not harmful to the patient, but it is dangerous since it may mask the presence of more serious antibodies. Therefore, it is necessary to work around this antibody when performing a crossmatch. The method that used to be employed was that of cold auto absorption in which the patient’s serum is incubated with its own (autologous) cells at 4°C. This procedure was repeated sufficient times that the auto antibody was removed while the other antibodies remained. Methods for this technique are available in almost all older textbooks of blood banking. One of the major problems with this technique occurred after the patient had been transfused. The patient still had the cold auto-agglutinin and may have been immunized by the transfused blood to produce another specific antibody. If the patient’s current blood is used for absorption, the specific antibody may be absorbed by the transfused cells at the same time that the patient’s own cells absorb the auto antibody. This is an unsatisfactory situation.

A ray of light seemed to appear when it was found that human breast milk contained the I substance, which is the usual cold agglutinin antigen. However, absorption with human milk, although successful in some cases, did not work in all instances. A way around this quandry was to begin with an autoabsorbed specimen, which was screened for antibodies, and store it. This could be used subsequently for crossmatching and was valid as long as the cold agglutinin did not reactivate (which it sometimes did), or a strong immune antibody did not develop in the patient owing to subsequent transfusions. If no transfusion was received for a while, a new sample could be drawn and used.

Another method that is sometimes helpful is to grade the reactions between the different cells which compose the red cell panel and to see if the strength of agglutination varies from one cell to another. From this, it is sometimes possible to see several different agglutination patterns which vary in strength and which show patterns of both the cold agglutinin and another specific antibody present.

Currently, the usual procedure used is to perform the crossmatch at 37°C which will prevent the reaction of most of the cold agglutinins. This is now considered the method of choice by most authors. It does have the danger though that if a clinically significant cold reactive antibody does exist, it will not be detected, and the transfusionist will be faced with trying to discover the cause of an unknown transfusion reaction.

A problem which was reported by us and which is seen occasionally is the presence of a blood group antigen which has been secreted by the tumor. In this case, the patient was originally grouped as O, since his red cells did not react with anti A or with anti B; however, the patient had only anti A in his serum. After considerable washing of the red cells, it was found that the red cells were indeed B, and the patient’s serum was found to inhibit anti B antiserum when it was added to it. Therefore, a soluble B substance was present in the serum. Other studies have also shown that tumors can secrete blood group substances and that
this can interfere with the blood grouping in the patient.\textsuperscript{13}

Another problem which can create a considerable difficulty in typing and crossmatching a cancer patient is the decrease in antibody levels seen in some cases. Antibody titer can decrease as a function of age, cachexia, effect of immunosuppression, or other factors. If this is sufficiently strong, antibodies can be completely suppressed. What is probably more comforting is that in these cases the antibody response is usually suppressed as well, and the patients do not respond to antigenic stimulus. On the other hand, all immunosuppressed patients should be followed with periodic antibody screens to determine if the antibody titers are rising and if any new antibodies have developed.

Finally, there have been occasional reports of carcinoma patients losing or gaining blood group antigens. In most of these cases where a blood group antigen is gained, the blood group antigen is a pseudo-B caused by the patient having an overwhelming sepsis or is a case of T activation owing to various bacteria\textsuperscript{16} (p. 406). In the case of lost blood group antigens, these may involve several blood group systems.\textsuperscript{5,12} Fortunately, the loss is only a partial diminution in reactivity, and blood grouping and crossmatching can still be performed.

**Blood Groups and Cancer**

A considerable amount of interest was raised in the mid 1950’s when Buckwalter\textsuperscript{5} and others\textsuperscript{11,13} found a correlation between blood group A and the incidence of gastric carcinoma as well as the correlation of other diseases. Although this correlation has been shown to be statistically valid, it is not strong. Subsequent studies on various diseases and blood groups have not been particularly helpful, and currently, there seems to be little interest in these investigations.\textsuperscript{17}

**References**


