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Autologous Stem-Cell Transplantation Can Be Performed Safely Without the Use of Blood-Product Support

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PURPOSE: Autologous stem-cell transplantation has been shown to be a curative procedure for a variety of leukemias and lymphomas. Most transplants require RBC and platelet support. We report the ability to perform autologous transplantation without blood-product support.

SUBJECTS AND METHODS: **In this study, we treated 26 patients with religious objection to blood products with autologous stem-cell support without the use of any blood products.** Patients received a combination of granulocyte colony-stimulating factor (G-CSF), erythropoietin, and interleukin-11 or G-CSF alone to mobilize stem cells. Post-transplant patients received intravenous iron, erythropoietin, G-CSF, and epsilon aminocaproic acid.

RESULTS: There were two major bleeding complications (8%), with two treatment-related deaths (8%). There were three minor bleeding complications (12%). The median fall in hemoglobin level was 4.7 g/dL; the median hemoglobin level 30 days after transplantation was 9.2 g/dL. The median total number of days with platelet count less than $10 \times 10^9/L$ was 4 days; the median days to platelet recovery greater than $20 \times 10^9/L$ was 12 days.

CONCLUSION: Autologous stem-cell transplantation can be performed safely without the use of any blood products.

High-dose chemotherapy followed by autologous stem-cell transplantation is

the only curative therapy for some patients with recurrent Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, and germ-cell tumors.¹⁻³

Autologous stem-cell transplantation has been shown to prolong survival in multiple myeloma.⁴ The risks of high-dose chemotherapy include bleeding from thrombocytopenia and severe anemia.⁵ Blood product support can be complicated by iron overload, infectious disease transmission, and transfusion reactions.⁶ Autologous stem-cell transplant recipients usually require 5 to 20 transfusions of RBCs or platelets.⁷

Jehovah's Witnesses are members of a religious group founded in the 1870s in Pennsylvania by Charles Taze Russell.⁸ There are an estimated 6 million Jehovah's Witnesses worldwide.

Most Jehovah's Witnesses will refuse transfusion of any major blood products, which they define as red cells, white cells, plasma, and platelets, on religious grounds, following a strict interpretation of the Biblical passages in Leviticus: "And you must not eat any blood in any places where you dwell... Any soul, who eats any blood, that soul must be cutoff from his people."⁹ However, many Jehovah's Witnesses will accept blood fractions that include stem cells, or purified derivatives such as albumin.¹⁰ There have been several approaches to "bloodless" surgery in Jehovah's Witness patients. Multidisciplinary bloodless medicine and surgery programs have been established to provide optimal medical and nursing care for patients with religious or other objections to blood products.^{11,12}

Despite the existence of more than 100 of these bloodless programs, very few transplant centers will consider Jehovah's Witness patients candidates for stem-cell transplant, and therefore, many of these patients will not be referred to a transplant team. In a study of 50 Jehovah's Witness patients scheduled to undergo cardiac surgery, patients received recombinant human erythropoietin alpha (erythropoietin) 500 units/kg every other day until the hematocrit level reached 36%. Intraoperative aprotinin was used to decrease bleeding, and the mean discharge hematocrit was greater than 30%.¹³ Another surgical team utilized vigorous volume replacement, nutritional support, iron replacement, and early surgical treatment for Jehovah's Witness patients with varices.¹⁴ However, despite data in the surgical literature, there are little published data on the care of Jehovah's Witness patients who require intensive medical procedures, such as high-dose chemotherapy. Many non-Witness patients are treated according to predefined transfusion "triggers," mandating transfusion below a certain hemoglobin or platelet count. **In this study, we describe the experience of 26 Jehovah's Witness patients, the largest experience to date, undergoing stem-cell transplantation without the use of any blood products.**

Study Subjects

Jehovah's Witness patients were referred to either the University of Massachusetts Memorial Care or Pennsylvania Hospital for consideration of bloodless autologous stem-cell transplant. Both institutions have established Bloodless Medicine and Surgery Programs. All patients had to meet usual eligibility criteria for transplantation, including chemotherapy-sensitive disease, ejection fraction greater than 50%, diffusing capacity of the lung for carbon monoxide greater than 50% predicted, creatinine clearance more than 60 mL/min, and Eastern Cooperative Oncology Group performance status 0 to 2 and normal clotting parameters (protime and partial thromboplastin time). Patients between the ages of 18 to 65 years were eligible. There were no additional eligibility criteria for bloodless transplantation compared with traditional autologous transplantation. Additional exclusion criteria for CNS malignancy and for a starting hemoglobin level less than 11 g/dL, were added later, as described in the Treatment Plan section. The programs did not retain data on the number of patients who were discussed or referred for transplantation but who did not meet eligibility criteria. This report

includes all consecutive bloodless transplantation patients at the two institutions between May 1996 and October 2002. Patients met with a counselor from the Bloodless Program before transplantation. All participants were informed of the increased risks of bloodless transplantation and signed a consent form approved by their local hospital institutional review boards. Patients were treated with similar, but not identical, regimens in the two centers, as described in the Treatment Plan section.

Treatment Plan

Routine blood conservation included the use of pediatric tubes for all blood sampling and the return of the discard from the central venous catheter into a closed system. In an effort to limit the toxicity and myelosuppression of further chemotherapy, no specific chemotherapy priming was administered. The last cycle of conventional chemotherapy was used to mobilize peripheral blood progenitor cells.

Peripheral blood stem cells were mobilized after the last dose of chemotherapy using granulocyte colony-stimulating factor (G-CSF) 10 µg/kg/d, recombinant human erythropoietin 150 U/kg/d and interleukin (IL) -11 50 U/kg/d or G-CSF alone 10 µg/kg/d.¹⁵ The target collection was a minimum of 2.5×10^6 CD34+ cells/kg. Patients received a second mobilization with G-CSF alone if the target dose was not achieved. Early in the study, the protocol was amended to delay the transplant admission until a hemoglobin level of 11 to 12 g/dL was achieved. The patients continued on erythropoietin during this time.

Patients received a standard high-dose chemotherapy conditioning regimen depending on their primary disease. Beginning on day +1 following transplantation, patients received a daily dose of erythropoietin 150 U/kg/d. After the **hemoglobin level fell to less than 10 g/dL, patients received weekly intravenous (IV) iron dextran at a dose calculated for the hemoglobin level.**¹⁶ IV use was chosen as oral preparations were poorly tolerated. G-CSF was given at a daily dose of 5 µg/kg beginning on day +1 (day +5 for patients at the University of Massachusetts Memorial Care Hospital) after transplantation. At Pennsylvania Hospital, patients also received IL-11 post-transplantation. Patients received epsilon aminocaproic acid (Amicar; Immunex, Seattle, WA) at a dose of 1 to 6 g orally every 6 hours during the period of thrombocytopenia, when the platelet count fell below $30 \times 10^9/L$. The dose was adjusted upward as needed for bleeding.¹⁷ IV infusion was initiated if oral medications could no longer be tolerated, and the maximum dose was IV 1 g/h. Desmopressin was used at a dose of IV 0.3 µg/kg every 12 hours for 36 hours if bleeding persisted, despite maximal doses of aminocaproic acid.¹⁸ All patients received prophylactic phytonadione, folic acid, and gastrointestinal bleeding prophylaxis, such as with a proton pump inhibitor. Menstruating women were treated with either oral contraceptives or Depo-Provera (Pfizer Pharmaceuticals Group, New York, NY). Protome (PT) and partial thromboplastin time (PTT) were both measured weekly.

Statistical Analysis

Time for the engraftment and survival parameters was measured from day 0 of transplantation and was estimated by the Kaplan-Meier method. Patients who died before the engraftment of a hematopoietic parameter were censored at the date of death. Patients who had not died were censored at the time of their most recent follow-up in the analysis of overall survival. Patients who had not died and had not recurred with cancer were censored at their last contact date with respect to progression-free and disease-free survivals.

Patient Characteristics

Twenty-six consecutive patients who elected to proceed to autologous stem-cell transplant without blood-product support were enrolled onto this study from May 1996 to October 2002. Patient characteristics are described in Table 1. The median age was 40 years (range, 21 to 54 years). Diagnoses included lymphoma (n = 14), multiple myeloma (n = 8), breast cancer (n = 3), and medulloblastoma (n = 1). All patients who were mobilized were able to proceed to transplantation. Only one patient with lymphoma required a second mobilization; two patients with lymphoma also required a bone marrow harvest to obtain sufficient stem cells. The median dose of CD34+ cells infused was 3.8×10^6 cells/kg with a range of 0.6 to 20.0×10^6 CD34+ cells/kg. Myeloablative conditioning regimens were administered according to protocols available for the specific diagnoses. Fourteen patients with lymphoma received cyclophosphamide 1,500 mg/m²/d for 4 days (total dose, 6 g/m²), etoposide 200 to 225 mg/m² bid for 4 days (total dose, 1,600 to 1,800 mg/m²), and carmustine 300 mg/m² for 1 day (total dose, 300 mg/m²); eight patients with myeloma received melphalan 75 to 100 mg/m²/d for 2 days (total dose, 150 to 200 mg); and the three patients with breast cancer were treated with cyclophosphamide 1,500 mg/m²/d for 4 days (total dose, 6 g/m²), carboplatin 200 mg/m²/d for 4 days (total dose, 800 mg/m²), and thiotepa 125 mg/m²/d for 4 days (total dose, 500 mg/m²). The patient with medulloblastoma was conditioned with cyclophosphamide 1,500 mg/m²/d for 4 days (total dose, 6 g/m²) and melphalan 60 mg/m²/d for 2 days (total dose, 120 mg/m²). **For one patient (the medulloblastoma patient described in more detail in Bleeding Complications), the patient's family elected to "switch" to a blood-product approach.**

Engraftment of RBCs, Platelets, and Neutrophils

Table 2 outlines the engraftment parameters for this patient population. All patients (except for the patient who died on day +7) had evidence of neutrophil engraftment. The average days to neutrophil engraftment (defined as the first of three days of absolute neutrophil count > 500/ μ L) was 10 days. The range was 8 to 13 days. The average starting hemoglobin level was 12.5 g/dL (range, 7.0 to 14.2 g/dL). The median decrease in hemoglobin was 4.7 g/dL, with a range of 2.0 to 9.2 g/dL. The median number of days of hemoglobin less than 8 g/dL was 3.5 days. The median hemoglobin on day +30 post-transplantation was 9.2 g/dL.

All patients experienced thrombocytopenia; the median decrease in platelet count was 150×10^9 /L (range, 72 to 343×10^9 /L). The median number of days of platelets below 10×10^9 /L was 4 days (range, 0 to 12 days). The platelet count decreased to a median of 6×10^9 /L (range, 1 to 36×10^9 /L). The median days to platelet engraftment (defined as first day of platelets count > 20×10^9 /L) was 12 days (range, 0 to 21 days). The median platelet count on day +30 after transplant was 121×10^9 /L, with a range of 17 to 547×10^9 /L.

Bleeding Complications

Bleeding complications are outlined in Table 3. There was one death attributable to bleeding. This patient, a 22-year-old man with a brain medulloblastoma, died of CNS bleeding on day +7 after transplantation. The patient received a cell dose of 4.0×10^6 CD34+ cells/kg. The patient also had persistent disease, documented histologically at the time of evacuation of the intracranial hemorrhage. The patient's family elected to proceed with platelet transfusion for a platelet count of 2×10^9 /L at the time of intracranial bleeding. PT and PTT were normal. After this event, the protocol was amended to exclude patients with CNS malignancy. Another patient with lymphoma had gastrointestinal bleeding, requiring admission

to the intensive care unit. The patient received a cell dose of 8.2×10^6 CD34+ cells/kg. The patient's platelet count was $< 10 \times 10^9/L$ for 7 days, and was $1 \times 10^9/L$ on day +6 post-transplantation. The patient had epistaxis, hematochezia, and hememetesis while on aminocaproic acid and phytonadione. PT and PTT were normal, and there was no evidence of disseminated intravascular coagulation. The hemoglobin levels dropped to 2.5 g/dL on day +9 post-transplantation, at which time cryoprecipitate was given empirically with immediate cessation of bleeding. The patient's platelet count recovered to $20 \times 10^9/L$ on day +11 post-transplantation, and hemoglobin level recovered to 9.1 g/dL by day +30 post-transplantation.

There were three minor bleeding complications, which included hematuria and epistaxis. One patient had epistaxis requiring nasal packing, with a platelet count of $2,000 \times 10^9/L$. Subsequent epistaxis was treated with intranasal vasoconstriction and humidified air to avoid the need for nasal packing. Another patient, a 29-year-old woman with breast cancer, had mild epistaxis and hematuria during her nadir. No significant bleeding occurred in this study when the platelet count was greater than $5 \times 10^9/L$.

Transplant-Related Mortality

One patient, a 21-year-old woman with Hodgkin's disease, died on day +15 from complications of anemia after transplantation. The patient had profound anemia, with a hemoglobin of 2.0 g/dL accompanied by fever and neutropenia, nausea, mucositis, and electrolyte disturbances. She died of respiratory failure. This patient received transplantation in 1997, with a starting hemoglobin level of 7.0 g/dL. After this patient, the protocol was amended to delay the start of conditioning until the hemoglobin reached 11 to 12 g/dL. In addition, the medulloblastoma patient discussed previously died of an intracranial bleed with persistent disease. **After this patient, the protocol was amended to exclude patients with CNS malignancy.** Including this case, the transplant-related mortality was 8%.

Relapse Rate and Survival **{Note from Dad; these numbers aren't up to date}** With a median follow-up of 30 months, to date, 18 patients are living. The overall survival was 81% at 1 year and 72% at 2 years for all patients. Overall survival is demonstrated in Figure 1. Figure 2 displays the progression-free survival for all patients. Progression-free survival was 65% at 1 year and 57% at 2 years. Progression-free survival for myeloma patients was 75% at 2 years, and for lymphoma patients, 49% at 2 years.

Blood transfusions were first performed in the 17th century, but they did not become part of routine clinical practice until the **establishment of the first blood bank in 1934.**¹⁹ The routine use of transfusions advanced surgical practice, allowing the development of successful procedures, such as coronary artery bypass and total hip replacement.²⁰ **The outbreak of AIDS in the 1980s heightened the awareness of the risks of transfusions.**²¹ Newer concerns over Jacob-Creuzfeldt disease and West Nile virus have limited the number of eligible donors and further strained the available blood supply.²² Therefore, **several strategies have been developed for blood conservation.**

Erythropoietin was initially used for anemia associated with chronic renal failure.²³ **After high-dose chemotherapy and autologous stem-cell transplantation, anemia develops rapidly,** and erythropoietin levels rise.²⁴ Serum erythropoietin levels may be disproportionately low for the degree of anemia and may remain low for as long as 1 year in some patients.²⁵ ,²⁶ Transfusion requirements were reduced in 50 allogeneic patients were randomized to receive post-transplantation erythropoietin.²⁷

However, the results in autologous transplantation patients have been less impressive. A prospective study of 10 solid tumor patients receiving erythropoietin for 28 days post-transplantation showed no decrease in RBC transfusion requirement compared with historical controls.²⁸ Similar results have been reported in retrospective studies.^{29,30}

Since post-transplantation erythropoietin is not very effective in the autologous setting, a better strategy may be to administer erythropoietin before high-dose chemotherapy, as we have undertaken in this study. This same priming concept has been used successfully in Jehovah's Witness patients preparing for surgery.^{13,14}

The bone marrow and erythroid precursors may be more responsive, and the patient's hematocrit level would rise, coming into the peripheral blood stem-cell mobilization and collection phase of the treatment, thereby reducing the degree of anemia and the need for post-transplantation RBC transfusion. The administration of supplemental iron with erythropoietin is also important to maintain iron stores.³¹ A recent study showed a benefit to IV iron given with erythropoietin in patients with chemotherapy-induced anemia.¹⁶ Early in the study, it was appreciated that starting the conditioning when the hemoglobin was 11 g/dL or greater also allowed the patients to handle the 4- to 5-point hemoglobin loss safely. Allowing the hemoglobin to rise resulted in an average delay of 13 days from collection to start of conditioning; there was no disease recurrence during this period. This short delay seemed unlikely to impact the success of the transplantation. **Another approach used in our study was to minimize extra blood loss by reducing the amount of blood lost by phlebotomy.** Smoller and Kruskall³² have reported that intensive care unit patients had a mean volume of 41.5 mL of blood drawn for diagnostic testing each day. The total average blood loss was 762 mL. Patients with arterial lines averaged 944 mL of blood loss. Use of pediatric tubes can decrease blood loss by 45%.¹¹ The discard from the central venous catheter can be returned to the patient via a closed system.

Thrombocytopenia following high-dose chemotherapy is also a significant problem. Results with thrombopoietin-like growth factors have been disappointing. A randomized study showed no benefit to the use of pegylated recombinant human megakaryocyte growth and development factor.³³ The use of IL-11 post-transplantation or during mobilization has been controversial, but has been shown to improve thrombopoiesis in some studies.^{15,34,35} Bleeding may be compounded by clotting factor abnormalities induced by poor oral intake and multiple antibiotics. Prophylactic phytonadione was used in our study, to help replete phytonadione-dependent clotting factors.

The use of other agents that have been shown to decrease bleeding in the surgical setting were used in this bloodless transplant approach.

Aminocaproic acid is an antifibrinolytic agent that binds to plasminogen, thereby blocking the binding of plasminogen to fibrin and fibrin activation.³⁶ Aminocaproic acid has been used to reduce blood loss in cardiac surgery. Three randomized studies have shown a reduction in blood loss by 30% to 40%.³⁷⁻³⁹ Aminocaproic acid has been shown in uncontrolled studies to decrease mucosal bleeding in patients with thrombocytopenia.¹⁷ Desmopressin, an analog of arginine vasopressin, has also been used to control bleeding.³⁶ Desmopressin has been used extensively in patients with hemophilia A and von Willebrand's disease, but also in patients with acquired bleeding disorders. The mechanism of action may be formation of high concentrations of von Willebrand's factor and the appearance of ultra-large multimers of von Willebrand's factor, which increases platelet adhesion to the vascular subendothelium.¹⁸

A limitation of our study is that the protocols used at the Pennsylvania Hospital and University of Massachusetts Memorial Care were not identical. The protocol used at University of Massachusetts Memorial Care was developed later, based on the earlier work by Ford et al.⁴⁰ Minor adjustments were made for institutional preferences. The differences included the use of IL-11 for mobilization (instead of post-transplantation), and the use of G-CSF beginning on day +5 (as opposed to day +1) post-transplantation in Massachusetts. **In both institutions, in an effort to decrease toxicity, no specific chemotherapy priming was used for mobilization.**

There were two treatment-related deaths in this study, for a transplant-related mortality of 8%. This mortality rate is higher than the 2% to 4% transplant-related mortality rate described in recent studies of autologous stem-cell transplantations for lymphoma and multiple myeloma using blood-product support.^{41,42} Excluding patients with CNS disease and allowing the hemoglobin to rise to 11 g/dL may decrease toxicity in the bloodless patients, but the transplant procedure is still riskier in patients who refuse blood products. However, **traditionally, Jehovah's Witnesses and other patients who object to blood products were excluded from transplantation procedures; the techniques discussed here may allow these patients to receive a curative procedure.** Our data do not support the need for more stringent organ function eligibility requirements for transplant.

Our study did not compare the cost of the cytokines used in the bloodless patients with the cost of blood and platelet transfusions. However, our earlier work indicated a potential cost savings of \$6,000 (US \$) per patient, using the average transfusion requirements of four platelet transfusions and five RBC transfusions for a lymphoma autologous transplant patient in one of the participating institutions.⁴³ A more detailed cost comparison could be the subject of continued investigation. Jehovah's Witnesses represent approximately 0.5% to 1% of the population in the United States. **Jehovah's Witness patients were referred to Pennsylvania Hospital or University of Massachusetts Memorial Care Hospital because of their established Bloodless Medicine and Surgery programs. The success and safety of the bloodless approach in transplantation** can also be extended to other clinical settings for these patients, such as care of the leukemic patient and the surgical patient.^{44,45} To our knowledge, this report is the only large series to date on autologous transplantation for patients without blood products; there have been three separate case reports, and two of these patients are included in this series.^{40,43,46} Mazza et al recently reported on four patients who underwent autologous stem-cell transplantation without any blood-product support.⁴⁷ **The techniques used here in the autologous setting may also apply to Jehovah's Witness patients receiving nonmyeloablative allogeneic transplants. The nonmyeloablative approach is now used in patients who may not be candidates for traditional, ablative allogeneic transplant due to age or comorbid diseases.**⁴⁸ Fewer transfusions are administered in recipients of nonmyeloablative transplants, with a median number of 2 to 6 RBC transfusions and 0 to 6 platelet transfusions per patient, depending on the disease and conditioning regimen.^{49,50} A recent case report describes a successful nonmyeloablative transplant for a Jehovah's Witness without the use of any blood products.⁵¹

The value of the bloodless approach is that it may have broader implications for transfusion reductions in all transplant patients.

Recently, the use of erythropoietin, given between first and second transplants, for patients receiving tandem transplants for multiple myeloma, decreased the transfusion requirements during the second transplant.⁵² At Pennsylvania Hospital, **preliminary observations show that the number of transfusions after autologous stem-cell transplantation in non-Jehovah's Witness patients decreased from 7.2 to 1.5 RBC transfusions after the start of the bloodless program.** In addition, the techniques described here to decrease bleeding may be helpful to patients who are alloimmunized and do not respond well to platelet transfusion. In our experience in the current study, when using aminocaproic acid and phytonadione, there were no bleeding complications with platelet counts more than $5 \times 10^9/L$. Patients remained clinically stable even with hemoglobin levels as low as 7 g/dL. We may be able to eliminate the usual transfusion "triggers" and decrease transfusions with the use of routine blood conservation techniques and alternatives such as erythropoietin, iron, and amicar, and increase the safety of transplantation for all patients.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

NOTES

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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