Haematologica 1999; 84:1085-1087 original paper

Allogeneic bone marrow transplantation for secondary leukemia or myelodysplasia

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ABSTRACT

Background and Objectives. **Marrow transplantation results in disease-free survival for less than one-third of patients treated for secondary leukemia. The objective of this report is to review results following allogeneic marrow transplantation for treatment of secondary leukemia or myelodysplasia at a single tertiary referral center to determine the patient characteristics which lead to better survival and lower relapse.**

Design and Methods. **The medical records of 99 patients with secondary leukemia or myelodysplasia transplanted consecutively at the Fred Hutchinson Cancer Research Center between 1971 and 1997 were reviewed. Prior to development of secondary leukemia or myelodysplasia, the patients' original diagnoses were hematopoietic malignancies, solid tumors, aplastic anemia, or miscellaneous individual disorders previously treated by chemotherapy alone, radiation alone, chemoradiotherapy, or immunosuppressive therapy. At the time of transplantation, at each stage of myelodysplasia the numbers of patients were 52 with acute myelogenous leukemia (AML), 15 with refractory anemia with excess blasts in transition (RAEB-T), 18 with refractory anemia with excess blasts (RAEB), 11 with refractory anemia (RA), 1 with refractory anemia with ringed sideroblasts (RARS), and 2 with hypoplastic unclassifiable hematologic disorders. Sixty-five patients received marrow from an HLA identical or *partially* identical family member, and 34 received marrow from an HLA identical unrelated donor after conditioning with chemotherapy and total body irradiation or chemotherapy alone.**

Results. **The Kaplan-Meier probability of survival after transplantation for all patients was 13%, and by stage of disease was 33% for RA/RARS, 20% for RAEB, and 8% for RAEB-T/AML. The probability of relapse for all patients was 47%, was 34% for RAEB, and 58% for RAEB-T/AML. None of the patients with RA/RARS has relapsed. The overall probability of non-relapse mortality was 78%, divided equally among infection or organ failure-related causes of death.**

Interpretation and Conclusions. **The main impediments to long-term survival after transplantation for secondary leukemia or myelodysplasia are relapse and mortality from infections or organ failure. The survival is better when transplantation is done during the early stages of myelodysplasia because it is then associated with a lower relapse rate. These data suggest that patients at risk of secondary myelodysplasia should be followed prospectively to detect the early stages of myelodysplasia, and be considered for transplantation at that time.**

Key words: secondary leukemia, secondary myelodysplasia, allogeneic bone marrow transplantation

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The prognosis of secondary leukemia is poor. Only a minority of patients who are treated with chemotherapy achieve a remission, and fatal infections from prolonged aplasia are frequent.[1,2] Marrow or blood stem cell transplantation offers the possibility of cure but results in disease-free survival in less than one-third of patients.[3-5] The best timing for transplantation for patients with secondary leukemia is controversial.[6,7] Although transplantation after successful remission induction often results in improved long-term disease-free survival for patients with spontaneous acute leukemia, patients with secondary leukemia may not survive the induction therapy and may never be able to receive transplant therapy. On the other hand, transplantation in acute blastic leukemia is associated with a high relapse rate after marrow or blood stem cell transplantation. We previously reported no statistically significant difference in outcome between patients with secondary acute myeloid leukemia who were transplanted as initial therapy or following induction chemotherapy.[3] Here we review data from patients transplanted after a diagnosis of secondary myelodysplasia or acute leukemia with the aim of identifying patient characteristics which are associated with a better long-term disease-free survival after hematopoietic stem cell transplantation.

Design and Methods

We reviewed the records of 99 patients who were consecutively transplanted at the Fred Hutchinson Cancer Research Center with allogeneic marrow for secondary leukemia or myelodysplasia from December 1971 through to May 1997 with follow-up through to July of 1998. Patients were between 5.4

and 61 years old. The original diseases and the number of patients each who were treated before development of secondary leukemia or myelodysplasia were Hodgkin's disease 33, non-Hodgkin's lymphoma 12, breast cancer 7, acute lymphocytic leukemia 5, polycythemia vera 4, multiple myeloma 2, ovarian carcinoma 2, aplastic anemia 2 and other miscellaneous individual diagnoses 32. Treatment of the original disease consisted of chemotherapy alone in 34 patients, radiation alone in 9 patients, chemoradiotherapy in 46 patients, immunosuppressive therapy in 4 patients, and for 6 patients the treatment details were unknown. The secondary diseases present at the time of transplantation were acute myelogenous leukemia (AML) in 52 patients, refractory anemia with excess blasts in transition (RAEB-T) in 15 patients, refractory anemia with excess blasts (RAEB) in 18 patients, refractory anemia (RA) in 11 patients, and 1 patient each with refractory anemia with ringed sideroblasts (RARS), panhypoplasia, and an unclassified hematologic disorder. Marrow donors consisted of HLA A, B and D locus matched siblings for 51 patients, phenotypically matched family members for 2 patients, haploidentical family members for 8 patients, syngeneic donors for 4 patients, and HLA phenotypically identical or partially identical unrelated donors for 34 patients. Conditioning regimens for grafting consisted of chemoradiotherapy, usually including 120 mg/kg cyclophosphamide and 9.6-15.75 Gy total body irradiation for 32 patients, chemotherapy alone, usually busulfan 14-16 mg/kg with cyclophosphamide 120 mg/kg for 39 patients and miscellaneous chemoradiotherapy or chemotherapy regimens for 28 patients.

Results

All patients were engrafted. Grades II-IV acute graft-versus-host disease (GvHD) occurred in 53 patients. At 6.4 years the Kaplan-Meier (KM) probability of survival for all patients was 13%. Of 12 patients transplanted in the RA or RARS stage, 5 are alive between 0.8 and 7.1 years after transplantation. Of 18 patients transplanted in RAEB, 4 are alive between 1.2 and 11.2 years. Of 67 patients transplanted with RAEB-T or AML, 9 are alive between 0.9 and 8.4 years. The KM probability of survival by stage of disease at transplantation was 33% for patients with RA or RS, 20% for those with RAEB, and 8% for those with RAEB-T or AML (Figure 1).

At 3.1 years the probability of relapse for all patients reached a plateau at 47%. None of the 12 patients in the combined RA/RS group relapsed. Four of the 18 patients with RAEB relapsed , and 24 of the 67 patients with RAEB-T/AML relapsed. The KM probability of relapse was 58% for the RAEB-T/AML group, 34% for the RAEB group, and zero percent for the RA/RS group (Figure 2). Relapse led to death in 27 patients.

Infection caused 18 deaths and was disseminated aspergillus in 8 patients, candida septicemia in 3 patients, bacterial septicemia or pneumonia in 4 patients, cytomegalovirus interstitial pneumonia in 2 patients, and disseminated varicella in 1 patient.

Organ failure cuased 17 deaths and was due to hepatic veno-occlusive disease in 5 patients, multiple organ failure in 4 patients, idiopathic pneumonia or diffuse alveolar damage in 3 patients, respiratory failure syndrome in 4 patients, and cardiomyopathy in 1 patient. Four patients died of acute GvHD and 3 of chronic GvHD. Central nervous system hemorrhage resulted in the death of 4 patients. Secondary cancers led to the death of 2 patients, and 4 other patients died of unknown causes. The probability of non-relapse mortality for all 99 patients was 78%.

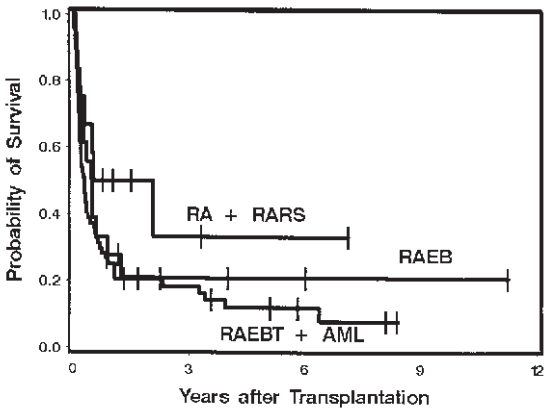

Figure 1. Kaplan-Meier probability of survival by stage of disease after transplantation. Tick marks indicate patients alive at last contact.

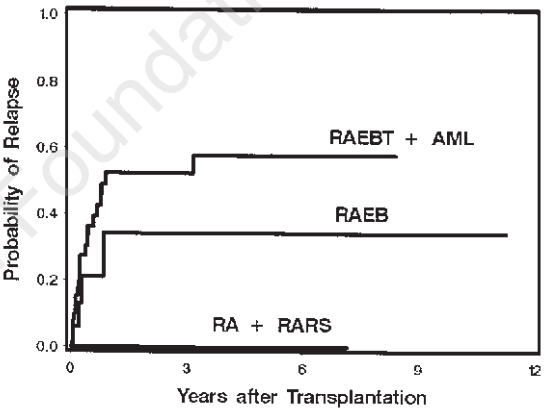

Figure 2. Kaplan-Meier probability of relapse by stage of disease at transplantation.

Discussion

These data show that while the probability of overall survival was 13%, and that of relapse 47%, patients transplanted during earlier stages of the evolution of

secondary myelodysplasia to leukemia had a better survival. Furthermore, none of the 12 patients transplanted at the RA or RARS stage relapsed during follow-up. Of 18 patients transplanted with RAEB, 4 relapsed and died, and 4 are alive between 1.2 and 11.2 years after their transplant. In contrast, for the 67 patients transplanted with RAEB-T or AML, 24 relapsed and died and only 9 are alive between 0.9 and 8.4 years later. These data suggest that patients with secondary myelodysplasia or leukemia should be considered for transplantation at the earliest stages of their disease.

Non-relapse mortality was a significant impediment to survival. For the entire group, the KM probability of death from infection was 27%. Of the 18 infection-related deaths, 10 occurred in patients who were transplanted when their disease had progressed to the RAEB-T or AML stage; 5 of the patients with RAEB died of infection, and 2 of the patients with RA or RARS died of infection. The probability of death from infection after transplantation in the RAEB-T or AML stage was 24%, in the RAEB stage 35%, and in the RA/RARS stage 24%. Perhaps this risk of infection is due to prolonged neutropenia before transplantation and inability to control opportunistic infection that later becomes manifest after transplantation. For the entire group the probability of death from organ failure was 24%. Of the 17 organ failure deaths, 14 occurred in patients who were transplanted in the RAEB-T or AML stage and resulted in a probability of organ failure related death, in this group, of 25%. No organ failure deaths occurred in patients transplanted with RAEB. Unfortunately, 3 organ failure deaths occurred in patients transplanted in the RA or RARS stage and resulted in a probability of organ failure related death of 45% in this group which had the best overall survival. The deaths from organ failure were not clearly related to the conditioning regimens of cyclophosphamide and total body irradiation, or chemotherapy conditioning regimen of busulfan and cyclophosphamide. Of the 4 patients who died of CNS hemorrhage, 3 were transplanted at the RAEB-T or AML stage. GVHD was not a major cause of non-relapse mortality. The risk of secondary cancer after transplantation in this group was similar to that in patients transplanted for a primary hematologic malignancy.

We conclude that impediments to a successful outcome of transplantation for secondary leukemia or myelodysplasia are mortality from relapse and non-relapse mortality from infection or organ failure. Innovative measures are needed to reduce the organ failure deaths. However, in spite of the significant treatment related-mortality, the disease-free survival was better when transplantation was done earlier in the evolution of the disease because it resulted in a lower relapse rate. Therefore patients who are at risk of developing secondary leukemia should be followed prospectively at intervals to identify the early development of myelodysplasia, and transplantation considered at that time.

Contributions and Acknowledgments

Both authors participated sufficiently in the manuscript entitled "Allogeneic Bone Marrow Transplantation for Secondary Leukemia or Myelodysplasia" to take public responsibility for its content. They reviewed the final version and agree with its contents. RPW, the first author, drafted the manuscript. The authors acknowledge the assistance of Gary Schoch, Clinical Computing Section, Clinical Research Division of the Fred Hutchinson Cancer Research Center for generation of the Kaplan-Meier probability plots.

Funding

Supported in part by HL36444 of the National Heart, Lung and Blood Institute, CA18029 and N01-CP51027 of the National Cancer Institute of the National Institutes of Health, Bethesda, MD, USA and the Gabriella Rich Foundation.

Disclosures

Conflict of interest: none

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received March 31, 1999; accepted August 31, 1999.

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