Marrow Transplantation for Patients in Accelerated Phase of Chronic Myeloid Leukemia


The records were reviewed of 58 patients receiving transplants in Seattle with unmanipulated marrow from HLA-identical siblings during the accelerated phase (AP) of chronic myeloid leukemia. Variables examined for association with survival and relapse included the interval from diagnosis to transplant, the reasons for categorization as AP, age, regimen, and cytomegalovirus serology. Four patients relapsed. The 4-year probabilities of survival, relapse-free survival, nonrelapse mortality, and relapse were 0.49, 0.43, 0.51, and 0.12, respectively. After completion of the stepwise multivariate analysis, age less than 38 years and categorization as AP solely on the basis of chromosomal abnormalities emerged as being independently significantly associated with improved survival. The 4-year probability of survival for the 16 patients categorized as AP because of chromosomal abnormalities and receiving transplant less than 1 year from diagnosis was 0.74. The low probability of relapse in these patients suggests that more aggressive preparative regimens are not indicated for patients receiving transplants in AP because of the increased risk of transplant-related mortality.

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MATERIALS AND METHODS

Patient accrual and categorization. From January 1986 through December 1992, 58 patients with Ph-positive CML in AP received transplants of unmodified marrow from genotypically HLA-identical siblings.

The diagnosis of AP was made before transplant after complete review of the pretransplant data. At least one of the following findings was required for categorization as AP: (1) the persistent presence of 10% to 30% myeloblasts in marrow or peripheral blood; (2) major perturbations of white blood cell (WBC) count (>50 × 10^9/L), platelet count (<100 or >1,000 × 10^9/L), and hematocrit (<0.25 uncontrolled by therapy with busulfan (BU), hydroxyurea (HU), or interferon (IFN); (3) progressive splenomegaly; (4) extramedullary tumor; (5) the presence of any nonconstitutional cytogenetic abnormality in addition to a single Ph chromosome; and (6) persistent unexplained fever or bone pain.

The reasons for categorization as AP were aberrations in WBC or platelet count for 24 patients, splenomegaly for 4, chloroma for 2, and bone pain for 1. The other 27 patients were classified as AP solely because of chromosomal abnormalities in addition to a single Ph chromosome demonstrated before transplantation. There was no earlier cytogenetic information available for 9 of these patients, but earlier studies were available for 18 patients and the abnormalities were newly detected in 8 of these. Among these, 16 patients had abnormalities such as an additional Ph chromosome, an extra chromosome 8, and/or the occurrence of i(17q) (major route secondary clonal abnormalities) generally accepted as indicative of acceleration.

Eleven patients were categorized as AP on the basis of chromosomal abnormalities other than these pathways, and each of these patients had different abnormalities. In 1 patient, the abnormality involved chromosome 14 and in another patient it involved chromosome 7. These 2 chromosomes have been reported occasionally in patients in lymphoid blast crisis; none of the other abnormalities not "major route clonal" in nature has been prominent in reports of patients with CML.

Twelve of the 31 patients categorized as AP for reasons additional to, or other than, cytogenetic abnormalities also had such abnormalities. Of the 19 patients with standard CP cytogenetics, 17 had at least 20 metaphases evaluated, 1 had 13 metaphases evaluated, and 1 had 11 metaphases evaluated.

Treatment regimen. The treatment regimen was determined by the protocol in effect at the time of transplant. None of the protocols involved randomization for the antileukemic component of the regimens (ie, the conditioning regimen), but for some patients the type

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of prophylaxis of acute graft-versus-host disease (GVHD) was determined by random allocation as part of a study protocol. Table 1 describes the number of patients prepared for transplantation with each conditioning regimen and prophylactic regimen against acute GVHD. Cyclophosphamide (CY) was administered intravenously on each of 2 successive days, with each dose either 60 mg/kg (regimens 1 through 4) or 25 mg/kg (regimen 5). Busulfan (BU) was administered orally 4 times daily on each of 4 successive days, with each dose either 1.0 mg/kg (regimen 4; total dose, 16 mg/kg) or 0.44 mg/kg (regimen 5; total dose, 7 mg/kg). Total body irradiation (TBI) was administered from dual 60Co sources at an exposure rate of 6 to 7 cGy per minute. The TBI exposure was either 1.2 Gy 3 times daily for a total of 11 fractions (regimen 1) or 2.0 Gy on each of 6 successive days (regimens 2 and 5) or 2.25 Gy on each of 7 successive days (regimen 3). Marrow was infused on the day after completion of this regimen (day 0), except in regimen 4, in which the marrow was infused 24 to 36 hours after the last dose of CY.

All patients received cyclosporine (CSP) as part of the GVHD prophylactic regimen. CSP administration started on the day before marrow infusion (day −1) with a dose of 3.0 mg/kg/day intravenously in 2 doses of 1.5 mg/kg each, infused over a period of 4 hours. Oral administration at a dose of 12.5 mg/kg/d replaced the intravenous route as soon as the patient could tolerate drugs orally.

After day 50, the dose of CSP was reduced by 5% per week and the drug was discontinued at approximately 6 months after transplant.13,14 Most patients also received intravenous methotrexate at 15 mg/m² administered on day 1 and at 10 mg/m² on days 3, 6, and 11 after transplant.13,14 Six patients on regimens 4 and 5 were randomized instead to receive a combination of CSP plus methylprednisolone (MP) at 0.25 mg/kg twice daily from day 7 to day 14, at 0.5 mg/kg twice daily on days 15 to 28, and then tapered to extinction on day 180. Acute GVHD was treated with prednisone, antithymocyte globulin, or monoclonal antibodies.13,16 Chronic GVHD was treated with prednisone alone or in combination with CSP.13,18

Histocompatibility testing. Typing for class I HLA-A, B, and C and class II HLA-DR and DQ antigens was by standard serologic methods supplemented by isoelectric focusing and molecular typing by sequence-specific oligonucleotide probe (SSOP)/polymerase chain reaction (PCR) techniques.18 Typing for DR was originally supplemented by using HLA homozygous typing cells in a modified mixed leukocyte culture assay or by typing with T-cell clones.20,21

Cytokines. As part of ongoing phase 1 and II studies, 2 patients received recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) posttransplant at a dose of 250 µg/m² daily from day 0 until either day 20 or day 27 posttransplant22 and 4 received recombinant granulocyte colony-stimulating factor (G-CSF) during the first 21 days after transplant.

Spleen size. Spleen size was evaluated on the day of diagnosis and on the day of transplant. Spleen status was characterized by palpation and history as unknown, splenectomized, not palpable, enlargement of unknown degree, slight splenomegaly (enlarged 4 cm or less), moderate splenomegaly (enlarged 4 to 8 cm), or massive splenomegaly (enlarged more than 8 cm).

Causes of death. Patients who died after posttransplant relapse were categorized as dying of leukemia irrespective of the proximate cause. Deaths of patients who had not relapsed were categorized as nonrelapse mortality. Infection was listed as the cause of death when a bacterial, viral, or fungal infection other than interstitial pneumonia (IP) was the proximate cause of death in patients who had not relapsed. Deaths caused by IP formed a separate category. Infections were further categorized as associated with or not associated with a history of acute or chronic GVHD.

Informed consent. Risks of the transplant procedure were explained fully by the transplant team to patients and relatives. Informed consent was obtained using forms and procedures approved by the institutional review board of the Fred Hutchinson Cancer Research Center.

Statistics. Events were recorded through February 1994. Table 2 describes patient and disease characteristics at the time of diagnosis and transplant-related variables. Relapse was defined as the posttransplant detection of Ph-positive metaphases in marrow.

Survival was measured from transplant to death censored by end of follow-up. relapse was measured from transplant to relapse censored by death or end of follow-up, event-free survival was measured from transplant to relapse or death censored by end of follow-up. and nonrelapse mortality was measured from transplant to death censored by relapse or the end of follow-up. The distributions of survival duration were estimated by the method of Kaplan and Meier23,24 and levels of statistical significance for differences between these curves were calculated by the Mantel-Cox statistic.25 Multivariate analysis was performed using the Cox proportional hazards model with stepwise regression. The analysis was performed in three layers. The first layer examined the influence of the pretransplant patient and disease characteristics. These characteristics were phase subcategorization (reasons for classification as is AP), patient and donor gender and cytomegalovirus (CMV) serology, patient age, spleen status at diagnosis and at the time of transplant, peripheral blood WBC count at the time of diagnosis, previous chemotherapy, and the interval from diagnosis to transplant, peripheral blood WBC count at the time of diagnosis, previous chemotherapy, and the interval from diagnosis to transplant, peripheral blood WBC count at the time of diagnosis, previous chemotherapy, and the interval from diagnosis to transplant.

Table 1. Conditioning Regimens

<table>
<thead>
<tr>
<th>Conditioning Regimen</th>
<th>Methotrexate</th>
<th>Cyclosporine</th>
<th>Cyclosporine Prednisone</th>
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<tbody>
<tr>
<td>1. Cyclophosphamide 60 mg/kg × 2</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>TBI 1.2 Gy × 11</td>
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<tr>
<td>2. Cyclophosphamide 60 mg/kg × 2</td>
<td>6</td>
<td>0</td>
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<tr>
<td>TBI 2.8 Gy × 6</td>
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<tr>
<td>3. Cyclophosphamide 60 mg/kg × 2</td>
<td>8</td>
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<tr>
<td>TBI 2.25 Gy × 7</td>
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<tr>
<td>4. Busulfan 1 mg/kg × 16</td>
<td>5</td>
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<tr>
<td>Cyclophosphamide 60 mg/kg × 2</td>
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<tr>
<td>5. Busulfan 0.44 mg/kg × 16</td>
<td>32</td>
<td>5</td>
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<tr>
<td>Cyclophosphamide 25 mg/kg × 2</td>
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<tr>
<td>TBI 2.0 Gy × 6</td>
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</table>

Results

Relationship between variables. There was an association between the interval from diagnosis to transplant and categorization as AP solely on the basis of cytogenetic abnormalities. Thus, 16 of 26 patients receiving transplants less than 1 year after diagnosis were categorized as AP because of chromosomal abnormalities, whereas this was true of 11 of 32 patients receiving transplants after an interval of more than 1 year (P = .04).
Table 2. Disease Characteristics and Transplant-Related Variables

<table>
<thead>
<tr>
<th>Gender (patient/donor)</th>
<th>No. of patients and donors:</th>
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<tr>
<td></td>
<td>Male/male*</td>
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<td>Male/female*</td>
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<td>Female/male*</td>
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<td>Female/female*</td>
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<td></td>
<td>Patient age</td>
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<td>Range (yr)</td>
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<td>Median (yr)*</td>
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<td></td>
<td>Over 50 yr of age (no. of patients)*</td>
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<td></td>
<td>CMV Serology</td>
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<tr>
<td></td>
<td>No. of positive patients*</td>
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<td>No. of negative patients with negative donors*</td>
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<td>Unknown</td>
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<td></td>
<td>Not palpable*</td>
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<td>Splenectomized</td>
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<td>Enlarged*</td>
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<td>Massive*</td>
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<td>Spleen size at diagnosis (no. of patients)</td>
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<td>Not palpable*</td>
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<td>Splenectomized</td>
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<td>Enlarged*</td>
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<td>Spleen size at transplant (no. of patients)</td>
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<td>Not palpable*</td>
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<td>Splenectomized</td>
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<td>Enlarged*</td>
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<td>Massive*</td>
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<td>Interval diagnosis to transplant</td>
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<td>Range (d)</td>
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<td>Median (d)</td>
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<td>Less than 1 yr (no. of patients)*</td>
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<td>1-3 yr (no. of patients)*</td>
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<td>More than 3 yr (no. of patients)*</td>
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<td>Transplanted within LAF isolation*</td>
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<td>Marrow cell dose (x10^8/kg)</td>
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<td>Range</td>
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<td>Median*</td>
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<td>Reason categorized as accelerated (no. of patients)</td>
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<td>WBC or platelet counts*</td>
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<td>Cytochromatics*</td>
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<td></td>
<td>Other*</td>
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<td>Previous therapy (no. of patients)</td>
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<td></td>
<td>Hydroxyurea</td>
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<td></td>
<td>Busulfan</td>
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<td></td>
<td>IFN</td>
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<td>Hydroxyurea alone*</td>
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<td></td>
<td>Busulfan alone</td>
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<td></td>
<td>IFN alone</td>
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<td></td>
<td>Peripheral WBC count at diagnosis (x10^9/L)</td>
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<td></td>
<td>Range</td>
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<td></td>
<td>Median*</td>
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</tbody>
</table>

* Categories used in the multivariate analysis.

Engraftment. Two patients died without signs of engraftment on day 28 with systemic candidiasis and on day 34 of venocclusive disease (VOD) of the liver. All other patients achieved successful and enduring engraftment.

Survival. The 4-year probabilities of survival and event-free survival for the entire group of patients was 0.49 and 0.43, respectively; the 4-year actuarial probability of relapse censoring for other causes of death was 0.12 (Fig 1). The 4-year actuarial probability of death censoring for relapse was 0.51. The 4-year probability of survival for patients aged 37 years or less was 0.66, compared with 0.30 for older patients (Fig 2, P = .01). The 4-year probability of survival for patients categorized as in AP because of factors other than cytogenetic abnormalities was 0.34, compared with 0.66 for patients whose only reason for categorization as AP was the presence of cytogenetic abnormalities other than a single Ph chromosome in marrow metaphases (Fig 3, P < .001). Six of 16 patients categorized as in AP because of major route secondary clonal abnormalities died, compared with 3 of 11 patients with other chromosomal abnormalities. The 4-year probability of survival for patients receiving transplants in AP less than 1 year from diagnosis of CML was 0.61, compared with 0.39 for patients who had delayed transplantation for more than 1 year (Fig 4, P = .03). The 4-year...
probability of survival for the 16 patients categorized as AP because of chromosomal abnormalities and receiving a transplant less than 1 year from diagnosis was 0.74.

In the multivariate analysis, the interval from diagnosis to transplant, age in years as a continuous variable, age 37 years or less at the time of transplant, and categorization as AP by cytogenetic abnormalities were the only significant variables in the univariate analysis. During the stepwise analysis, the interval from diagnosis to transplant and age as a continuous variable ceased to be significant when the variable representing categorization as AP by cytogenetic abnormalities was entered.

Table 3. Influence of Pretransplant Characteristics on Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>Relative Risk</th>
<th>Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 37 years or less</td>
<td>.04</td>
<td>0.34</td>
<td>0.15-0.78</td>
</tr>
<tr>
<td>Classified as AP because of</td>
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<td></td>
<td></td>
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<tr>
<td>cytogenetics only</td>
<td>.004</td>
<td>0.38</td>
<td>0.17-0.84</td>
</tr>
<tr>
<td>Major route</td>
<td>.04</td>
<td>0.38</td>
<td>0.15-0.94</td>
</tr>
<tr>
<td>Others</td>
<td>.02</td>
<td>0.24</td>
<td>0.07-0.82</td>
</tr>
</tbody>
</table>

After completion of the stepwise multivariate analysis, patient and donor gender and CMV serology, age as a continuous variable, age greater than 50 years, spleen status at diagnosis and at the time of transplant, peripheral blood WBC count at the time of diagnosis, previous chemotherapy, the interval from diagnosis to transplant, regimen, and acute or chronic GVHD were not significantly independently associated with survival or nonrelapse mortality. Age 37 years or less at the time of transplant and classification as AP solely on the basis of cytogenetic abnormalities emerged as factors independently significantly associated with improved survival and reduced nonrelapse mortality. The probabilities, relative risks, and confidence levels for the instantaneous relative risks are described in Table 3. Sample size considerations undermined confident assessment of the relative influence of different chromosomal abnormalities.

Relapse. Four patients relapsed after transplantation on days 69, 185, 427, and 695, respectively. One of these patients had been conditioned for transplantation with regimen 3 and 3 had been conditioned with regimen 5 (Table 1). Two of these patients had been categorized as in AP because of unresponsive high WBC count, 1 because of additional chromosomal abnormalities, and 1 because of progressive splenomegaly. Three of the relapsed patients had received pretransplant treatment with HU and 1 had received pretransplant treatment with BU.

One patient died from the complications of CMV pneumonia on day 185 and had Ph-positive metaphases in the marrow at autopsy. This patient has been considered to be in relapse for the purpose of determining the probability of relapse and as dying of CMV pneumonia in Table 4. One patient relapsed hematologically on day 427 posttransplant and received a second transplant from the same donor 21
days later. This patient again relapsed hematologically 665 days after the second transplant, received IFN without response, and died nearly 5 years after the first transplant. The other 2 patients relapsed on days 69 (cytogenetically) and 695 (hematologically) have failed to respond to IFN therapy and survive in clinical relapse at 5.5 and 3.2 years after transplantation.

Causes of death. Twenty-nine patients died from causes other than relapse. Thirteen deaths occurred during the first 100 days after transplant (5 VOD, 3 adult respiratory distress syndrome [ARDS], 2 CMV pneumonia, 3 infection). Sixteen patients (4 of whom had chronic GVHD) died between day 100 and day 666 from causes other than relapse. Four of these deaths were from CMV pneumonia (on days 108, 127, 185, and 216), 6 were from other forms of respiratory disease, 5 were from infection (2 fungal and 3 bacterial), and 1 patient died of traumatic hemorrhage. Table 4 lists the causes of death and their association with a history of GVHD.

DISCUSSION

In the previous Seattle report of transplantation in AP, splenomegaly at diagnosis was associated in multivariate analysis with an increased mortality from causes other than relapse. This effect was mainly caused by infections other than interstitial pneumonia. In the current study, this relationship could not be shown and the reasons for this discrepancy could not be determined.

The AP of CML is transitional between CP and BP, and the category is less well-defined than either of the other phases. Some characteristics used to define the phase, such as the proportion of blasts and promyelocytes in marrow and peripheral blood, can be evaluated readily, whereas others, such as bone pain, fever, and response to chemotherapy, are defined less objectively. There is no firm agreement on the cytogenetic characteristics that indicate a worse prognosis for a patient otherwise in CP. Certain chromosomal abnormalities generally have been accepted as “major route clonal abnormalities” specifically associated with a worsening prognosis when patients are treated with conventional (not transplant) therapy. The Seattle group has accepted the presence of any chromosomal abnormalities additional to a single Ph chromosome as an indication of AP. In the present study, there was no significant difference in survival between patients with major route clonal abnormalities and those with other chromosomal abnormalities, but the number of patients involved is very small. The paucity of the data did not permit useful statistical evaluation of the influence of newly acquired cytogenetic abnormalities, which would need to take into account the time frame over which these developments occurred or were recognized.

All the characteristics that are used to define AP have been shown to be prognostic for the survival of patients receiving conventional therapy. Studies of factors predictive of outcome of transplantation have identified phase as the most influential disease-related variable and have shown that survival is worse for patients receiving transplants in AP than for those receiving transplants during CP, with increased probabilities of relapse and of nonrelapse death. However, the indicators used to categorize patients as being in AP have not been examined for their isolated influence on the outcome of transplantation. The multivariate analysis performed in this study showed that categorization as AP solely because of the presence of chromosomal abnormalities was associated with a significantly better survival than other indicators of acceleration. This finding does not prove that chromosomal abnormalities are irrelevant to the outcome of transplantation. To examine this question would require demonstration that patients otherwise in CP did not have a worse probability of survival when chromosomal abnormalities were present.

Results in the previous Seattle report were heavily influenced by the use of T-cell depletion, which was associated with a very high probability of relapse. Subsequent regimens did not involve T-cell depletion and were directed at the premise that relapse risk was higher in AP than in CP. With overall 4-year probabilities of survival and relapse of 0.49 and 0.12, the use of these regimens has been accompanied by a marked reduction in relapse and improvement in survival. However, it is not clear that the probability of relapse after transplantation is intrinsically higher for patients treated during AP than for those transplanted in CP. Biggs et al. reported a series of 26 patients receiving transplants in AP with the regimen described as regimen 4 in Table 1. The 4-year probabilities of survival and relapse were 0.41 and 0.12. Regimens 2 and 4 in the present study are those currently used in Seattle for patients receiving transplants in CP, and none of the 11 AP patients who received these regimens relapsed. Unfortunately 6 of these patients died from causes other than relapse during the first 3 months after transplantation. However, the low probability of relapse described in these patients indicates that more aggressive preparative regimens should not be used in view of the risk of increasing the incidence of nonrelapse mortality. Furthermore, relapse can now be treated with IFN or with infusions of donor lymphocytes. Antiviral agents are now available to prevent CMV disease, and this should produce an improvement in survival for patients receiving transplants in AP CML.

Currently in Seattle, patients in AP receive transplants with the same regimen used for patients receiving transplants in CP (regimen 4). This should permit an assessment of any associations between chromosomal abnormalities or of phase categorization as AP and survival after transplantation.

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