Allogeneic Stem Cell Transplantation for Philadelphia Chromosome–Positive Acute Myeloid Leukemia

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Abstract
Philadelphia chromosome–positive acute myeloid leukemia (Ph+–AML) has a poor response to anthracycline- and cytarabine-containing regimens, high relapse rate, and dismal prognosis. Although therapy with imatinib and allogeneic stem cell transplantation (allo-SCT) is promising, relatively short follow-up limits understanding of long-term results of these therapies. This report describes the outcomes of 3 cases of Ph+–AML diagnosed and transplanted at the University of Nebraska Medical Center between 2004 and 2011. These patients, young and without major comorbidities, received induction therapy with 7 days of cytarabine and 3 days of idarubicin along with imatinib and consolidation therapy with high-dose cytarabine (with or without imatinib). All patients underwent 10/10 HLA-matched peripheral blood allo-SCT (sibling donor for first and third patients and unrelated donor for the second patient); all had acute graft-versus-host disease (GVHD), and the first and third patients had chronic GVHD. All patients are currently alive and experiencing complete remission at 116, 113, and 28 months after diagnosis, respectively. This report shows that the use of allo-SCT with resultant graft-versus-leukemia effect and the addition of imatinib can result in long-term remission and possible cure in some patients with Ph+–AML. (J Natl Compr Canc Netw 2014;12:963–968)

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Learning Objectives
Upon completion of this activity, participants will be able to:

• Discuss the rationale for the use of imatinib in the treatment of patients with Ph+–AML
• Identify the evidence supporting clinicopathologic distinction between Ph+–AML and chronic blast phase CML
• Discuss the role of SCT in the treatment of Ph+–AML

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Philadelphia chromosome–positive acute myeloid leukemia (Ph⁺-AML) is rare, accounting for approximately 1% of all cases of AML. Whether Ph⁺-AML is distinct from the blast phase of chronic myeloid leukemia (CML) was controversial until recently. A 2013 study showed that NPM1 mutations are seen exclusively in Ph⁺-AMLs (22%; n=9) whereas ABL1 mutations are exclusive to the blast phase of CML (20%; n=5), suggesting that Ph⁺-AML is distinct from blast phase CML. These mutational analyses can be helpful in clinical practice or research trials to distinguish between the entities. Clinical characteristics might also be helpful in making the distinction, including no history of CML or myeloproliferative disorder, no evidence of chronic or accelerated phases of CML after induction therapy, and no characteristics of CML, such as splenomegaly and basophilia. In addition, compared with the blast phase of CML, Ph⁺-AML is associated with very high leukocytosis, the p210 BCR-ABL protein (vs p190 BCR-ABL protein), and the coexistence of normal metaphases in addition to Ph⁺ metaphases. The presence of dwarf megakaryocytes in bone marrow; additional cytogenetic aberrations, such as an extra copy of Ph chromosome, trisomies 8 and 19, and isochromosome 17q; and the persistence of t(9;22) after induction therapy are more common in the blast phase of CML than in Ph⁺-AML. None of these features, however, are diagnostic of blast-phase CML or Ph⁺-AML.

The presence of the Ph chromosome in acute lymphoblastic leukemia is a poor prognostic factor leading to the recommendation of allogeneic stem cell transplantation (allo-SCT) whenever possible, but its prognostic significance and the optimal treatment of Ph⁺-AML are not clear. With the current treatment options, the outcome is dismal (with a median overall survival of 9 months in one study). Although several therapy options are promising, including imatinib and allo-SCT, relatively short follow-up limits understanding of long-term results of these therapies. This report describes the outcomes of 3 cases of Ph⁺-AML diagnosed and transplanted at the University of Nebraska Medical Center between 2004 and 2011. Despite the lack of consensus on accurate case definition, the lack of prior history of CML or myeloproliferative disorder, and the absence of the evidence of chronic or accelerated phases of CML after induction therapy seem to be the most important diagnostic criteria for Ph⁺-AML and were used for case definition in this and other reports. All patients reported had palpable spleens and absolute basophilia. Although strict case definition of Ph⁺-AML for research purposes may exclude patients with splenomegaly or basophilia, approximately one-quarter of patients with Ph⁺-AML are reported to have either splenomegaly or basophilia.

Case Report

The details of each patient are described in Tables 1 and 2. All patients, young and without comorbidities, presented with acute to subacute symptoms. The third patient had a history of stage IB right breast cancer diagnosed 3 years before presentation, which was treated with mastectomy, sentinel lymph node dissection, and adjuvant cyclophosphamide and doxorubicin (4 cycles); the patient subsequently underwent maintenance therapy with oral tamoxifen. All 3 patients had splenomegaly. The WBC count at presentation was 143,000/µL (66% blasts; 5% basophils) in the first patient (Figure 1); 159,000/µL (36% blasts; 0%–2% basophils) in the second patient; and 96,900/µL (12% blasts; 1% basophils) in the third patient. Bone marrow aspirate and biopsy revealed increased myeloblasts (>20%) in all patients; additionally the first patient had increased basophils (Figure 2). Immunophenotyping confirmed myeloid lineage and ruled out biphenotypic acute leukemia. Conventional cytogenetics and fluorescence in situ hybridization (FISH) studies detected a t(9;22)(q34;q11.2), consistent with the Ph chromosome, in the first and the second patients (Figure 3A). In addition, studies detected a subclone further characterized by a t(14;17)(q32;q24) in the first patient, which was confirmed by FISH to include disruption of the IGH locus at 14q32 (Figure 3B). FISH showed the presence of BCR-ABL in 17 of 17 cells in the third patient; however, a lack of mitotic cells prohibited conventional cytogenetic analysis. All of the patients received induction therapy with 7 days of cytarabine and 3 days of idarubicin along with imatinib, and consolidation therapy with high-dose cytarabine (± imatinib). The first and the third patients did not receive imatinib during consolidation because of grade 3 hepatotoxicity and grade 3 diarrhea, respectively. The cytogenetic abnormalities had resolved at the time of allo-SCT in the first and the third patients, but persisted in
Table 1 Characteristics of the Patients With Philadelphia Chromosome–Positive Acute Myeloid Leukemia Who Underwent SCT

<table>
<thead>
<tr>
<th>Age (y)/Sex</th>
<th>19/M</th>
<th>22/M</th>
<th>46/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral WBCs/blasts</td>
<td>143,000/mcL; 66% blasts</td>
<td>159,000/mcL; 36% blasts</td>
<td>96,900/mcL; 12% blasts</td>
</tr>
<tr>
<td>Immunophenotype of blasts</td>
<td>Myeloid (positive: dim CD45, dim CD7, CD13, and bright CD 34)</td>
<td>Myeloid (positive: dim CD45, HLA-DR, dim CD7, dim and partial CD11c, CD13, CD33, and CD 34)</td>
<td>Myeloid (positive: CD45, dim CD7, CD11b, CD13, partial CD34, and CD117)</td>
</tr>
<tr>
<td>Cytogenetics at diagnosis</td>
<td>46,XY,t(9;22)(q34;q11.2) [16]/46, idem,t(14;17)(q32;q24)[4]</td>
<td>46,XY,t(9;22)(q34;q11.2)[20]</td>
<td>See footnote a</td>
</tr>
<tr>
<td>Induction</td>
<td>7 + 3 + imatinib</td>
<td>7 + 3 + imatinib</td>
<td>7 + 3 + imatinib</td>
</tr>
<tr>
<td>Consolidation chemotherapy</td>
<td>1 cycle HDAC</td>
<td>3 cycles HDAC + imatinib</td>
<td>1 cycle HDAC</td>
</tr>
<tr>
<td>Type/timing of SCT</td>
<td>MRD; 3 mo in CR1</td>
<td>MRD; 9 mo in morphologic but not cytogenetic remission</td>
<td>MRD; 4 mo in CR1</td>
</tr>
<tr>
<td>OS</td>
<td>116 mo</td>
<td>113 mo</td>
<td>28 mo</td>
</tr>
</tbody>
</table>

Abbreviations: CR1, first complete remission; F, female; HDAC, high-dose cytarabine; M, male; MRD, matched related donor; MUD, matched unrelated donor; OS, overall survival from the time of diagnosis; SCT, stem cell transplantation; WBC, white blood cell.

*Timing of SCT is calculated from the time of diagnosis.
*7-day cytarabine and 3-day idarubicin.
*For all patients, antigen matching was 10/10.
*All patients are currently alive and experiencing complete remission.

Discussion

The t(9;22)(q34;q11.2) translocation, which results in the Ph chromosome, can occur in AML as a de novo chromosomal aberration with or without additional abnormalities or as a therapy-related event. In the present report, the first and the second patients had de novo chromosomal aberrations, whereas the third patient had therapy-related Ph+-AML. The occurrence of the Ph chromosome in AML with core-binding factor leukemia or with certain genetic aberrations, such as NPM1 mutations, may indicate a role as a cooperating mutation that enhances cell proliferation (class I mutation). Ph+-AMls display varying degrees of maturation, are classifiable into different French-American-British types, frequently express lymphoid markers, and demonstrate clonal rearrangement of the immunoglobulin or T-cell receptor genes.

The few publications available on the treatment and outcome of patients with Ph+-AML suggest a poor response to anthracycline- and cytarabine-containing regimens, high relapse rate, and dismal outcomes.
Although a transient response with imatinib alone (n=2) and with chemotherapy (n=5) have been reported,1 several case reports have shown good responses to imatinib as a first-line therapy (initial dose, 400 mg/d)12 and as a salvage therapy after chemotherapy failure (initial dose, 600 mg/d).13,14 Use of imatinib for postremission maintenance therapy after induction chemotherapy has resulted in complete remissions lasting for 10 to 19 months.15,16 In one instance, combination leukemia-type chemotherapy and imatinib after failure of induction therapy with single-agent imatinib resulted in a complete cytogenetic response. Consolidation chemotherapy and imatinib followed by postremission imatinib led to a complete molecular response, which continued 15 months from diagnosis.17 Taken together, these results indicate that imatinib can play a valuable role in postremission therapy, even when Ph⁺-AML is resistant to first-line single-agent imatinib.

Ph⁺-AML with additional abnormalities, rather than Ph⁺-AML alone, may behave differently. Ph⁺-
AML with monosomy 7 is considered to be a worse risk and is associated with poor response to therapy and short duration of remission. Conversely, the presence of favorable-risk cytogenetics may be associated with better outcomes. Two cases of Ph+–AML in association with inv(16) had excellent outcomes with chemotherapy (alive in remission 3 years after diagnosis) and allo-SCT (alive in complete remission 18 months post-SCT), respectively. Similarly, allo-SCT and chemotherapy with or without imatinib resulted in complete remission at 22 and 70 months after diagnosis in 2 patients with Ph+–AML with t(8;21). A patient with acute promyelocytic leukemia with a Ph chromosome experienced complete remission with all-trans retinoic acid and chemotherapy for 4 years from diagnosis. Additionally, the presence of a Ph chromosome in patients with otherwise good-risk AML may indicate a poor prognosis.

Only a few instances of allo-SCT have been reported in Ph+–AML. In one study, allo-SCT (n=7) resulted in a median overall survival of 12 months (patients’ characteristics are not available). In another study, 4 men (age, 18–44 years) were treated with AML-type induction chemotherapy, with further augmentation chemotherapy in 3 patients, followed by imatinib and consolidation chemotherapy. Two patients experienced molecular remission, whereas the other 2 experienced complete hematologic remission. Subsequently, these patients received a cyclophosphamide (120 mg/kg) and total body irradiation (1320 cGy) preparative regimen, and sibling (n=2) or unrelated (n=2) peripheral (n=1) or bone marrow (n=3) allo-SCT. Two patients had acute GVHD and 3 had chronic GVHD, whereas 1 did not have either acute or chronic GVHD. At 6 to 24 months’ follow-up, all of the patients were alive in molecular remission; however, the long-term outcome was not reported.

The present report shows that allo-SCT can result in long-term remission and possible cure in some patients with Ph+–AML. The second patient had experienced morphologic complete remission but not cytogenetic remission at the time of allo-SCT, thus suggesting that allo-SCT can achieve cure even in such a setting. In addition to the overall advancement in the techniques of allo-SCT and supportive care, the young age, absence of comorbidities and additional high-risk cytogenetics, incorporation of imatinib, and occurrence of GVHD (suggesting graft-versus-leukemia effect) in the present patients may have contributed to the excellent outcomes. Although the benefit of consolidation with high-dose cytarabine with or without imatinib before allo-SCT is unclear, this should at minimum be considered as an interim therapy while awaiting allo-SCT. The NCCN Clinical Practice Guidelines in Oncology for AML recommend treating Ph+–AML as myeloid blast-phase CML with tyrosine kinase inhibitor (alone or in combination with AML-type induction chemotherapy) followed by hematopoietic SCT, if feasible, or enrollment in a clinical trial (available at NCCN.org).

In conclusion, Ph+–AML is a rare condition that is incompletely studied. Available reports, including this one, suggest that long-term remission is possible. The use of allo-SCT, with resultant graft-versus-leukemia effect, and the addition of imatinib provide potentially curative properties.

References


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**Posttest Questions**

1. Several clinical and laboratory features, albeit not diagnostic, may help to differentiate between Ph+ -AML and blast crisis of CML. Which of the following features is suggestive of Ph+ -AML and not blast crisis of CML?
   a. Presence of NPM1 mutation
   b. Presence of ABL1 mutation
   c. History of myeloproliferative disorder
   d. Presence of lymphoid markers

2. True or False: Additional cytogenetic abnormalities may affect the prognosis of patients with Ph+ -AML.

3. Treatment of Ph+ -AML may include which of the following treatments?
   a. Anthracycline + cytarabine
   b. Imatinib
   c. Stem cell transplant
   d. All of the above