Chronic myelogenous leukemia (CML) is a hematologic malignancy characterized by excessive growth of myeloid cells and their progenitors. The disease was originally described in 1845 by Craigie, Bennett, and Virchow, who noted the classic features of “purulence” of the blood and marked splenomegaly. CML is the first human neoplasm to be associated with a consistent chromosome abnormality, the Philadelphia chromosome (Ph'), which is present in over 90% of cases. Cytogenetic studies and glucose-6-phosphate dehydrogenase (G6PD) isoenzyme and analyses have demonstrated that CML is a clonal disorder of pluripotent hematopoietic stem cells. The Ph' chromosome or a monoclonal pattern of G6PD isoenzyme expression has been identified in granulocytes, monocytes, macrophages, erythrocytes, megakaryocytes, eosinophils, basophils, and their committed progenitors. Mixed colony-forming cells, CFU-GEMM, also contain the Ph' chromosome. B lymphocytes and some null cells are also derived from the neoplastic clone. It is unclear to what extent T lymphocytes are involved in the malignant process. Peripheral blood T cells responding to lectin have not been reported to contain the Ph' chromosome. It is possible, however, that small numbers of Ph'-positive T cells are present but cannot be detected among a predominance of normal long-lived T lymphocytes. Recently, Marmont et al reported a patient who developed recurrent CML with the Ph' chromosome present in donor cells following allogeneic bone marrow transplantation. This intriguing observation suggests that the original oncogenic agent may persist in some patients or that exposure to environmental factors may reinduce the disease. Alternatively, relapse in donor cells could result from "transfection" of oncogenic material between residual host leukemic cells and donor cells.

CML results from neoplastic transformation of a pluripotent stem cell. Although multiple cell lineages are involved, the clinical features are usually limited to excessive granulocytosis alone or with thrombocytosis. CML results from neoplastic transformation of a pluripotent stem cell. Although multiple cell lineages are involved, the clinical features are usually limited to excessive granulocytosis alone or with thrombocytosis. The increased myelopoiesis is not due to an accelerated proliferative rate as measured by doubling time or labeling index of myeloid cells. Rather, the disease is characterized by massive expansion of pools of committed myeloid progenitors. Growth of the neoplastic cells in CML is not autonomous. For example, leukemic CFU-GM require colony-stimulating activity for growth in vitro and erythropoiesis in CML is generally erythropoietin dependent.

ETIOLOGY AND PATHOGENESIS
CML may develop following exposure to radiation. No other environmental factors have been definitively implicated and in the vast majority of cases, the cause is unknown. A transmissible oncogenic agent or virus has not been detected and the disease does not appear to be contagious. Recently, Marmont et al reported a patient who developed recurrent CML with the Ph' chromosome present in donor cells following allogeneic bone marrow transplantation. This intriguing observation suggests that the original oncogenic agent may persist in some patients or that exposure to environmental factors may reinduce the disease. Alternatively, relapse in donor cells could result from "transfection" of oncogenic material between residual host leukemic cells and donor cells.

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Untreated patients do not have unlimited granulocytosis; granulocyte counts typically stabilize at an abnormally high level, generally peaking at 100 to 400 x 10⁶ per liter and may spontaneously oscillate through 30- to 60-day cycles.³³,³⁴ This phenomenon is important to recognize, since it can give a false clinical impression of drug resistance or response during treatment.

The leukemic cells have a growth advantage over normal bone marrow progenitors. The proportion of Ph¹ chromosome-positive cells progressively increases over time to typically involve >99% of dividing bone marrow cells. Philadelphia chromosome-negative cells persist in the bone marrow but their growth is apparently suppressed by the malignant clone.¹⁴,³⁵ A number of inhibitors have been proposed including chalone, cell-associated inhibitors, isoferitins, and prostaglandin E,³⁶,³⁷ but there is no convincing evidence that humoral suppression of normal hematopoiesis is important in the pathogenesis of CML.

Myeloid cells mature normally during the chronic phase of CML. There are subtle abnormalities of granulocyte³⁸,³⁹ and platelet⁴⁰ function, but these rarely lead to symptomatic complications. CML cells are minimally invasive in the chronic phase. The malignant cells generally remain restricted to hematopoietic tissues, the marrow, spleen, and cords of the liver. Extramedullary involvement is uncommon and, if present, often indicates evolution to acute phase.⁴¹,⁴²

The chronic phase of CML is unstable. At some point, the disease undergoes transformation to an aggressive leukemia. Transformation may be clinically manifest by a picture of acute leukemia (acute phase or blastic crisis) or by progression of symptoms and resistance to chemotherapy (accelerated phase).⁴³ Features associated with transformation include systemic symptoms (fever, sweats, or weight loss), increasing organomegaly, or extramedullary leukemia. The granulocyte and/or platelet count typically becomes less responsive to chemotherapy and the proportion of blasts and promyelocytes increases, often associated with the development of anemia and/or thrombocytopenia. In more than 75% of patients, transformation is accompanied by karyotypic evolution with development of additional abnormalities superimposed upon the Ph¹ chromosome, most commonly trisomy 8, isochromosome 17, or duplication of the Ph¹ chromosome.⁴⁴,⁴⁵

Most patients ultimately develop acute phase (blast crisis), in which the disease resembles acute leukemia. The cells no longer differentiate to mature granulocytes; maturation arrest occurs at the level of the blast or promyelocyte.⁴⁶ Blast crisis can be divided into two general forms: lymphoid and myeloid.⁴⁷,⁴⁸ Lymphoid blast crisis develops in approximately one quarter of patients. In this variant, the blast cells are phenotypically similar to the common form of acute lymphoblastic leukemia; the cells generally contain terminal deoxynucleotidyl transferase and express DR (Iα) and common acute lymphoblastic leukemia antigens (CALLA).⁵⁰,⁵¹ They typically have immunoglobulin light chain rearrangement and may express cytoplasmic Fc-alpha chains characteristic of pre-B cells.⁵² Myeloid blast crisis is heterogeneous. The blasts appear to be morphologically similar to myeloblasts and express myeloid antigens and cytoplasmic enzymes. Erythroid and megakaryocytic variants of blast crisis also occur.⁵₃,⁵⁴ It is important to distinguish myeloid ν lymphoid blast crisis, since the latter often responds to chemotherapy with vincristine and prednisone and the former is largely resistant to treatment.⁴⁹,⁵¹

THE PHILADELPHIA CHROMOSOME (Ph¹)

The Ph¹ chromosome is a cardinal feature of CML. It was originally described by Nowell and Hungerford as a small chromosome 22 and Rowley later demonstrated that it typically results from a specific balanced (reciprocal) translocation t(9;22)(q34.1;q11.21).³⁹ In approximately 5% of patients, the Ph¹ chromosome results from anomalous complex translocations, but detailed studies using in situ hybridization have demonstrated that chromosomes 9 and 22 are usually involved. Translocations between chromosome 22 and a chromosome other than 9 rarely occur.⁵⁷

The translocation producing the Ph¹ chromosome is of particular interest with regard to the location of two cellular oncogenes (Fig 1).⁵⁸,⁵⁹ The breakpoints of the translocation vary among patients but occur within a small region on chromosomes 9 and 22, resulting in the translocation of the proto-oncogenes c-abl and c-sis.⁶⁰,⁶¹ C-sis, the cellular homologue of the Simian sarcoma virus oncogene, is normally located in the region q12.3 to q13.1 on chromosome 22, a substantial
distance from the translocation breakpoint; it is translocated to chromosome 9 with formation of the Philadelphia chromosome.\(^5\)\(^6\)\(^3\) C-sis encodes sequences for platelet-derived growth factor.\(^4\)\(^4\)\(^6\)\(^6\) Although the expression of c-sis is not generally detectable in cells from patients with CML, a c-sis gene product and/or platelet-derived growth factor could play a role in the myelofibrosis that frequently accompanies CML. C-abl, the cellular homologue of the murine Abelson leukemia virus oncogene, is normally located on the long arm of chromosome 9. With the formation of the Ph\(^1\) chromosome, c-abl is translocated to a very limited region on chromosome 22, where it is inserted near the gene encoding the \(\lambda\)-immunoglobulin light chain.\(^6\)\(^0\)\(^2\)\(^3\) The translocated c-abl is rearranged and amplified four- to eightfold in the CML cell line K562.\(^6\)\(^7\) K562 cells and fresh Ph\(^1\)-positive CML cells also have an anomalous 8-kb c-abl RNA transcript.\(^6\)\(^8\)\(^9\) Abnormal transcription of c-abl is highly associated with the Ph\(^1\) chromosome and is absent in cells from patients who lack the Ph\(^1\) chromosome. Recent studies with K562 cells and cells from patients with Ph\(^1\) chromosome-positive CML have shown a novel c-abl gene product with tyrosine kinase activity similar to the viral Abelson oncogene product.\(^7\)\(^0\)\(^7\)\(^1\) This anomalous product may result from transcription of a chimeric gene including DNA from chromosome 22 and the translocated portion of chromosome 9.\(^5\)\(^3\) These observations suggest that translocation of c-abl may lead to both gene amplification and rearrangement, with altered transcription causing production of a protein with kinase activity typical of a viral transforming protein. While these findings may not have primary etiologic importance, they shed light on potential pathogenetic mechanisms involved in the disease.

Although the Ph\(^1\) chromosome is a consistent feature of CML, it is uncertain whether all of the malignant cells are Ph\(^1\)-positive. Also, the acquisition of the Ph\(^1\) chromosome may not be the seminal oncogenic event. Several interesting patients have been reported, who presented with the clinical diagnosis of CML but with a normal karyotype in dividing myeloid cells.\(^7\)\(^2\)\(^7\)\(^5\) Each of these patients was later found to develop the Ph\(^1\) chromosome, suggesting that acquisition of Ph\(^1\) is not the primary event in the development of the disease. Other patients with typical Ph\(^1\) chromosome-positive CML have been reported who entered blast crisis with blast cells lacking the Ph\(^1\) chromosome, consistent with the presence of Ph\(^1\) chromosome-negative leukemic cells.\(^6\)\(^7\)\(^6\) Fialkow and co-workers have also presented evidence of monoclonal lymphocytes by G6PD analysis which lack the Ph\(^1\) chromosome.\(^7\)\(^1\) These data suggest a multistep pathogenesis for CML, in which the acquisition of the Ph\(^1\) chromo-

some is a second or subsequent event in the oncogenic process.

### PROGNOSIS IN CML

There has been considerable recent interest in defining prognostic factors in patients with CML. After the first year, there is a relatively constant risk of transformation to blast crisis; approximately 25% of patients surviving at any point will evolve into blast crisis over the ensuing year. Median survival is three to four years in most series. Less than 30% of patients survive five years.\(^7\)\(^9\) Several factors present at the time of diagnosis are associated with early transformation to blast crisis, including a high WBC count, a large proportion of immature cells, large spleen or liver size, and large numbers of eosinophils or basophils. Several investigators have identified high-risk, average, and low-risk groups based on these clinical features, with median survivals of approximately 2, 3½, and 5 years, respectively.\(^6\)\(^0\)\(^6\)\(^2\) The total dose of busulfan required in the first year to control the leukemia is also of prognostic importance; large dose requirements are associated with a short duration of chronic phase.\(^8\)\(^8\) Patients with a normal karyotype may have a worse prognosis than patients with the typical Ph\(^1\) chromosome abnormality, and patients presenting with other chromosome abnormalities may also have a worse prognosis.\(^8\)\(^8\)\(^8\)

### TREATMENT

The treatment of CML traditionally has had palliative intent.\(^1\)\(^2\)\(^3\)\(^6\)\(^7\) The major obstacle to the treatment of CML relates to the lack of differential sensitivity to chemotherapy between the malignant cells and their normal hematopoietic counterparts.\(^8\) The results of various treatments during the chronic phase of CML are summarized in Table I. During chronic phase, the growth of the malignant cells can be suppressed by a number of single agents. Treatment with either an alkylating agent or an anti-metabolite is generally effective in controlling the granulocytosis and thrombocytosis. The two most commonly used drugs are busulfan and hydroxyurea.\(^8\)\(^9\)\(^8\) Busulfan affects primitive stem cells and has a prolonged duration of effect. The blood counts must be carefully monitored, since overdosage of busulfan may produce protracted life-threatening pancytopenia. Prolonged survival has occasionally been reported in patients who, after inadvertent overtreatment with busulfan, developed mosaicism with partial recovery of normal (Ph\(^1\)-negative) bone marrow cells.\(^9\)\(^5\)\(^9\) Busulfan may rarely produce severe nonhematopoietic toxicity after prolonged use, particularly pulmonary fibrosis or a wasting syndrome mimicking Addison's disease. Hydroxyurea is equally effective in suppressing myelopoiesis and is preferred.
Table 1. Treatment of Chronic-Phase CML

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n</th>
<th>Median Survival From Initiation of Treatment</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>52</td>
<td>31</td>
<td>100</td>
</tr>
<tr>
<td>Splenic irradiation</td>
<td>54</td>
<td>28</td>
<td>100, 101</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>118</td>
<td>22</td>
<td>99</td>
</tr>
<tr>
<td>Busulfan</td>
<td>351</td>
<td>35–48</td>
<td>92, 93, 100, 104</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>122</td>
<td>48–56</td>
<td>90, 92, 94</td>
</tr>
<tr>
<td>Other alkylating agents</td>
<td>106</td>
<td>29–43</td>
<td>98, 99</td>
</tr>
<tr>
<td>Splenectomy and chemotherapy</td>
<td>358</td>
<td>36–45*</td>
<td>103, 104</td>
</tr>
<tr>
<td>Intensive combination chemotherapy</td>
<td>149</td>
<td>45–65</td>
<td>106–110</td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td>&gt;100</td>
<td>Not reached</td>
<td>120–131</td>
</tr>
</tbody>
</table>

55%–70% disease-free survival at >3 yr

*There was no advantage for splenectomy v controls in the two randomized controlled trials sited.

by some hematologists, since it is less toxic than busulfan. Hydroxyurea is a cell cycle-specific antagonist of DNA synthesis that is relatively short-acting and must be given continuously. Other alkylating agents and $^{32}$P are also effective in suppressing excessive hematopoesis in CML but have no therapeutic advantage over busulfan or hydroxyurea.

These agents suppress the growth of the malignant clone but cannot eradicate the disease. Patients who achieve "clinical remission," ie, normal blood counts, continue to have predominantly Ph' chromosome-positive cells in the bone marrow. Although chemotherapy will relieve the symptoms of the disease, there is no evidence that treatment with any chemotherapeutic agent delays the development of blast crisis or prolongs survival compared with previous studies involving no treatment or splenic irradiation.

Elective splenectomy has also been proposed as a potential treatment for CML. The rationale for this approach is based on the observation that blastic transformation may originate in the spleen. Splenectomy would remove this site as well as a large number of leukemic cells, which may delay the evolution to acute phase. Unfortunately, several large controlled trials have failed to demonstrate any benefit from splenectomy with regard to the duration of chronic phase, survival, or response to chemotherapy.

Splenectomy should be reserved for patients with painful splenomegaly or hypersplenism producing anemia or thrombocytopenia. Splenectomy may be hazardous in patients with CML; in addition to the operative risks, extreme thrombocytosis and infectious complications may develop postoperatively.

Because of the failure of single agents to significantly affect survival in CML, a number of investigators have evaluated the use of more intensive combination chemotherapy similar to that used for remission induction of acute myelogenous leukemia (AML). The goal of this therapy is to eradicate the malignant clone or to at least reduce the proportion of Ph' chromosome-positive cells and prevent the progression to blast crisis. Unfortunately, this approach has been only transiently successful. Intensive therapy with cytarabine-, daunorubicin-, and/or cyclophosphamide-based regimens may reduce the proportion of Ph' chromosome cells in a minority of patients, but the duration of this effect is usually brief.

This intensive approach is associated with substantial toxicity and there is no convincing evidence that the duration of chronic phase is prolonged or survival improved.

Interferon has recently been evaluated for the treatment of CML. Interferon has antiproliferative activity and also affects cellular differentiation. In preliminary studies, leukocyte interferon has been effective in controlling the WBC count and has been reported to be particularly useful in suppressing thrombocytosis. Unlike single-agent chemotherapy, treatment with leukocyte interferon was reported to increase the proportion of Ph' chromosome-negative bone marrow cells. If this finding is confirmed, interferon may then have promise to facilitate re-emergence of presumably normal clones. The effect of interferon on overall survival is unknown and its use in this disease may be limited by side effects of fever and malaise.

Another innovative treatment involves the clinical use of agents that induce cellular differentiation in vitro, such as retinoids, in an attempt to prevent or delay the development of blast crisis. Several trials involving retinoids are in progress, but there is no convincing evidence to date that this form of therapy is effective in CML.

Patients who progress to acute phase of CML have a poor prognosis; the results of current treatments of the acute phase are summarized in Table 2. It is important to distinguish the lymphoid variant from other forms of acute phase. Approximately 60% of lymphoid blast crises achieve remission after treatment with vincristine and prednisone. It is unclear if addition of
CHRONIC MYELOGENOUS LEUKEMIA

Table 2. Treatment of Acute-Phase CML

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Complete Remission (%)</th>
<th>Median Survival (mo) Responders</th>
<th>Median Survival (mo) All Patients</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine/prednisone</td>
<td>&gt;40</td>
<td>20–30</td>
<td>7</td>
<td>5</td>
<td>47, 49, 51, 86, 115</td>
</tr>
<tr>
<td>TRAMPCOL</td>
<td>19</td>
<td>42</td>
<td>7</td>
<td>7</td>
<td>114</td>
</tr>
<tr>
<td>Cytarabine/anthracyline ± others</td>
<td>&gt;100</td>
<td>10–20</td>
<td>4–6</td>
<td>2–3</td>
<td>41, 116</td>
</tr>
<tr>
<td>5-azacytidine plus VP-16-213</td>
<td>27</td>
<td>3</td>
<td>7.5</td>
<td>1.5</td>
<td>117</td>
</tr>
<tr>
<td>Cytarabine and carmustine ± vincristine/prednisone</td>
<td>86</td>
<td>5</td>
<td>5–8</td>
<td></td>
<td>118</td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td>53</td>
<td>&gt;90</td>
<td>3*</td>
<td>3</td>
<td>120</td>
</tr>
</tbody>
</table>

Approximately 10% are long-term survivors.

TRAMPCOL, 6-thioguanine, daunorubicin, cytarabine, methotrexate, prednisone, cyclophosphamide, vincristine, L-asparaginase.

other agents improves this response rate or if maintenance therapy is beneficial. Unfortunately, the median duration of remission is only four to six months and <20% survive for one year. The myeloid forms of acute phase respond poorly to treatment; <30% achieve remission with intensive chemotherapy, and these remissions are generally brief. Clearly, more effective therapy is required for patients in acute phase, particularly for the myeloid variant. Because of the poor response to intensive therapy, several investigators have proposed less toxic palliative outpatient regimens for patients with acute-phase CML, involving agents such as hydroxyurea, 6-mercaptopurine, and prednisone. This approach is unlikely to induce complete remission, but does result in survival comparable with more intensive chemotherapy.

BONE MARROW TRANSPLANTATION FOR CML

One potential approach to overcome the lack of differential sensitivity to chemotherapy and irradiation between the leukemic and normal hematopoietic cells is to use very high-dose “marrow-ablative” chemoradiotherapy, followed by bone marrow transplantation to restore hematopoiesis. Three sources of hematopoietic stem cells have been used: cryopreserved autologous peripheral blood or bone marrow cells, syngeneic marrow from an identical twin, or allogeneic bone marrow generally from HLA-identical sibling donors.

In order to perform autologous transplants, large numbers of bone marrow and/or peripheral blood cells are collected during the chronic phase of CML and cryopreserved. Patients who progress to the acute phase may then receive marrow-ablative chemoradiotherapy and reinfusion of the stored autologous cells. The objective of this approach is to restore the chronic phase. Since Ph1 chromosome-positive cells are reinfused, cure of the disease is not possible. The major limitation of this technique is the resistance of the acute-phase cells to supralethal therapy. Although most patients achieve a second chronic phase, they usually relapse with acute phase within four months and <20% survive for one year. This approach is clearly of marginal benefit and cannot be routinely recommended.

Encouraging results have been obtained with high-dose chemoradiotherapy, followed by syngeneic or allogeneic bone marrow transplantation. This is the only treatment capable of eradicating the leukemic clone. Fefer et al. initially reported prolonged disease-free survival in patients with CML receiving high-dose cyclophosphamide, total body irradiation, and syngeneic bone marrow transplants. Approximately 65% of patients receiving syngeneic transplants in chronic phase and 20% of those treated while in blast crisis have achieved complete remission free of Ph1 chromosome-positive cells and have survived for over five years free of disease.

Based on these reports, a large number of centers have evaluated similar therapy with allogeneic marrow transplantation. Again, the best results have been achieved in patients treated while in chronic phase. A recent report from the International Bone Marrow Transplant Registry noted three-year disease-free survival in 63% of patients transplanted while in chronic phase compared with 36% and 12% for patients transplanted in accelerated or acute phases, respectively. The actuarial leukemic recurrence rate has been surprisingly low for patients transplanted in chronic phase (7%) but increases to over 40% in patients with more advanced disease. The major causes of treatment failure with allogeneic bone marrow transplantation are graft-vs-host disease and interstitial pneumonitis. The most important prognostic factor for transplant outcome appears to be patient age; pediatric and adolescent patients fare better than older adults and most centers will not perform bone marrow transplants.
in patients over 45 years of age. Preliminary data also suggests that patients transplanted within one year of the diagnosis of CML have better results than patients transplanted after longer intervals. Although these results are very promising, more time is required to confirm that the remissions following marrow transplantation are indeed durable. In addition, bone marrow transplantation has yet to be compared with conventional treatment in a prospective controlled trial.

Which patients should receive bone marrow transplantation and at what point in their disease? From the data available, the best chance for success lies with bone marrow transplantation during the chronic phase. The potential benefit of marrow transplantation must be weighed against the risks of the procedure. Even among optimal candidates, approximately 30% of patients will die within six months of transplant-related complications. This risk must be balanced against the known natural history of the disease, with the virtual certainty of ultimate transformation to acute phase. Delaying the procedure carries the risk to the patient of entering acute phase and losing the opportunity for a successful bone marrow transplant.

Our approach is to offer early bone marrow transplantation to patients under 45 years of age who have average or poor-risk prognostic features. Patients with “good-risk” clinical parameters have median survivals exceeding five years with conventional management, and it is unclear whether early marrow transplantation is more beneficial for this group than delaying the procedure until the development of adverse clinical features.

Unfortunately, only a minority of patients are currently candidates for bone marrow transplantation. Most patients either lack an HLA-identical sibling donor or are too old to be considered. Possibly, the use of unrelated HLA-matched donors or techniques to prevent graft-vs-host disease with HLA-mismatched marrow transplants will expand the eligible patient population. Nonetheless, alternative forms of therapy are required for most patients. Hopefully, the recent fundamental advances in our understanding of the biology of CML will lead to the development of effective and less toxic approaches to treatment capable of selectively eradicating the malignant clone or preventing transformation of chronic phase CML to the acute phase.

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Chronic myelogenous leukemia: recent advances

RE Champlin and DW Golde