Chronic Myelogenous Leukemia

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Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder resulting from the neoplastic transformation of the primitive hemopoietic stem cell [1-4]. The disease is monoclonal in origin, affecting myeloid, monocytic, erythroid, megakaryocytic, B-cell, and, sometimes, T-cell lineages [4,5]. Bone marrow stromal cells are not involved [6]. CML has a very significant historical relevance, because it was the first disease in which a specific chromosomal abnormality was linked to its pathogenesis, implicating activation of a specific oncogene in the chromosomal rearrangement [7-10]. At the therapeutic level, it is also historically important, because it is one of the first neoplastic diseases for which the use of a biologic agent (ie, interferon) could suppress the neoplastic clone [11] and prolong survival [12]. Some of the most impressive results with bone marrow transplantation (BMT) also come from studies of patients with CML [13].

Introduction

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder resulting from the neoplastic transformation of the primitive hemopoietic stem cell [1-4]. The disease is monoclonal in origin, affecting myeloid, monocytic, erythroid, megakaryocytic, B-cell, and, sometimes, T-cell lineages [4,5]. Bone marrow stromal cells are not involved [6]. CML has a very significant historical relevance, because it was the first disease in which a specific chromosomal abnormality was linked to its pathogenesis, implicating activation of a specific oncogene in the chromosomal rearrangement [7-10]. At the therapeutic level, it is also historically important, because it is one of the first neoplastic diseases for which the use of a biologic agent (ie, interferon) could suppress the neoplastic clone [11] and prolong survival [12]. Some of the most impressive results with bone marrow transplantation (BMT) also come from studies of patients with CML [13].

Epidemiology

CML accounts for 7% to 15% of all leukemias in adults, with approximately 1 to 1.5 cases per 100,000 population [14-16]. There is a male predominance, with a male to female ratio of 1.4–2.2 to 1 [15-17]. The incidence of CML has remained steady for the last 50 years [16]. The median age at presentation is 50 to 60 years [15,17], but the disease can be seen in all age groups. In earlier reports, 54% to 63% of patients were 60 years old and older [15,18], but the incidence has decreased in more recent reports to as low as 12% [3]. This may be a consequence of earlier detection in recent years or the exclusion of patients having CML-like pictures (ie, other myeloproliferative disorders, Philadelphia [Ph] chromosome-negative CML, chronic myelomonocytic leukemia), who are usually significantly older.

Etiology

The etiology of CML is not clear. There is little evidence for genetic factors linked to CML. Offspring of parents with CML do not have a higher incidence of CML than does the general population [19]. There is also no correlation in monozygotic twins, suggesting that CML is an acquired disorder [19]. However, there may be some correlation with human leukocyte antigens (HLAs) CW3 and CW4 [20]. Survivors of the atomic disasters at Nagasaki and Hiroshima had a significantly higher incidence of
CML [21]. Therapeutic radiation has also been associated with increased risk of CML [22]. This was the case in patients with ankylosing spondylitis treated with spinal irradiation [23] and in women with uterine cervical cancer given radiation therapy [24]. Chemicals have not been associated with increased risk for CML.

Clinical Characteristics

The disease usually has a biphasic, and sometimes triphasic, course. The initial phase is the chronic phase, which is frequently asymptomatic. The incidence of asymptomatic cases has increased over the last decade from 15% to about 40% of all cases [3] as a result of more widespread use of routine blood testing. Patients with symptoms usually have a gradual onset of fatigue, anorexia, weight loss, increased sweating, left upper quadrant discomfort, and early satiety as a result of splenic enlargement [25]. Rare patients with very high counts of white blood cells (WBCs) may have manifestations of hyperviscosity, including priapism, tinnitus, stupor, visual changes from retinal hemorrhages, and even cerebrovascular accidents [26]. There are a few case reports of CML presenting as diabetes insipidus [27]. On physical exam, splenomegaly was documented in approximately 70% of the patients in older series, but its incidence has decreased to 30% in more recent series. Sometimes the spleen may be massive. The liver is also enlarged in 10% to 40% of cases.

The accelerated phase is an ill-defined transitional phase [28] that is frequently asymptomatic. The diagnosis is made from changes in peripheral blood or bone marrow. Some patients may have fever, night sweats, and progressive enlargement of the spleen. At least 20% of patients enter a blastic phase without evidence of having had accelerated phase [3].

Patients in the blastic phase are more likely to have symptoms, including weight loss, fever, night sweats, and bone pains [17]. Symptoms of anemia, infectious complications, and bleeding are commonly seen. Subcutaneous nodules or hemorrhagic tender skin lesions and lymphadenopathy are more common in this phase, and signs of central nervous system (CNS) leukemia can also be seen [17]. In the blastic phase, tissue infiltration can occur, most frequently to the lymph nodes, skin, subcutaneous tissues, and bone.

Laboratory Features

Peripheral Blood

The most common feature of CML is an elevated WBC count, usually above 25,000/µL, and frequently above 100,000/µL [29]. Some patients have wide cyclic variations in their WBC count, with peak counts every few days or separated by up to 70 days [30]. The WBC differential usually shows granulocytes in all stages of maturation, from blasts to mature granulocytes that look morphologically normal. The number of basophils is usually increased from that normally expected, but only 10% to 15% of patients have 7% or more basophils in peripheral blood; a very high proportion (ie, 20% or more) of basophils in the peripheral blood usually signals acceleration of CML [28]. The number of eosinophils is also frequently higher than normal, but to a smaller degree. The absolute lymphocyte count is usually elevated, mostly representing an expansion of T-lymphocytes [31]. The platelet count is elevated in 30% to 50% of patients and is higher than 1,000,000/µL in a few patients. Thrombocytopenia can also be seen and usually signals acceleration of the disease [28]. Most patients have mild anemia at diagnosis, but untreated patients may be severely anemic. The neutrophil function is usually normal or only mildly impaired [32]. Patients in the chronic phase do not have an increased risk for infections. However, the activity of their natural killer cells is impaired because of the defective maturation of these cells [33]. Platelet function is frequently abnormal as measured in the laboratory and most frequently shows a decreased secondary aggregation with epinephrine, but this usually does not have clinical significance.

Bone Marrow

The bone marrow is hypercellular, with cellularity of 75% to 90% and very little fat. The myeloid to erythroid ratio is 10:1 to 30:1 rather than the normal 2:1 to 5:1 [34]. The myelocyte is the predominant cell in the bone marrow during the chronic phase, with promyelocytes and blasts accounting for less than 10% of all cells. Megakaryocytes are increased early in the disease and may show dysplastic features. Cells mimicking Gaucher cells can be seen in 10% of cases, as can “sea-blue” histiocytes [35]. Fibrosis may be evident at diagnosis and increases with disease progression [36]. Surprisingly, reticulin fibrosis grades 3 to 4 are seen in up to 30% to 40% of cases and has been associated with a worse prognosis [36].
The activity of leukocyte alkaline phosphatase is reduced in nearly all patients at diagnosis [37]. The significance of this finding is unclear, but, interestingly, the activity can be restored after transfusing leukocytes from patients with CML to neutropenic patients, which suggests extrinsic regulation [38]. Granulocyte colony-stimulating factor can induce synthesis of leukocyte alkaline phosphatase in vitro [39]. The activity of leukocyte alkaline phosphatase also increases with infections, stress, and upon achievement of remission or progression to the blastic phase.

Serum levels of vitamin B12 and transcobalamin are increased, sometimes up to 10 times the normal levels. Although this is, in part, due to the high WBC count, these levels may remain high even after hematologic remission. Serum levels of uric acid and lactic dehydrogenase are also frequently elevated.

CML Phases
As mentioned, CML has a bi- or triphasic course. There is an initial chronic phase that eventually leads to a blastic phase, sometimes preceded by an intermediate or accelerated phase. The chronic phase, if untreated, has a median duration of 3.5 to 5 years before evolving to the more aggressive phases. The diagnosis is based on the characteristics mentioned above.

The blastic phase resembles an acute leukemia. Its diagnosis requires the presence of at least 30% of blasts in the bone marrow or peripheral blood [40]. In some patients, the blastic phase is characterized by extramedullary deposits of leukemia called myeloblastomas [41]. These usually appear in the CNS, lymph nodes, or bones and occasionally occur in the absence of blood or bone marrow evidence of blastic transformation. Most of these cases, however, will have hematologic manifestations within a few months [42]. Patients in the blastic phase usually die within 3 to 6 months. Approximately 50% of patients have a myeloid blastic phase, 25% lymphoid, and 25% undifferentiated [43]. Although median survival is slightly better for patients with a lymphoid blastic phase than for those who have myeloid or undifferentiated cases (9 vs 3 months), the outcome is still very poor [43]. Seventy-five to 80% of patients go through an accelerated phase before entering the blastic phase [3]. The definition for the accelerated phase is not uniform [28]. Specific criteria associated with a survival shorter than 18 months by multivariate analysis have been proposed, including the presence of 15% or more blasts in peripheral blood, 30% or more blasts and promyelocytes in the blood, 20% or more basophils in the blood, or a platelet count less than 100,000/µL (Table 1) [28]. Cytogenetic clonal evolution has been considered a criterion for acceleration. Recent analysis suggests that its prognostic effect depends on the specific abnormality, its predominance in marrow metaphases, and the time of appearance [44]. Patients with chromosome 17 abnormalities, 25% or more abnormal metaphases, clonal evolution longer than 25 months after diagnosis, and no prior therapy with alpha interferon (IFN-alfa) have the worst outcome. The median survival for patients with none of these features is 51 months compared with 24, 14, and 7 months when 1, 2, or 3 or 4 features, respectively, are present [42].

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of Patients With Different Phases of Chronic Myelogenous Leukemia</th>
</tr>
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<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Age &gt; 60 yr</td>
</tr>
<tr>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Hemoglobin &lt; 12 g/dL</td>
</tr>
<tr>
<td>WBC count &gt; 100,000/µL</td>
</tr>
<tr>
<td>Platelet count &gt; 700,000/µL</td>
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</tbody>
</table>
Chronic Myelogenous Leukemia

Several clinical characteristics have been identified to have prognostic significance in CML. These include age, spleen size, liver size, platelet count, WBC count, percentages of blasts and basophils in blood or bone marrow, number of nucleated red blood cells, and cytogenetic clonal evolution. These factors have been incorporated in staging systems [45-48]. A synthesis staging system has incorporated factors from all these systems and resulted in a simple model for staging that can identify four CML stages with different outcomes (Table 2) [49]. The stage at diagnosis has been identified as one of the most important predictors of survival after treatment with interferon-α (IFN-α) therapy [50,51] but is somehow less predictive for patients treated with chemotherapy alone [52]. The response to therapy with IFN-α is a significant prognostic factor for long-term survival and will be discussed later in this review.

Table 2. Synthesis Staging System for Chronic Myelogenous Leukemia Criteria Stage Definition

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>For chronic phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>1</td>
<td>0 or 1 characteristic</td>
</tr>
<tr>
<td>Spleen &gt; 10 cm</td>
<td>2</td>
<td>2 characteristics below costal margin</td>
</tr>
<tr>
<td>Blasts &gt; 3% in blood</td>
<td>3</td>
<td>&gt; 3 characteristics or &gt; 5% in marrow</td>
</tr>
<tr>
<td>For accelerated phase</td>
<td>4</td>
<td>&gt; 1 characteristic</td>
</tr>
<tr>
<td>Cytogenetic clonal evolution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blasts &gt; 15% in blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blasts + promyelocytes &gt; 30% in blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basophils &gt; 20% in blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets &lt; 100,000/µL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other factors have been suggested to be predictive of response to therapy and survival. The site of the breakpoint in the \( bcr \) gene has been thought to have prognostic significance [53,54], but large studies show a lack of correlation with response to therapy or survival [55].

Cytogenetic and Molecular Changes

Ninety to 95% of all patients with CML have the Ph chromosome [56]. Initially identified as a short
Conventional Therapy and Other Chemotherapy

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Chromosome 22, it actually represents a balanced translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11) [56]. The c-abl proto-oncogene located on chromosome 9q34 is homologous to the transforming element of the Abelson murine leukemia virus, v-abl. It codes for a nonreceptor protein–tyrosine kinase expressed in most mammalian cells, but its normal function is unknown. In the Ph chromosome, the breakpoint occurs within the first intron of c-abl, therefore translocating exons 2 through 11 to chromosome 22 [56]. In chromosome 22, the breakpoint occurs within the bcr gene, a large 70-kb gene with 20 exons. The breakpoint usually involves a 5.8-kb area known as the breakpoint cluster region, either between exons b3 and b4 or b2 and b3 [56]. Therefore, two different fusion genes can be formed, both of them joining exon 2 of abl with either exon 2 of bcr (b2a2) or exon 3 of bcr (b3a2). This hybrid gene is then transcribed into an 8.5-kb mRNA, in contrast to the normal c-abl, which is 6 to 7 kb [57].

Upon translation, a new protein is synthesized that has a molecular mass of 210 kDa (p210bcr/abl); the normal c-abl is 145 kDa. The normal tyrosine kinase activity of c-abl is dysregulated as a consequence of its binding to bcr, with markedly increased autophosphorylating activity [58]. The binding to bcr also activates an actin-binding function associated with c-abl [59]. The expression of p210bcr/abl is sufficient to induce leukemic transformation of transfected cells [60] and can induce leukemia in transgenic mice [61]. Although the mechanism by which this new protein can induce transformation is not well known, recent data have clarified this issue to some extent. The first exon of bcr is essential for the transforming ability of bcr/abl and binds to an ABL SH2 domain in a phosphotyrosine-independent manner [62]. Disruption of this binding eliminates the transforming activity of bcr/abl. Upon autophosphorylation, several tyrosine residues are phosphorylated. The most critical one seems to be Y177, which then links p210bcr/abl to a 26-kDa protein with SH2 and SH3 domains called GRB-2 [63]. This protein links tyrosine kinases to ras signaling [64]. Ras activation is in fact required for transformation by several tyrosine kinases [65], and suggests that it also plays a major role in bcr/abl directed transformation. The actin-binding function of abl seems to be important for the transforming ability [66]. Other proteins may also be bound and phosphorylated by bcr/abl. One such protein is CRKL, which is the most abundant phosphorylated protein in some CML cell lines [67], but its specific role in leukemic transformation is not yet clear. It is likely, however, that more than one pathway is involved in leukemic transformation after bcr/abl autophosphorylation. When the bcr/abl SH2 domain (ie, the major tyrosine autophosphorylation site of the kinase domain) is mutated, transforming activity is lost, but it can be restored by the overexpression of c-myc [68]. It is not known whether signals generated through GRB-2 feed into both pathways (ie, ras and myc) or whether other pathways are involved. It has also been suggested that the activation of the tyrosine kinase activity may suppress apoptosis in hemopoietic cells [69]. The reciprocal fusion gene (ie, abl/bcr) is transcribed in approximately two thirds of patients with CML, but the significance of this event is not clear [70].

As mentioned earlier, additional chromosomal abnormalities are a marker of acceleration of the disease. The most common events are the appearance of an additional Ph chromosome, trisomy 8, and isochromosome 17q. The molecular events of acceleration, however, are not well defined [71]. Mutations of p53 have been found frequently by some investigators [72], but others found mutations a less common event, whereas deletions and rearrangements may occur during the blastic phase [73]. Overall, loss of function of p53 is probably associated with disease progression in approximately 25% of CML patients [74].

Besides the intrinsic abnormalities of CML cells determined by the bcr/abl and associated intracellular signal elements, external regulatory factors are also affected in CML. Cells from CML patients have a defect in cellular adhesion to stromal cells that affects the regulation of myeloid cell growth [75]. CML progenitor cells are deficient in the expression of the cytoadhesion molecule lymphocyte function antigen-3 [76]. This deficiency is corrected by exposure to IFN-alfa [76]. IFN-alfa can also increase adhesion to stroma by a mechanism that can be blocked by antibodies to integrins a4, a5, and b1 [77]. This is not related to a deficient expression of the integrins but to a functional defect of these molecules [77]. More evidence for the dysregulation of CML cells by external influences was provided by studies on interleukin-1. Levels of interleukin-1-b have been reported to be elevated in patients with CML, and inhibitors of interleukin-1 can suppress CML clonogenic growth [78]. Elevated levels of interleukin-1 have been correlated with an adverse prognosis [79].

Therapy

Conventional Therapy and Other Chemotherapy
For a long time, therapy for CML has consisted mostly of busulfan (Myleran) or hydroxyurea (Hydrea). Busulfan allows long periods of hematologic control and is not expensive, making it attractive for use when socioeconomic issues are important or in patients for whom follow-up is erratic. Busulfan therapy is associated with lung, marrow, and heart fibrosis and can cause Addison-like disease; in 10% of patients, prolonged myelosuppression may be observed. The dose of busulfan is usually 0.1 mg/kg/d until the WBC counts decrease by 50%, and then the dose is reduced by 50%. Therapy is discontinued when the WBC count drops below 20,000/µL and is restarted when it increases above 50,000/µL.

Hydroxyurea has a lower toxicity profile but shorter control of hematologic manifestations, requiring more frequent follow-up [80]. It is usually given at a dose of 40 mg/kg/d and is reduced by 50% when the WBC count drops below 20,000/µL. The dose is then adjusted individually to keep the WBC count at 5 to 10,000/µL. One study used higher doses of hydroxyurea (2 g/m²/d) until the absolute neutrophil count reached <1,000/µL [81]. Patients achieving a cytogenetic response were given additional cycles until maximal response. Fourteen of 25 cycles administered to 14 patients in the chronic phase resulted in 25% Ph-chromosome-negative cells. In one patient, a complete cytogenetic remission was achieved. In all cases, however, the responses were transient [81].

Both drugs can control the hematologic manifestations of the disease in more than 70% of all patients. A recent large randomized study prospectively compared these two agents in patients with chronic-phase CML [82]. Patients treated with hydroxyurea had a longer median duration of the chronic phase (47 months vs 37 months, \( P = .04 \)) and a longer overall survival (58 months vs 45 months; \( P = .008 \)) than those treated with busulfan [82]. The toxicity profile was also better for hydroxyurea. Hematologic improvements were not accompanied by a significant reduction in the percentage of cells bearing the Ph chromosome. Therefore, while disease control can be achieved with these agents, the ability to regress the disease to the acute phase remains unchanged.

One recent study used continuous infusion of low-dose cytarabine in patients with chronic-phase CML [83]. Five patients received 15 to 30 mg/m²/d of cytarabine. The hematologic manifestations of the disease were controlled in all patients, and all achieved some cytogenetic response, including one complete response and one partial response [83]. This approach, however, is still experimental. Other chemotherapeutic agents such as mercaptopurine (Purinethol), melphalan (Alkeran), and thioguanine have been used less frequently, sometimes in combination with busulfan [84]. Thiotepa has been used to treat excessive thrombocytopenia associated with CML [85].

Homoharringtonine is a promising agent in CML. Patients in early chronic phase who have been treated with homoharringtonine have a complete hematologic response (CHR) rate of 95%, with 24% entering major cytogenetic remission [86]. In patients in the late chronic phase, these rates are 68% and 17%, respectively, despite the fact that two thirds of the patients were refractory to IFN-alfa [87].

### Interferon

In the early 1980s, IFN-alfa was introduced into the therapy for CML following observations of in vitro inhibition of myeloid colony formation when normal or CML progenitors were cultured in its presence [88]. The first reports in humans used partially pure IFN-alfa to treat 51 patients in chronic phase [88]. A CHR was achieved in 71%. More important, however, was the fact that cytogenetic responses (ie, suppression of the Ph-positive clone) were observed in 39% of patients [89]. Recombinant human IFN-alfa soon became available and had similar results to those achieved with natural IFN-alfa. This was confirmed in several trials. In the last update from The University of Texas M.D. Anderson Cancer Center, 274 patients treated with IFN-alfa-based were reported [50]. Eighty percent of the patients achieved a CHR with cytogenetic responses rates of 40% to 60% and a major cytogenetic response rate of 38%. Twenty-six percent of the patients achieved a complete cytogenetic response (Table 3).

| Table 3. Results of Treatment With IFN-alfa for Patients in Early Chronic-Phase CML |
|-----------------------------------|------------|------------|
| Response            | Category   | N           |
| Hematologic         | Complete   | 2           |
|                     | Partial    |             |
|                     | Resistant   |             |
| Cytogenetic         | Any        | 1           |
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Cytogenetic responses are considered complete if Ph-positive cells constitute 0% of all cells, partial if they represent between 1% and 34% of all cells, and minor if they represent 35% to 90% of all cells. Complete and partial cytogenetic responses constitute major cytogenetic responses [91]. Other studies have used different criteria, making comparisons of results among studies difficult. Standard response criteria, as proposed in Table 4, will help such comparative studies in the future, because CHR and cytogenetic responses have prognostic relevance. The median time to achieve a hematologic remission is 6 to 8 months [51,91]. For cytogenetic responses, the median time is 22 to 24 months for a complete response, 12 to 18 months for a partial response, and 8 to 14 months for a minor response [3,51,91]. Responses may be faster with recombinant than with natural IFN-alfa [91]. The cytogenetic responses achieved with IFN-alfa are durable in > 50% of patients achieving them, or in about 25% to 30% of all patients in the early chronic phase [3]. The durability is greater in patients who achieve complete or partial responses than in those with lesser degrees of major cytogenetic responses. Several other groups have confirmed these observations, but the results vary [51,92-96]. In analyzing these results, several factors must be considered, including the dose, the patients selected for treatment trials and their phase of disease, the type of therapy given, and the toxic effects patients experience.

Table 4. Criteria for Response to IFN-alfa in CML

<table>
<thead>
<tr>
<th>Response</th>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic remission</td>
<td>Complete</td>
<td>Normalization of WBC counts to &lt; 9,000/µL with normal differential</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>Decrease in WBC to &lt; 50% of pretreatment level and to &lt; 20,000/µL, or normalization of WBC with persistent splenomegaly or immature peripheral cells</td>
</tr>
<tr>
<td>Cytogenetic response</td>
<td>Complete</td>
<td>No evidence of Ph-positive cells</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>5% to 34% of metaphases Ph-positive</td>
</tr>
<tr>
<td></td>
<td>Minor</td>
<td>35% to 90% of metaphases Ph-positive</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Persistence of Ph chromosome in all analyzable cells</td>
</tr>
</tbody>
</table>

Dose: There is a dose-response effect with IFN-alfa in CML. The dose used in most studies that documented significant response is 5,000,000 U/m²/d [51]. With lower doses the results are inferior [3]. In one study, patients were randomized to receive 2,000,000/U/m² three times a week or 5,000,000/U/m² three times a week [97]. The CHR rate was lower with the lower dose (24% vs 47%; $P = .06$). Patients who did not respond to the lower dose still achieved a CHR with the higher dose. The same group observed a CHR rate of 87% when they used a daily schedule [97]. One recent report suggests that low doses are as effective as high doses [93]. These results may be influenced by patient selection and should be considered cautiously. At this point, the recommended dose is
therefore 5,000,000 U/m²/d or the maximally tolerated individual dose, not to exceed 5,000,000 U/m²/d.

**Patient Selection:** Several patient characteristics are associated with failure to achieve a major cytogenetic response and with worse survival after treatment with IFN-alfa. These include poor performance status, the presence of symptoms at diagnosis, splenomegaly, anemia, leukocytosis, a high percentage of blasts in the peripheral blood, peripheral nucleated red blood cells, and marrow basophilia [50]. The stage of disease, whether staged with Sokal’s model [47] or the synthesis staging system [49], is strongly predictive of response and survival [50]. Patients at low risk have a CHR rate of 80% to 90%, with 40% having major cytogenetic responses compared with 50% to 60% and 20% to 30%, respectively, for patients at intermediate risk and 20% to 60% and 5% to 10%, respectively, for patients at high risk [3] (Table 5). Age is a significant survival factor, with patients 60 years old and older having a worse prognosis [47,49]. However, a recent report from M.D. Anderson Cancer Center suggests that patients in this age group may have responses to IFN-alfa similar to those in younger patients, albeit with more toxic effects [98].

**Table 5. Response to Alpha Interferon (IFN-alfa) Therapy With Different Dose Schedules**

<table>
<thead>
<tr>
<th>Study</th>
<th>IFN-alfa dose</th>
<th>CHR (%)</th>
<th>Any</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC</td>
<td>5,000,000 U/m²/d Daily</td>
<td>274</td>
<td>80</td>
<td>58</td>
</tr>
<tr>
<td>Schofield et al</td>
<td>2,000,000 U/m²/d Daily</td>
<td>27</td>
<td>70</td>
<td>33</td>
</tr>
<tr>
<td>Alimena et al</td>
<td>5,000,000 U/m² 2,000,000 U/m² TIW</td>
<td>30</td>
<td>30</td>
<td>63</td>
</tr>
<tr>
<td>Freund et al</td>
<td>5,000,000 U TIW</td>
<td>10</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Anger et al</td>
<td>3,000,000 U TIW</td>
<td>9</td>
<td>22</td>
<td>20</td>
</tr>
</tbody>
</table>

CHR = complete hematologic response
MDACC = M.D. Anderson Cancer Center
NS = not stated
TIW = three times a week

**CML Phase:** The phase of the disease at the time of treatment is a major determinant of response. Patients in the chronic phase have the best response to IFN-alfa [3]. Among those in the chronic phase, patients treated within 1 year from diagnosis (ie, early chronic phase) have a CHR rate of 60% to 80%, and 20% to 30% of them have major cytogenetic responses compared with a CHR rate of 50% to 60% in fewer than 10% of patients treated more than 1 year from diagnosis. Patients in the accelerated or blast phase have CHR rates of less than 40% and only occasionally have a cytogenetic response (Table 7) [3].

**Table 7. Response to Alpha Interferon by Chronic Myelogenous Leukemia Phase**

<table>
<thead>
<tr>
<th>Phase</th>
<th>CHR (%)</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early chronic</td>
<td>60–80</td>
<td>40–50</td>
</tr>
</tbody>
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Several groups have documented a survival advantage for patients treated with IFN-alfa compared with conventional chemotherapy [50,51,94-96]. Time to progression to blastic phase was also prolonged. In all three randomized studies [51,94,96], IFN-alfa produced higher rates of major and complete cytogenetic remission compared with conventional chemotherapy, but one of these studies showed no survival advantage over that achieved with hydroxyurea [96]. The recent update from the Italian Cooperative Study Group on CML [51], which compared treatment with IFN–a vs conventional chemotherapy, documented a longer median survival for patients treated with IFN-alfa (median 72+ vs 52 months; \( P = .002 \)). The 6-year survival rate was 50% vs 29% for patients treated with IFN-alfa and chemotherapy, respectively (\( P = .002 \)). The time to the acceleration or blastic phase was also significantly prolonged for the IFN-alfa group (72+ vs 45 months; \( P < .001 \)) [51]. Similar results were reported by Allan et al [94]. A recent study by Hehlmann et al [96] randomized patients to receive IFN-alfa or conventional chemotherapy. Patients treated with IFN-alfa had a median survival of 5.5 years (5-year survival rate of 59%) compared with 3.8 years (32%) for those treated with busulfan (\( P = .008 \)) and 4.7 years (44%) for those treated with hydroxyurea (not statistically significant). Several points may explain the findings: (1) some patients entered on the IFN-alfa arm may not have been in the chronic phase (blasts up to 35%, platelets less than 100,000/µL) (2) the actual dose–schedule of IFN-alfa delivered was 2,000,000 U/m²/d after the initial 4 weeks and (3) the complete and major cytogenetic response rates were low (7% and 10%, respectively). The latter two observations are important because some studies show superior survival only with achievement of a major cytogenetic response, which is enhanced by higher dose schedules of IFN-alfa. Achievement of a cytogenetic response is associated with a survival advantage in several studies. However, two studies failed to document such a correlation [92,96]. These studies had a low rate of major cytogenetic responses, possibly because of the patients selected or because the actual doses of IFN-alfa administered were lower [92,96]. Two other studies show that patients who achieve a cytogenetic response have a survival advantage, whereas those who fail to achieve such a response have a survival similar to that of patients treated with conventional chemotherapy [50,51]. In a trial from the Medical Research Council, even though patients who did not respond to IFN-alfa had a shorter survival than did responders, they still showed a survival advantage over those treated with chemotherapy [94]. Multivariate analysis has not been completed in this study [94].

**Combination Therapy Using IFN:** IFN-alfa-based combinations have attempted to improve on the results of single agent trials. Initial studies with IFN-gamma documented a CHR rate of 23%, and some patients who were refractory to one type of IFN-(alfa or gamma) responded to the other [99]. These results prompted the use of a combination of IFN-alfa and IFN-gamma [100,101]. The combination is well tolerated, but the results are not better than those achieved with IFN-alfa alone [100,101].

Cytarabine has selective in vitro activity against CML, and preliminary studies reported cytogenetic responses in patients treated with it alone [83]. The combination of cytarabine and IFN-alfa in patients in late chronic phase achieved a CHR rate of 55% and a cytogenetic response rate of 15%, which compares favorably with the 28% (\( P < .01 \)) and 5% (not significant), respectively, achieved with IFN-alfa alone. Survival rates were also better with the combination. For patients in the accelerated phase, no improvement in the response rate was observed [102]. Among patients in the early chronic phase, Arthur and Ma reported a CHR rate of 93%, a cytogenetic response rate of 67%, and a complete cytogenetic response rate of 30% [103]. Guilhot et al randomized patients to receive IFN-alfa alone or with low-dose cytarabine and reported a trend for a higher complete cytogenetic response rate in patients treated with the combination schedule (23% vs 14%; \( P < .24 \)) [104]. Other combinations are less effective. The use of busulfan with IFN-alfa can be complicated by prolonged myelosuppression. Hydroxyurea can be given safely with IFN-alfa and is popular in clinical practice because CHR is achieved faster; however, the cytogenetic response rates are similar. With the results reported by Hehlmann et al [96], this combination may be investigated further in future.
Trials. Intensive chemotherapy can produce complete and major cytogenetic responses in 30% to 50% of patients who have chronic-phase CML [105], but these responses are transient and last only for 3 to 9 months. The use of IFN-alfa as a maintenance drug following the induction of intensive chemotherapy does not improve the survival rate or the durability of cytogenetic responses over those achieved with IFN-alfa alone [106].

Toxicity of IFN: Most patients treated with IFN-alfa experience a transient flu-like syndrome with fever, chills, malaise, fatigue, and anorexia. These are transient, not dose-limiting, and manageable symptomatically. Simple measures such as starting with 25% to 50% of the dose of IFN-alfa for the first week, giving it at night, reducing the initial WBC count to between 10,000 and 20,000/µL with other chemotherapy before the start of IFN-alfa, and premedicating with acetaminophen can help control these symptoms [3].

With long-term administration of IFN-alfa, late side effects occur that may be dose-limiting in 10% to 25% of patients [3]. The most common are chronic fatigue (61% of patients) and weight loss (50%). Less frequent (ie, less than 20%) side effects include diarrhea, alopecia, stomatitis, and neurotoxicity, usually in the form of recent memory loss or depression [91]. Patients 60 years old and older experience more side effects with IFN-alfa, particularly neurotoxicity [98,107]. Fewer than 2% of patients develop bone marrow aplasia, particularly when they had received prior busulfan therapy [108]. Autoimmune phenomena occur in fewer than 5% of patients and include hemolytic anemia, thrombocytopenia, hypothyroidism, Raynaud's phenomenon, arthritis, lupus erythematosus, and cardiac problems such as arrhythmias and congestive heart failure [109]. Interestingly, 91% of patients with hypothyroidism and 75% of those with diseases involving connective tissue had some degree of cytogenetic response [109].

When side effects develop, dose reduction may be indicated as follows: (1) for grade-3 or -4 toxicity, hold therapy until recovery and restart at 50% of the dose; (2) for persistent grade-2 toxicity, reduce the dose by 25%; and (3) for WBC counts lower than 2,000/µL or platelet counts less than 60,000/µL, reduce the dose by 25%.

Allogeneic BMT

Another treatment used in patients with CML is allogeneic BMT, which is curative. Results are more encouraging for patients in chronic than accelerated or blastic phase. Several studies have reported long-term survival rates of 50% to 80% and disease-free survival rates of 30% to 70% in patients with chronic-phase CML [110-117]. The results, however, are not uniform in all studies and are dependent on the patient's age at the time of BMT, the stage of disease, regimens used to prepare patients for BMT, and manipulation of bone marrow to enhance the chances of a good response.

Age at Time of Transplant: Younger patients have a better outcome with allogeneic BMT, but the age cutoff is controversial. Patients younger than 20 years have the best outcome, with long-term disease-free survival of 60% to 70% in most studies and a very low incidence of transplant-related mortality (approximately 10%) and leukemia relapse (20%) [110,115]. With increased age, the rate of complications increases, but the relapse rate remains similar. Data from the International Bone Marrow Transplant Registry suggest that after age 20, there is a significant drop in the disease-free survival rate [110,115]. Data from a Seattle study show that selected patients age 50 to 60 years may have 4-year disease-free survival rates of greater than 80% [13]. Most studies, however, show a decline in long-term survival after age 20 to 30 years [114,117]. Until the results from Seattle can be reproduced more widely, patients older than 20 to 30 years, depending on the experience at each institution, should be considered to have a higher risk of transplant-related complications.

Stage of Disease: The results with allogeneic BMT are also better for patients in the chronic phase than for those in the accelerated or blastic phase. Long-term survival rates are 50% to 60%, 15% to 40%, and less than 15% for those three groups, respectively [110,115]. Among patients in the chronic phase, early transplantation is important in achieving good results. Some groups advocate that transplantation within 1 year from diagnosis produces better results than later transplant [111,116]. This may be influenced by prior therapy: patients previously treated with busulfan do worse because of higher transplant-related morbidity; when these patients are excluded, the difference is less significant [111]. Prior treatment with IFN-alfa, however, does not adversely affect overall survival, disease-free survival, time to neutrophil or platelet recovery, incidence of graft-vs-host disease (GVHD), or the 100-day BMT-related mortality [114]. Data from the International Bone Marrow Transplant Registry show only a significant trend for better outcome for patients who undergo BMT within 1 year from diagnosis compared with those who have BMTs 1 to 3 years or more than 3 years after diagnosis [114], but this has not been confirmed in the European Bone Marrow Transplant Registry [110]. Recent data from Seattle suggest that patients who undergo BMT 1 to 2 years after diagnosis have a similar outcome to those who have BMT within the first year.
of diagnosis [11]. Even when the difference is found to be significantly in favor of transplantation during the first year, the disease-free survival rate improves by less than 10% [118] and may be less with time [119]. Interestingly, this difference is not due to more resistant disease, but to a higher BMT-related mortality.

**Preparative Regimens:** The initial studies of allogeneic BMT in patients with CML used conditioning regimens containing cyclophosphamide and total body irradiation [115,116]. An escalation in the dose of total body irradiation resulted in a decrease in the relapse rate but increased the risk of death due to causes other than relapse [112]. Substituting busulfan for total body irradiation resulted in an outcome comparable with that of patients whose regimens included total body irradiation [111]. In a randomized trial comparing the two alternatives, the busulfan-containing regimen resulted in a nonsignificant trend to better overall and disease-free survivals [113]. The use of total body irradiation was associated with significantly more patients with GVHD, fever, and prolonged hospitalization [113]. A recent report suggests that patients with advanced disease treated with busulfan may have more early toxic effects and increased transplant-related mortality [120]. Other preparative regimens produce similar results [121].

**Bone Marrow Manipulation:** Several groups have used T-cell depletion in an effort to decrease the incidence of GVHD in patients undergoing allogeneic BMT [122,123]. Although this approach can in fact reduce the incidence of GVHD, it also leads to an increased risk of relapse and graft failure [117,122,123]. More selective depletion of specific subtypes of T-cells may preserve the cells responsible for the graft-vs-leukemia effect [124]. Selective T-cell purging is an encouraging investigational trend.

Several approaches have become available for patients whose disease relapses after allogeneic BMT. A second transplant has been used with some success, particularly among patients who received a second BMT 1 year after the first [125]. Recent investigations have focused on immune-mediated mechanisms to control relapse. For instance, the infusion of leukocytes from the original bone marrow donor after disease relapses in patients with CML [126-130] has resulted in the disappearance of the malignant clone [126-129] even when assessed with the polymerase chain reaction (PCR) [126]. Another approach is to give IFN-alfa therapy to patients whose disease recurs after BMT [130,132]. In two studies using this alternative, 6 of 18 patients who had a hematologic relapse and 8 of 11 who had a cytogenetic-only relapse [132] responded to IFN. A recent study combined IFN-alfa and donor leukocyte infusions to treat eight patients with chronic-phase CML that recurs after BMT [133]. PCR showed no evidence of cells bearing the Ph chromosome in six of these patients [133].

Because only a small fraction of patients have donors for an allogeneic BMT, interest has focused on BMT using matched unrelated donors [134,135]. The 2-year disease-free survival rate is 37% to 45% [134,135], with better results among patients who receive transplants when the disease is in the early chronic phase (45% vs 36%) [134]. The best results are obtained in children [135]. Acute GVHD grades II to IV was seen in 77% to 82% [134,135], and extensive chronic GVHD was seen in more than 50%. One disadvantage to this approach is the long time to identify a donor; in one study, the median time from the start of the search to the BMT was 8.4 months [135]. Thus, although a promising alternative for patients without family donors, allogeneic BMT with matched unrelated donors is still a high-risk procedure with significant mortality and morbidity that is related to GVHD, which is most prevalent in patients 30 years or older and those with a mismatch of one or more antigens.

**Autologous BMT**

Some patients with CML have early progenitors (ie, CD34+, DR- cells) that do not express the bcr/abl gene and are thus probably unaffected by CML [136]. The early progenitors allow normal hematopoiesis to exist in these patients’ bone marrows, even though the marrow is dominated by the malignant CML clone. The normal early progenitors can be collected by leukapheresis during early recovery following intensive chemotherapy [137,138].

Cells collected in this way are more frequently Ph-negative than cells harvested from the bone marrow [138]. This has led to investigations on autologous BMT as a therapeutic alternative in these CML patients. Although 40% to 70% of these patients can achieve some degree of suppression of Ph-positive cells upon engraftment after the transplant, this is usually a short-lived phenomenon, and disease in most patients eventually recurs [137,139-142]. The use of stem cells may enable faster engraftment but does not prolong survival [142].

Interestingly, some patients previously refractory to IFN-alfa may regain sensitivity after autologous BMT [139]. Patients who receive a BMT with unpurged bone marrow show no survival advantage over those who receive conventional chemotherapy only [143]. Studies using retrovirus-marked...
autologous bone marrow have shown that the disease recurs at least in part from infused leukemic cells [144]. This suggests the need for better bone marrow purging. Several approaches have been used for this purpose [145], including the use of a long-term bone marrow culture that can select Ph-negative cells [146], although usually significant numbers of Ph-positive cells are still detectable [147]. In vitro purging with mafosfamide [148,149], interferon-γ [150], antisense oligodeoxynucleotides to c-myb [151] or bcr/abl [152-154], and other immunologic approaches [155] are also used, as is in vivo purging using intensive chemotherapy and early stem-cell collection. The ideal purging technique is not yet known, and active research in this area is currently being conducted. The use of IFN-alfa for maintenance therapy after autologous BMT has not resulted in sustained remissions.

**Minimal Residual Disease**

With the availability of more sensitive techniques, detection of minimal residual disease in CML, which has the advantage of having a specific marker (ie, Ph chromosome), has become possible [120]. However, the information regarding methods to detect minimal residual disease and its significance may be confusing, and the clinician has to be careful with interpretation of the results. After treatment with IFN-alfa, the bcr/abl gene can be detected in nearly all patients with the PCR [156,157], even although a few patients do become negative for this gene [158]. However, most patients will remain in complete remission even if bcr/abl is still present [157]. This may be explained by the extreme sensitivity of this technique, which may detect bcr/abl-positive cells that are either not clonogenic or not myeloid (eg, T-cells) long-lived cells. Some investigators have advocated the use of a semiquantitative PCR procedure that would identify an increase in the expression of bcr/abl, which may predict relapse [159,160]. The use of fluorescent in situ hybridization may reveal the Ph chromosome in proliferating cells, which may be more useful for predicting relapse [161,162], but this hypothesis needs further testing. Hypermetaphase fluorescent in situ hybridization is a technique that allows the analysis of 500 or more metaphases and thus offers an intermediate level of sensitivity between cytogenetics and the PCR. Interestingly, patients treated with IFN-alfa may continue to show bcr/abl-positive cells on PCR tests for some time [158] after they achieve a cytogenetic response [158]. Some patients have turned negative as late as 5 years after the initial response, but even after becoming negative on PCR tests, residual disease may be detected in some patients by clonogenic assay [158], which suggests a state of tumor dormancy. Unlike the situation with IFN-alfa, the PCR test has been more predictive of long-term outcome when used on samples from patients who have had a BMT, particularly when done 1 year after the BMT. Ph-positive cells may be detected soon after BMT, but they frequently disappear [163]. Persistent or increasing proportions of Ph-positive cells, however, may herald a relapse [163]. Single positive results on PCR within the first 6 months after BMT do not predict relapse [164-166], but positive PCR samples after 6 months may be predictive [167]. When serial studies are performed, persistent positivity on PCR tests will be followed by a relapse in 75% of patients, whereas disease in only 20% with both positive and negative results and in none with all negative results will recur [168]. Patients who receive unmanipulated BMT may still eventually become bcr/abl negative despite positive results on PCR tests after 1 year from the transplant [169,170].

**Patients in the Accelerated or Blastic Phase**

Patients in the accelerated or blastic phase of CML respond poorly to therapy. Regimens including high-dose cytarabine and daunorubicin induce remissions in only 25% to 35% of patients, with a median survival of 8 to 18 months for those in the accelerated phase and 3 months for those in the blastic phase [171]. Regimens that do not contain cytarabine produce similarly poor results in these patients [172]. Results with allogeneic BMT are also worse than for patients in the chronic phase. The 4-year survival rate is 20% to 40% [111,173]. Some studies report more optimistic results [174], but patient selection may be different. Patients who are in the accelerated phase only on the basis of clonal evolution and who undergo BMT less than 1 year after diagnosis of CML have a 4-year probability of survival of 74% [173]. As mentioned earlier, this is a group with a good outcome [44]. Autologous BMT has been used with the intention of reinitiating a second chronic phase [175]. Although most patients achieve this status, their disease eventually recurs after a median disease-free survival of 8 months [175].

**Ph-Negative CML**
In 5% to 10% of patients with otherwise typical clinical features of CML, the Ph chromosome is not found in cytogenetic studies [176-179]. One third of these patients have evidence of the \textit{bcr/abl} translocation when analyzed at the molecular level [177]. These patients have similar clinical features, response to IFN therapy, and long-term prognosis similar to those of patients with Ph-positive disease [178]. Patients without molecular evidence of the translocation are older, have a higher incidence of thrombocytopenia, lower WBC counts, and fewer basophils than Ph-positive or Ph-negative, \textit{bcr}-positive patients. Their median survival is significantly shorter than that of patients with Ph-positive or Ph-negative, \textit{bcr}-positive CML (25 months vs 73 and 68 months, respectively) [178]. However, disease in these patients does not evolve to a blastic phase as it does in Ph-positive or Ph-negative, \textit{bcr}-positive patients. Instead, their natural history is characterized by increasing leukemia burden, with progressive leukocytosis, organomegaly, extramedullary infiltrates, and bone marrow failure without a significant increase in blasts [179].

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Links: