CHRONIC MYELOGENOUS leukemia (CML) is a clonal myeloproliferative disorder of the primitive hematopoietic stem cell.\(^1\)\(^2\)\(^3\) It involves the myeloid, erythroid, megakaryocytic, B-, and sometimes T-lymphoid elements, but not the marrow fibroblasts.\(^4\)\(^5\)\(^6\) CML is characterized by (1) the heterogeneity of the disease among patients, (2) a biphasic or triphasic course, and (3) the presence of a chromosomal marker, the Philadelphia chromosome (Ph), in the leukemic cells.\(^1\)\(^2\)\(^3\) Proliferation is a shared feature of CML and other myeloproliferative disorders such as essential thrombocytosis, polycythemia vera, and myeloid metaplasia/myelofibrosis. Although these entities are usually distinct, overlap in presentation is occasionally observed, resulting in diagnostic confusion. Thus, it is important to confirm the diagnosis of CML by cytogenetic (Ph chromosome) or molecular studies, because the natural history and treatment of the myeloproliferative disorders are different.

PROGNOSTIC FACTORS AND MODELS IN CML

The disease heterogeneity led to analyses of the prognostic factors in CML (Table 1)\(^6\)\(^7\)\(^8\) and to the development of prognostic models that categorize patients into good-, intermediate-, or poor-risk groups with different survival expectations (median survival 2, 3 to 4, 4 to 5 to 6 years, respectively). A synthesis prognostic model, based on these studies, was proposed\(^9\) (Table 2).

CML PHASES AND DEFINITIONS

CML initially presents in an indolent or chronic phase course, easily controlled with therapy. With conventional treatment, it progresses into an accelerated phase that lasts for less than 1 to 1.5 years, and is followed by a blastic phase resulting in the patient's death within 3 to 6 months. Twenty percent to 25% of patients die from complications of accelerated phase, while another 20% to 25% develop a blastic phase without the intermediate accelerated phase events. The definition of accelerated phase is vague.\(^15\)\(^16\)

With more therapies reporting success in accelerated phase, a standardized definition, within which different approaches could be compared, is needed (Table 3).

CURRENT PROGNOSIS IN CML

In the past, the prognosis of patients with CML was poor. The expected median survival was 3 years, and less than 20% of patients were alive 5 years after diagnosis. Prognosis has improved in recent cohorts of CML patients because of (1) earlier diagnosis, (2) improved anti-CML therapy, and (3) better supportive care. With routine screening tests, more patients are detected in the asymptomatic phase of CML, and with lesser degrees of tumor burden (Table 4). In contrast to the previous limited number of effective anti-CML agents (hydroxyurea or busulfan), several additional active drugs and combinations are now available that may improve patient prognosis. These include interferons, low-dose cytosine arabinoside (ara-C), intensive chemotherapy, and autologous bone marrow transplantation (BMT). Presently, the median survival in CML is about 60 to 65 months. The survival rates are 75% to 85% at 3 years, and 50% to 60% at 5 years (Fig 1). With alpha interferon (IFN-\(\alpha\)) regimens, 20% to 25% of all patients remain alive with major durable cytogenetic responses on therapy, as discussed later.

PHILADELPHIA CHROMOSOME, MOLECULAR ABNORMALITIES, AND DISEASE PATHOPHYSIOLOGY

The Ph chromosome initially described a shorter long arm of chromosome 22. It is the result of breaks on chromosome 9 and 22, with a reciprocal translocation of the distal genetic material, t(9;22)(q34;ql1).\(^7\)\(^8\) This translocation transposes the c-\(\text{abl}\) proto-oncogene from its normal location, on chromosome 9, to a new position on chromosome 22, in proximity to the breakpoint cluster region (\(\text{bcr}\)) (Fig 2). A new hybrid BCR-ABL oncogene is formed. It produces an abnormal 8.5-kb RNA that encodes for a 210-Kd (p210) fusion protein. The latter, presumably through its increased tyrosine kinase activity, changes normal hematopoietic cells into CML cells.\(^9\)

In Ph-positive CML, the breakpoints within BCR have been assigned to 3' or 5' locations. Depending on whether the joinings are between exon 3 or exon 2 of the BCR and exon 2 of ABL, two different RNA messages are formed: b3a2 and b2a2. While the 3' breakpoints often result in b3a2 and 5' breakpoints in b2a2 messages, some patients with 5' breakpoints (zone 3) produce the b3a2 message. These abnormalities at the DNA and RNA levels have been associated with different prognostic implications, but the findings remain controversial.\(^20\)\(^24\)

In Ph-positive acute leukemia, 50% to 80% of patients have a breakpoint proximal to the BCR region, which results in a smaller 7.5-kb RNA and 190-Kd (p190) message.\(^19\)\(^25\) These changes have been associated with lymphoid lineage-specific involvement (in contrast to multilineage involvement with p210 disease), and with shorter periods to acute transformation in animal models. However, except for the development of second chronic phase disease in p210 Ph-positive acute leukemia, the clinical features and prognoses are similar in p210 versus p190 acute leukemias.\(^76\)

From the Sections of Leukemia and Biological Studies, the Division of Medicine, M.D. Anderson Cancer Center, Houston, TX. Submitted February 5, 1993; accepted April 30, 1993.

H.M.K. is a Scholar of the Leukemia Society of America.

Address reprint requests to Hagop M. Kantarjian, MD, M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Box 61, Houston, TX 77030.

© 1993 by The American Society of Hematology.

0006-4971/93/8203-0043$3.00/0

Blood, Vol 82, No 3 (August 1), 1993: pp 691-703

691
The mechanisms underlying the growth advantage of CML over normal hematopoietic cells are unknown. The Ph-associated molecular abnormalities reduce the adherence of CML cells to the stromal matrix, thus decreasing the time of stroma: hematopoietic cell interaction. This abrogates the normal maturation of cell surface signals (cytoadhesion molecules, HLA-DR) required for the normal proliferation-maturation sequence, allowing CML cells to remain longer in the late progenitor proliferative phase before differentiation. A discordant nuclear:cytoplasmic maturation in CML may also provide a growth advantage over normal hematopoietic cells. Although increased proliferation is proposed as the mechanism of CML growth advantage, CML cells may live longer than normal cells, and not undergo programmed cell death, or apoptosis, to the same degree. Thus, approaches that induce (1) suppression of Ph-positive cells or (2) normalization of their behavior via adherence to the stroma, maturation of deficient cell surface signals, differentiation of late progenitor cells, or induction of apoptosis, may be helpful and should be investigated.

RATIONAL FOR INVESTIGATIONAL TREATMENTS IN CML

In the 1970s, intensive chemotherapy was developed, as for acute leukemia, to attempt elimination of the Ph-positive CML clones. The degree of Ph suppression, or cytogenetic response, was intense but brief. It was also argued that the Ph-positive event was a late phenomenon, and that the Ph-negative cells obtained were still clonal. Thus, suppressing Ph-positive cells would not be therapeutically beneficial. This was later refuted by in vitro and in vivo studies showing that the Ph-negative cells were normal, nonclonal hematopoietic stem cells. This strengthened the rationale for attempts to suppress or eliminate the Ph-positive CML cells. It was postulated that while the bone marrow of patients with CML is overwhelmed by the growth advantage of the Ph-positive CML cells, a suppressed normal stem cell pool persisted, which could be exploited therapeutically. Treatments that reversed the growth advantage in favor of normal over Ph-positive cells would hopefully change the course of CML, and improve patient prognosis.

Preclinical models have established the causal association between the Ph-associated molecular events and the initiation and perpetuation of CML disease. In one such model, cDNA encoding p210BCR-ABL was introduced into mouse marrow cells, which were reinfused into lethally irradiated mice. After 2 to 8 weeks, some of the mice developed CML-like disorders, including (1) leukocytosis and splenomegaly, (2) monocytic and macrophage extramedullary tu-

---

**Table 1. Poor Prognostic Factors in CML**

<table>
<thead>
<tr>
<th>A. Clinical</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td></td>
</tr>
<tr>
<td>Symptoms at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Significant weight loss</td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
</tr>
<tr>
<td>Poor performance</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Laboratory</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Thrombocytosis, thrombocytopenia, megakaryocytopenia</td>
<td></td>
</tr>
<tr>
<td>Increased blasts, or blasts + promyelocytes in blood or marrow</td>
<td></td>
</tr>
<tr>
<td>Increased basophils in blood or marrow</td>
<td></td>
</tr>
<tr>
<td>Collagen or reticulum fibrosis grade 3-4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Treatment-associated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer time to achieve hematologic remission with busulfan chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Short remission duration</td>
<td></td>
</tr>
<tr>
<td>Total dose of busulfan or hydroxyurea therapy required in the first year to control the disease</td>
<td></td>
</tr>
<tr>
<td>Lack of significant suppression of Ph-positive metaphases with intensive chemotherapy or IFN-α therapy</td>
<td></td>
</tr>
<tr>
<td>Poor initial response to IFN-α therapy</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 2. Synthesis Prognostic Staging System for CML**

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Poor-Prognosis Characteristics</th>
<th>Prognostic Determinants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 or 1</td>
<td>Poor-Prognosis Characteristics</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1. Age &gt; 60 yrs</td>
</tr>
<tr>
<td>3</td>
<td>≥3</td>
<td>2. Spleen ≥10 cm below costal margin</td>
</tr>
<tr>
<td>4</td>
<td>Any accelerated phase characteristic</td>
<td>3. Blasts ≥3% in blood or ≥3% in marrow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Basophils ≥7% in blood or ≥3% in marrow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Platelets ≤700 x 10^3/μL</td>
</tr>
</tbody>
</table>

---

**Table 3. Definitions of Accelerated and Blastic Phases of CML**

<table>
<thead>
<tr>
<th>A. Blastic CML</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>30% or more blasts in the marrow or peripheral blood</td>
<td></td>
</tr>
<tr>
<td>Extramedullary disease with localized immature blasts</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Accelerated phase CML</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Multivariate analysis-derived criteria</td>
<td></td>
</tr>
<tr>
<td>Peripheral blasts 15% or more</td>
<td></td>
</tr>
<tr>
<td>Peripheral blasts plus promyelocytes 30% or more</td>
<td></td>
</tr>
<tr>
<td>Peripheral basophils 20% or more</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia &lt;100 x 10^3/μL unrelated to therapy</td>
<td></td>
</tr>
<tr>
<td>Cytogenetic clonal evolution</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Other criteria used in common practice</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing drug dosage requirement</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly unresponsive to therapy</td>
<td></td>
</tr>
<tr>
<td>Marrow reticulin or collagen fibrosis</td>
<td></td>
</tr>
<tr>
<td>Marrow or peripheral blasts ≥10%</td>
<td></td>
</tr>
<tr>
<td>Marrow or peripheral basophils ≥ eosinophils 10% or greater</td>
<td></td>
</tr>
<tr>
<td>Triad of WBC &gt;50 x 10^9/L, hematocrit &lt;25% and platelets ≤100 x 10^9/μL not controlled with therapy</td>
<td></td>
</tr>
<tr>
<td>Persistent unexplained fever or bone pain</td>
<td></td>
</tr>
</tbody>
</table>
CHRONIC MYELOGENOUS LEUKEMIA

CHRONIC MYELOGENOUS LEUKEMIA

quently used in countries where socioeconomic consider-
pression (10% or less of patients); organ fibrosis (lungs,
treated patients show persistence of Ph-positive cells in the
candidates for BMT because of its better toxicity profile. It
droxyurea has been the drug of choice in patients who are
but was associated with unpredictable prolonged myelosup-
Asymptomatic diagnosis
Splenomegaly
Hepatomegaly

Table 4. Changing Presentation of Patients With Ph-Positive
Chronic Phase CML by Year of Referral

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before 1983 (N = 326)</th>
<th>Since 1993 (N = 494)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>≥60</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Asymptomatic diagnosis</td>
<td>Yes</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>Hemoptorygaly</td>
<td>Yes</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Yes</td>
<td>76</td>
<td>54</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&lt;12</td>
<td>58</td>
<td>48</td>
</tr>
<tr>
<td>WBC count (&lt;10^9/μL)</td>
<td>≥100</td>
<td>69</td>
<td>56</td>
</tr>
<tr>
<td>Platelet count (10^11/μL)</td>
<td>≥700</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Peripheral blasts</td>
<td>Yes</td>
<td>65</td>
<td>56</td>
</tr>
<tr>
<td>Peripheral basophils (%)</td>
<td>≥7</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Marrow blasts (%)</td>
<td>≥5</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Marrow basophils (%)</td>
<td>≥3</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Additional chromosomal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormalities other than Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>from diagnosis</td>
<td>Yes</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

Chronic Phase

Cytogenetic responses were categorized as complete if Ph-
positive cells were 0%, partial if they were 1% to 34%, and
minor if they were 35% to 90%. The median survival of
patients treated with IFN-α in early chronic phase
CML is shown in Fig 1.

Results of IFN-α therapy in CML have now been re-
ported by several investigators. Differences in CHR and
cytogenetic response rates in various trials may be
related to (1) the CML phase in which patients are treated,
(2) the patient risk group and pretreatment characteris-
tics, and (3) the dose-schedule of IFN-α. Alimena et
al.42 randomized patients to receive IFN-α 2 × 10^6 U/m2
two times weekly, or 5 × 10^6 U/m2 three times weekly.
Among 33 patients treated at the lower dose schedule, 8
(24%) achieved CHR, compared with 14 of 30 patients
(47%) treated at the higher dose schedule (P = .06). Among
21 patients who failed to achieve a response at the lower
dose schedule and who were treated at the higher dose sched-
ule, 8 (38%) achieved CHR. On the daily dose schedule that
they used subsequently, 7 of the first 8 patients treated

has been observed occasionally when unpredictable pro-
longed myelosuppression is induced by busulfan therapy.
With hydroxyurea therapy, the cytogenetic responses are
minor and transient. While these treatments offer effective
disease control and survival prolongation, they have not
altered the inexorable transformation of CML into the ter-

IFN-α

therapy with the partially pure human leukocyte IFN, in
patients with chronic phase CML, demonstrated a complete
hematologic response (CHR) rate of 70%, and a cytogenetic
response rate of 40%. This was followed by several trials
with the recombinant α interferons (IFN-α) alone, or in
combinations with other biologic agents (IFN-γ, DFMO),
with initial or later cyclic intensive chemotherapy, hydroxy-
urea, and low-dose ara-C. These studies have confirmed
that CHRs are achieved in 70% to 80% of patients, cytoge-
netic responses in 40% to 60%, and major cytogenetic
responses (Ph suppression to <35%) in 30% to 40% (Table 5).
Cytogenetic responses were categorized as complete if Ph-
positive cells were 0%, partial if they were 1% to 34%, and
minor if they were 35% to 90%. The median survival of
patients treated with IFN-α regimens in early chronic phase
CML is shown in Fig 1.

until 1980, hydroxyurea and busulfan were the two most
effective anti-CML agents. They were superior to irradiation
or other drugs such as melphalan, 6 mercaptopurine,
and chlorambucil, provided excellent disease control with
minimal toxicity, were inexpensive, and were administered
orally. Busulfan provided longer periods of disease control,
but was associated with unpredictable prolonged myelosup-
pression (10% or less of patients); organ fibrosis (lungs,
heart, marrow); and Addison's-like disease. It is still fre-
quently used in countries where socioeconomic consid-
erations prevail, and in older patients who are not candidates
for BMT, and who do not want frequent follow-ups. Hy-
droxyurea has been the drug of choice in patients who are
candidates for BMT because of its better toxicity profile. It
is used in intermittent schedules to keep the white blood cell
(WBC) count below 10,000/μL, and in continuous
exposure schedules to control the WBC count at a range of 2
to 5 × 10^9/μL, ie, a minimal CML tumor burden.
Both agents produce hematologic remissions in 70% to
80% of patients with chronic phase CML. However, these
are "pseudoremissions" because cytogenetic studies in
treated patients show persistence of Ph-positive cells in the
majority (>90%) of marrow metaphases. Ph suppression

THERAPY OF CML

Conventional Therapy

Until 1980, hydroxyurea and busulfan were the two most
effective anti-CML agents. They were superior to irradiation
or other drugs such as melphalan, 6 mercaptopurine,
and chlorambucil, provided excellent disease control with
minimal toxicity, were inexpensive, and were administered
orally. Busulfan provided longer periods of disease control,
but was associated with unpredictable prolonged myelosup-
pression (10% or less of patients); organ fibrosis (lungs,
heart, marrow); and Addison's-like disease. It is still fre-
quently used in countries where socioeconomic consid-
erations prevail, and in older patients who are not candidates
for BMT, and who do not want frequent follow-ups. Hy-
droxyurea has been the drug of choice in patients who are
candidates for BMT because of its better toxicity profile. It
is used in intermittent schedules to keep the white blood cell
(WBC) count below 10,000/μL, and in continuous
exposure schedules to control the WBC count at a range of 2
to 5 × 10^9/μL, ie, a minimal CML tumor burden.
Both agents produce hematologic remissions in 70% to
80% of patients with chronic phase CML. However, these
are "pseudoremissions" because cytogenetic studies in
treated patients show persistence of Ph-positive cells in the
majority (>90%) of marrow metaphases. Ph suppression
achieved CHR (87%). In early chronic phase CML, IFN-α at $5 \times 10^6$ U/m$^2$ daily, or at the lower maximally tolerated individual dose, is associated with better hematologic and cytogenetic response rates.

Side effects. IFN-α is associated with early flulike side effects (fever, chills, postnasal drip, anorexia, lack of appetite) in most patients, which (1) are not dose-limiting, (2) can be managed symptomatically (bedtime dose, acetaminophen), and (3) are minimized by starting IFN-α at 50% of the dose for the first week. Reducing the initial WBC counts to 10 to 20 $\times 10^3$/$\mu$L with chemotherapy also reduces the leukocytosis-associated side effects (fever, chills, musculoskeletal pains). Tachyphylaxis develops within 1 to 2 weeks. Late side effects are dose-limiting in 10% to 25% of patients, and include persistent fatigue; weight loss; neurotoxicity (depression); a triad of depression, fatigue, and insomnia (manageable with small doses of antidepressants at bedtime); and occasional immune-mediated complications. These have included immune-mediated hemolysis or thrombocytopenia, collagen vascular disorders such as rheumatoid arthritis and systemic lupus erythematosus, and immune-mediated nephrotic syndrome and hypothyroidism. Rare cases of cardiac dysfunction (arrhythmias, congestive heart failure) have been reported and may be immune-mediated. These necessitate immediate discontinuation of IFN-α, standard treatment for heart failure, and steroid ther-

**Table 5. Results of IFN-α Studies in CML at MDACC**

<table>
<thead>
<tr>
<th>Study-Year (reference)</th>
<th>No. Patients</th>
<th>CHR</th>
<th>Any</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human IFN-α–1982 (40)</td>
<td>51</td>
<td>71</td>
<td>41</td>
<td>18</td>
</tr>
<tr>
<td>Recombinant IFN-α–1984 (41)</td>
<td>35</td>
<td>80</td>
<td>54</td>
<td>40</td>
</tr>
<tr>
<td>IFN-α + IFNγ–1985</td>
<td>36</td>
<td>68</td>
<td>47</td>
<td>31</td>
</tr>
<tr>
<td>IFN-α ± cyclic intensive chemotherapy–1986</td>
<td>68</td>
<td>82</td>
<td>66</td>
<td>43</td>
</tr>
<tr>
<td>IFN-α + hydrea–1988</td>
<td>79</td>
<td>86</td>
<td>62</td>
<td>41</td>
</tr>
<tr>
<td>IFN-α + low-dose ara-C–1989</td>
<td>44</td>
<td>70</td>
<td>55</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>313</td>
<td>77</td>
<td>56</td>
<td>35</td>
</tr>
</tbody>
</table>

**Table 6. Results of IFN-α Studies in CML**

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>No. Patients</th>
<th>CHR</th>
<th>Ph Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.D. Anderson Cancer Center</td>
<td>313</td>
<td>240 (77)</td>
<td>175 (56)</td>
</tr>
<tr>
<td>Alimena et al (42)</td>
<td>63</td>
<td>29 (46)</td>
<td>27 (43)</td>
</tr>
<tr>
<td>Niederle et al (43)</td>
<td>41</td>
<td>23 (56)</td>
<td>14 (34)</td>
</tr>
<tr>
<td>Ozer et al (44)</td>
<td>107</td>
<td>63 (59)</td>
<td>31/80 (44)</td>
</tr>
<tr>
<td>Freund et al (45)</td>
<td>27</td>
<td>10 (37)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Montastruc et al (46)</td>
<td>38</td>
<td>32 (84)</td>
<td>24 (63)</td>
</tr>
</tbody>
</table>
apy if indicated. Immune-mediated hypothyroidism does not require IFN-α discontinuation and is managed by replacement therapy.

Dose reductions are required for (1) grade 3 or 4 toxicity (hold therapy until recovery then start at 50%), (2) persistent grade 2 toxicity not improved with symptomatic support (25% dose reduction), or (3) if the WBC count decreases to below 2 x 10^3/µL or platelets below 60 x 10^3/µL (25% dose reductions). Elderly patients (age 60 years or older) tolerate therapy less well than younger patients.

**Long-term follow-up of cytogenetic responses.** To evaluate the long-term course of patients, and allow for maturation and follow-up of cytogenetic responses, patients treated until 1988 were reviewed. Cytogenetic studies were performed every 3 months in the first 2 years, then every 4 to 6 months. The duration of cytogenetic response is calculated from the time of achievement of any cytogenetic response (Fig 3, A and B), or from the time of achievement of the best cytogenetic response (Fig 3, C), until recurrence of more than 90% Ph-positive cells. Durable cytogenetic responses were noted in about 30% of patients (Table 8). Of 49 patients achieving complete cytogenetic remission (CR), 45 (92%) have durable cytogenetic responses for periods ranging between 2 and 8 years, whereas 4 have lost their cytogenetic response (ie, reverted back to 90% or more Ph-positive metaphases) (Table 8). Thirty-four of the 49 patients were in a continuous cytogenetic CR (ie, Ph status 0%) with repeated studies. Sixteen of the 34 patients were taken off IFN-α because of toxicities (5 patients) or patient or physician choice (11 patients); continuous cytogenetic CR for more than 2 years: 7 of the 16 continue in cytogenetic CR for 12+ to 56+ months (median 34 months); 6 had Ph recurrence but went back to 0% Ph-positivity (3 patients) or less than 35% Ph-positive (3 patients) with reinstitution of IFN-α; and 3 had recurrence of Ph-positive metaphases but are on observation off IFN-α therapy (cytogenetic but not hematologic relapse). Among the remaining 11 patients, 6 fluctuate with Ph-positive metaphases of 0% to 10%, whereas 5 have more than 10% Ph-positive metaphases, but are in continuous cytogenetic response on IFN-α therapy (2 with less than 35% Ph-positive metaphases). Thus, currently 28 (18 + 7 + 3) of the 49 patients (57%) are in continuous cytogenetic CR on or off IFN-α therapy; while 39 patients (28 cytogenetic CR, 11 cytogenetic PR) (80% of total) are in a durable major cytogenetic response.

**Associations of cytogenetic responses with prognosis.** Accounting for the time to achieve the best cytogenetic response (median time 22 months for complete, 18 months for partial, 12 months for minor cytogenetic responses, respectively), the duration of cytogenetic response was longest in patients achieving a complete cytogenetic response (Fig 3). This is not surprising because, in most other tumors, the lowest detectable tumor burden achieved (ie, CR) is the only response that is associated with durable remissions and with prolongation of survival or disease-free survival. Once such a low tumor burden is obtained in a substantial fraction of patients (40% to 60%), significant survival prolongation may be observed for the total population under treatment. A similar significant association between the cytogenetic response at 12 months and survival was also reported by the Italian Cooperative Study Group in CML. Using a landmark analysis, Ozer et al did not find a significant correlation between cytogenetic response and remission duration or survival. However, their analysis combined cytogenetic CR and PR as one category (which might have diluted the association), and only 14 patients were in cytogenetic CR.

Zuffa et al updated their comparative study that randomized patients to IFN-α at 5 x 10^6 U/m² daily (218 patients) or hydroxyurea (104 patients). The long-term follow-up showed major cytogenetic response at 4 years in 25% of patients receiving IFN-α and in 0% of those treated with hydroxyurea. The median survivals were significantly better in IFN-α-treated patients overall (not reached v 49 months, P = .004), and within low-intermediate (not reached v 50 months, P = .04), and high-risk groups (56 v 38 months, P = .02).

Investigating the long-term prognosis of patients, Lazzarino et al analyzed IFN-α as a treatment variable for prognosis, showing it to be significantly favorable in good- and intermediate-risk patients, but not in those with poor-risk disease.

**Interpretation of the maturing experience.** While the results of Zuffa and Lazzarino et al support association between IFN-α and improved survival, the fact that only 25% of patients have complete responses suggests that the beneficial effect on survival in the total denominator may not be reproducible in other studies. In general, to observe the effect in the whole population, at least 40% of patients should achieve a minimal tumor burden (ie, CR for solid tumors, cytogenetic CR for CML) if that response is associated with at least a 25% improvement in prognostic.is (10% overall improvement; P = .05; power 80%; 100 patients in study and control groups).

These findings have important therapeutic implications. If the positive effect of IFN-α on survival of the total population is shown in other studies, the treatment recommendations might change to advise continuing IFN-α therapy in all patients with CML, regardless of the cytogenetic response, aiming for the survival benefit. However, if the survival association is not solidly confirmed, then only patients

**Table 8. Parameters Associated With Differences in Response to IFN-α in Ph-Positive CML**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category</th>
<th>CHR</th>
<th>Any</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML phase (IFN-α 5 x 10^6 U/m² daily)</td>
<td>Early chronic</td>
<td>60-80</td>
<td>40-50</td>
<td>20-30</td>
</tr>
<tr>
<td></td>
<td>Late chronic</td>
<td>50-60</td>
<td>10-20</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>Accelerated</td>
<td>30-40</td>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Blastic</td>
<td>20-30</td>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
<td>Risk category in early chronic phase</td>
<td>Low</td>
<td>80-90</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>50-60</td>
<td>40</td>
<td>20-30</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>20-60</td>
<td>10-20</td>
<td>5-10</td>
</tr>
<tr>
<td>Dose of IFN-α</td>
<td>5 x 10^6 U/m² daily</td>
<td>80</td>
<td>50-60</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>5 x 10^6 U/m² Tw</td>
<td>70</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>2 x 10^6 U/m² Tw</td>
<td>30-40</td>
<td>20</td>
<td>5-10</td>
</tr>
<tr>
<td></td>
<td>&lt;2 x 10^6 U/m² Tw</td>
<td>20-30</td>
<td>&lt;10</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: Tw, 3 times weekly.
who achieve a major cytogenetic response would continue on IFN-α therapy (discussed later under "Proposed Sequence of Treatments in CML"). Future studies with IFN-α combinations would then aim to achieve complete cytogenetic response rates of 40% or more before other randomized clinical trials are planned.

In summary, the maturing experience with IFN-α regimens (1) shows median survivals of 60 to 65 months with 25% of patients being in durable cytogenetic remissions, and (2) suggests the superiority of IFN-α over conventional therapy, as measured by cytogenetic response and survival.

**Other IFNs**

The promising results with IFN-α encouraged the search for other IFNs or biologic agents with potential anti-CML activity. IFN-γ differs from α and β IFNs in its biologic properties, mechanisms of action, and cell surface receptors. Studies investigating γ-IFN in CML have shown definite but modest activity, with a CHR rate range of 20% to 30%. Combining IFN-α with γ-IFN in (1) a simultaneous dose schedule using the full dose of IFN-α and a low (in vitro synergistic) dose of IFN-γ, or (2) in a sequential fashion using alternate-day or alternate-week schedules of the two IFNs, has produced disappointing results. IFN-β has had limited investigation in CML with negative results. Studies with the "consensus" IFN, a synthetized molecule that presumably incorporates the active moieties of different subspecies of α IFNs, are underway.

**Combinations of IFN-α and Other Agents**

To improve the prognosis beyond that obtained with IFN-α alone, investigations have combined it with other...
CHRONIC MYELOGENOUS LEUKEMIA

The combination of IFN-α and hydroxyurea is attractive in clinical practice because of its ease of administration. This regimen provides (1) rapid disease control, (2) a better CHR rate, (3) a lower incidence of side effects attributed to leukocytosis (fever, chills, musculoskeletal syndrome), and (4) a longer duration of disease control. However, it is not associated with improved cytogenetic response rates (overall, major, durable).

Ara-C was combined with IFN-α because of its selective anti-CML effect in vitro, and its capacity to induce cytogenetic remissions in treated patients.58,59 With low-dose ara-C therapy in chronic phase CML, Sokal and Bigner58 and Cannistra et al59 observed cumulatively Ph suppression down to a median of 27% Ph-positive metaphases (range 0% to 84%) in 6 of 8 patients. Low-dose ara-C is associated with less myelosuppressive side effects than intensive chemotherapy, and provides longer exposure of CML cells to the effect of chemotherapy (only 3 initial courses, or once every 6 months) mandated by the serious myelosuppressive side effects.57

The combination of IFN-α and hydroxyurea is attractive in clinical practice because of its ease of administration. This regimen provides (1) rapid disease control, (2) a better CHR rate, (3) a lower incidence of side effects attributed to leukocytosis (fever, chills, musculoskeletal syndrome), and (4) a longer duration of disease control. However, it is not associated with improved cytogenetic response rates (overall, major, durable).

Ara-C was combined with IFN-α because of its selective anti-CML effect in vitro, and its capacity to induce cytogenetic remissions in treated patients.58,59 With low-dose ara-C therapy in chronic phase CML, Sokal and Bigner58 and Cannistra et al59 observed cumulatively Ph suppression down to a median of 27% Ph-positive metaphases (range 0% to 84%) in 6 of 8 patients. Low-dose ara-C is associated with less myelosuppressive side effects than intensive chemotherapy, and provides longer exposure of CML cells to the treatment (about 1 week every month) and, hence, potentially better suppression of CML clonal evolution. In late chronic-phase CML, the combination of IFN-α and low-dose ara-C was associated with significantly higher CHR rates compared with IFN-α alone, a trend for better cytogenetic response rates, and with significantly longer survival60 (Table 9). It also induced suppression of clonal evolution in 5 of 20 patients (25%) treated in accelerated phase (16 patients with clonal evolution only, see Table 11; 4 patients with other accelerated phase features with or without clonal evolution).

In a randomized study, Guilhot et al61 treated patients with early chronic-phase CML with IFN-α plus low-dose ara-C (39 patients) or with IFN-α alone (36 patients). Both groups had received hydroxyurea during remission induction to achieve rapid cytoreduction until CHR was obtained. Compared with IFN-α therapy alone, the combination of IFN-α plus low-dose ara-C was associated with a higher complete cytogenetic response rate (8% v 28%; P < .01) and with nonsignificant trends for a higher major cyto-

| Table 9. Therapy With IFN-α Alone or With Low-Dose ara-C in Late Chronic-Phase CML |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| CML Phase | Therapy | No. Patients | CHR | Cytogenetic Response | 3-yr Survival (%) |
| Late chronic | IFN-α + ara-C | 40 | 22 (55) | 6 (15) | 75 |
| | IFN-α | 39 | 11 (28) | 2 (5) | 44 |
| Accelerated (clonal evolution only) | IFN-α + ara-C | 16 | 8 (50) | 4 (25) | 74 |
| | IFN-α | 9 | 6 (66) | 2 (22) | 49 |

Allogeneic BMT

Allogeneic BMT is curative in CML, with significantly better disease-free survival rates in chronic, compared with accelerated or blastic phases (Table 10). Candidate patients should be offered matched or one antigen-mismatched related allogeneic BMT in chronic phase, before disease transformation.

The timing of allogeneic BMT in chronic phase is more controversial because of the risks of the procedure. In chronic phase CML, better results are achieved (1) in younger patients, (lower risk of early and graft-versus-host disease [GVHD]-associated mortality), (2) when BMT is performed in early chronic phase, and (3) in patients not exposed to busulfan therapy.62,66 A lower incidence of BMT morbidity and mortality from GVHD has been observed with T-cell-depleted BMT, which was counterbalanced by the higher incidence of graft failure and leukemia relapse.66,67

The lower disease-free survival rates with transplantation later in chronic phase CML are not due to a higher incidence of leukemia relapse (ie, more resistant clones from longer disease duration), but to a higher BMT mortality. This suggests that host- (age, organ function) or treatment-related factors (prior busulfan exposure) are partly responsible for this difference. This difference in survival rates, while statistically significant in the international BMT registry (IBMTR) in over 1,000 patients evaluated, is in the range of 5% to 10%, and may not be relevant to individual patients,68 particularly when accounting for age and prior therapy considerations. In a subset analysis of patients receiving non-T-cell–depleted allogeneic BMT, Goldman et al69 reported both the duration of chronic phase, and exposure to busulfan therapy, to be independent prognostic factors for patient outcome. The European BMT Registry (EBMTR) has not shown a survival difference by time to BMT, but patients

| Table 10. Results of Allogeneic BMT in CML |
|---------------------------------|-----------------|-----------------|-----------------|
| CML Phase | Disease-free Survival | Leukemia Relapse | Parameter | % With Parameter by Age of Patients (yrs) |
| A. Results by CML Phase | | | | |
| Chronic | 40-60 | 5-30 | <20 | 20-29 |
| Accelerated | 15-25 | 50-60 | >30 | |
| B. Results by Age in Chronic-Phase CML | | | | |
| Early mortality | 5-10 | 10-20 | 10-25 | |
| Late mortality | 5-10 | 10-20 | 10-25 | |
| Leukemia relapse | 20 | 20 | 20 | |
| Disease-free survival | 60-70 | 40-50 | 40 | |
with worse expected prognosis may have received transplants earlier in chronic-phase CML. The long-term follow-up studies from both registries show disease-free survival rates of 38% at 5 years, a figure lower than projections from earlier reports, with a continuous pattern of late relapses (relapse rates 10% at 2 years, 25% at 5 years). This late relapse pattern, not seen in acute leukemia, may be caused by the more primitive stem cell involvement in CML. Both of these updates have included patients who had undergone T-cell-depleted allogeneic BMT, and the disease-free survival rates in non-T-cell-depleted BMT are higher. In the EBMTR studies, patients with prior IFN exposure and those who underwent splenectomy before BMT did not have different outcomes compared with those who had not.

Allogeneic BMT with matched unrelated donors (MUD) has yielded encouraging results. The median time from the start of the search to BMT was 8.4 months. The procedure was associated with (1) a higher incidence of graft failure (16%), and (2) higher incidences of grade III and IV acute GVHD (54%) and of extensive chronic GVHD (52%). Overall, the 2-year disease-free survival rate was 31%, and ranged from 14% to 43% depending on the patient age and degree of HLA-matching. Thus, while promising, MUD allogeneic BMT is presently associated with significant morbidity and mortality, particularly in older patients. It is indicated in patients with a poor prognosis (acute leukemia in first relapse, CML transformation). Its benefit versus risk should be carefully weighed in chronic-phase CML, particularly among older patients, in relation to other investigational modalities, and to the natural course of the disease with current treatments.

Proper Sequence of Treatments in CML

All patients with CML transformed (accelerated, blastic) phases and those with a syngeneic donor should be offered allogeneic BMT if they are candidates for the procedure (age less than 50 to 55 years, available matched or one antigen mismatched related donor).

Younger patients (age cut-off defined by investigators according to their experience in different age subgroups) would be offered related allogeneic BMT in early chronic phase when possible, because of the high disease-free survival rates and low morbidity and mortality in these age groups.

For the remaining patients, an initial trial of IFN-α-containing regimen may be indicated. If patients achieve a significant response (any cytogenetic response at 6 months, Ph-positive cells less than 50% to 65% at 12 months) they will continue on therapy unless the response is lost. The others will be offered allogeneic BMT from related donors, or investigational treatments such as MUD allogeneic BMT, autologous BMT, or new agents (homoharringtonine, others) or combinations (Fig 4).

Patients who achieve a complete durable cytogenetic response documented over a 6-month period should have an autologous marrow storage. In them, IFN-α therapy should be held for at least 1 month before autologous marrow preservation for ease of procedure and storage of an adequate marrow for BMT (3 x 10⁶ nucleated cells or more/kg, 10⁴ or more G M C F C / kg).

IFN-α therapy was thought not to benefit patients in late chronic-phase CML. Recent studies showing a survival advantage of IFN-α versus hydroxyurea and of IFN-α plus low-dose ara-C in late chronic phase CML suggesting otherwise. Patients in late chronic-phase CML who are not candidates for allogeneic BMT (related, MUD), should consider an investigational trial before deciding on maintenance with IFN-α therapy (IFN-α plus low-dose ara-C or hydroxyurea) for optimal benefit (Fig 4).

Autologous BMT

Autologous BMT in CML transformed phases was associated with a high rate of reestablishment of a short-lasing second chronic phase. In chronic-phase CML, autologous BMT with infusions of predominantly Ph-positive autologous stem cells (peripheral, marrow) produced transient cytogenetic remissions. Follow-up studies have suggested a longer survival with autologous BMT. However, similar to autologous BMT studies in other tumors (acute leukemia in first CR, multiple myeloma, breast and lung cancers), it is difficult to dissociate the effect of patient selection, and lead time bias, from that of BMT. Comparative studies with patients treated with other modalities and matched for age, organ function, and time to BMT may help clarify the issue.

Autologous stem cell transplant using in vivo (chemotherapy, IFN) or in vitro purging (chemotherapy, IFNs, long-term liquid cultures, positive selection for CD34-positive normal stem cells, negative selection for CML cells) is an exciting strategy. The purpose is to infuse stem cells maximally enriched with normal hematopoietic cells and depleted of Ph-positive clones.

Using long-term liquid (Dexter) cultures for in vitro purging of CML marrows, Barnett et al screened 88 patients and identified 33 (38%) to be suitable for the large-scale purging procedure. Twenty of the 33 patients underwent purged autologous BMT (14 in first chronic phase; 6 in later...
phases). Graft failure was noted in 5 patients (20%). Of 14 evaluable patients by cytogenetic studies, 12 (86%; 60% of total) achieved a cytogenetic CR, and the other 2 had a cytogenetic PR. After a median follow-up of 16 months (range 6 to 51 months), Ph-positive recurrence was observed in 8 of the 12 patients, and 6 received IFN-α therapy. Five patients (20% of total) are currently disease free for 16 to 50 months, the latter 2 with IFN-α therapy.

Alimena summarized the Italian experience in patients with CML who underwent autologous BMT intensification if they had not achieved a desirable cytogenetic response with IFN-α therapy. Fifteen patients, whose median percent of Ph-positive cells was 72% after a median duration of 20 months of IFN-α therapy, had harvest and underwent autologous BMT; 5 remain in cytogenetic remission (Ph-positive less than 35% in 2, and more than 35% in 3). In that same analysis, of a total of 48 patients undergoing autologous BMT before (26 patients) or after IFN-α therapy (22 patients), 11 (23%) achieved favorable cytogenetic responses. These relatively mature studies, as well as others using different forms of in vitro purging (IFN-γ, CD34-positive stem cell selection, negative selection of Ph-positive cells), or in vivo purging (intensive chemotherapy), encourage further investigations of purged autologous BMT programs as an intensification procedure to increase the rate of durable cytogenetic responses and to prolong survival.

The potential use of oncogene-targeted approaches (antisense oligonucleotides, conjugated toxins) for in vitro purging or in vivo therapy in autologous BMT are of interest. Combinations of these approaches may result in selective relatively nontoxic anti-CML therapies.

Other Investigational Modalities

New agents such as homoharringtonine have shown promising anti-CML efficacy. Homoharringtonine, used in a low-dose prolonged-infusion schedule in patients with late chronic-phase CML, resulted in CHR in 68% of patients, and in cytogenetic responses in 31% (17% major). Its activity in combination with IFN-α in early chronic-phase CML is under investigation.

Other approaches of interest include differentiating agents (retinoids), agents that block cytokines that may mediate CML progression (interleukin-1 [IL-1] receptor antagonists; IL-1 soluble receptors), and new chemotherapeutic drugs.

QUESTIONS OF INTEREST IN THE MANAGEMENT OF CML

Ph Chromosome-Negative CML

About 10% of patients with a morphologic picture of CML do not have the Ph chromosome by cytogenetic analysis. One third of them will have BCR rearrangement by Southern blot molecular analysis (Ph-negative BCR-positive CML) and have a similar clinical picture, response to therapy, and outcome as Ph-positive CML. The remaining patients have a spectrum of disorders including myelodysplastic syndrome with a myeloproliferative component, chronic myelomonocytic leukemia, and true “Ph-negative, BCR-negative CML.” The latter, unlike Ph-positive CML, may have a low propensity for blastic transformation (25% to 50%), and an intermediate prognosis between chronic myelomonocytic leukemia (CMML) and Ph-positive CML.

Thrombocytosis in CML

Thrombocytosis in CML is a poor prognostic feature, and may be associated with thromboembolic or bleeding complications. In most patients, thrombocytosis responds to the regimen used in controlling CML. IFN-α is effective in controlling thrombocytosis in more than three quarters of patients. Angrelide, an agent that prevents megakaryocytic maturation, also reduces the platelet counts, but has no effect on marrow megakaryocytosis. In patients refractory or intolerant to the above treatments, thiopeta is effective at doses of 75 mg/m² intravenously every 2 to 3 weeks until response occurs.

CML and Pregnancy

Pregnant women with CML may be managed with repeated leukophereses during the first one or two trimesters of pregnancy. Leukopheresis may be performed when the WBC count exceeds 70 to 100 × 10⁹/L, or in symptomatic conditions. Hydroxyurea has been used in the later stages of pregnancy without untoward or teratogenic effects on the fetus. IFN-α is teratogenic in animal models. Two of our patients became pregnant while undergoing IFN-α therapy; the treatment was discontinued, and both delivered normal babies. However, patients on IFN-α therapy should have adequate contraception, because the treatment has the potential of inducing serious complications in the newborn (underweight babies, malformations).

Role of Splenectomy in CML

The spleen may be an initial site of CML transformation in a minority of patients (≤ 10%). These may be the patients with persistent significant splenomegaly despite adequate disease control in the BM and blood. Studies randomizing patients to splenectomy or no splenectomy in early chronic phase, or before allogeneic BMT have not shown a survival advantage. Splenectomy before allogeneic BMT may result in earlier hematopoietic recovery, but is associated with a higher incidence of GVHD in patients without palpable splenomegaly. Based on current knowledge, splenectomy in chronic-phase CML may be considered for persistent significant splenomegaly on optimal therapy, particularly with evidence of hypersplenism, or with suboptimal treatment delivery because of anemia or thrombocytopenia. Splenectomy in CML transformation may be associated with increased morbidity and mortality without an obvious therapeutic benefit.

When Should Molecular Studies Be Performed in CML?

In patients with a morphologic picture of CML but no Ph-positive metaphases, Southern blot analysis for BCR rearrangement will identify the subset of Ph-negative, BCR-positive CML patients. This will help direct their therapy (as for Ph-positive CML) and prognosticating on the course of the disease.
The value of molecular studies to detect 3’ versus 5’ breakpoints, or b3a2 versus b2a2 messages, is controversial. It should be pursued in investigational studies, but not as routine tests in clinical practice.

In the follow-up of patients on treatment, BCR rearrangement quantification has not yet been standardized in relation to cytogenetic studies. Once the equivalence of the two studies for measuring the degree of Ph-suppression is established, serial follow-ups with BCR quantification may be easier, faster, and less expensive. The test is currently useful to monitor the effect of therapy in patients with Ph-negative BCR-positive disease. Southern blot analysis is equivalent, but not superior, to cytogenetic studies in assessing minimal residual disease (ie, Ph-positive 0%).

Polymerase chain reaction (PCR) studies to detect residual disease at 10−4 to 10−3 level is an important investigational tool in Ph-positive CML. In our experience, PCR studies for BCR-ABL were positive in all 40 patients who had 0% Ph-positive metaphases by cytogenetic studies after IFN-α therapy. Other groups have reported some cases with PCR-negativity. Detection of residual disease at this level may not be clinically relevant because it has not predicted consistently for subsequent relapse. Among patients studied after allogeneic BMT, more than 75% will have at least one PCR-positive test within 12 months post BMT, and 40% to 50% will be positive at 12 months. Only 25% of the latter group will have CML relapse. Consequently, PCR studies for BCR-ABL should be pursued in investigational studies of therapeutic interventions in CML, but not in current community practice.

FUTURE DIRECTIONS

Future investigations should aim at improving and maximizing the intensity and duration of cytogenetic responses in CML, ie, suppressing the Ph-positive clones responsible for disease propagation and progression. This could be achieved through (1) optimizing IFN-α combination regimens (with low-dose ara-C, homoharringtonine, or other agents); (2) investigating new approaches in allogeneic BMT that improve the efficacy and safety of the procedure; (3) pursuing the leads in purged autologous BMT as an intensification procedure, followed by IFN-α or other maintenance therapies; (4) developing selective antioncogene targeted therapies; and (5) discovering new agents with specific anti-CML efficacy. The sum of such programs will hopefully improve significantly the prognosis in CML over the next decade.

REFERENCES

23. Mills KL, Birnie GD: Does the breakpoint within the major breakpoint cluster region (M-bcr) influence the duration of the chronic phase in Philadelphia-positive CML patients? Blood 78:3125, 1991
24. Clark SC, McLaughlin J, Crist WM: Unique forms of the abl...
59. Cannistra S, Tantravahi R, Robertson MJ, Griffin J, Canellos GP: Low-dose cytotoxic arabinoside induces cytogenetic remis-
sions in patients with stable phase chronic myeloid leukemia. Blood 76:259a, 1990 (abstr, suppl 1)


67. Advisory Committee of the International Bone Marrow Transplant Registry: Report from the International Bone Marrow Transplant Registry. Bone Marrow Transplant 4:221, 1989


70. Gratwohl A: Bone marrow transplantation for chronic myelogenous leukemia. The European Bone Marrow Transplantation Experience in Chronic Myelogenous Leukemia. 2nd International Conference. Bologna, Italy, 1992


72. Hughes T, Brito-Babapulle F, Marcus RE: Transient Ph negativity after autografting with blood-derived stem cells for patients with chronic myeloid leukemia in chronic phase. Bone Marrow Transplant 4:51, 1989 (suppl 1)


86. The Italian Cooperative Study Group on Chronic Myeloid Leukemia: Results of a prospective randomized trial of early splenectomy in chronic myeloid leukemia. Cancer 54:333, 1984


94. Hughes T, Gareth JM, Martiat P, Goldman JM: Detection


Chronic myelogenous leukemia: a concise update

HM Kantarjian, A Deisseroth, R Kurzrock, Z Estrov and M Talpaz