Chronic Myelogenous Leukemia: Update on Biology and Treatment

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Chronic myelogenous leukemia (CML) is a myeloproliferative disorder that follows a characteristic clinical course in which a chronic phase of variable duration precedes an accelerated, and ultimately blastic, phase.

Introduction

Chronic myelogenous leukemia (CML) accounts for 15% to 20% of leukemias in adults and occurs with an incidence of 1 to 2 cases per 100,000 population. This myeloproliferative disorder results from neoplastic transformation of hematopoietic progenitor cells and affects myeloid, monocytic, erythroid, megakaryocytic, and lymphoid lineages.

Chronic myelogenous leukemia occurs more frequently in males than in females (ratio of 1.3 to 1). Incidence increases with age, and the median age at presentation is between 45 and 55 years. Up to 30% of patients with CML are 60 years or older, which is an important consideration for the selection of therapeutic strategies, such as stem-cell transplantation and treatment with interferon-alfa (Intron A, Roferon-A).

The outlook for patients with CML has improved dramatically over the last decade, thanks to refinements in allogeneic stem-cell transplantation and growing expertise in the use of interferon-alfa. This review provides a concise update of the biology of CML, as well as current therapeutic options and management strategies.

Clinical Course

Chronic myelogenous leukemia typically follows a biphasic or triphasic course. A chronic phase of variable length precedes an accelerated phase, which is often followed by a blastic phase.

Chronic Phase

Chronic-phase disease is indolent, and up to 50% of patients in this stage have no symptoms and are diagnosed by routine blood testing. Among those who have symptoms, fatigue and anorexia, weight loss, abdominal fullness, left upper quadrant discomfort, early satiety, bleeding, and sweats are encountered most frequently. In the rare patient with very high white blood cell (WBC) counts, symptoms of hyperviscosity may occur; these include visual changes from retinal hemorrhage, headaches, stupor, tinnitus, and priapism. Physical examination reveals splenomegaly in 50% of patients with CML and hepatomegaly in a lesser percentage.

Marked leukocytosis, anemia, and thrombocytosis are common laboratory features at presentation. Granulocytes are present in all stages of maturation. The activity of leukocyte alkaline phosphatase (LAP score) is reduced in almost all patients and can be used to distinguish CML from other myeloproliferative disorders. The bone marrow of patients with CML is usually hypercellular and may reveal reticulin fibrosis, especially with disease progression.

Accelerated and Blastic Phases

Chronic myelogenous leukemia invariably transforms and becomes refractory to therapy with such agents as hydroxyurea (Hydrea) and busulfan (Myleran). It then enters an accelerated phase, which is characterized by basophilia and increases in peripheral blood blast and promyelocyte counts. The definition of accelerated-phase disease is vague and relies on several generally accepted clinical and laboratory criteria (Table 1).

In about 75% of patients, accelerated-phase disease is followed, after 3 to 18 months, by a blastic phase, which resembles acute leukemia and causes the death of the patient within 3 to 6 months. One-fourth of patients develop blastic-phase disease without an intervening accelerated phase.
The blast phase of CML is usually defined by the presence of extramedullary infiltrates of leukemic cells or blast counts in excess of 30% in peripheral blood or marrow. In one-third of cases, blasts are characterized by lymphoid morphology and expression of lymphoid markers, such as terminal deoxynucleotidyl transferase (TdT) or CD10 (common acute lymphoblastic leukemia antigen [CALLA]). The remaining two-thirds of patients have either the acute myeloblastic leukemia (AML) or acute undifferentiated leukemia (AUL) phenotype and form a heterogeneous group.[5] Patients with lymphoid blastic-phase CML may respond to treatment with regimens active against acute lymphoid leukemia (ALL).[6] The complete response rates with such therapies are 50% to 60%, and median survival durations range from 9 to 12 months.

Initial Diagnostic Work-up

The essential diagnostic work-up for CML at presentation includes a complete blood count (CBC) with platelets and differential blood count, marrow aspiration for morphology (percentages of blasts and basophils) and biopsy, and cytogenetic studies to demonstrate the Philadelphia (Ph) chromosome and other markers of clonal evolution. Approximately 5% of patients present with a morphologic picture consistent with CML without documentation of the Ph chromosome by cytogenetic studies. In these cases, molecular studies, either Southern blot analysis for detection of the bcr-abl rearrangement or assays (eg, Western blot analysis to detect the bcr-abl protein) to characterize the specific fusion messenger RNA (mRNA) and protein product (p210bcr-abl, p190bcr-abl, or p230bcr-abl), should be performed.

The Philadelphia Chromosome

The Ph chromosome results from a reciprocal translocation between the long arms of chromosome 9 and chromosome 22. This transposes the large 3' segment of the c-abl gene from chromosome 9q34 to the 5' part of the bcr gene on chromosome 22q11 in a head-to-tail fashion, creating a hybrid bcr-abl gene that is transcribed into a chimeric bcr-abl mRNA (Figure 1). Initially described by Nowell and Hungerford in 1960, the Ph chromosome became the first chromosomal abnormality to be associated with a specific neoplastic disorder.[7] Translocation t(9;22)(q34;q11) can be demonstrated in more than 90% of patients with CML. It is also seen in up to 5% of children and 15% to 30% of adults with ALL and in 2% of patients with AML who showed no evidence of a preceding CML phase.[8]

Role of the bcr-abl Fusion Gene in CML Pathogenesis

The c-abl gene is a proto-oncogene that encodes a nonreceptor tyrosine kinase with a molecular mass of 145 kd (p145c-abl) that is localized in both cytoplasm and nucleus. It consists of 11 exons (also referred to as a1 to a11) and spans 230 kilobases (kb). Exon 1 has two alternative forms, 1a and 1b. In most cases, the breakpoint in the abl gene occurs in the 5' part of abl exon a2, within the segment between exons 1a and 1b.[8] Abl exons a2 to a11 are transposed into a region of the bcr gene between exons 12 and 16 (also referred to as b1 to b5) on chromosome 22, which extends over 5.8 kb and is called the major breakpoint cluster region (M-bcr). The breakpoint locations fall either 5' between exons b2 and b3 or 3' between exons b3 and b4, creating a bcr-abl fusion mRNA of 8.5 kb with either a b2a2 or b3a3 junction (Figure 1). The fusion mRNAs are translated into a 210-kd chimeric protein called p210bcr-abl.[8] In about 50% of children and 80% of patients with Ph-positive ALL, the breakpoint on chromosome 22 falls 5' of the M-bcr within a long intron segment separating alternative exon e2' from exon e2; this is called the minor breakpoint cluster region (m-bcr).[9] Splicing out exons e1' and e2' creates an e1a2 junction of the bcr-abl transcript and a smaller bcr-abl fusion protein of 190 kd termed p190bcr-abl.

A third breakpoint location in the bcr gene is identified 3' from the M-bcr region, between exons e19 and e20 (also referred to as c3 and c4); this breakpoint creates a fusion transcript with an e19a2 junction. The translation product is a 230-kd protein termed p230bcr-abl. Although expression of these proteins is rare in CML, association of the p190bcr-abl variant with a prominent monocytic component and of p230bcr-abl with the chronic neutrophilic leukemia variant have been described.[10,11]

Both p210bcr-abl and p190bcr-abl demonstrate significantly higher tyrosine phosphokinase activity than the normal c-abl protein.[8] Several other functional sequences of the bcr-abl protein assume transforming capacity by generating multiple protein-protein interactions that initiate diverse signaling pathways.[12] Evidence for a direct link between the expression of bcr-abl fusion gene products and abnormal
proliferation and malignant behavior of hematopoietic progenitor cells comes from experiments using in vitro and in vivo models of tumor development. In vitro bone marrow culture assays have shown that \textit{bcr-abl} causes factor-independent and leukemogenic cell growth in hematopoietic cell lines.[13]

Several in vivo animal systems using transgenic mouse models or retrovirus-mediated gene transfer of \textit{bcr-abl} into murine hematopoietic cells have demonstrated that diverse hematologic malignancies can be generated, among them a syndrome that closely resembles the chronic phase of human CML (reviewed in reference 14). These data support the hypothesis that the \textit{v-abl} and \textit{bcr-abl} gene transcripts are central mediators of myeloid proliferation and transformation in CML.

**Detection of \textit{bcr-abl}**—Cytogenetic analysis demonstrates the Ph chromosome in 90% of patients with CML. Such analysis is tedious and time-consuming, allows the examination of only 20 to 25 metaphases per bone marrow sample, and misses the 5% of patients who are Ph-negative but \textit{bcr-abl}-positive. Despite these shortcomings, cytogenetic analysis is the gold standard in the diagnosis of CML.

Molecular tools are important for detecting the molecular abnormalities associated with Ph and also for monitoring the course of disease during treatment. These include polymerase chain reaction (PCR), as well as Southern blot and Western blot analyses. Quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) is the method of choice for following patients with CML after stem-cell transplantation.[15] Its use for monitoring patients receiving interferon-alpha is not well-defined.

Fluorescence in situ hybridization (FISH) allows for the analysis of both metaphase and nondividing interphase cells.[16] Results of FISH studies are easily quantifiable. Interphase fluorescence in situ hybridization (i-FISH) is performed on peripheral blood specimens and, thus, avoids the need for bone marrow aspirations. It is fast and permits the analysis of more cells than is possible with conventional cytogenetics. Interphase FISH has a false-positive incidence of up to 10%.

Hypermetaphase fluorescence in situ hybridization (h-FISH) analyzes up to 500 metaphases per sample. In contrast to i-FISH, h-FISH produces no false-positive results. However, peripheral blood samples are not suitable for analysis with h-FISH.[17]

A recently introduced FISH technique uses double-color probes for the detection of Ph-positive leukemias.[18] Despite promising results, not enough data are available to validate its impact on disease monitoring.

**Cytogenetic Events in Disease Transformation**

The Ph chromosome is the predominant cytogenetic abnormality during chronic phase. Clonal evolution is observed in 50% to 80% of patients during the transition from chronic to accelerated and blastic phase (Table 2). These changes may precede the hematologic and clinical manifestations of transformed CML.

Mitelman[19] described cytogenetic route changes in CML evolution. Minor changes were monosomies of chromosomes 7, 17, and Y; trisomies of chromosomes 17 and 21; and translocation t(3;21)(q26;q22). Major changes were trisomy 8, isochromosome i(17q), trisomy 19, and an extra Ph chromosome (double Ph). Trisomy 8 is most common, especially during myeloid transformation. Isochromosome i(17q) is seen almost exclusively in myeloid-type blastic phase.

In some cases, alterations in molecular mechanisms correspond to cytogenetic changes during the progression of CML. These include abnormalities of p53 (on chromosome 17p13), RB1 (13q14), \textit{c-myc} (8q24), p16\textsuperscript{NK4A} (9p21), \textit{ras}, and AML/EVI-1, a fusion protein resulting from translocation t(3;21)(q26;q22). The incidence of these molecular abnormalities appears to be low, however.

**Treatment**

The natural history of CML has changed over the last decade. In the past, median survival time in CML was 3 years, with fewer than 20% of patients alive at 5 years following diagnosis. Currently, median survival duration is approximately 5 to 7 years, with 50% to 60% of patients alive at 5 years and over 30% alive at 10 years following diagnosis.[1] The factors responsible for this change include: earlier diagnosis, better supportive care, and more effective anti-CML therapies. Prognostic models derived from multivariate analyses allow stratification of treatment options to a patient’s risk profile (Table 3).[20,21]

**Conventional Therapy**

Both busulfan, an alkylating agent, and hydroxyurea, a cell-cycle–specific inhibitor of DNA synthesis,
achieve hematologic control in 50% to 80% of patients. However, cytogenetic remissions are rare, and both agents have little or no effect on disease progression. Patients treated with these drugs will inevitably experience transformation to the blastic phase and die from its complications after a median of 3 to 6 years.

Busulfan has considerable side effects (eg, delayed myelosuppression, idiosyncratic pulmonary reactions, and myelofibrosis) and has largely been superseded by hydroxyurea. Median survival times and median duration of chronic phase CML are longer with hydroxyurea than with busulfan. In contrast to busulfan, exposure to hydroxyurea prior to stem-cell transplantation has no adverse effects and is associated with better post-transplant outcome in patients undergoing allogeneic transplantation.[22,23]

Splenectomy has little role in the management of patients with CML. It may be beneficial in the occasional patient with persistent massive or symptomatic splenomegaly and refractory cytopenias.

**Interferon-Alfa**

The interferons are a family of naturally occurring proteins that are produced by eukaryotic cells in response to exposure to antigens and mitogens, such as occurs in viral infections and malignant diseases. Interferons have pleiotropic biological effects that include inhibition of cellular proliferation, regulation of cytokine expression, and modulation of the immune surveillance system.[24] Of the three groups of distinct interferon species that have been identified—interferon-alfa, interferon-beta, and interferon-gamma—interferon-alfa has been used most extensively in the treatment of solid and hematologic malignancies.

Talpaz et al[25] first described the therapeutic benefits of interferon-alfa in patients with CML. They later reported cytogenetic remissions in CML patients treated with interferon-alfa, and, thus, identified it as the first agent capable of achieving cytogenetic responses in CML outside of trials of allogeneic stem-cell transplantation.

Numerous studies have since been conducted by several groups. These include single-arm trials of interferon-alfa, randomized trials comparing interferon-alfa with conventional therapy, and trials of interferon-alfa in combination with other agents, such as cytarabine (Ara-C). The use of unified response criteria for hematologic and cytogenetic remissions allows for more accurate comparisons among studies (Table 4).

**Single-Arm Trials**—Initial studies with interferon-alfa in early chronic-phase CML reported promising results. In studies conducted at the M. D. Anderson Cancer Center, 274 patients received interferon-alfa daily at a dose of 5 MU/m² or the maximally tolerated lower dose. Complete hematologic responses (Table 4) were seen in 80% of patients and cytogenetic responses in 58% (complete in 26% and major in 38%).[26] The estimated median survival was 89 months. Achieving a cytogenetic response after 12 months of therapy conferred a statistically significant survival benefit: 5-year survival rates were 90% for patients with a complete cytogenetic response, 88% for those with a partial cytogenetic response, 76% for those with a minor cytogenetic response, and 38% for those in other response categories (Table 4).

Three other trials reported similar results, thus confirming higher response rates with higher doses of interferon-alfa and the influence of achievement of a cytogenetic response on survival (Table 5).[27-29]

**Interferon-Alfa vs Conventional Therapy**—Four recent randomized trials compared interferon-alfa therapy with conventional chemotherapy (Table 6).[30-33] In all four trials, patients treated with interferon-alfa achieved higher rates of hematologic response and of major and complete cytogenetic responses.

A meta-analysis of seven randomized trials comparing interferon-alfa vs chemotherapy for CML confirmed that patients treated with interferon-alfa had a significantly better survival than those given either hydroxyurea (P = .001) or busulfan (P = .00007) alone.[34] Five-year survival rates were 57% with interferon-alfa vs 42% with chemotherapy.

**Interferon-Alfa Combined With Ara-C**—The combination of interferon-alfa and Ara-C demonstrates further effectiveness in the treatment of early as well as late chronic and accelerated phases of CML. In a recent study from M. D. Anderson Cancer Center, Kantarjian et al[35] analyzed the efficacy of daily treatment with interferon-alfa (5 MU/m²) combined with low-dose Ara-C (10 mg) in 140 patients with Ph-positive early chronic CML. Results were compared with those in patients receiving interferon-alfa with or without intermittent Ara-C (7 d/mo).

Complete hematologic responses were observed in 92% of patients treated with interferon-alfa plus daily Ara-C and cytogenetic responses in 74% (major in 50%, complete in 31%). The estimated 4-year survival rate was 70%. The incidence of complete hematologic response was higher with
interferon-alfa plus daily Ara-C than with intermittent or no Ara-C. (92% vs 84% vs 80%; P = .01); similar results were noted for cytogenetic response (74% vs 73% vs 58%; P = .03) The time to achievement of a major cytogenetic response was significantly shorter than that obtained with previous interferon-alfa regimens. Guilhot et al[36] randomized 721 patients with Ph-positive early chronic-phase CML to treatment with either hydroxyurea (50 mg/kg) and interferon-alfa (5 MU/m²/d) or hydroxyurea, interferon-alfa, and monthly courses of Ara-C (20 mg/m² for 10 d/mo). The rate of complete hematologic response was 66% in the interferon-alfa/Ara-C group vs 55% in the interferon-alfa/hydroxyurea group (P = .003). The cytogenetic response rate was 66% in patients treated with low-dose Ara-C (major in 41%, complete in 15%), which was significantly lower than the 52% rate (major in 24%, complete in 9%) in patients treated with interferon-alfa/hydroxyurea (P < .001). Patients in the interferon-alfa/Ara-C group had significantly a better survival rate than patients in the interferon-alfa/hydroxyurea group (3-year survival rates, 86% vs 79%; P = .02).

Summary—Data from the aforementioned trials confirm: (1) the achievement of cytogenetic responses with interferon-alfa; (2) a survival advantage among patients overall, as well as among those who attain a cytogenetic response; (3) and a positive correlation between interferon-alfa dose and cytogenetic response.

Practical Issues in Managing Patients Receiving Interferon-Alfa

Selection of Patients and Definition of End Points—At diagnosis, it is difficult to predict which patients will benefit from interferon-alfa. Even patients with poor prognostic features, such as age, splenomegaly, thrombocytosis, and high blast and basophil counts, may achieve a major cytogenetic response. Consequently, all eligible patients should be offered the option of interferon-alfa therapy, provided that they have certain responses at defined time points. Achieving a complete hematologic response at 6 to 8 months, a cytogenetic response at 12 months, or a major cytogenetic response at 24 months is associated with a significantly better outcome.[37] Determining whether or not a patient responds to interferon-alfa may require prolonged administration and follow-up (ie, 12 to 18 months). Patients who do not achieve a cytogenetic response within that time period may be taken off interferon-alfa therapy and treated with alternative modalities, such as allogeneic stem-cell transplantation.

Starting Therapy With Interferon-Alfa—Initial, rapid tumor reduction is not the objective of interferon-alfa therapy. In fact, interferon-alfa is poorly tolerated if started in the presence of elevated WBC counts, which, in patients with CML, are frequently > 100 x 10⁹/L. Hydroxyurea should be used to lower WBC counts to < 20 x 10⁹/L, at which point interferon-alfa can be safely initiated (Table 7). Hydroxyurea can be continued during the initial phase of interferon-alfa therapy to prevent rebound leukocytosis and minimize associated toxicities. However, the need for more than 3 months of hydroxyurea therapy to control blood counts in the presence of full-dose interferon-alfa (ie, 5 MU/m²/d) may be a poor prognostic sign.

Interferon-alfa should be started at 25% of the target dose (3 MU/d) and gradually increased to the maximally tolerated dose over 2 to 4 weeks (Table 7).[38]

Dose Modifications and Duration of Therapy—Effective tumor reduction and control of minimal disease burden have significant effects on survival. Achievement of a major cytogenetic response and complete hematologic response is dose-dependent.[26] The dose of interferon-alfa should not be reduced in patients, except for WBC counts of < 2 x 10⁹/L and platelet counts of < 50 x 10⁹/L. In patients who experience grade 3 to 4 toxicities, interferon-alfa should be withheld until symptoms resolve; it can then be restarted at 50% of the previous dose, to be escalated to 75% of that dose. Although higher doses of interferon-alfa are associated with better cytogenetic responses, the optimal dose of interferon-alfa is still controversial, and combination regimens (interferon-alfa and Ara-C) may allow reductions in interferon-alfa dose while improving response.

Interferon-alfa therapy should continue for 2 to 3 years after achievement of a complete cytogenetic remission. Therapy may then be stopped, to be resumed in case of cytogenetic relapse. It is uncertain how long cytogenetic remissions last and whether premature discontinuation of the drug may jeopardize treatment success. If the decision is made to stop therapy, careful follow up and regular cytogenetic analysis are important in order to resume treatment promptly if disease recurs. Polymerase chain reaction and FISH are sensitive techniques for following patients. Fluorescence in situ hybridization may become the standard of monitoring patients during therapy. At M. D. Anderson Cancer Center, CML patients receiving therapy with interferon-alfa undergo cytogenetic studies of bone marrow aspirates every 3 to 6 months. Interphase FISH studies are performed on
peripheral blood specimens every 3 months until the level of Ph-positive cells decreases below 10%; after that, h-FISH studies are done.

**Side Effects of Interferon-Alfa**—Interferon-alfa has to be discontinued because of severe side effects in 10% to 15% of patients, and up to 50% require dose reductions due to poor tolerance. Early, flu-like symptoms include fever, chills, postnasal drip, and anorexia. These are not dose-limiting, can be managed symptomatically (Table 7), and abate within 1 to 2 weeks. Common chronic side effects are fatigue, depression, insomnia, weight loss, alopecia, reduced libido, and impotence (Table 7). Neurotoxicity (lack of concentration, depression, and psychosis) is more common in patients with previous psychiatric problems and those ≥ 60 years old. Autoimmune phenomena are observed in < 5% of patients treated with interferon-alfa. These include hemolytic anemia and thrombocytopenia, Raynaud’s phenomenon, collagen vascular disorders (lupus erythematosus, rheumatoid arthritis), hypothyroidism, and nephrotic syndrome. Cardiac arrhythmias and manifestations of congestive heart failure are rare but mandate discontinuation of therapy, as do severe autoimmune phenomena, severe neurotoxicity, and refractory depression.[39]

Extreme caution and close follow-up should be exercised when treating pregnant women with interferon-alfa (if it is used at all). Alternative treatments for pregnant patients with CML include supportive care, or pheresis in the first 3 months, followed by hydroxyurea until delivery and resumption of interferon-alfa thereafter.

**Allogeneic Stem-Cell Transplantation**

Allogeneic stem-cell transplantation achieves long-term overall survival rates of 40% to 80% and disease-free survival rates of 30% to 70%; relapse rates range from 15% to 30%. Relapse events plateau at approximately 5 years post-transplant. Late relapses can occur up to 9 years following transplantation.[40]

The applicability of allogeneic stem-cell transplantation is limited by the availability of matched siblings and by age restrictions that preclude this option in many cases. Only a fraction of patients (< 30% in Europe and North America) receive bone marrow transplants from matched sibling donors.

**Factors Influencing Outcome**—Several factors influence the outcome of stem-cell transplantation.[41] First, younger patients (< 50 years old) do best; disease-free survival is 60% to 70%, transplant-related mortality is 10%, and probability of relapse is 20%. The decrease in disease-related survival rates in older patients is due to increased transplant-related mortality, not higher relapse rates.[1]

Studies from Seattle reported outcome data for patients ≥ 50 years old that are as favorable as data for younger patients.[42] These results have not been reproduced by other transplant centers. Second, disease phase determines the outcome of stem-cell transplantation: Disease-free survival rates decrease from 40% to 60% in chronic-phase disease to < 15% in blastic-phase disease.[1,23,42] Post-transplant outcome is better when clonal evolution is the single criterion for accelerated-phase disease. Timing of stem-cell transplantation in chronic-phase disease is more controversial. Most centers propose transplantation in early chronic phase, ie, within 1 year of diagnosis; otherwise, increases in transplant-related mortality may diminish the success of stem-cell transplantation. However, data from the European Bone Marrow Transplant Registry (EBMTR)[41] show similar rates of 5-year disease-free survival in patients with chronic-phase disease who underwent transplantation at different times after diagnosis. Clift et al[42,43] updated the Seattle data and identified a critical cut-off point at approximately 2 years.

Third, chemotherapy prior to transplantation influences post-transplant disease-free survival. Data from the International Bone Marrow Transplant Registry (IBMTR) show that the disease-free survival rate at 5 years is significantly higher in patients who are pretreated with hydroxyurea than in those who receive busulfan pretreatment (61% vs 45%). A similar adverse effect of pretransplant interferon-alfa has not been observed.[44] Interestingly, in the updated IBMTR data, outcome of transplant within or after 12 months of diagnosis did not differ.

Fourth, outcome is influenced by the preparative regimen and prophylaxis for graft-vs-host disease (GVHD).

**Salvage Therapy**

Rates of relapse after allogeneic stem-cell transplantation range from 10% in chronic phase to 70% in accelerated phase.[45] Prognosis in such cases is not as poor as was previously reported, and several salvage treatment modalities are available.

**Second Transplants**—The outcome of second transplants from HLA-identical siblings depends on the interval between initial transplant and relapse. Mrsic et al[46] analyzed 114 recipients of second matched-related stem-cell transplants. In patients whose disease relapsed < 6 months after their
first transplant, the rate of disease-free survival was 7%, transplant-related mortality was 69%, and the probability of relapse was 77%. Among patients who relapsed > 6 months after the first transplant, disease-free survival rate was 28%, transplant-related mortality was 30%, and the probability of relapse was 59%.

**Interferon-alfa** may induce long-lasting cytogenetic remissions in 20% to 40% of patients who have a cytogenetic relapse in chronic phase following an allogeneic stem-cell transplant.[47]

**Donor lymphocyte infusions** are the most effective form of adoptive salvage immunotherapy for patients who relapse after allogeneic stem-cell transplantation.[48] Cytogenetic response and complete hematologic response rates range from 60% to 80% and appear to be durable, with 3-year disease-free survival rates of 38% to 87%. Responses are less frequent and short-lived in transformed CML phases.

Toxicities of donor lymphocyte infusions can cause substantial morbidity and mortality, and include myelosuppression and severe GVHD. The reported 1-year mortality for CML patients treated with donor lymphocyte infusions can be as high as 20%.[49] Strategies to mitigate these toxicities include: (1) separation of graft-vs-leukemia (GVL) and GVHD effects by selective depletion of CD8-positive T-lymphocytes; (2) earlier infusion at cytogenetic relapse; and (3) use of lower or gradually incremental donor lymphocyte infusion cell doses.[48]

**Suggested Management Approach for Newly Diagnosed Patients**

The results of interferon-alfa in early chronic-phase CML should be evaluated in the context of the potentially curative role of allogeneic stem-cell transplantation. Other factors to consider are the morbidity and mortality associated with transplantation in some patients, especially those of advanced age and/or those with other comorbid conditions.

The estimated median survival of patients receiving interferon-alfa therapy is 7 years, and the estimated median survival of “good-risk” patients (50% of patients) is 9 years, without associated transplant-related mortality.[50] In patients who achieve a major cytogenetic response at 12 months of interferon-alfa therapy, the projected 6- to 8-year survival rate is > 85%.[26,36,51] However, delaying allogeneic stem-cell transplantation raises some concerns. These include: (1) the unpredictable disease course and sudden transformation; (2) the worsening of stem-cell transplant outcome; (3) the induction of fibrosis by interferon-alfa; and (4) the adverse effect of interferon-alfa itself on the outcome of related-donor or unrelated-donor stem-cell transplantation.

In our studies, the incidence of blastic transformation was only 4% in the first year; half of the patients had lymphoid transformation and underwent effective salvage therapy.[6] Whether delaying stem-cell transplantation worsens outcome is a controversial issue.[49] Most studies evaluating the outcome of allogeneic stem-cell grafting failed to confirm any adverse effect of interferon-alfa and timing in the setting of matched-related transplants.[42,43,52-54] The effect of interferon-alfa in patients who undergo matched-unrelated donor (MUD) transplants remains questionable, and is currently being investigated in the setting of transplant registries.[55,56] Finally, our studies showed no induction of fibrosis with interferon-alfa therapy.[57] **Figure 2** summarizes a proposed treatment algorithm for newly diagnosed patients with CML.

**New Treatment Strategies**

**Matched-Unrelated Donor Transplantation**

Disease-free survival rates at 2 years following transplant vary from 14% to 43%, depending on patient age and degree of matching. Relapse is rare.[55,58,59] However, morbidity and mortality of MUD transplants are significant. Transplant-related mortality is well above 50% in certain subgroups.[55]

Patients at good risk for receiving unrelated donor transplants are younger (< 30 years old), are in early chronic phase, are matched at the HLA-DRB1 locus, are seronegative for cytomegalovirus (CMV), and have received non-T-cell-depleted marrow infusions. Carefully selected patients may achieve 5-year survival rates of > 70%, a likelihood of relapse not more than 10%, rates of graft failure < 10%, and rates of severe acute GVHD below 50%.[58]

**Autologous Transplantation**

Despite the presence of a fully predominant Ph clone at diagnosis of CML, normal marrow hematopoiesis still exists, and early hematopoietic progenitors that do not express p210b<sup>cr-abl</sup> can be identified. This provides the rationale for the collection of marrow or peripheral blood stem cells from patients prior to high-dose therapy, followed by reinfusion of the previously collected and preserved progenitor cells. Although cytogenetic responses can be obtained with unpurged marrow, they are transient. A survival advantage has been suggested[60] but not proven. Relapse due to reinfused,
Ph-positive cells may occur.[61]

To reduce contaminating Ph-positive leukemic cells, purging strategies, both ex vivo and in vivo, have been developed.[62] These include hyperthermia, manipulations with cyclophosphamide derivatives, and biological response modifiers (e.g., interferon-gamma [Actimmune], interleukin-2 [Proleukin]), the use of tyrosine kinase inhibitors, antisense oligonucleotides, and ribozymes, and positive or negative selections based on either phenotype determination or long-term bone marrow cultures.[62] Results from such investigations are encouraging.[62]

**New Agents and Investigational Approaches**

**Homoharringtonine** is a plant alkaloid derived from the *Cephalotaxus fortuneii* tree. Using a low-dose continuous infusion schedule in patients with late chronic-phase CML who were resistant to interferon-alpha, O'Brien et al.[63] reported complete hematologic responses in 71% of patients and cytogenetic responses in 31% (major in 15%). In early chronic-phase disease, homoharringtonine was given for 6 cycles to induce remission and then followed by interferon-alpha maintenance: the complete hematologic response rate was 92% and the cytogenetic response rate was 68% after treatment with homoharringtonine alone.[64]

These results suggest that homoharringtonine has activity in early and late chronic phases of CML, in which it can achieve cytogenetic remissions and possibly prolong survival in patients who have become resistant to interferon-alpha. Combinations of homoharringtonine with interferon-alpha and Ara-C have shown promising preliminary results in the clinical setting.[65]

**Decitabine**—5-Aza-2'-deoxycytidine (decitabine) is a cytidine analog that forms covalent bonds with the enzyme DNA methyltransferase and exerts a potent hypomethylating effect on DNA. Hyper-methylation of DNA is a mechanism of tumor progression that is observed in half of patients with CML.[66]

Decitabine produces responses in 25% of patients with blastic-phase CML and 53% with accelerated-phase disease.[67] Therapy with decitabine is characterized by an unusual pattern of slow and gradual clearing of blasticosis and prolonged myelosuppression. Clinical trials now in progress include decitabine in combination with busulfan and cyclophosphamide (Cytoxan, Neosar) as part of a preparative regimen for allogeneic transplantation, and decitabine in combination with stem-cell rescue as salvage therapy after relapse from allogeneic stem-cell transplantation.

**Antisense oligonucleotides** are short DNA sequences modified to bind target RNA sequences within the cell and thereby prevent translation of the RNA message into functional proteins. Effective targets for antisense approaches are bcr-abl itself, Ras, Pl-3-kinase, c-Myb, and c-Myc.[68] Bcr-abl antisense oligonucleotides alone or in combination with sequences targeted against additional oncogenes reduce the level of p210bcr-abl in CML cells and slow the rate of growth and proliferation. Use of antisense sequences directed against bcr-abl is also being tried for ex vivo purging in the context of autologous bone marrow transplants.

**Tyrosine Kinase Inhibitors**—Although many targets along the signaling cascade (SH3 blockers, Ras, farnesyl transferase, and further downstream targets) can be considered for inhibition, phosphotyrosine kinase activity has been studied most extensively and may hold the greatest promise for future trials.[69] Natural inhibitors of tyrosine kinases (herbimycin A, genistein, erbstatin, lavendustin A) have been extracted from fungal sources and exhibit only broad specificity for a variety of enzyme substrates. To improve target specificity, synthetic compounds have been modeled after the naturally occurring kinase inhibitors (reviewed in reference 69). More than 20 of these tyrphostin compounds are known today. Analysis of some of these compounds demonstrated a growth-inhibitory effect on CML cell lines in vitro,[70] and clinical trials with bcr-abl-specific tyrosine kinase inhibitors are underway.

**Adaptive Immunotherapy**—That leukemic cells are under regulatory influences by the immune system is based on several observations: (1) Donor lymphocyte infusions reestablish cytogenetic remissions in a high percentage of patients who relapse after an allogeneic transplant. (2) There is a positive correlation between GVHD and reduced risk of relapse after transplantation. (3) There is an increased frequency of disease recurrence with T-cell–depleted stem-cell transplantation. (4) Cytogenetic response correlates with the grade of interferon-associated autoimmune phenomena. Considerable research is now focusing on the identification of specific T-cell clones that can eliminate leukemic progenitors, as well as the identification of proteins that can serve as targets, even though very few tumors have been shown to express unique structures. Chronic myelogenous leukemia is a good model, however, because it expresses p210bcr-abl, which is uniquely associated with the Ph translocation. Specific cytotoxic T-cell responses can be generated against leukemia-associated antigens,[71] and expansion of leukemia-reactive T-cells ex vivo has been achieved by coincubation with combinations of cytokines.
In one study, cultures of CD34-positive CML progenitor cells incubated with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-4 (IL-4), and tumor necrosis factor (TNF) stimulated the formation in vitro of dendritic cells, leukemic-antigen-presenting cells that are strong inducers of T-cell responses in vitro.[72] It is hoped that identification of leukemia-specific antigens and stimulation of leukemia-specific T-cell responses will allow us to use the immunogenicity of CML cells for other approaches, such as immune gene therapy and peptide vaccination.

Conclusions

Chronic myelogenous leukemia is an intriguing disease. No other leukemia is so consistently associated with a single chromosomal translocation and the expression of a protein product intricately involved in its pathogenesis. Knowledge accumulated over the last few years has increased our understanding of CML leukemogenesis and has led to targeted, effective treatment strategies. Already, patients live longer with a disease that was once invariably fatal after 3 to 4 years and had no prospect of cure. Refinements in transplantation techniques and supportive care have contributed to this development, as has the introduction of new agents, most prominently, interferon-alfa. We also know more about immunologic mechanisms that underlie the CML disease process. Exploiting leukemic cell-specific immunoreactivity may benefit patients, and success with donor lymphocyte infusions promises further progress with immunomodulation, including vaccine-based strategies. Finally, transplantation may no longer be the only modality with curative potential. Indeed, more targeted, less toxic therapies hold great promise for the future.

References:


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