The Biology and Treatment of Chronic Myelogenous Leukemia

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Over the past 2 decades, our understanding of the pathobiological events underlying chronic myelogenous leukemia (CML) has grown. At the same time, effective transplant and nontransplant treatment approaches to

Introduction

Chronic myelogenous leukemia (CML) is a malignancy of the human hematopoietic stem cell. It is characterized clinically by the presence of increased immature and mature granulocytes in the peripheral blood. Red blood cell and platelet numbers may also be abnormal. Myeloid hyperplasia is the dominant feature in the marrow. The characteristic cytogenetic abnormality is a deletion of the short arm of chromosome 22 (22q-) known as the Philadelphia chromosome (Ph) and is often found as a balanced translocation with chromosome 9, abbreviated t(9;22). This abnormal chromosome is present in all myeloid lineages, in some B lineage lymphoid cells, and occasionally, in T lymphocytes. At the molecular level, this translocation is recognized as a fusion between the breakpoint cluster region (BCR) on chromosome 22 and the Abelson gene (ABL) on chromosome 9, thus resulting in the BCR-ABL oncogene and its protein product, p210BCR-ABL. [1,2]

The median age at onset is 50 years, although children may also be affected by CML.[2] Asymptomatic patients may be discovered through abnormalities in routine blood tests. Alternatively, patients may present with leukocytosis, splenomegaly, fatigue, anorexia, weight loss, or other signs of systemic disease.[2] As many as 50% of patients will have splenomegaly at presentation. Clinical features at presentation may have prognostic importance (Table 1).[3]

The majority of newly presenting patients experience a "chronic phase" during which signs and symptoms of leukemia can be controlled with hydroxyurea (Hydrea) or interferon-alpha. In many patients, CML eventually progresses to an "accelerated phase" characterized by cytogenetic evidence of clonal evolution, further blood count abnormalities, increased drug dosage requirements, and/or worsening clinical symptoms. Eventually, patients may enter a "blast crisis," defined by the presence of 30% or more myeloblasts or lymphoblasts in the blood or marrow.[4,5] Certain cytogenetic abnormalities involving chromosomes 7, 8, 9, 17, and 21 may herald progression to the accelerated phase or blast crisis.[4,6]

Biology

The hybrid mRNA created by the fusion of the BCR and ABL genes encodes the p210BCR-ABL. At least two other isoforms of the fusion protein may be created. A breakpoint upstream of the one observed in the p210 results in p190, while a breakpoint downstream results in p230. The p190 is commonly found in acute lymphocytic leukemia (ALL),[7] while the p230 is observed in chronic neutrophilic leukemia (CNL).[8]

The p210 is a cytoplasmic protein with tyrosine kinase activity that stimulates transcription of several target genes. The net result is abnormal adhesion, proliferation, differentiation, and apoptosis of malignant cells containing the BCR-ABL gene. These abnormalities lead to an increase in circulating immature myeloid progenitors. Prolonged survival of CML cells may allow acquisition of additional cytogenetic mutations, resulting in resistance to chemotherapy and evolution to blast crisis.[1,9-12]

Conventional Therapy With Busulfan or Hydroxyurea
Busulfan (Myleran) is an alkylating agent that was initially used to treat CML in the early 1950s.[13] It is an effective therapeutic agent in CML; however, fatal marrow suppression and lung fibrosis may result from busulfan administration.[5]

Hydroxyurea is a cycle-specific inhibitor of DNA synthesis with biological activity in CML. Hydroxyurea provides disease control rates similar to or better than those achieved with busulfan but with less toxicity.[14,15] Myelosuppression, a major problem with busulfan, is usually transient with hydroxyurea.[5] Other side effects of hydroxyurea include nausea and anorexia, skin atrophy, alopecia, macrocytosis, megaloblastic changes in the marrow, and rarely, skin or mucosal ulcers.[5]

Complete cytogenetic responses seldom occur with either hydroxyurea or busulfan. However, a randomized study demonstrated significantly longer median survival and duration of chronic phase with hydroxyurea.[15]

Interferon-Alpha

Interferon-alpha is a naturally occurring cytokine introduced into CML therapy in the early 1980s.[16] Many investigators now consider it to be the treatment of choice for newly diagnosed chronic-phase patients ineligible for allogeneic hematopoietic stem cell transplantation. Interferon-alpha used as a single agent for initial therapy yields complete hematologic response rates in up to 80% of cases, and major cytogenetic responses (> 66% Ph-negative metaphases) in up to 38% of selected, newly diagnosed patients.[17] Results of randomized trials comparing interferon-alpha to conventional therapy are described in Table 2.[18-22]

Most investigators recommend subcutaneous administration of interferon-alpha on a daily basis at a dose of 5 million U/m²/d. To avoid toxicity, treatment should be initiated at 25% of the target dose, increased gradually over 1 month, and adjusted according to blood counts. Use of an intermittent treatment schedule or a lower target dose may not produce sustained remissions as effectively. Prolonged administration of interferon (12 to 18 months) may be necessary to achieve a complete or major cytogenetic remission.[5]

Patients who attain a major cytogenetic response on interferon-alpha therapy may experience long-term hematologic remissions and, rarely, the disappearance of the BCR-ABL gene abnormality. It is not yet known how long interferon-alpha therapy should be continued in responding patients to avoid disease recurrence; however, administration for at least several years after cytogenetic remission seems prudent.

Failure to achieve a major cytogenetic remission after treatment with recommended doses of interferon-alpha for 1 to 2 years is considered a poor prognostic indicator (Figure 1).[23] In such cases, patients may be eligible for experimental therapy, or use of hydroxyurea may be warranted to reduce cost and toxicity.

Several clinical trials suggest that interferon-alpha is superior to busulfan and/or hydroxyurea therapy for the treatment of CML.[18-22] A meta-analysis of trials found that CML patients treated with interferon-alpha achieve a superior 5-year survival, when compared with busulfan and/or hydroxyurea (57% vs 42%). The absolute improvement in the 5-year survival rate was 20% in trials of interferon vs busulfan and 15% in trials of interferon vs hydroxyurea.[24]

Combination Therapy

Combination therapy consisting of interferon-alpha and cytarabine in newly diagnosed chronic-phase CML patients may be more effective than therapy with interferon-alpha alone. Oral cytarabine is administered daily at a dose of 10 mg/m² (or according to other low-dose schedules) in combination with daily subcutaneous interferon-alpha, 5 million U/m. Combination therapy has resulted in major cytogenetic response rates in up to 50% of patients as well as significantly improved long-term survival rates, compared to interferon-alpha alone. However, toxicity with the combined therapy regimen may also be greater.[23,25]
Related-Donor Hematopoietic Stem Cell Transplantation

At present, allogeneic hematopoietic stem cell transplantation is the only proven curative therapy for CML. Patients transplanted during chronic phase and within 1 year of diagnosis (early chronic phase) report the most favorable outcome. The reported incidence of long-term disease-free survival for these patients ranges from 50% to more than 80%, whereas for patients undergoing transplantation in accelerated phase or in blast crisis, the survival rate is only approximately 40% and 15%, respectively.

The incidence of relapse among patients receiving transplants in the chronic phase is approximately 10%; however, the relapse rate increases to approximately 60% when transplantation is performed in blast crisis. Other patient characteristics that contribute to an adverse effect on outcome include older recipient age and a prolonged interval from the time of diagnosis to transplant. Modifications to traditional transplantation approaches—eg, use of blood rather than marrow as a source of donor stem cells, removal of total-body irradiation from the preparative regimen, and use of hematopoietic growth factor support—may improve outcome.[26,27]

Graft-vs-Host Disease

Graft-vs-host disease (GVHD) is the primary cause of death in related-donor hematopoietic stem cell transplantation. Better GVHD prophylaxis regimens using cyclosporine (Neoral, Sandimmune) and short-course methotrexate have improved outcome, and preparative regimens that minimize inflammatory damage to normal tissue may also reduce the clinical effects of GVHD.[28]

Although GVHD may be deleterious to the patient, an immune-mediated antileukemia effect (graft-vs-leukemia) is important in preventing relapse after human leukocyte antigen (HLA)-identical sibling transplants for CML and possibly other malignancies. Graft-vs-leukemia effects are mediated at least in part by T lymphocytes and, possibly, by other immune effector cells. Consequently, relapse rates after T-cell-depleted allogeneic hematopoietic stem cell transplantation may be higher than in the non-T-cell-depleted transplant setting.

The efficacy of hydroxyurea or interferon-alpha therapy vs related-donor hematopoietic stem cell transplantation has not been investigated in randomized trials. However, retrospective analyses suggest an improved long-term survival advantage for CML patients receiving related-donor transplantation, compared to patients receiving hydroxyurea or interferon-alpha. A lower early mortality rate has been observed in interferon-alpha/hydroxyurea-treated patients, although long-term survival rates fall because of continued late relapse.

In the hematopoietic stem cell transplantation group, there is a high early mortality associated with transplant-related complications. However, the survival curve then reaches a plateau because few late relapses or other fatal complications occur. As a result, the survival curves cross at 2 to 6 years, depending on the risk categories studied, and long-term survival for transplant recipients proves superior (Figure 2).[29] Of course, such analyses do not take into account more elusive end points such as long-term side effects, quality of life, and cost of therapy, which may differ with hematopoietic stem cell transplantation and interferon-alpha therapy for CML.

One seemingly logical approach to the treatment of CML is a trial of interferon-alpha followed by relatively early intervention with allogeneic stem cell transplantation in patients who do not tolerate interferon-alpha therapy or in whom such therapy fails. This approach has been controversial because some investigators report an adverse effect from previous interferon-alpha therapy on allogeneic transplant outcome,[30] while others find no such effect.[31-33] A recent European report suggests that an adverse effect on subsequent stem cell transplantation for CML can be avoided if interferon-alpha therapy is curtailed at least 3 months before transplant therapy is initiated.[34]

Unrelated-Donor Hematopoietic Stem Cell Transplant

Unrelated donors are an alternative source of hematopoietic stem cells for allogeneic transplantation. Over the past 15 years, an international network of computerized registries has
been developed. In the United States, the National Marrow Donor Program has access to approximately 4 million unrelated donors typed by HLA. This program can locate suitably matched donors for more than one-third of potential recipients and, in most cases, can procure marrow donations within 4 months of the initial search request.

Survival rates after HLA-matched unrelated-donor transplant in CML may approach those observed after related-donor transplant.[35] In a recent retrospective analysis, the incidence of long-term survival was over 60% in a highly selected subset of good-risk CML unrelated-donor transplant recipients (Figure 3).[36] However, as in related-donor stem cell transplantation, outcome is highly dependent on patient characteristics. Older recipient age, prolonged interval to transplant, advanced disease, and donor/recipient HLA mismatch adversely affect outcome.[36]

Donor Lymphocyte Infusions After Allogeneic Transplant

Depletion of T lymphocytes from the donor stem cell inoculum reduces the incidence of GVHD; however, the incidence of relapse may be markedly increased. This observation led to the understanding that the antileukemic effect of allogeneic stem cell transplantation in CML depends less on the high-dose preparative regimen and more on the immune-mediated suppression of residual host malignant progenitors by donor effector cells. One strategy that has evolved from these observations is the use of "donor lymphocyte infusions" to prevent or treat relapse after allogeneic stem cell transplantation.[37]

Donor lymphocyte infusions can induce cytogenetic and hematologic remissions in patients relapsing after allogeneic transplant. Approximately two-thirds of relapsing posttransplant CML patients will have a complete hematologic and cytogenetic response to donor lymphocyte infusions. Treatment with donor lymphocyte infusions is more effective when initiated before hematologic progression has occurred, and may even be useful as prophylaxis against relapse when used in combination with T-lymphocyte-depleted transplants. Unfortunately, approximately one-third of donor lymphocyte infusion recipients will develop GVHD, which may be fatal. Aplasia may also occur.[37-40]

Nonmyeloablative Hematopoietic Stem Cell Transplants

High peritransplant morbidity associated with allogeneic transplant therapy for CML is related to the toxicity of the preparative regimen and to the development of GVHD. A nonmyeloablative preparative regimen (also known as a "mini-transplant" or "transplant-lite") reduces myelosuppression and organ toxicity. Graft-vs-host disease may also be reduced with this strategy, because it is triggered to some extent by tissue inflammation.[41]

Preparative regimens used in nonmyeloablative transplants have included a purine analog (fludarabine [Fludara] or cladribine [Leustatin]) with immunosuppressive properties and, in some centers, low-dose total-body irradiation. Additional peritransplant immunosuppression may be needed to ensure donor engraftment.

Very preliminary reports on this new transplant approach suggest that sustained engraftment, complete cytogenetic and hematologic remission, and low peritransplant morbidity can be achieved.[41-45] Because the nonmyeloablative regimens are less toxic, they may extend the option of allogeneic stem cell transplantation to older or sicker patients who otherwise would not be considered for conventional transplants. This is particularly relevant in CML, for which the median age at presentation is over 50 years.

The long-term efficacy of nonmyeloablative transplants, however, has not been determined. Optimal use of immunosuppressive agents in nonmyeloablative conditioning is not yet understood, and the preparative regimen may need tailoring according to the disease type and HLA matching. Acute and chronic GVHD do occur after nonmyeloablative conditioning and can result in serious or fatal complications.

Autologous Hematopoietic Stem Cell Transplants
The marrow and blood of at least some CML patients contain coexistent benign and malignant hematopoietic progenitor populations. Investigators have capitalized on this observation by administering high-dose chemoradiotherapy followed by infusion of autologous marrow or blood cells. In some cases, the inoculum has been "purged" ex vivo with chemotherapeutic agents, interferon, or antisense agents to selected gene targets such as the \( BCR-ABL \) oncogene. More recently, in vivo purging has been achieved by "priming" patients with high-dose chemotherapy, followed by the collection of blood cells enriched for benign progenitors.[46,47]

Autologous transplant therapy for CML can effect partial or complete cytogenetic remissions, and may prolong survival. Peritransplant complications and mortality are reduced, compared to allogeneic stem cell transplantation. The role of autologous stem cell transplantation in CML is not yet fully understood. In most cases, autologous stem cell transplantation is not curative and may serve best as a "platform" for subsequent chemotherapy, cytokine therapy, or immunotherapy.

**Tyrosine Kinase Inhibitors and STI-571**

Perhaps one of the most exciting occurrences in the treatment of CML is the development of tyrosine kinase inhibitors such as STI-571. The agent STI-571 "targets" specific tyrosine kinases encoded by the \( BCR-ABL \) oncogene and disrupts their intracellular signals. Incubation of normal and CML progenitors with STI-571 in culture results in selective suppression of malignant cells and survival of normal progenitors.[48]

Phase I dose-escalation studies demonstrate little toxicity at oral daily doses of 400 mg, and have not yet determined the maximum tolerated dose. Preliminary results of phase II studies suggest that STI-571 therapy can induce hematologic remissions in the majority of CML patients and cytogenetic responses in some.[49-51] A phase III, prospective, randomized trial has been initiated to compare the efficacy of interferon-alpha plus cytarabine vs STI-571 in newly diagnosed CML patients.

Although the results of STI-571 therapy are exciting, the long-term benefits of this agent are not yet known. Optimal dose and dose schedules and dose-limiting or idiosyncratic toxicities have not been fully determined. The promising strategy of combining STI-571 with other therapeutic agents or with hematopoietic stem cell transplantation awaits exploration.

**Approach to Therapy in the Patient With CML**

A patient with newly diagnosed chronic-phase CML now has several therapeutic options. The advent of the promising but not yet fully tested tyrosine kinase inhibitor STI-571 further complicates the decision-making process. One approach to therapy is described in Figure 4.

Newly diagnosed patients presenting with extreme leukocytosis or thrombocytosis may benefit from immediate therapy with hydroxyurea and pheresis. Allopurinol and vigorous hydration should be administered to prevent complications of hyperuricemia. After stabilization, potential hematopoietic stem cell transplant candidates and their siblings should be typed for HLA. Eligible patients may elect to undergo immediate transplant.

The majority of patients, however, will not be eligible for or elect early transplant therapy. These patients should be offered a course of interferon-alpha and cytarabine administered daily as described above, or they should be entered into STI-571 trials, if available.

Patients receiving a trial of interferon-alpha plus cytarabine who develop unacceptable toxicity or who do not achieve a major cytogenetic response within 1 year, as well as those entered into STI-571 trials who experience disease progression, may choose alternative approaches. These approaches include treatment with hydroxyurea, and novel nontransplant therapy such as arsenic trioxide (Trisenox) or homoharringtonine (HHT). Eligible patients may consider allogeneic or autologous hematopoietic stem cell transplantation. Therapy with interferon-alpha should be discontinued for at least 3 months prior to allogeneic stem cell transplantation.
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