Chronic Myeloid Leukaemia (CML, So): An overview and advancement in the treatment

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Background

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. Consequently, the peripheral blood cell profile shows an increased number of granulocytes and their immature precursors, including occasional blast cells. The Philadelphia Chromosomes is present in more than 85% cases. This translocation relocates an oncogene called abl from the long arm of chromosome 9 to the long arm of chromosome 22 in the bcr region. The presence of bcr-abl rearrangement is the hallmark of CML, although this rearrangement has also been described in other diseases. It is considered diagnostic when present in a patient with clinical manifestations of CML.

Age & Frequency

In general, this disease occurs in the fourth and fifth decades of life. Younger patients aged 20-29 years may be affected and may present with a more aggressive form, such as in accelerated phase or blast crisis. Uncommonly, CML may appear as a disease of new onset in elderly individuals. CML accounts for 20% of all leukemia's affecting adults. It typically affects middle-aged individuals. Although uncommon, the disease also occurs in younger individuals. Increased incidence was reported among individuals exposed to radiation in Nagasaki and Hiroshima after the dropping of the atomic bomb.

Mortality / Morbidity

Generally, 3 phases of the disease are recognized. The general course of the disease is characterized by an eventual evolution to a refractory form of acute myelogenous or, occasionally, lymphoblastic leukemia. The median survival of patients using older forms of therapy was 3-5 years. Most patients present in the chronic phase, characterized by splenomegaly and leukocytosis (see Image 1) with generally few symptoms.

Image 1: This blood film at 400x magnification demonstrates leukocytosis with the presence of precursor cells of the myeloid " lineage. In addition, basophilia, eosinophilia, and thrombocytosis can be seen (photographed by U. Woermann, MD, Division of Instructional Media, Institute for Medical Education, University of Bern, Switzerland).

This phase is easily controlled by medication. The major goal of treatment during this phase is to control symptoms and complications resulting from anemia, thrombocytopenia, leukocytosis, and splenomegaly. Newer forms of therapy aim at delaying the onset of the accelerated or blastic phase. After an average of 3-5 years, the disease usually evolves into the blast crisis, which is marked by an increase in the bone marrow or peripheral blood blast count or by the development of soft tissue or skin leukemic infiltrates. Typical symptoms are due to increasing anemia, thrombocytopenia, basophilia, a rapidly enlarging spleen and failure of the usual medications to control leukocytosis and splenomegaly. The manifestations of blast crisis are similar to those of acute leukemia. Treatment results are unsatisfactory, and most patients succumb to the disease once

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this phase develops. In approximately two thirds of cases, the blasts are myeloid. However, in the remaining one third of patients, the blasts exhibit a lymphoid phenotype, further evidence of the stem cell nature of the original disease. Additional chromosomal abnormalities usually are found at the time of blast crisis, including additional Ph chromosomes or other translocations.

In many patients, an accelerated phase occurs 3-6 months before the diagnosis of blast crisis. Clinical features in this phase are intermediate between the chronic phase and blast crisis.

**History**

The clinical manifestations of CML are insidious and often are discovered accidentally when an elevated WBC count is revealed by a routine blood count or when an enlarged spleen is revealed during a general physical examination. Nonspecific symptoms of tiredness, fatigue, and weight loss may occur long after the onset of the disease. Loss of energy and decreased exercise tolerance may occur during the chronic phase after several months. Symptoms related to enlargement of the spleen and/or the liver often are present. The large spleen may encroach on the stomach and cause early satiety and decreased food intake. Left upper quadrant abdominal pain described as "gripping" may occur due to spleen infarction. The enlarged spleen also may be associated with a hypermetabolic state, fever, weight loss, and chronic fatigue. The enlarged liver may contribute to the patient's weight loss. Low-grade fever and excessive sweating related to hyper metabolism may occur in some patients. The disease has 3 clinical phases, and it follows a typical course of an initial chronic phase, in which the disease process is easily controlled; followed by a transitional and unstable course (accelerated phase); and, finally, a more aggressive course (blast crisis), which usually is fatal. The majority of patients are diagnosed while still in the chronic phase. The WBC count usually is controlled with medication (hematologic remission). This phase varies in duration depending on the maintenance therapy used. It usually lasts 2-3 years with Hydroxyurea or busulfan therapy and has lasted for longer than 9.5 years in patients who respond well to alpha-interferon therapy. Some patients progress to a transitional or accelerated phase, which may last for several months. The survival of patients diagnosed in this phase is 1-1.5 years. This phase is characterized by poor control of the blood counts with myelosuppressive medication and the appearance of peripheral blast cells (~15%), promyelocytes (~30%) (see Image 3), basophils ~20%, and platelet counts less than 100,000 cells/µL unrelated to therapy. Usually, the doses of the medications need to be increased; splenomegaly may not be controllable by medications, and anemia can worsen. Bone pain and fever, as well as an increase in bone marrow fibrosis are harbingers of the last phase.

Acute phase, or blast crisis, is similar to acute leukemia, and survival is 3-6 months at this stage. Bone marrow and peripheral blood blasts of 30% or more are characteristic. Skin or tissue infiltration also defines blast crisis. Cytogenetic evidence of another Ph-positive clone (double) or clonal evolution (other cytogenetic abnormalities such as trisomy 8, 9, 19, or 21, isochromosome 17, or deletion of y chromosome) usually is present. In some patients who present in the accelerated, or acute, leukemia phase of the disease (skipping the chronic phase), bleeding, petechiae, and ecchymoses may be the prominent symptoms. In these situations, fever usually is associated

![Image-3: Blood film at 1000x magnification shows a promyelocyte, an eosinophil, and 3 basophils](photographed by U. Woermann, MD, Division of instructional Media, Institute for Medical Education, University of Bern, Switzerland)
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with infections.

Physical
Splenomegaly is the most common physical finding in patients with CML. In more than half of patients with CML, the spleen extends more than 5 cm below the left costal margin at time of discovery. The size of the spleen correlates with the peripheral blood granulocyte counts (see Image 2), with the biggest spleens being observed in patients with high white cell counts.

Image 2: This blood film at 1000x magnification demonstrates the whole granulocytic lineage, including an eosinophil and a basophil (photographed by U. Woermann, MO, Division of Instructional Media, Institute for Medical Education, University of Bern, Switzerland)

Very large spleen usually is a harbinger of transformation into an acute blast crises form of the disease. Hepatomegaly also occurs, although less commonly than splenomegaly. Hepatomegaly usually is part of the extramedullary hematopoiesis occurring in the spleen. Physical findings of leukostasis and hyperviscosity can occur in some patients with extraordinary elevation of their WBC counts, exceeding 300,000-600,000 cells/µL. Upon funduscopy, the retina may show papilledema, venous obstruction, and hemorrhages.

Causes
The initiating factor of CML still is unknown, but exposure to irradiation has been implicated, as observed in the increased incidence among survivors of the atomic bombing of Hiroshima and Nagasaki. Other agents, such as benzene, are suspected causes.

D/D
Agnogenic Myeloid Metaplasia with Myelofibrosis
Myelodysplastic Syndrome
Myeloproliferative Disease
Polycythemia Vera

Other problems to be considered.
Leukemoid reactions from infections (chronic granulomatous, such as tuberculosis)
Myelodysplasia
Tumor necrosis
Essential thrombocytosis/thrombocythemia
Chronic neutrophilic leukemia
Chronic myelomonocytic leukemia
Acute myeloid leukemia

Lab studies
Peripheral blood findings show a typical leukoerythroblastic blood picture, with circulating immature cells from the bone marrow (see Image 4).

Image 4: This bone marrow film at 400x magnification demonstrates clear dominance of granulopoiesis. The number of eosinophils and megakaryocytes is increased (photographed by U Woermann, MD, Division of Instructional Media, Institute for Medical Education, University of Bern, Switzerland).

Increase in mature granulocytes and normal lymphocyte counts (low percentage due to dilution in the differential count) results in a total white cell count of 20,000-60,000 cells/µL. A mild increase in basophils and eosinophils is present and becomes more prominent during the transition to acute leukemia.

These mature neutrophils, or granulocytes, have decreased apoptosis (programmed cell death), resulting in accumulation of long-lived cells with low or absent enzymes, such as alkaline phosphatase. Consequently, the leukocyte alkaline phosphatase (LAP) stains very-low-to-absent in most cells, resulting in a low score. Early myeloid cells such as myeloblasts, myelocytes, metamyelocytes, and nucleated
red blood cells commonly are present in the blood smear, mimicking the findings in the bone marrow. The presence of the different mid stage progenitor cells differentiates this condition from the acute myelogenous leukemias, in which a leukemic gap (maturation arrest) or hiatus exists that shows absence of these cells. A mild-to-moderate anemia is very common at diagnosis, which usually is normochromic and normocytic. The platelet counts at diagnosis can be low, normal, or even increased in some patients (>1 million in some). Bone marrow characteristically is hypercellular, with expansion of the myeloid cell line (eg, neutrophils, eosinophils, basophils) and its progenitor cells. Megakaryocytes (see Image 5) are prominent and may be increased. Mild fibrosis often is seen in the reticulin stain.

Cytogenetic studies of the bone marrow cells, and even peripheral blood, should reveal the typical Philadelphia (Ph1) chromosome, which is a reciprocal translocation of chromosome material between chromosomes 9 and 22. This is the hallmark of CML, found in almost all patients with CML, and is present in CML throughout its entire clinical course.

The Philadelphia translocation is the translocation of the cellular oncogene c-abl from the 9 chromosome, which encodes for a tyrosine protein kinase, with a specific breakpoint cluster region (bcr) of chromosome 22, resulting in a chimeric bcr-c-abl messenger RNA that encodes for a mutation protein with much greater tyrosine kinase activity compared to the normal protein (see Image 5). The latter presumably is responsible for the cellular transformation in CML. This m-RNA can be detected by polymerase chain reaction (PCR).

In a sensitive test that can detect it in a few cells. This is useful in monitoring minimal residual disease (MRD) during therapy. Karyotypic analysis of bone marrow cells requires the presence of a dividing cell without loss of viability because the material requires that the cells go into mitosis to obtain individual chromosomes for identification after banding, which is labor intensive and a slow process. The new technique of fluorescence in situ hybridization (FISH) (see Image 6) uses labeled probes that are hybridized to either metaphase chromosomes or interphase nuclei, and the hybridized probe is detected with fluorochromes. This technique is a rapid and sensitive means of detecting recurring numerical and structural abnormalities.

Two forms of the bcr-abl mutation are present, depending on the location of their joining regions on bcr 3’ domain. Approximately 70% of patients who have the 5’ DNA breakpoint have a b2a2 RNA message, and 30% of patients have a 3’DNA breakpoint and a b3a2 RNA message. The latter is associated with a shorter chronic phase, shorter survival, and thrombocytosis. CML should be differentiated...
from Ph-negative diseases with negative PCR for bcr-abl m-RNA. These diseases include other myeloproliferative disorders and chronic myelomonocytic leukemia, which now is classified with the MDSs.

Additional chromosomal abnormalities, such as an additional or double Ph+ or trisomy 8,9,19, or 21, isochromosome 17, or deletion of Y chromosome, have been described as the patient enters a transitional form or accelerated phase of the blast crisis as the Ph chromosome persists.

Patients with conditions other than chronic-phase CML, such as newly diagnosed acute lymphocytic leukemia (ALL) or nonlymphocytic leukemia (ANLL), also may have a positive Ph chromosome. Some consider this the blastic phase of CML without a chronic phase. The chromosome rarely has been found in patients with other myeloproliferative disorders, such as polycythemia vera or essential thrombocythemia, but these probably are misdiagnosed CML. It rarely has been observed in myelodysplastic syndrome.

Other laboratory abnormalities include hyperuricemia, which is a reflection of high bone marrow cellular turnover and markedly elevated serum B12-binding protein (TC-I). The latter is synthesized by the granulocytes and reflects the degree of leukocytosis.

**Imaging Studies**

Typical hepatomegaly and splenomegaly may be imaged by using a liver/spleen scan. Most often, these are so obvious that radio imaging is not necessary.

**Histologic Findings**

Diagnosis is based on the histopathologic findings in the peripheral blood and the Ph 1 in the bone marrow cells.

**Medical Care**

The 3-fold goals of treatment of CML have changed markedly in the past 10 years; they are to achieve a hematologic remission (normal CBC) and physical examination (no organomegaly), to achieve cytogenetic remission (normal chromosome returns with 0% Ph-positive cells), and, most recently, to achieve molecular remission (negative PCR for the mutational bcr-abl m-RNA). The latter is an attempt for cure and prolongation of patient survival.

A new approach to treatment of this disease is to directly inhibit the molecular cause of the disease, i.e., using a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome translocation abnormality. ST1571 or imatinib mesylate inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for bcr-abl and also fresh leukemic cells in CML positive for the Philadelphia chromosome. This drug was approved rapidly by the US Food and Drug Administration because of the following results:

In patients in the chronic phase who were previously treated with interferon and whose treatment failed or who were unable to tolerate therapy, a complete hematologic remission was achieved in 88% (532 patients), with a major cytogenetic response (i.e., complete remission was 0%, partial remission was 1–35%, Ph+ metaphases) in 49% of patients. Among 235 patients in the accelerated phase, the hematologic response was 65% (28% complete remission), and the cytogenetic response was 21%. Patients in myeloid blast crisis (260 patients) achieved a 26% hematologic response (4% complete remission) and a 13.5% major cytogenetic response (5% complete remission).

The decision to choose the initial treatment or primary therapy for chronic-phase CML is difficult since the advent of the tyrosine kinase inhibitor Imatinib (formerly ST1571). For patients with chronic-phase CML, Imatinib at 400 mg/d is the best candidate for primary therapy since it induces complete hematologic response in almost all patients and causes a high cytogenetic response rate,
although overall survival data comparing it to interferon are still pending.

Treatment of CML patients in the accelerated phase or in blast crisis has been dismal. However, recent data show that Imatinib can induce hematologic response in 52-82%, but the response is sustained for at least 4 weeks in 31-64%. Complete response is lower at 7-34%. Karyotypic response occurs in 16-24%, and complete cytogenetic response is observed in only 17%. Higher doses (ie, 600 mg/d) resulted in improved response rates, cytogenetic response, and disease free and overall survival.

Myelosuppressive therapy, which was formerly the mainstay of converting a patient with CML from an individual with an uncontrolled initial presentation to one with hematologic remission with normalization of the physical and laboratory findings, may soon disappear as the new agents prove to be more effective with fewer adverse events and longer survival.

Hydroxyurea, an inhibitor of deoxynucleotid synthesis, is the most common myelosuppressive agent used to achieve hematologic remission. The initial blood count is monitored every 2-4 weeks, and the dose is adjusted depending on the white cell and platelet counts. Most patients enter hematologic remission within 1-2 months. This medication has a short duration for myelosuppression, so even if the counts go lower than intended, stopping or decreasing doses usually controls the blood counts. Maintenance with hydroxyurea rarely results in cytogenetic or molecular remissions.

Busulfan is an alkylating agent that traditionally has been used to keep the white cell counts less than 15,000 cells/II.L. However, the myelosuppressive effects may occur much later and persist longer, making maintaining the numbers within normal limits more difficult. Long-term use can cause pulmonary fibrosis, hyperpigmentation, and prolonged marrow suppression lasting for months.

Leukapheresis using a cell separator can lower WBC counts rapidly and safely in patients with WBC counts of higher than 300,000 cells/II.L, and it can alleviate acute symptoms of leukostasis, hyperviscosity, and tissue infiltration. Leukapheresis usually reduces the white cell count only temporarily and often is combined with cytoreductive chemotherapy for more lasting effects.

Alpha interferon is the treatment of choice for the majority of patients with CML who are too old or do not have a matched bone marrow donor. This is given at an average of 3-5 million international units (MIU) per day subcutaneously after hematologic remission with hydroxyurea.

The cytogenetic response is monitored every 3-6 months by karyotyping or by FISH to count the percentage of bone marrow cells with Ph-positive cells. The goal is 100% normal cells after 1-2 years of therapy. Patients with MRO (bcr-abl positive) should be kept on maintenance therapy as long as MRO exists.

Cytogenetic improvement has been observed in 70% of patients treated for longer than 3 months, with the median of Ph'-positive cells declining from 100% to 65% (range 0-95%). Complete suppression of Phi chromosome was observed in 20% of patients. Bone marrow transplantation (BMT) should be considered early in young patients (355 y) who have a matched sibling donor.

All siblings should be typed for human leukocyte antigen (HLA) A, B; and OR. If no match is available, the HLA type can be entered into a bone marrow registry for a completely matched unrelated donor.

The mortality rate of BMT is 10-20% or less with a matched sibling and 30-40% with an unrelated donor. The bone marrow registry approximates the cure rate for patients with CML at 50%. Transplantation is recommended within 1 year of diagnosis or
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after a 1-year trial of interferon therapy without a complete or significant cytogenetic remission.

Most patients with MRO after transplantation may require interferon maintenance therapy anyway, or they may require reinfusion of T cells collected from the donor.

Treatment decisions involving the use of interferon, BMT, or investigative options for younger patients with CML are extremely complex and in constant flux. Individualized decisions should be made in conjunction with consultation with physicians familiar with the recent literature.

Surgical Care
Splenectomy and splenic irradiation have been used for large painful spleens, usually in the late phase of the disease. This rarely is needed in patients whose disease is well controlled. Some authors believe that splenectomy accelerates the onset of myeloid metaplasia in the liver. Splenectomy carries high perioperative morbidity and mortality due to bleeding or thrombotic complications.

Consultations
These patients should be under the care of hematologists and oncologists. Selected patients should be seen by experts in a bone marrow transplantation program in a tertiary care center. The medications used for patients in chronic-phase CML include a myelosuppressive agent to achieve hematologic remission, which requires 1-2 months of treatment. Once the patient goes into hematologic remission, the goal of treatment is to suppress the Ph-positive hematopoietic clone in the bone marrow for a cytogenetic remission and, hopefully, a molecular remission. This entails the use of alpha interferon or a BMT. The following factors determine the treatment: (1) age of the patient, (2) HLA-matched donor willing to donate bone marrow, and (3) the Sokal score. The Sokal score falls into 3 categories: (1) low risk is less than 0.8, (2) intermediate risk is 0.8-1.2, and (3) high risk is greater than 1.2. The Sokal score is calculated for patients aged 5-84 years by hazard ratio = exp (0.011 (age-43) + 0.0345 (spleen - 7.5 cm) + 0.188 [(platelets/700)2 .0563 + 0.0887 (% blasts in blood -2.1 ). The choice of treatment is determined by the prognosis and the age of the patient. Most patients have no matched donor or are too old for BMT; alpha interferon is the drug of choice in these patients.

Drug Category: Myelosuppressive agents
To control the underlying hyperproliferation of the myeloid elements, a myelosuppressive agent is necessary to bring down the WBC counts and, occasionally, the elevated platelet counts. The size of the spleen correlates with the WBC counts, and it shrinks as the WBC counts approach normal range. Also, the intermediate and myeloblast cells disappear from the circulation.

Hydroxyurea
Inhibitor of deoxynucleotide synthesis and DOC for inducing a hematologic remission in CML. This agent is less leukemogenic than alkylating agents such as busulfan, Alkeran, or chlorambucil. Myelosuppressive effects last a few days to a week and are easier to control than with alkylating agents; busulfan is associated with prolonged marrow suppression and also can cause pulmonary fibrosis. Adult dose: Initially dose- 30 mg/kg/d at an average of 1000-1500 mg/d PO in 500-mg tablets can be given at higher doses in patients with extremely high WBC counts (>300,000) and adjusted accordingly as counts fall and platelet counts drop; the dose can be given as a single daily dose or divided into 2-3 doses at higher dose ranges. Contraindications: Documented hypersensitivity; thrombocytopenia is dose-limiting factor in using hydroxyurea; do not administer if platelet counts <50,000; administer under advisement in patients with counts <100,000/uL; anemia may be aggravated by medications, and concomitant irradiation is contraindicated. Interactions: Neurotoxicity can occur when administered concurrently with fluorouracil. In Pregnancy -
Safety for use during pregnancy has not been established. Precautions: Monitor blood counts and adjust doses accordingly; some patients may be sensitive and present with fever, chills, and elevation of liver enzymes, which disappear after stopping drug; skin ulcers may be seen in long-term use of drug; caution in patients diagnosed with renal impairment

**Busulfan**
Potent cytotoxic drug that, at recommended dosage, causes profound myelosuppression. As alkylating agent, mechanism of action of active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells. Adult dose: 4-8 mg/d pa; may administer up to 12 mg/d; maintenance dosing range is 1-4 mg/d to 2 mg/wk; discontinue regimen when WBC reaches 10,000-20,000 cells/mm³; resume therapy when WBC reaches 50,000/mm³. Pediatric dose: 0.06-0.12 mg/kg/d or 1.8-4.6 mg/m³/d; titrate dose to maintain WBC >40,000/mm³; reduce dose by 50% if WBC is 30,000-40,000/mm³; discontinue if WBC <20,000/mm³. Contraindications: Documented hypersensitivity; severely depressed bone marrow function; women who are breast feeding; failure to respond to previous treatment. Interactions: CYP3A3/4 enzyme substrate; acetaminophen, cyclophosphamide, itraconazole, and thioguanine may increase toxicity; phenytoin may decrease levels. In Pregnancy: Contraindicated in pregnancy. Precautions: Regularly examine hematologic profile (particularly neutrophils and platelets) to monitor for hematopoietic suppression; may cause pulmonary fibrosis; if WBC count is high, hydration and allopurinol should be used to prevent hyperuricemia.

**Drug Category: Tyrosine kinase inhibitors**
Imatinib mesylate or STI571 in oral formulation is an agent with strong tyrosine kinase inhibition activity of the bcr-abl abnormality in all phases of CML.

**Imatinib** mesylate
Specifically designed to inhibit tyrosine kinase activity of the bcr-abl kinase In Ph+ leukemic CML cell lines. Well absorbed after oral administration, with maximum concentrations achieved within 2-4 hours. Elimination is primarily in feces in form of metabolites. Adult dose: In chronic phase: 400 mg/d pa with food and large glass of water; may increase to 600 mg/d if no severe adverse effects or severe non-leukemia-related neutropenia or thrombocytopenia, disease continues to progress (any time), hematologic response is not satisfactory (after at least 3 month treatment), or a loss of previously achieved hematologic response occurs. Accelerated phase or blast crisis: 600 mg/d pa with food and large glass of water; may increase to 800 mg/d (400 mg bid) if no severe adverse effects or severe non-leukemia-related neutropenia or thrombocytopenia, disease continues to progress (any time), hematologic response is not satisfactory (after at least 3 month treatment), or a loss of previously achieved hematologic response occurs. Pediatric dose: Not established

Contraindications: Documented hypersensitivity. Interactions: CYP3A4 inhibitors (ketoconazole increases distribution of imatinib); CYP3A4 substrates (simvastin increases maximum concentration of imatinib by a 2-3.5-fold factor); CYP3A4 inducers (phenytoin decreases AUC by approximately one fifth of typical AUC); likely to increase blood levels of drugs that are substrates of CYP2C9, CYP2D6, and CYP3A4/5. In Pregnancy: Contraindicated in pregnancy. Precautions: Dose must be reduced if grade 3-4 neutropenia or thrombocytopenia develops or levels of transaminases or bilirubin become elevated

**Drug Category: Interferons**
Alpha, beta, and gamma are the 3 types known to date. Alpha group has been found to inhibit propagation of Ph-positive hematopoietic clone, allowing return of normal cells in the bone marrow.

**Interferon alfa-2a or alfa-2b**
Both are recombinant alpha interferons with
some minor amino acid differences but are considered equivalent modalities in the treatment of CML. INF alfa2a comes in single (3-MIU, 6-MIU, 9- MIU, 36-MIU strength) or multidose vials (9-MIU, 18-MIU strength). INF alfa2b comes in multidose pens of 18 MIU (delivers 3 MIU/dose), 30 MIU (5 MIU/dose), and 60 MIU (10 MIU/dose) with each pen good for 6 doses. Elderly patients who cannot tolerate adverse effects of alpha interferon may be started at one half the recommended starting dose. Adult dose: Approximately 5 million/m2/d SC until complete cytogenetic remission (100% Ph-negative BM cells by FISH). Remission can occur within 1-2 years from onset of therapy; an individual maximally tolerated dose can be obtained by starting at 3 million or 1.5 million qd and increasing by 3 million/d each month until tolerance or cytogenetic remission. Pediatric dose: Not established. Contraindications: Documented hypersensitivity. Interactions: Theophylline may increase toxicity; cimetidine may increase antitumor effects; zidovudine and vinblastine may increase toxicity. In Pregnancy- Safety for use during pregnancy has not been established. Precautions: Elderly patients do not tolerate treatment as well as younger individuals; caution in brain metastases, severe hepatic or renal insufficiencies, seizure disorders, multiple sclerosis, or compromised CNS; can cause severe mood disturbance in some patients, including clinical depression; caution in history or predisposition to depression; most acute adverse effects are flu like symptoms, which can be alleviated by taking acetaminophen for fever and muscle aches and giving injections at night before bedtime; occasionally, patients may have some psychiatric effects (psychoses) or intolerance due to chronic fatigue; liver function test may be affected with liver enzyme elevation, which is alleviated by decreasing total dose and allowing for fever.

Further Inpatient Care

Allogeneic bone marrow or stem cell transplantation is the best treatment for cure of this disease. This procedure has a high mortality rate because of the induction and long-term complications. Several types of BMT are available, and most of the data are in allogeneic transplants from an HLA-matched sibling donor and a few syngeneic from an identical twin. The data show that allogeneic transplants have better results than syngeneic transplants because of some graft-versus-leukemia effects. Allogeneic BMT currently is the only proven cure for CML. Ideally, it should be performed in the chronic phase of the disease rather than in transformation phase or in blast crisis. Candidate patients should be offered the procedure if they have a matched or single-antigen-mismatched related donor available. In general, younger patients fare better than older patients. Allogeneic BMT with matched unrelated donors has yielded very encouraging results in this disease. The procedure has a higher incidence of early and late graft failures (16%), grade III-IV acute graft-versus-host disease (GVHD) (50%), and extensive chronic GVHD (55%). The overall survival rate ranges from 31-43% for those younger than 30 years and from 14-27% for older patients.

Benefits and risks should be assessed carefully with the patient. Autologous BMT is investigational, but, recently, chemotherapy combinations or interferon have been found to induce a cytogenetic remission and allow harvesting of Ph-negative CD34 hematopoietic stem cells from the patient's peripheral blood. Other attempts to collect specifically normal stem cells currently are being investigated.

Prognosis

Historically, the median survival of patients with CML from time of diagnosis was 3-5 years, and no known therapy was shown to alter this survival rate until the onset of new modes of treatment. As treatment improved, the need to stage patients according to their prognosis became necessary to determine justification of procedures with high morbidity and mortality, such as BMT. Staging of patients comes from several analyses using multiple variate analysis between the association of pretreatment host and leukemic cell characteristics and their corresponding patient's survival. The findings...
from these studies classify patients into good, intermediate, or poor-risk groups, with an average survival of 5-6 years, 3-4 years, and 2 years, respectively. A combined prognostic model, incorporating previous models such as Sokal score, has been devised using the number of poor-prognosis characteristics; stage 1 is for 0 or 1 +, stage 2 is for 2+, stage 3 is for 3 or more, and stage 4 is for diagnosis at blastic phase. Poor prognosis in patients with CML is associated with several clinical and laboratory factors, including older age, symptomatic presentation, poor performance status, African-American descent, hepatomegaly, splenomegaly, negative Ph chromosome or bcr-abl, anemia, thrombocytopenia, thrombocytosis, decreased megakaryocytes, basophilia, or myelofibrosis (increased reticulin and/or collagen). Several therapy-associated factors may indicate poor prognosis in patients with CML, including longer time to hematologic remission with myelosuppression therapy, short duration of remission, total dose of hydroxyurea or busulfan, or poor suppression of Ph-positive cells by chemotherapy or interferon alfa therapy. Recently, the prognosis of patients with CML has improved from an expected median survival of 3 years and a 5-year survival rate of less than 20% to a median survival of 5 or more years and a 5-year survival rate of 50-60%. The improvement is due to early diagnosis, improved therapy with interferon and BMT, and better care. A German study of 139 low-risk patients with CML, according to the Sokal index, shows that the median survival with busulfan is 6 years (50 patients), with hydroxyurea is 6.5 years (55 patients), and with alpha interferon is approximately 9.5 years (34 patients), indicating improvement in survival with new therapy. Some patients with molecular remissions from alpha interferon may be cured, but this will only be established over time. The new and active tyrosine kinase inhibitor, Imatinib, is associated with a higher response rate and better tolerance of adverse effects. It may replace interferon as first-line therapy. long-term remissions remain to be seen, and Imatinib will be reevaluated in the near future to determine its role in the treatment.

Miscellaneous Medical/legal Pitfalls: Failure to diagnose and treat early with new modalities may be a cause for malpractice charges.

Conclusion
The discovery of new agents presently under study, such as tyrosine kinase inhibitor therapy, may prove valuable in prolonging the survival of this group of patients and may provide them with an eventual cure. Physicians should refer their patients to tertiary care and specialized centers for clinical trials involving these therapies under the guidance of Haematology-Oncologists. Currently in Bangladesh all kinds of facilities for CML (except ABMT) is present. The Government should come forward to fulfill these measures for the overall benefit of the patients.

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