Chronic Myelogenous Leukemia: Molecule to Man

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Chronic myelogenous leukemia (CML) is a malignancy of myeloid cells and their progenitors. CML is divided into two phases, a chronic phase in which the myeloid mass is markedly increased but cell maturation appears normal, and an acute phase with impaired maturation. This latter phase resembles acute leukemia. This review considers four aspects of CML: cell biology, molecular biology, treatment, and bone marrow transplantation.

Cell Biology

The characteristic feature of CML is a marked increase in myeloid cells and their progenitors. The underlying pathophysiology is not understood. Some data suggest a slight maturational defect in CML cells which results in the occurrence of several additional cell divisions before cells enter the nonproliferative, nonmitotic pool. The hierarchical structure of hematopoiesis amplifies this modest abnormality resulting in production of substantially more end cells which correspond to the clinical phenotype of CML. For example, it is estimated that each progenitor cell may produce as many as $10^6$ end cells. This would involve about 17 cell divisions. A small increase in proliferation of these myeloid progenitor cells, by three or four divisions, would increase granulocytes tenfold to sixteenfold.

CML is a clonal disorder. The Philadelphia (Ph) chromosome, resulting from a reciprocal translocation between chromosomes 9 and 22, is found in granulocyte progenitors, macrophages, RBC progenitors, megakaryocytes, and some B lymphocytes (1-4). However, it is not typically found in T-cells or their progenitors (5-10). These data suggest that transformation occurs within a progenitor cell to myelopoiesis and B-cell (but not T-cell) development. T-cells are sometimes involved in the CML clone. In such an instance a less mature progenitor cell is probably transformed. Data regarding sites of transformation have been confirmed by molecular studies of the BCR and ABL genes (vide infra) and by studies of polymorphic genetic systems on the X chromosome.

The clonal increase in myelopoiesis typical of CML is accompanied by decreased normal polyclonal hematopoiesis. The reason for this decrease is uncertain. One possibility is that regulatory mechanisms operate effectively to suppress proliferation by normal (but not CML) progenitor cells. It is also possible that cells of the CML clone release factors that suppress normal hematopoiesis. Cytogenetic analyses of bone marrow from persons with CML often show only cells derived from the CML clone. However, considerable data show that normal stem cells persist; normal metaphases can be detected under a variety of circumstances. These include the following: overdoses of busulfan, intensive chemotherapy, treatment with interferon, and in vitro bone marrow culture. Furthermore, normal metaphases have been observed in persons with CML receiving autotransplants (11).

A third aspect of the cell biology of CML is the inevitable progression to acute phase. When this occurs, cell maturation that characterizes the chronic phase is lost. Myeloid cells remain within the proliferative pool. Progression to acute phase occurs at a rate of approximately 10% in the first year following diagnosis and approximately 25% per year thereafter. By eight years, less than 20% of persons with CML remain in chronic phase. Several mechanisms might explain progression to acute phase. One possibility is that the duration of chronic phase is genetically predetermined. It is also possible that progression is a
Fig 1—Evolution of chronic myelogenous leukemia. N = normal hematopoiesis; X = clonal hematopoiesis; Ph = Ph-positive clone; Ph* = Ph clone with additional changes. a: An event occurs in a hematopoietic stem cell leading to proliferation of that clone X, while normal hematopoiesis N is suppressed. b: The t(9;22) occurs in the X clone leading to CML, the WBC increases, and clinical features of the disease develop while normal hematopoiesis is further suppressed. c: The diagnosis is made and the disease treated, clinical features resolve with partial recovery of normal hematopoiesis N. d: The disease is controlled with chemotherapy for a median period of 3½ years; eventually it becomes more difficult to control. Accelerated phase is indicated by the jagged line. e: Additional abnormalities occur in the Ph clone leading to acute phase disease Ph* with an increasing WBC and loss of maturation of the cells; normal clones N are again suppressed, as is the Ph clone. f: The disease becomes uncontrollable, leading to death. The issue of whether clonal hematopoiesis precedes the Ph chromosome is controversial. (From Gale RP, Chronic myelogenous leukemia: A model for human cancers. Ballière’s Clinical Hematology 1987;1:869-86. Reprinted with permission.)

Molecular Biology

Investigations in our laboratory as well as in others have determined the molecular basis of CML (15,16) (Fig 2). The 3' portion of the ABL proto-oncogene is translocated into the 5' portion of the BCR gene. In CML, breakpoints in BCR occur within a specific region of the BCR gene designated M-BCR. Within this region, breakpoints occur either between the second and third or third and fourth exons. Breaks within the ABL gene typically occur between the two alternative first exons designated 1α and 1β. The chimeric BCR-ABL gene is transcribed to an 8.3 kilobase (kb) chimeric mRNA and translated to a chimeric 210 kilodalton (kd) protein. This protein, unlike the normal 145 kd ABL gene product, has prominent tyrosine kinase activity. This increased kinase activity is thought to result from the amino terminal modification of the normal ABL protein and resembles activation of ABL by gag sequences in acutely transforming retroviruses. The substrate of the 210 kd BCR/ABL protein is unknown but it is capable of autophosphorelation. Transformation of rat embryo fibroblasts has been observed following infection with a retrovirus containing a DNA construct of the rearranged human BCR/ABL gene. Recently, infection of murine bone marrow with this construct was shown to cause a disease resembling CML. These data suggest that the rearranged BCR-ABL gene causes CML. Whether its introduction results in chronic and acute phase or chronic phase only is unknown.

A different rearrangement of BCR and ABL is found in about one-half of cases of Ph1-chromosome positive acute leukemias, predominantly acute lymphoblastic leukemia (ALL). In ALL, only the first exon of BCR is linked to the same exons of ABL. This results in a chimeric gene transcribed into a 7.0 kb chimeric
mRNA and translated into a 190 kd chimeric protein, also with increased tyrosine kinase activity. The other half of cases of Ph-chromosome ALL have the 210 kd type of rearrangement. Some data suggest that younger persons may be more likely to have the 190 kd type rearrangement but this is uncertain.

The molecular basis of transition to acute phase is less certain. There is no evidence that further rearrangement within the BCR-ABL chimeric gene coincides with transition to acute phase. Some recent reports indicate rearrangement of the P53 antioncogene in acute phase CML while others found no rearrangement. The P53 antioncogene maps to chromosome 17p, a region involved in isochromosome 17 rearrangement which is associated with acute phase. The emerging of isochromosome 17 results in loss of one allele of P53; rearrangement or mutation of the remaining allele may inactivate P53. Since isochromosome 17 occurs in only about 15% to 20% of persons with acute phase CML, other mechanisms are likely to be involved in transition to acute phase in most cases. Other cytogenetic abnormalities typical of acute phase of CML are reviewed elsewhere (17). Based on these data we suggest that these additional cytogenetic abnormalities may determine the phenotype of acute phase.

**Therapy**

Since transition to acute phase results in death within one year, duration of chronic phase is the major determinant of survival in CML. There are two possible objectives of CML therapy: increasing the duration of chronic phase, and increasing likelihood of cure. These objectives differ. Increasing duration of chronic phase would result in increased survival but need not be accompanied by increased cures. In contrast, cure requires preventing transition to acute phase.

Drugs used to treat CML include busulfan, hydroxyurea, cytarabine, anthracyclines, purines, and others (16,18). Busulfan and hydroxyurea control myeloid mass in chronic phase but have no effect on duration nor do they reduce the likelihood of transition to acute phase. Multidrug chemotherapy is no more effective than single drugs. Recently interferon has been shown to control myeloid mass in chronic phase CML. Interferon treatment reduces the portion of Ph1-chromosome positive cells detected in the bone marrow. However, it is unknown whether this effect correlates with a reduced number of myeloid progenitor cells at risk for transformation to acute phase. Furthermore, there are no convincing data that the duration of chronic phase or the likelihood of transition to acute phase is affected by interferon therapy.

**Transplants**

Several types of bone marrow transplants are performed in persons with CML including those from human lymphocyte antibody (HLA)-identical related donors (typically siblings), transplants from HLA-matched unrelated donors, and autotransplants. Data from the International Bone Marrow Transplantation Registry in about 1,200 persons with CML receiving HLA-identical transplants indicate five-year disease-free survival of about 45% in chronic phase, 30% in accelerated phase, and 20% in acute phase (19). Results are best in young persons, in those receiving posttransplant immune suppression with cyclosporine and methotrexate, in those not receiving T-cell depleted transplants, in persons with chronic but not acute graft-versus-host disease (GvHD), and in those in whom transplants were performed within one year of diagnosis (20). Outcomes of transplants in different phases of disease reflect predominantly different risks of leukemia recurrence: about 20% in chronic phase and about 60% in more advanced CML.

Detailed analysis of relapse rates in persons with CML in chronic phase receiving bone marrow transplants under diverse circumstances suggests that the major means of leukemia eradication is probably an immune mechanism. Recipients of HLA-identical transplants who develop chronic GvHD have a substantially lower risk of leukemia relapse than those without it (21). Also, recipients of T-cell depleted transplants have a markedly increased risk of leukemia relapse (22). There is a similarly high relapse rate in persons receiving transplants from genetically identical twins (23). Analysis of these data suggests that for CML in chronic phase the major means of leukemia eradication are chronic GvHD and a T-cell effect of GvHD. Genetic differences between donor and recipient may also be beneficial in view of the high relapse rate in twins. Probably several mechanisms operate.

The notion that leukemia eradication is not a direct result of high doses of chemotherapy and radiation is confirmed by analyses of bone marrow cells from persons with CML who receive transplants. Sensitive techniques, including the polymerase chain reaction, can detect cells with the BCR-ABL gene rearrangement up to five years posttransplant; most of these persons have not yet developed clinical evidence of recurrent CML (24-26). These data suggest that immune or other regulatory mechanisms controlled residual CML cells during the time these subjects were observed.

Most subjects with CML lack a HLA-identical sibling or a twin donor. Recently, these persons have received transplants from nonsibling HLA-identical or matched related or unrelated donors (27-29). Results are slightly inferior to those observed using perfectly matched donors. However, in view of the incurability of CML by other approaches, transplantation from a suitably matched unrelated donor seems reasonable.

Autotransplants have also been reported in CML (30). These are performed in acute or chronic phase using blood- or bone marrow-derived progenitor cells. Sometimes the bone marrow has been treated in vitro to decrease or eliminate Ph-chromosome positive cells. Techniques to remove CML cells from the bone marrow to be reinfused include short-term bone marrow culture, interferon, and anti-leukemia drugs such as hydroxyurea. In some instances, the subject has received chemotherapy or interferon prior to bone marrow procurement resulting in a decrease in Ph1-chromosome positive cells in the harvested bone marrow. Encouraging preliminary results have been reported with several of these approaches. The high relapse rates in persons without GvHD after receiving allogeneic transplants for CML in chronic phase and in recipients of transplants from twins suggest that eradication of leukemia in the recipient is a major obstacle to success of autotransplants. None of the techniques reported to eliminate CML cells in vitro...
has been studied in randomized trials; consequently, their efficacy is unknown. Although transplants in acute phase typically restore chronic phase, its duration is invariably brief. Most data suggest that the acute phase recurs from cells persisting in the recipient rather than in the graft. Results of autotransplants in chronic phase indicate that a small proportion of subjects become partially Ph1-chromosome negative for a brief period; a few are Ph1-chromosome negative for two or three years.

**Summary**

Substantial progress has been made in our understanding and treatment of CML. The molecular basis of CML is clear, but the precise mechanism by which the chimeric BCR-ABL tyrosine kinase results in an expansion of the myeloid mass in chronic phase is unknown. The molecular basis of the acute phase of CML is less well studied but the P53 antioncogene may play a role in some cases.

Progress in treating CML is less rapid. Interferon therapy decreases the proportion of Ph1 chromosome positive cells in the blood and bone marrow. Whether it affects CML progenitor cells is unknown. Consequently, its effect on prolonging duration of chronic phase or reducing the likelihood of transition to acute phase is unproved. Bone marrow transplantation, particularly from a HLA-identical sibling, results in about 50% five-year disease-free survival when performed in chronic phase. Results are less impressive in more advanced CML but are clearly better than any alternative. Despite some interesting outcomes following autotransplants, it is unlikely that this approach can cure CML. The efficacy of transplants in CML relates more to immunological or regulatory factors affecting hematopoiesis than to high-dose chemotherapy and/or radiation. These data may provide interesting insights into future control and/or treatment of CML.

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**References**