Focus on acute leukemias

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Epidemiology

Acute leukemias are a heterogeneous group of malignant diseases of hematopoietic progenitor cells with different molecular genetic abnormalities, clinical characteristics, and variable outcomes with currently available treatments. Age-specific incidence of acute myeloid leukemia (AML) rises linearly after age 40 with a median age of approximately 65 years. Most cases are sporadic, but congenital disorders such as Fanconi's, Bloom's, Down's, Kostmann's, and Diamond-Blackfan syndromes can increase the relative risk of developing AML (Scheinberg et al., 2001). Risk is also increased in individuals with acquired hematologic disorders including the myeloproliferative and myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria. Therapy-related AML (t-AML) may develop as a consequence of exposure to chemotherapy, including alkylating agents, epipodophyllotoxins, and ionizing radiation (Scheinberg et al., 2001). The age-specific incidence of acute lymphoblastic leukemia (ALL) peaks between the ages of 2 and 4, declines during late childhood adolescence and young adulthood, and peaks again among older adults. Mortality from ALL has declined dramatically during the last 25 years due to improvements in chemotherapy, particularly among children.

Classification, diagnosis, and prognosis

The French-American-British (FAB) classification, described approximately 25 years ago, remains the foundation on which the morphologic diagnosis of AML and ALL is based. However, the new World Health Organization (WHO) classification takes into account cytogenetics, molecular genetics, and morphologic and immunophenotypic findings not previously described (Harris et al., 1999). The diagnosis of AML is now established when at least 20% of the cells identified in the blood or bone marrow are blasts of myeloid origin. Precursor B cell acute lymphoblastic leukemia is now defined by cytogenetic and molecular genetic subgroups since these impart important prognostic information.

Diagnosis of acute leukemias requires morphologic evaluation of the peripheral blood smear, bone marrow aspirate and core biopsy, cytogenetics, molecular genetics, and immunophenotyping. The latter is particularly important in the subclassification of patients with ALL. In AML patients, cytogenetics are important prognostic factors in predicting response to treatment (Grimwade et al., 1998; Mrozek et al., 2000). Patients with AML whose leukemic cells have translocations t(8;21), t(15;17), t(16;16), or inv(16) have a favorable outcome with induction chemotherapy and intensive postremission consolidation chemotherapy. However, abnormalities of chromosomes 5 or 7,11q23 or complex karyotypes have a very poor outcome with currently available induction and postremission chemotherapy. Patients with a normal karyotype or with trisomy 8 have an intermediate prognosis. Among adults with ALL, t(9;22) or t(4;11) confer a very poor prognosis. Patients with t(9;22) ALL are rarely, if ever, cured with chemotherapy alone. The immunophenotypic determination of surface antigens expressed on leukemic blast cells may aid in diagnosis and has important implications for treatment and prognosis of myeloid, T, and B lineage leukemias.

FISH, SKY, CGH, MRD monitoring, and DNA microarrays

New techniques have begun to revolutionize diagnosis, prognosis, and classification of leukemias. Fluorescence in situ hybridization (FISH) allows for rapid testing for specific chromosomal translocations in both metaphase and interphase cells. Spectral karyotyping (SKY) uses 24 different fluorescently labeled chromosome painting probes to generate automated color display of all chromosomes, enhancing accuracy and sensitivity of cytogenetic analysis, especially with complex karyotypes. Comparative genomic hybridization (CGH) provides a sensitive method for identification of regions of genomic deletion or amplification and may identify new disease genes at these loci. Minimal residual disease (MRD) monitoring using sensitive RT-PCR-based amplification and quantitation of fusion genes may be useful to predict relapse. Finally, DNA microarray analysis of gene expression profiles may enhance conventional diagnostic and prognostic testing. For example, expression arrays can delineate AML versus ALL samples based solely on patterns of gene expression (Golub et al., 1999). Furthermore, expression array analysis has demonstrated that ALL associated with MLL translocations is a distinct subtype of acute leukemia, readily distinguished from either AML or ALL (Armstrong et al., 2002). In addition, expression profiling is a valuable tool for classification, subtype discovery, and prediction of outcome in pediatric B and T lymphoid leukemias (Ferrando et al., 2002; Yeoh et al., 2002).

Disease mechanisms and molecular targets

Chromosomal translocations

Cloning of recurring chromosomal translocation breakpoints associated with acute leukemias has provided valuable insights into disease mechanisms, as well as identification of therapeutic targets. More than 100 have been cloned, and although genotypically diverse, many translocations target similar signal transduction and transcriptional activation pathways. For example, acute promyelocytic leukemia (APL) is associated with t(15;17)(q22;q12) giving rise to the PML/RARα fusion, but the same phenotype is observed with at least four other chromosomal translocations involving the *RARα* gene. PML/RARα is a dominant-negative inhibitor of transcription through aberrant recruitment of the nuclear corepressor complex (NCoR), including histone deacetylase (HDAC). Patients with acute promyelocytic leukemia (APL) respond dramatically to the differentiating effects of all-*trans* retinoic acid (ATRA) (Fenaux et al., 1999; Tallman et al., 1997). ATRA binding to the PML/RARα fusion

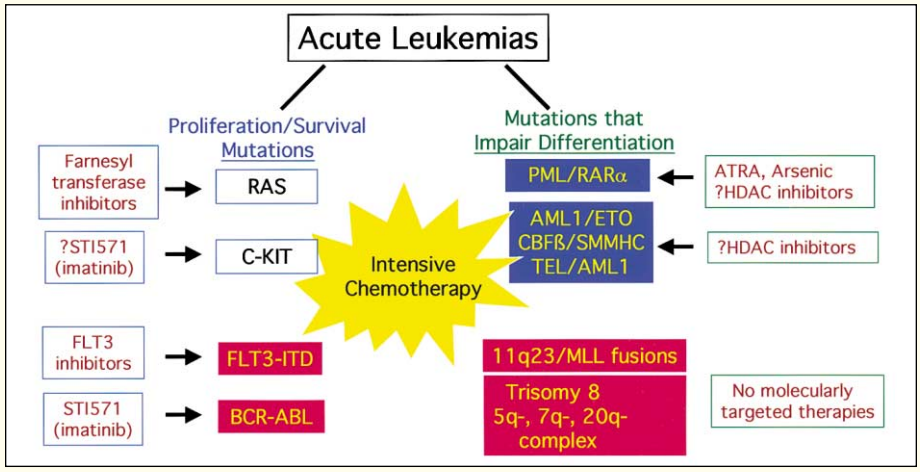

Figure 1. Pathogenesis and treatment of acute leukemias

As indicated by the yellow star, intensive cytotoxic chemotherapy remains the mainstay of treatment for all acute leukemias. Good prognosis leukemias are indicated in blue, poor prognosis leukemias are in red, and intermediate or unknown are in white. There are two classes of cooperating mutations in acute leukemia, those that confer proliferation and/or survival and those that impair hematopoietic differentiation. Targeted therapies have been developed or are being tested for many of these, including ATRA, arsenic, and HDAC inhibitors for APL associated with the PML/RARα fusion. HDAC inhibitors may also have utility for treating core binding factor leukemias such as AML1/ETO. STI571 (Gleevec, imatinib) is a selective inhibitor of BCR/ABL tyrosine kinase activity and has activity in CML blast crisis and in BCR/ABL-positive ALL. STI571 may also have activity in leukemias with activating mutations in c-KIT, although the most common of these, D816Y, is STI571 resistant. FLT3 inhibitors and farnesyl transferase inhibitors are also being tested in acute leukemia associated with FLT3 (Kelly et al., 2002b; Weisberrg et al., 2002 [both this issue of *Cancer Cell*]) and RAS mutations, respectively.

results in release of NCoR and restoration of normal transcriptional differentiation programs. The clinical success of "differentiation" therapy has stimulated enthusiasm for identification of other agents that target the NCoR complex, including HDAC inhibitors (Figure 1).

The AML1 and CBFβ components of the heterodimeric transcription factor core binding factor (CBF) are targeted by a dozen different translocations and result in loss of function of CBF. These include the t(8;21)(q22;q22) and inv(16)(p13q22) that result in expression of the AML1/ETO and CBFβ/SMMHC fusions and account for about 20%–25% of adult AML. The TEL/AML1 fusion in t(12;21)(p13;q22) pediatric ALL accounts for about 25% of childhood ALL. CBF is essential for normal hematopoietic development, and translocations involving CBF result in expression of dominant-negative inhibitors of CBF (Okuda et al., 1998; Yergeau et al., 1997). Like PML/RARα, dominant-negative activity of CBF fusions is mediated by aberrant recruitment of the NCoR/HDAC complex, suggesting that differentiation therapy with HDAC inhibitors might also be effective in this group of leukemias. Other transcription factors that are important in normal hematopoietic development are also targeted by translocations, including HOX family members and transcriptional regulatory and coactivating proteins such as MLL, CBP, p300, and TIF2 (Mrozek et al., 2000).

Rare cases of pediatric ALL and about 30% of adult ALL harbor t(9;22)(q34;q11) giving rise to the BCR/ABL fusion. In addition, the MLL-AF4 fusion associated with t(4;11)(q21;q23) occurs in the majority of cases of infant ALL, and this distinct clinical entity is associated with overexpression of FLT3 (Armstrong et al., 2002).

Point mutations

Point mutations also play an important role in pathogenesis of acute leukemia. Activating mutations have been identified in RAS (20%), FLT3 (30%–35%), and c-KIT (5%) as well as loss of function mutations in the hematopoietic transcription factors AML1 and C/EBPα.

Deletions

Identification of the gene(s) responsible for acute leukemias associated with recurrent deletions, including 5q–, 7q–, and 20q–, has been difficult. Efforts have focused on identification of classical tumor suppressor genes at these loci, in which there is loss of function of one allele due to deletion and of the other due to mutation. The lack of success thus far and recent observations that half gene dosage can contribute to hematopoietic phenotype suggest that haploinsufficiency of one or more genes in the deleted regions may contribute to the leukemic phenotype.

Cooperating mutations in acute leukemia

No single mutation is sufficient to cause acute leukemia. For example, expression of PML/RARα, AML1/ETO, or inv(16) alone impairs hematopoietic development and may contribute to expansion of the stem cell pool but is not sufficient to cause acute leukemia (Castilla et al., 1999; Grisolano et al., 1997; He et al., 1997; Higuchi et al., 2002). Similarly, expression of BCR/ABL, activated RAS, or activated FLT3 can cause myeloproliferative disease (Kelly et al., 2002a) but is not sufficient to cause acute leukemia. Accumulating experimental and epidemiologic evidence suggests a model of cooperation between two classes of mutations in acute leukemia (Dash and Gilliland, 2001). One class of mutations, exemplified by activating mutations in RAS, FLT3, or KIT, confers a proliferative and/or survival benefit to hematopoietic progenitors but does not affect differentiation. A second class of mutations, exemplified by PML/RARα, AML1/ETO, HOX gene fusions or MLL gene rearrangements, impairs hematopoietic differentiation and may contribute to expansion of hematopoietic progenitors (Figure 1). Acute leukemia, characterized by enhanced proliferation and survival of cells *and* impaired differentiation, is the consequence of expression of both classes of mutations. One important implication of this hypothesis is that there may be therapeutic synergy achieved by targeting each class of mutation, such as a combination of FLT3 inhibitors and ATRA in treatment of APL.

Current therapeutic strategies

During the past 40 years, treatment for both AML and ALL has been based on empirically derived cytotoxic chemotherapy. The best treatment for the majority of adults with AML, except those with APL, includes induction chemotherapy with an anthracycline or anthracenedione plus cytarabine followed by multiple cycles of intensive postremission chemotherapy, usually with high-dose cytarabine (Mayer et al., 1994). Patients with CBF leukemias [t(8;21) and inv(16) or t(16;16)] have an excellent outcome with this strategy, and a five-year disease-free survival (DFS) of 60%–70% has been achieved (Bloomfield et al., 1998). Randomized clinical trials have not shown any benefit for the

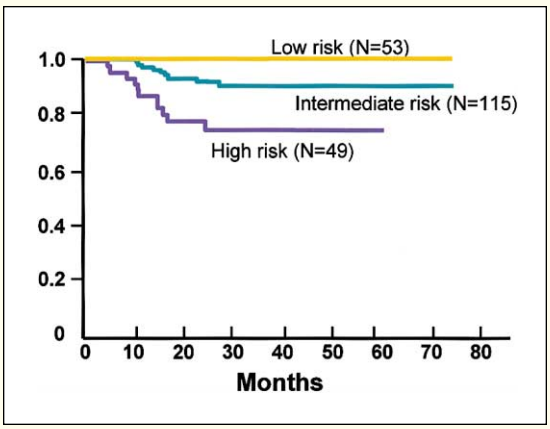

Figure 2. Kaplan-Meier product limit estimate of relapse-free survival for acute promyelocytic leukemia according to risk groups defined by a predictive model

Low risk: WBC ≤ 10,000/μl, platelet count > 40,000/μl; intermediate risk: WBC ≤ 10,000/μl, platelet count < 40,000/μl; high risk: WBC ≥ 10,000/μl, platelet count < 40,000/μl (reproduced with permission from Sanz et al., 2000).

addition of other agents or high-dose cytarabine in induction (Buchner et al., 1999). With the exception of the CBF leukemias, which have the most favorable outcome with at least three courses of intensive high-dose cytarabine as postremission chemotherapy, the optimal number of courses has not been determined. Older adults (≥55–60) do not benefit from intensive postremission chemotherapy following successful induction (Mayer et al., 1994). The most curable subtype of AML in adults is APL. The important advance is the incorporation of ATRA in induction and maintenance therapy, and five-year DFS of 75%–85% is now anticipated (Figure 2; Fenaux et al., 1999; Tallman et al., 1997). In patients with AML, attempts to exploit potential graph-versus-leukemia effect have yielded moderate success. Although hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched sibling donor is associated with the most potent antileukemic effect, treatment-related mortality remains approximately 20%, offsetting the benefits of the antileukemic effect in historical randomized clinical trials (Cassileth et al., 1998). However, this approach may be the only curative one for patients who fail induction or have unfavorable cytogenetics (Slovak et al., 2000). Similarly, in prospective randomized trials during the last decade, autologous HSCT has not consistently led to a better outcome than intensive postremission chemotherapy in randomized trials but may offer an advantage following multiple cycles of intensive postremission chemotherapy (Burnett et al., 1998). Low-intensity nonmyeloablative HSCT attempts to decrease the intensity of chemotherapy and increase immunosuppression in order to minimize toxicity and permit a graft-versus-tumor effect (Giralt et al., 1997). Haploidentical HSCT is a promising strategy, although profound immunosuppression with late opportunistic infections remains problematic (Aversa et al., 1998).

The principal phases of treatment for adults with ALL include remission induction with a vincristine-prednisone-based regimen and an anthracycline, multiple postremission cycles of chemotherapy variously designated as intensification or consolidation, with a variety of agents including high-dose methotrexate, high-dose cytarabine, alkylating agents, epipodophyllotoxins, L-asparaginase, central nervous system (CNS) treatment or prophylaxis, and maintenance therapy with vincristine and prednisone-based chemotherapy (Larson et al., 1995). Approximately 35% of adults with ALL are alive and free of disease at 5 years and beyond in large cooperative group trials. Historically, although HLA-matched sibling allogeneic HSCT has been reserved for patients at high risk of recurrence, contemporary studies suggest a benefit in all risk groups when carried out in first complete remission. The role of autologous HSCT has not been established and remains an area of investigation.

Recent advances in therapy

Insights into molecular pathogenesis have led to development of a spectrum of new targeted therapies for leukemia. Gemtuzumab ozogamicin, an anti-CD33 monoclonal antibody chemically linked to the potent cytotoxic agent calicheamicin, has activity in CD33-positive AML (Sievers et al., 2001). Arsenic trioxide has potent activity in APL, in part through effects on PML/RARα stability and through induction of apoptosis (Soignet et al., 2001). STI571 (Gleevec, imatinib mesylate), a small-molecule inhibitor of the ABL kinase, has activity in CML, CML blast crisis, and in BCR/ABL-positive ALL. Farnesyl transferase inhibitors (FTIs) impair prenylation and targeting of RAS to the plasma membrane and are being tested in AML patients with activating mutations in RAS. In addition, because BCR/ABL activates RAS, FTIs are being tested in concert with imatinib in BCR/ABL-positive leukemias and in imatinib-resistant leukemias. Activated FLT3 is an exceptionally attractive target for therapy as the single most commonly mutated gene in AML and is associated with a poor prognosis (Kottaridis et al., 2001). Selective inhibitors of FLT3 (Kelly et al., 2002b; Weisberg et al., 2002 [both in this issue of *Cancer Cell*]) have been developed and are entering clinical trials in AML. HDAC inhibitors are currently being tested in AML in an attempt to induce differentiation and apoptotic cell death, analogous to the effect of ATRA in APL.

Future challenges

Progress toward cure of acute leukemia is likely to occur with new therapies directed at specific molecular targets, such as BCR/ABL, FLT3, RAS, and the NCor/HDAC complex. This goal may be facilitated by modern genomic approaches to acute leukemia, including use of DNA microarray and proteomic strategies for identification of novel targets and prognostic indicators. In addition, to the extent that molecularly targeted therapies are effective, resistance mechanisms will develop that must be addressed and circumvented. Successful solutions to these challenges will require continued cooperation between laboratory scientists and clinical investigators and improved accrual to clinical trials evaluating the benefits of new targeted treatments.

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