Combinations of tretinoin, arsenic trioxide, and/or chemotherapy and/or gemtuzumab ozogamicin have shown favorable responses in high-risk APL patients at diagnosis.

Assessment of residual disease by RT-PCR amplification of the t(15;17) chimeric gene product *PML-RARA* following the final cycle of chemotherapy is an important step in the management of APL patients. Disappearance of the signal is associated with long-term disease-free survival; its persistence documented by two consecutive tests performed 2 weeks apart invariably predicts relapse. Sequential monitoring of RT-PCR for *PML-RARA* is now considered standard for postremission monitoring of APL, especially in high-risk patients.

The benefit from maintenance therapy with tretinoin has been documented in some studies and not in others. Thus, the use of tretinoin depends on which regimen has been used for induction and consolidation treatment and the risk category of the patients, with those with high-risk disease seemingly benefiting the most from maintenance therapy.

Patients in molecular, cytogenetic, or clinical relapse should be salvaged with arsenic trioxide with or without tretinoin; it produces meaningful responses in up to 85% of patients and can be followed by autologous or, less frequently, especially if RT-PCR positive for *PML-RARA*, allogeneic HSCT.

133 Chronic Myeloid Leukemia

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Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder. The disease is driven by the *BCR-ABL1* chimeric gene product, a constitutively active tyrosine kinase, resulting from a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, t(9;22) (q34;q11.2), cytogenetically detected as the Philadelphia chromosome (Ph) (Fig. 133-1). Untreated, the course of CML may be biphasic or triphasic, with an early indolent or chronic phase, followed often by an accelerated phase and a terminal blastic phase. Before the era of selective BCR-ABL1 tyrosine kinase inhibitors (TKIs), the median survival in CML was 3–7 years, and the 10-year survival rate was 30% or less. Introduced into CML therapy in 2000, TKIs have revolutionized the treatment, natural history, and prognosis of CML. Today, the estimated 10-year survival rate with imatinib mesylate, the first BCR-ABL1 TKI approved, is 85%. Allogeneic stem cell transplantation (SCT), a curative but risky treatment approach, is now offered as second- or third-line therapy after failure of TKIs.

INCIDENCE AND EPIDEMIOLOGY

CML accounts for 15% of all cases of leukemia. There is a slight male preponderance (male:female ratio 1.6:1). The median age at diagnosis is 55–65 years. It is uncommon in children; only 3% of patients with CML are younger than 20 years. CML incidence increases slowly with age, with a steeper increase after the age of 40–50 years. The annual incidence of CML is 1.5 cases per 100,000 individuals. In the United States, this translates into 4500–5000 new cases per year. The incidence of CML has not changed over several decades. By extrapolation, the worldwide annual incidence of CML is about 100,000 cases. With a median survival of 6 years before 2000, the disease prevalence in the United States was 20,000–30,000 cases. With TKI therapy, the annual mortality has been reduced from 10–20% to about 2%. Therefore, the prevalence of CML in the United States is expected to continue to increase (about 80,000 in 2013) and reach a plateau of approximately 180,000 cases around 2030. The worldwide prevalence will depend on the treatment penetration of TKIs and their effect on reduction of worldwide annual mortality. Ideally, with full TKI treatment penetration, the worldwide prevalence should plateau at 35 times the incidence, or around 3 million patients.

ETIOLOGY

There are no familial associations in CML. The risk of developing CML is not increased in monozygotic twins or in relatives of patients. No etiologic agents are incriminated, and no associations exist with exposures to benzene or other toxins, fertilizers, insecticides, or viruses. CML is not a frequent secondary leukemia following therapy of other cancers with alkylating agents and/or radiation. Exposure to ionizing radiation (e.g., nuclear accidents, radiation treatment for ankylosing spondylitis or cervical cancer) has increased the risk of CML, which peaks at 5–10 years after exposure and is dose-related. The median time to development of CML among atomic bomb survivors was 6.3 years. Following the Chernobyl accident, the incidence of CML did not increase, suggesting that only large doses of radiation can cause CML. Because of adequate protection, the risk of CML is not increased in individuals working in the nuclear industry or among radiologists in recent times.

PATHOPHYSIOLOGY

The t(9;22) (q34;q11.2) is present in more than 90% of classical CML cases. It results from a balanced reciprocal translocation between the long arms of chromosomes 9 and 22. It is present in hematopoietic cells (myeloid, erythroid, megakaryocytes, and monocytes; less often mature B lymphocytes; rarely mature T lymphocytes, but not stromal cells), but not in other cells in the human body. As a result of the translocation, DNA sequences from the cellular oncogene *ABL1* are translocated next to the major breakpoint cluster region (*BCR*) gene on chromosome 22, generating a hybrid oncogene, *BCR-ABL1*. This fusion gene codes for a novel oncoprotein of molecular weight 210 kDa, referred to as $p210^{BCR\text{-}ABL1}$ (Fig. 133-1*B*). This BCR-ABL1 oncoprotein exhibits constitutive kinase activity that leads to excessive proliferation and reduced apoptosis of CML cells, endowing them with a growth advantage over their normal counterparts. Over time, normal hematopoiesis is suppressed, but normal stem cells can persist and may reemerge following effective therapy, for example with TKIs. In Ph-positive acute lymphocytic leukemia (ALL) and in rare cases of CML, the breakpoint in *BCR* is more centromeric, in a region called the minor *BCR* region (*mBCR*). As a result, a shorter sequence of *BCR* is fused to *ABL1*, with a consequent smaller BCR-ABL1 oncoprotein, $p190^{BCR\text{-}ABL1}$. When occurring in Ph-positive CML, this translocation may predict for a worse outcome. A third rare breakpoint in *BCR* occurs telomeric to the major *BCR* region and is called *micro-BCR* (μ-BCR). It juxtaposes a larger fragment of the *BCR* gene to ABL1 and produces a larger $p230^{BCR\text{-}ABL1}$ oncoprotein, which is associated with a more indolent CML course.

The constitutive activation of *BCR-ABL1* results in autophosphorylation and activation of multiple downstream pathways that modify gene transcription, apoptosis, skeletal organization, and degradation of inhibitory proteins. These transduction pathways may involve RAS, mitogen-activated protein (MAP) kinases, signal transducers and activators of transcription (STAT), phosphatidylinositol-3-kinase (PI3k), MYC, and others. These interactions are mostly mediated through tyrosine phosphorylation and require binding of BCR-ABL1 to adapter proteins such as GRB-2, CRK, CRK-like (CRK-L) protein, and Src homology containing proteins (SHC). BCR-ABL1 TKIs bind to the *BCR-ABL1* kinase domain (KD), preventing the activation of transformation pathways and inhibiting downstream signaling. As a result, proliferation of CML cells is inhibited and apoptosis induced, leading to the reemergence of normal hematopoiesis. A plethora of signaling pathways have been implicated in BCR-ABL1-mediated cellular transformation. The emerging picture is a complex and redundant transformation network. An additional layer of complexity is related to differences in signal transduction between CML differentiated cells and early progenitors. Beta-catenin, Wnt1, Foxo3a, transforming growth factor β, interleukin-6, PP2A, SIRT1, and others have been implicated in CML stem cell survival.

Experimental models have established the causal relationship between the Ph-related *BCR-ABL1* molecular events and the development of CML. In animal models, expression of *BCR-ABL1* in normal hematopoietic cells produced CML-like disorders or lymphoid leukemia, demonstrating the leukemogenic potential of *BCR-ABL1* as a single oncogenic abnormality.