may have other RNA fusion types (e.g., e1a2, e13a3, or e14a3). In these patients, the routine PCR primers may not amplify the *BCR-ABL1* transcripts, thus leading to false-negative results. Therefore, molecular studies at diagnosis are important to document the type and presence of *BCR-ABL1* transcripts to avoid erroneously "undetectable" *BCR-ABL1* transcripts on follow-up studies, with the misconception of a complete molecular response.

Both FISH and PCR studies can be falsely positive at low levels or falsely negative because of technical issues. Therefore, a diagnosis of CML must always rely on a marrow analysis with routine cytogenetics. The diagnostic bone marrow confirms the presence of the Ph chromosome, detects clonal evolution, i.e., chromosomal abnormalities in the Ph-positive cells (which may be prognostic), and also quantifies the percentage of marrow blasts and basophils. In 10% of patients, the percentage of marrow blasts and basophils can be significantly higher than in the peripheral blood, suggesting poorer prognosis or even disease transformation.

Monitoring patients on TKI therapy by cytogenetics, FISH, and molecular studies has become an important standard practice to assess response to therapy, emphasize compliance, evaluate possible treatment resistance, change TKI therapy, and order mutational analysis studies. It is thus important to recognize the comparability of these measures in monitoring response. A partial cytogenetic response is defined as the presence of 35% less Ph-positive metaphases by routine cytogenetic analysis. This is roughly equivalent to *BCR-ABL1* transcripts by the International Scale (IS) of 10% or less. A complete cytogenetic response refers to the absence of Ph-positive metaphases (0% Ph positivity). This is approximately equivalent to *BCR-ABL1* transcripts (IS) of 1% or less. A major molecular response refers to *BCR-ABL1* transcripts (IS) ≤0.1%, or roughly a 3-log or greater reduction of CML burden from baseline. A complete molecular response usually refers to *BCR-ABL1* transcripts (IS) <0.0032% (undetectable by current techniques), roughly equivalent to a more than 4.5-log reduction of CML burden from baseline.

Findings in CML Transformation Progression of CML is usually associated with leukocytosis resistant to therapy, increasing anemia, fever and constitutional symptoms, and increased blasts and basophils in the peripheral blood or marrow. Criteria of accelerated-phase CML, historically associated with median survival of less than 1.5 years, include the presence of 15% or more peripheral blasts, 30% or more peripheral blasts plus promyelocytes, 20% or more peripheral basophils, cytogenetic clonal evolution (presence of chromosomal abnormalities in addition to Ph), and thrombocytopenia <100 × 10^9/L (unrelated to therapy). About 5–10% of patients present with de novo accelerated phase or blastic phase. The prognosis of de novo accelerated phase with TKI therapy has improved significantly, with an estimated 8-year survival rate of 75%. The median survival of accelerated phase evolving from chronic phase has also improved from a historical median survival of 18 months to an estimated 4-year survival rate of 70% on TKI therapy. Therefore, the criteria for accelerated-phase CML should be revisited because most have lost much of their prognostic significance. Blastic-phase CML is defined by the presence of 30% or more peripheral or marrow blasts or the presence of sheets of blasts in extramedullary disease (usually skin, soft tissues, or lytic bone lesions). Blastic-phase CML is commonly myeloid (60%) but can present uncommonly as erythroid, promyelocytic, monocytic, or megakaryocytic. Lymphoid blastic phase occurs in about 25% of patients. Lymphoblasts are terminal deoxynucleotide transferase positive and peroxidase negative (although occasionally with low positivity up to 3–5%) and express lymphoid markers (CD10, CD19, CD20, CD22). However, they also often express myeloid markers (50–80%), resulting in diagnostic confusion. This is important because, unlike other morphologic blastic phases, lymphoid blastic-phase CML is quite responsive to anti-ALL-type chemotherapy (e.g., hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, and dexamethasone]) in combination with TKIs.

PROGNOSIS AND CML COURSE

Before the imatinib era, the annual mortality in CML was 10% in the first 2 years and 15–20% thereafter. The median survival time in CML was 3–7 years (with hydroxyurea-busulfan and interferon α). Without a curative option of allogeneic SCT, the course of CML was inexorable toward transformation to, and death from, accelerated or blastic phases. The disease stability was unpredictable, with some patients demonstrating sudden transformation to a blastic phase. With imatinib therapy, the annual mortality in CML has decreased to 2% in the first 12 years of observation. Half of the deaths are from factors other than CML, such as old age, accidents, suicides, other cancers, and other medical conditions (e.g., infections, surgical procedures). The estimated 8- to 10-year survival rate is now 85%, or 93% if only CML-related deaths are considered (Fig. 133-2). The course of CML has also become quite predictable. In the first 2 years of TKI therapy, rare sudden transformations are still noted (1–2%), usually lymphoid blastic transformations that respond to combinations of chemotherapy and TKIs followed by allogeneic SCT. These may be explained by the intrinsic mechanisms of sudden transformation already existing in the CML clones before the start of therapy that were not amenable to TKI inhibition, in particular imatinib. Second-generation TKIs (nilotinib,

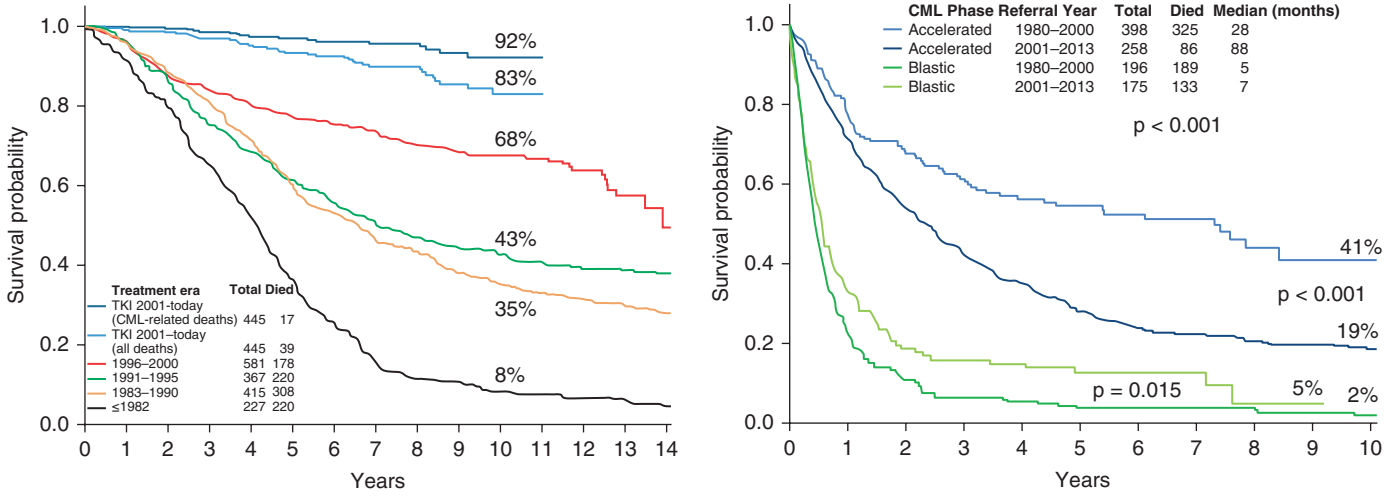

FIGURE 133-2 ***A.*** Survival in newly diagnosed chronic-phase chronic myeloid leukemia (CML) by era of therapy (M.D. Anderson Cancer Center experience from 1965 to present). Causes of non-CML deaths in 22 patients were other cancers (n = 7), postsurgical complications (n = 3), car accident (n = 2), suicide (n = 1), neurologic events (n = 3), cardiac (n = 3), pneumonia (n = 1), and unknown (n = 2). ***B.*** Survival in patients with accelerated- and blastic-phase CML referred to M.D. Anderson Cancer Center by era of therapy, demonstrating the significant survival benefit in the tyrosine kinase inhibitor (TKI) era in accelerated-phase CML but the modest benefit in blastic-phase CML. Referred cases included de novo and post-chronic-phase transformations.