responses, particularly complete cytogenetic responses, are uncommon (10–30%) and transient in blastic phase. Studies of TKIs in combination with chemotherapy are ongoing; the general experience suggests that combined TKI-chemotherapy strategies increase the response rates and their durability and improve survival. In CML lymphoid blastic phase, the combination of anti-ALL chemotherapy with TKIs results in complete response rates of 60–70% and median survival times of 2–3 years (compared with historical response rates of 40–50% and median survival times of 12–18 months). This allows many patients to undergo allogeneic SCT in a state of minimal CML burden or secondary chronic phase, which are associated with higher cure rates. In CML nonlymphoid blastic phase, anti-AML chemotherapy combined with TKIs results in CR rates of 30–50% and median survival times of 9–12 months (compared with historical response rates of 20–30% and median survival times of 3–5 months). In accelerated phase, response to single TKIs is significant in conditions where "softer" accelerated phase criteria are considered (e.g., clonal evolution alone, thrombocytosis alone, significant splenomegaly or resistance to hydroxyurea, but without evidence of high blast and basophil percentages). In accelerated phase, combinations usually include TKIs with low-intensity chemotherapy such as low-dose cytarabine, low-dose idarubicin, decitabine, interferon α, hydroxyurea, or others.

OTHER TREATMENTS AND SPECIAL THERAPEUTIC CONSIDERATIONS

Interferon α Interferon α was a standard of care before 2000. Today, it is considered in combination with TKIs (an investigational approach), sometimes after CML failure on TKIs, occasionally in patients during pregnancy, or as part of investigational strategies with TKIs to eradicate residual molecular disease.

Chemotherapeutic Agents Hydroxyurea and busulfan were commonly used chemotherapeutic agents in the past. Hydroxyurea remains a safe and effective agent (at daily doses of 0.5–10 g) to reduce initial CML burden, as a temporary measure in between definitive therapies, or in combination with TKIs to sustain complete hematologic or cytogenetic responses. Busulfan is often used in allogeneic SCT preparative regimens. Because of its side effects (delayed myelosuppression, Addison-like disease, pulmonary and cardiac fibrosis, myelofibrosis), it is now only rarely used in the chronic management of CML. Low-dose cytarabine, decitabine, anthracyclines, 6-mercaptopurine, 6-thioguanine, thiotepa, anagrelide, and other agents are useful in different CML settings to control the disease burden.

Others Splenectomy is occasionally considered to alleviate symptoms of massive splenomegaly and/or hypersplenism. Splenic irradiation is rarely used, if at all, because of the postirradiation adhesions and complications. Leukapheresis is rarely used in patients presenting with extreme leukocytosis and leukostatic complications. Single doses of high-dose cytarabine or high doses of hydroxyurea, with tumor lysis management, may be as effective and less cumbersome.

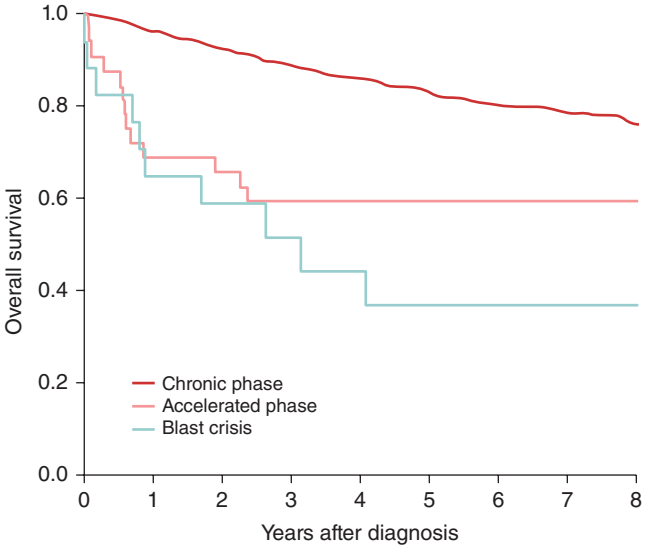
Special Considerations Women with CML who become pregnant should discontinue TKI therapy immediately. Among 125 babies delivered to women with CML who discontinued TKI therapy as soon as the pregnancy was known, three babies were born with ocular, skeletal, and renal malformations, suggesting the uncommon teratogenicity of imatinib. There are no or little data with other TKIs. Control of CML during pregnancy can be managed with leukapheresis for severe symptomatic leukocytosis in the first trimester and with hydroxyurea subsequently until delivery. There are case reports of successful pregnancies and deliveries of normal babies with interferon α therapy and registry studies in essential thrombocytosis of its safety, but interferon α can be antiangiogenic and may increase the risk of spontaneous abortions.

Patients on TKI therapy may develop chromosomal abnormalities in the Ph-negative cells. These may involve loss of chromosome Y, trisomy 8, 20q–, chromosome 5 or 7 abnormalities, and others. Most chromosomal abnormalities disappear spontaneously on follow-up and may be indicative of the genetic instability of the hematopoietic stem cells that predispose the patient to develop CML in the first place. Rarely, abnormalities involving chromosomes 5 or 7 may be truly clonal and evolve into myelodysplastic syndrome or acute myeloid leukemia. This is thought to be part of the natural course of patients in whom CML was suppressed and who live long enough to develop other hematologic malignancies.

GLOBAL ASPECTS OF CHRONIC MYELOID LEUKEMIA

Routine physical exams and blood tests in the United States and advanced countries result in early detection of CML in most patients. About 50–70% of patients with CML are diagnosed accidentally, and high-risk CML as defined by prognostic models (e.g., Sokal risk groups) is found in only 10–20% of patients. This is not the same situation in emerging nations (e.g., India, China, African countries, the Middle East), where most patients are diagnosed following evaluation for symptoms and many present with high tumor burdens, such as massive splenomegaly, and advanced phases of CML (high-risk CML documented in 30–50%). Therefore, the prognosis of such patients on TKI therapy may be worse than the published experience.

The high cost of TKI therapies (annual costs of $90,000–$140,000 in the United States; lower but variable in the rest of the world) makes the general affordability of such treatments difficult. Although TKI treatment penetration is high in nations where cost of therapy is not an issue (e.g., Sweden, European Union), it may be less so in other nations, even in advanced ones like the United States, where out-of-pocket expenses may be prohibitive to a subset of patients (perhaps 10–20%). Based on the sales of imatinib worldwide and charity free drug supplies, it is estimated that less than 30% of patients are treated with imatinib (or other TKIs) consistently. Although the estimated 10-year survival in CML is 85% in single-institution studies (e.g., M.D. Anderson Cancer Center), in national studies in countries with TKI affordability (Sweden) (Figs. 133-2 and **133-3**) or in company-sponsored studies (where all patients have access to TKIs throughout their care), the estimated 10-year survival worldwide, even 12 years after the introduction of TKI therapies, is likely to be less than 50%. The Surveillance, Epidemiology, and End Results (SEER) data from



No. at risk

CP	699	672	631	530	446	365	278	212	144
AP	32	22	21	18	14	10	5	4	2
BC	17	11	10	7	6	5	4	4	1

FIGURE 133-3 Survival in chronic (CP), accelerated (AP), and blastic crisis (BC) phases of chronic myeloid leukemia (CML) in the population-based Swedish national registry study. The accelerated- and blastic-phase cases are de novo presentations. The favorable outcome with de novo blastic phase may be due to use of 20% blasts or more to define blastic phase. *(With permission from Dr. Martin Hoglund, Swedish CML Registry, 2013.)*