dasatinib) used as frontline therapy have reduced the incidence of transformation in the first 2–3 years from 6–8% with imatinib to 2–4% with nilotinib or dasatinib. Disease transformation to accelerated or blastic phase is rare on continued TKI therapy, estimated at <1% annually in years 4–8 of follow-up on the original imatinib trials. Patients usually develop resistance in the form of cytogenetic relapse, followed by hematologic relapse and subsequent transformation, rather than the previously feared sudden transformations without the warning signals of cytogenetic-hematologic relapse.

Before the imatinib era, several pretreatment prognostic factors predicted for worse outcome in CML and have been incorporated into prognostic models and staging systems. These have included older age, significant splenomegaly, anemia, thrombocytopenia or thrombocytosis, high percentages of blasts and basophils (and/or eosinophils), marrow fibrosis, deletions in the long arm of chromosome 9, clonal evolution, and others. Different risk models and staging systems, derived from multivariate analyses, were proposed to define different risk groups. As with the introduction of cisplatin into testicular cancer therapy, the introduction of TKIs into CML therapy has nullified or lessened the prognostic impact of most of these prognostic factors and the significance of the CML models (e.g., Sokal, Hasford, European Treatment and Outcome Study [EUTOS]). Treatment-related prognostic factors have emerged as the most important prognostic factors in the era of imatinib therapy. Achievement of complete cytogenetic response has become the major therapeutic endpoint and is the only endpoint associated with improvement in survival. Achievement of a major molecular response is associated with decreased risk of events (relapse) and CML progression, may predict for differences in event-free survival (depending on the definition of an event) and for small differences in transformation rates, but has not been associated with survival prolongation. Among patients in complete cytogenetic response, survival is similar independent of whether they achieve a major molecular response or not. This may be due to the efficacy of salvage TKI therapies, which are and should be implemented at the first evidence of cytogenetic relapse. Achievement of complete molecular response (undetectable *BCR-ABL1* transcripts), particularly when durable (>2 years), may offer the possibility of durable molecular response (molecular cure rather than functional cure) in the context of investigational trials and may allow temporary therapy interruption in women eager to have babies. The lack of achievement of major or complete molecular responses should not be considered as "failure" of a particular TKI therapy and/or an indication to change the TKI or to consider allogeneic SCT.

Pretreatment prognostic factors and prognostic models have lost much of their clinical relevance to define prognosis and to select different therapies. However TKI-associated therapeutic responses have gained major clinical relevance and dictate appropriate and careful monitoring of patients to optimize their treatment.

TREATMENT CHRONIC MYELOID LEUKEMIA

The introduction of TKI therapy, first in the form of imatinib mesylate in 2001, has revolutionized the treatment and prognosis in CML. Before 2000, allogeneic SCT was frontline therapy, when available, because of its potentially curative capacity. Otherwise, patients were offered interferon α therapy (approved for the treatment of CML in 1986), which had modest benefits (improving survival from a median of 3–4 years with hydroxyurea-busulfan to a median of 6–7 years), but also significant side effects. Other alternatives included hydroxyurea, busulfan, and other nonspecific chemotherapies. With TKI therapy, the estimated 10-year survival in CML is 85%. Since 2001, six agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of CML. These include five oral BCR-ABL1-selective TKIs: imatinib (Gleevec), nilotinib (Tasigna), dasatinib (Sprycel), bosutinib (Bosulif), and ponatinib (Iclusig). Imatinib 400 mg orally daily, nilotinib 300 mg orally twice a day (on an empty stomach), and dasatinib 100 mg orally daily are approved for frontline therapy of CML. All three are also approved for salvage therapy (nilotinib 400 mg twice daily), in addition to bosutinib (500 mg daily) and ponatinib (45 mg daily). Imatinib, dasatinib (140 mg daily), bosutinib, and ponatinib are also approved for the treatment of CML transformation (accelerated and blastic phase), whereas nilotinib is only approved for chronic and accelerated phase. Dasatinib, nilotinib, and bosutinib are referred to as second-generation TKIs; ponatinib is referred to as a third-generation TKI. The sixth approved agent is omacetaxine (Synribo), a protein synthesis inhibitor with presumed more selective inhibition of the synthesis of the BCR-ABL1 oncoprotein. It is approved for the treatment of chronic- and accelerated-phase CML after failure of two or more TKIs, at 1.25 mg/m^2 subcutaneously twice a day for 14 days for induction and for 7 days for consolidation-maintenance. Nilotinib is similar in structure to imatinib but 30 times more potent. Dasatinib and bosutinib are dual SRC-ABL1 TKIs (dasatinib is reported to be 300 times more potent and bosutinib 30–50 times more potent than imatinib). Ponatinib is effective against wild-type and mutant *BCR-ABL1* clones. It is unique in being the only currently available BCR-ABL1 TKI that is active against T315I, a gatekeeper mutant resistant to the other four TKIs **(Table 133-2)**.

Imatinib, nilotinib, and dasatinib are all acceptable frontline therapies in CML. The long-term results of imatinib are very favorable. The 8-year follow-up results show a cumulative complete cytogenetic response rate (occurring at least once) of 83%, with 60–65% of patients being in complete cytogenetic response at 5-year follow-up. The estimated 8-year event-free survival rate is 81%, and the overall survival rate is 85%. Among patients continuing on imatinib, the annual rate of transformation to accelerated-blastic phase in years 4–8 is <1%. In two randomized studies, one comparing nilotinib 300 mg twice daily or 400 mg twice daily with imatinib (ENEST-nd) and the other comparing dasatinib 100 mg daily with imatinib (DASISION), the second-generation TKIs were associated with better outcomes in early surrogate endpoints, including higher rates of complete cytogenetic responses (85–87% vs 77–82%), major molecular responses (65–76% vs 46–63%), and undetectable *BCR-ABL1* transcripts (IS) (32–37% vs 15–30%), and lower rates of transformation to accelerated-blastic phase (2–4% vs 6%). However, neither study showed a survival benefit with second-generation TKIs (median follow-up times of 4–5 years). This may be because salvage

TABLE 133-2 MEDICAL THERAPEUTIC OPTIONS IN CHRONIC MYELOID LEUKEMIA

Agent (Brand Name)	Approved Indications	Dose Schedule	Notable Toxicities
Imatinib mesylate (Gleevec)	All phases	400 mg daily	See text
Dasatinib (Sprycel)	All phases	First-line: 100 mg daily Salvage: 140 mg daily	Myelosuppression; pleural and pericardial effusions; pulmonary hypertension
Nilotinib (Tasigna)	All phases except blastic phase	First-line: 300 mg twice daily Salvage: 400 mg twice daily	Diabetes; vasoocclusive disease; pancreatitis
Bosutinib (Bosulif)	All phases except frontline	500 mg daily	Diarrhea
Ponatinib (Iclusig)	All phases except frontline	45 mg daily (may consider lower starting doses in the future, e.g., 30 mg daily)	Skin rashes, pancreatitis; vasoocclusive disease (10–20%)
Omacetaxine mepesuccinate (Synribo)	Failure ≥2 tyrosine kinase inhibitors	1.25 mg/m^2 subcutaneously twice daily for 14 days for induction; 7 days of maintenance every month	Myelosuppression