CML, the cure rates with allogeneic SCT are 20–40%, depending on the definition of acceleration. Patients with clonal evolution as the only criterion have cure rates of up to 40–50%. Patients undergoing allogeneic SCT in second chronic phase have cure rates of 40–50%. The cure rates with allogeneic SCT in blastic phase CML are ≤15%. Post–allogeneic SCT strategies are now implemented in the setting of molecular or cytogenetic relapse or in hematologic relapse/transformation. These include the use of TKIs for prevention or treatment of relapse, donor lymphocyte infusions, and second allogeneic SCTs, among others. TKIs appear to be highly successful at reinducing cytogenetic/molecular remissions in the setting of cytogenetic or molecular relapse after allogeneic SCT.

Choice and Timing of Allogeneic SCT Allogeneic SCT was considered first-line CML therapy before 2000. The maturing positive experience with TKIs has now relegated its use to after first-line TKI failures. An important question is the optimal timing and sequence of TKIs and allogeneic SCT (whether allogeneic SCT should be used as second- or third-line therapy). Among patients who present with or evolve to blastic phase, combinations of chemotherapy and TKIs should be used to induce remission, followed by allogeneic SCT as soon as possible. The same applies to patients who evolve from chronic to accelerated phase. Patients with de novo accelerated-phase CML may do well with long-term TKI therapy (estimated 8-year survival rate 75%); the timing of allogeneic SCT depends on their optimal response to TKI (achievement of complete cytogenetic response). Among patients who relapse in chronic phase, the treatment sequence depends on several factors: (1) patient age and availability of appropriate donors; (2) risk of allogeneic SCT; (3) presence or absence of clonal evolution and mutations; (4) patient's prior history and comorbidities; and (5) patient and physician preferences **(Table 133-3)**. Patients with T315I mutations at relapse should be offered ponatinib and considered for allogeneic SCT (because of the short follow-up with ponatinib). Patients with mutations involving Y253H, E255K/V, and F359V/C/I respond better to dasatinib or bosutinib. Patients with mutations involving V299L, T315A, and F317L/F/I/C respond better to nilotinib. Comorbidities such as diabetes, hypertension, pulmonary hypertension, chronic lung disease, cardiac conditions, and pancreatitis may influence the choice for or against a particular TKI. Patients with clonal evolution, unfavorable mutations, or lack of major/complete cytogenetic response within 1 year of salvage TKI therapy have short remission durations and should consider allogeneic SCT as more urgent in the setting of salvage. Patients without clonal evolution or mutations at relapse and who achieve a complete cytogenetic response with TKI salvage, have long-lasting complete remissions and may delay the option of allogeneic SCT to third-line therapy. Finally, older patients (age 65–70 years or older) and those with high risk of mortality with allogeneic SCT may forgo this curative option for several years of disease control in chronic phase with or without cytogenetic response (Table 133-3). Historically, before the availability of TKIs, patients without cytogenetic response on interferon α or hydroxyurea had expected short median survival times (2–3 years) with expected rapid disease transformation. The maturing experience with TKIs suggests a different course, whereby patients may remain in chronic phase on TKI-based therapies (combinations including hydroxyurea, cytarabine, decitabine, and others), with or without cytogenetic response, for many years. Table 133-3 summarizes a general guidance to the choice of TKIs versus allogeneic SCT.

TABLE 133-3 GENERAL SUGGESTIONS REGARDING THE USE OF TYROSINE KINASE INHIBITORS (TKIS) AND ALLOGENEIC STEM CELL TRANSPLANTATION (SCT) IN CHRONIC MYELOID LEUKEMIA (CML)

CML Phase	Use of TKI	Consideration of Allogeneic SCT
Accelerated or blastic	Interim therapy to achieve minimal CML burden	As soon as possible (exception: de novo accelerated phase)
Imatinib failure in chronic phase; T315I mutation	Ponatinib to achieve minimal CML burden	Depends on longer term follow-up results of ponatinib efficacy
Imatinib failure in chronic phase; no clonal evolution, no mutations, good initial response	Second-line kinase inhibitors long-term	Third-line after second-line TKI failures
Imatinib failure in chronic phase; clonal evolution or mutations, or no cytogenetic response to second-line TKI	Interim therapy to achieve minimal CML burden	Second-line
Older patients (≥65–70 years) after imatinib failure in chronic phase	Salvage TKIs as longer-term therapy	May forgo allogeneic SCT in favor of good quality of life and survival in chronic phase

Note: Mutations involving Y253H, E255K/V, or F359V/C/I: prefer dasatinib or bosutinib. Mutations involving V299L, T315A, or F317L/F/I/C: prefer nilotinib.

MONITORING THERAPY IN CML

Achievement of complete cytogenetic response by 12 months of imatinib therapy and its persistence later, the only consistent prognostic factor associated with survival, is now the main therapeutic endpoint in CML. Failure to achieve a complete cytogenetic response by 12 months or occurrence of later cytogenetic or hematologic relapse is considered as treatment failure and an indication to change therapy. Because salvage therapy with other TKIs reestablishes good outcome, it is important to ensure patient compliance to continued TKI therapy and change therapy at the first sign of cytogenetic relapse. Patients on frontline imatinib therapy should be closely monitored until documentation of complete cytogenetic response, at which time they can be monitored every 6 months with peripheral blood FISH and PCR studies (to check for concordance of results), or more frequently if there are concerns about changes in *BCR-ABL1* transcripts (e.g., every 3 months). Monitoring by molecular studies only is reasonable in patients who are in major molecular response. Cytogenetic relapse on imatinib is an indication of treatment failure and need to change TKI therapy. Mutational analysis in this instance helps in the selection of the next TKI and identifies mutations in 30–50% of patients. Mutational studies in patients in complete cytogenetic response (in whom there may be concerns of increasing *BCR-ABL1* transcripts) identify mutations in ≤5% and are therefore not indicated. Earlier response has been identified as a prognostic factor for long-term outcome, including achievement of partial cytogenetic response (*BCR-ABL1* transcripts ≤10%) by 3–6 months of therapy. Failure to achieve such a response on imatinib therapy has been associated with significantly worse survival in some studies (particularly when second-generation TKIs were not readily available as salvage therapy), but not in others (when they were).

The use of second-generation TKIs (nilotinib, dasatinib) as frontline therapy changed the monitoring approach slightly. Patients are expected to achieve complete cytogenetic response by 3–6 months of therapy. Failure to do so is associated with worse event-free survival, transformation rates, and survival. However, the 3- to 5-year estimated survival among such patients is still high, around 80–90%, which is better than what would be anticipated if such patients were offered allogeneic SCT at that time. Thus, this adverse response to therapy is considered a warning signal, but it is not known whether changing therapy to other TKIs at that time would improve longer term outcome.

TREATMENT OF ACCELERATED AND BLASTIC PHASES

Patients in accelerated or blastic phase may receive therapy with TKIs, preferably second- or third-generation TKIs (dasatinib, nilotinib, bosutinib, ponatinib), alone or in combination with chemotherapy, to reduce the CML burden, before undergoing allogeneic SCT. Response rates with single-agent TKIs range from 30 to 50% in accelerated phase and from 20 to 30% in blastic phase. Cytogenetic