therapy with other TKIs (following close observation and treatment change at progression) provides highly effective salvage therapy that rebalances the negative effect of the relapse.

Salvage therapy in chronic phase with dasatinib, nilotinib, bosutinib, or ponatinib is associated with complete cytogenetic response rates of 30–60% of patients, depending on the salvage status (cytogenetic vs hematologic relapse), prior response to other TKIs, and the mutations at the time of relapse. Complete cytogenetic responses are generally durable, particularly in the absence of clonal evolution and mutations. Ponatinib is the only TKI active in the setting of T315I mutation, with complete cytogenetic response rates of 50–70%. The estimated 3- to 5-year survival rates with new TKIs as salvage are 70–80% (compared with <50% before their availability). For example, with dasatinib salvage after imatinib failure in chronic-phase CML, the major molecular response rates were 40–43%, the estimated 6-year survival rates were 74–83%, and progression-free survival rates were 40–51%. Thus, TKIs in the salvage setting have already reduced the annual mortality from the historical rate of 10–15% to ≤5%.

The goal of CML therapy is viewed differently in the context of research versus standard practice. In current practice, functional cure, defined as survival with CML similar to survival among normal individuals, is the current goal of therapy. CML is now considered an indolent disease, which, with appropriate TKI therapy, treatment compliance, careful monitoring, and early change to other TKIs as indicated, can be associated with close to normal survival. Therefore, in standard practice, achievement and maintenance of a complete cytogenetic response are the aims of therapy, because complete cytogenetic response is the only treatment-related factor associated with survival prolongation. Lack of achievement of a major molecular response (protects against events; associated with longer event-free survival) or of negative *BCR-ABL1* transcripts (offers the potential of TKI interruption on investigational studies) should not be considered indications to change TKI therapy or to consider allogeneic SCT. A general practice rule is to continue the particular TKI chosen at the most tolerable dose schedule not associated with grade 3–4 side effects or with bothersome chronic side effects, for as long as possible, until either cytogenetic relapse or the persistence of unacceptable side effects. These two factors (i.e., cytogenetic relapse and intolerable side effects as judged by the patient and treating physician) are the indicators of "failure" of a particular TKI therapy. Because of the increasing prevalence of CML (cost of TKI therapy) and the emerging long-term low rates of significant organ toxicities, the ultimate goal of CML therapy in the research setting is to achieve eradication of the disease (molecular cure) that is prolonged and durable, with recovery of nonneoplastic, nonclonal hematopoiesis off TKI therapy. The first step toward this aim is to obtain the highest rates of undetectable *BCR-ABL1* transcripts lasting for at least 2 or more years.

Recommendations provided by the National Comprehensive Cancer Network (NCCN) and by the European LeukemiaNet (ELN) discuss optimal/expected, suboptimal/warning, and failure response scenarios at different time points of TKI treatment duration. Unfortunately, they may have been misinterpreted in current practice, because oncologists often report that their aim of treatment is the achievement of major molecular response and disease eradication. Significantly, a substantial proportion of oncologists consider a change of TKI therapy in a patient in complete cytogenetic response if they note "loss of major molecular response" (increase of *BCR-ABL1* transcripts ([IS] from <0.1% to >0.1%). This perception may be the result of confusion regarding the NCCN and ELN guidelines, which have been updated often as a result of maturing data and have multiple treatment endpoint considerations. Although such endpoints have been suggested by these recommendations as possible criteria for failure, it is important to emphasize that no randomized study has yet shown that a change of TKI treatment in patients with complete cytogenetic response because of a loss of major molecular response, versus changing at the time of cytogenetic relapse, has been shown to improve survival. This is likely because of the high efficacy of salvage TKI therapy at the time of cytogenetic relapse.

Side effects of TKIs are generally mild to moderate, although with long-term TKI therapy, they could affect the patient's quality of life. Serious side effects occur in less than 5–10% of patients. With imatinib therapy, common mild to moderate side effects include fluid retention, weight gain, nausea, diarrhea, skin rashes, periorbital edema, bone or muscle aches, fatigue, and others (rates of 10–20%). In general, second-generation TKIs are associated with lower rates of these bothersome adverse events. However, dasatinib is associated with higher rates of myelosuppression (20–30%), particularly thrombocytopenia, and with pleural (10–25%) or pericardial effusions (≤5%). Nilotinib is associated with higher rates of hyperglycemia (10–20%), pruritus and skin rashes, and headaches. Nilotinib is also associated with rare events of pancreatitis (<5%). Bosutinib is associated with higher rates of early and self-limited gastrointestinal complications like diarrhea (50–70%). Ponatinib is associated with higher rates of skin rashes (10–15%), pancreatitis (5%), elevations of amylase/lipase (10%), and vasospastic/vasoocclusive events (10–20%). Nilotinib and dasatinib may cause prolongation of the QTc interval; therefore, they should be evaluated cautiously in patients with prolonged QTc interval on electrocardiogram (>470–480 ms), and drugs given for other medical conditions should have relatively smaller or no effects on QTc. These side effects can often be dose-dependent and are generally reversible with treatment interruptions and dose reductions. Dose reductions can be individualized. However, the lowest estimated effective doses of TKIs (from different studies and treatment practices) are imatinib 300 mg daily; nilotinib 200 mg twice daily; dasatinib 20 mg daily; bosutinib 300 mg daily; and ponatinib 15 mg daily.

With long-term follow-up, rare but clinically relevant serious toxicities are emerging. Renal dysfunction and renal failure (creatinine elevations >2–3 mg/dL) are observed in 2–3% of patients and reverse with TKI discontinuation and empirical use of other TKIs. Pulmonary hypertension has been reported with dasatinib (<1–2%) and should be considered in a patient with shortness of breath and a normal chest x-ray (echocardiogram with emphasis on measurement of pulmonary artery pressure). This may be reversible with dasatinib discontinuation and occasionally the use of sildenafil citrate. Systemic hypertension has been observed more often with ponatinib therapy, as well as other TKIs. Hyperglycemia and diabetes have been noted more frequently with nilotinib. Finally, mid- and small-vessel vasoocclusive and vasospastic events have been reported at low but significant rates with nilotinib and ponatinib and should be considered possibly TKI-related and represent indications to interrupt or reduce the dose of the TKI. These events include angina, coronary artery disease, myocardial infarction, peripheral arterial occlusive disease, transient ischemic attacks, cerebral vascular accidents, Raynaud's phenomenon, and accelerated atherosclerosis. Although these events are uncommon (<5%), they are clinically significant for the patient's long-term prognosis and occur at significantly higher rates than in the general population (5–20 times more often).

ALLOGENEIC STEM CELL TRANSPLANT

Allogeneic SCT, a curative modality in CML, is associated with long-term survival rates of 40–60% when implemented in the chronic phase. It is associated with early (1-year) mortality rates of 5–30%. Although the 5- to 10-year survival rates were reported to be around 50–60% (and considered as cure rates), about 10–15% of patients die in the subsequent 1–2 decades from subtle long-term complications of the transplant (rather than from CML relapse). These are related to chronic graft-versus-host disease (GVHD), organ dysfunction, development of second cancers, and hazard ratios for mortality higher than in the normal population. Other significant morbidities include infertility, chronic immune-mediated complications, cataracts, hip necrosis, and other morbidities affecting quality of life. The cure and early mortality rates in chronic-phase CML are also associated with several factors: patient age, duration of chronic phase, whether the donor is related or unrelated, degree of matching, preparative regimen, and others. In accelerated-phase