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# Second Generation TKI before and after Stem Cell Transplant for CML Blast Crisis in the Era of Precision Medicine, Where Do We Go from There?

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Despite the great advances in Tyrosine Kinase Inhibitors (TKI) in treatment of Chronic Myeloid Leukemia (CML) and great improvement in patients quality of life, those who progress to blast crisis still have dismal outcome [1]. The pathogenesis and mechanisms of progression of CML from chronic phase to Advance Phase (AP) or Blast Crisis (BC), including genetic instability and centrosomal aberrations, is complex and still not fully understood [2]. Hence, consensus on an optimal treatment approach has not been achieved.

Yu and colleagues [3] presented clinical outcome of four young patients (age 28-52) with CML-BC. Three of these patients received imatinib and progressed on it. Two of the 4 patients received second generation TKI to reduce the burden of disease before Stem Cell Transplant (SCT) while the other two patients received second generation TKI to treat relapse of BC after SCT and help revert to complete donor chimerism. After SCT, the first 2 patients were free of progression for almost 2 years (22 and 23 months) and the last 2 patients were also free of progression after second generation TKI for almost 2 years (21 and 25 months). It is safe and reasonable approach to use second generation TKI pre SCT without adverse effect on liver or engraftment [4]. SCT with individualized intervention after TKI therapy is superior to TKI alone for CML-BC [5]. Other than being young, these 4 patients did not have any evidence of clonal evolution or other genetic abnormalities and they were able to receive myoablative conditioning regimen before SCT. In a study in which the outcomes of 28 patients receiving reduced intensity conditioning were compared to those of 56 recipients of myeloablative SCT matched for disease severity and stage, reduced intensity recipients had higher rates of relapse [6], In a multivariate analysis done by Jain and colleagues on 477 patients with CML-BC, myeloid immunophenotype, prior TKI, age >58 years, lactate dehydrogenase level >1227 IU/L, platelet count <102 K/lL, no history of stem cell transplantation, transition to BC from chronic phase/AP, and the presence of chromosome 15 aberrations predicted for a significantly increased risk of death [7]. Interestingly, the first two patients described by Yu et al. had almost 2 years of no progression post SCT without prophylactic or maintenance TKI post SCT. Zhao et al. reported outcome of 12 patients (8 BC and 4 AP) who were treated with second generation TKI, followed by allo-SCT. However, prophylactic dasatinib or nilotinb was administrated after transplantation in 9 patients. After a median follow-up of 28 months after SCT, 8 (66.7%) were alive [8]. The benefit of prophylactic versus the preemptive use of TKI post SCT is not clear. Nowadays especially that most patients with CML BC referred to SCT are high risk patients and the use of reduced intensity regimens for older patients are on the rise, most centers use the prophylactic approach. However if maintenance is not performed, mandatory close monitoring of the bcr-abl transcript is required although fluctuation of levels is common as late as 10 years post SCT [9]. But there is no prospective data on what is the best approach regarding effect on survival, graft versus host disease (GVHD), quality of life or cost.

Yu [3] and others [10] demonstrated encouraging responses to TKI therapy in selected patients with AP or BC relapse of CML after SCT. Dasatinib inhibits Src family tyrosine kinases and T cell receptor-mediated signal transduction and cytokine production [11] and was proposed as a new therapeutic opportunity for GVHD. However, in this report patient number 3 had relapse of GVHD but control of CML after starting dasatinib. In this report patient 4 and others reported durable response using nilotinib for relapse, associated with reconstitution of full-donor chimerism without any signs of GVHD [12].

Further preclinical and clinical studies are needed to assess the pathogenesis of CML BC, high risk features, and individual influence of different TKIs on chimerism, graft versus leukemia, GVHD and other transplant-related toxicity and outcome (Figure 1).

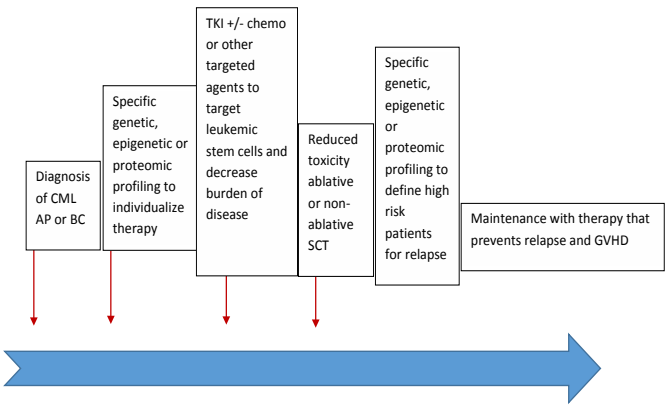


**Figure 1:** Potential future treatment schema.

AP: Accelerated Phase; BC: Blast Crisis; GVHD: Graft Versus Host Disease; SCT: Stem Cell Transplant; TKI: Tyrosine Kinase Inhibitor.

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## Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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