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Early switch in tyrosine kinase inhibitor therapy for patients with chronic myeloid leukemia: An emerging clinical question

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ABSTRACT

Response to frontline BCR-ABL1-targeted tyrosine kinase inhibitor (TKI) therapy is associated with an improved prognosis for patients with chronic myeloid leukemia (CML). Accordingly, the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) recommend the use of specific response milestones (eg, *BCR-ABL1* $\leq$ 10% on the International Scale at 3 months) to assess treatment success and inform follow-up care, including potentially switching to another TKI therapy. However, prior to any treatment change, the potential benefits and risks of each TKI and the goals of the patient must be considered. Here we review current NCCN and ELN response recommendations for patients with CML, highlight the impact of early responses on long-term prognosis, and discuss several reasons patients may consider a switch in TKI therapy. We also review completed and ongoing clinical studies involving a switch in frontline therapy for patients with CML, including those with a treatment-free remission phase.

1. Introduction

Tyrosine kinase inhibitors (TKIs) targeting the oncoprotein BCR-ABL1 have become an essential component in chronic myeloid leukemia (CML) therapy due to their success in improving patient outcomes (O'Brien et al., 2003; Kantarjian et al., 2012). There are currently several TKIs approved by the US Food and Drug Administration (FDA) for the treatment of patients with Philadelphia chromosome–positive (Ph+) CML in chronic phase (CML-CP) in the frontline, second-line, and later-line settings. Imatinib, nilotinib, and dasatinib are each FDA approved for the treatment of adult patients with newly diagnosed Ph+ CML-CP (Tasigna, 2015; Sprycel, 2015; Gleevec, 2015); nilotinib and dasatinib are also approved for the treatment of adults with Ph+ CML-CP with resistance to or intolerance of prior therapy including imatinib (Tasigna, 2015; Sprycel, 2015). Bosutinib is approved by the FDA for adult patients with Ph+ CML in any phase with resistance to or intolerance of prior therapy (Bosulif, 2013), and ponatinib is approved for the treatment of any-

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phase CML in adult patients with the T315I mutation or for whom no other TKI is indicated (Iclusig, 2015).

Many patients with CML-CP treated with frontline imatinib achieve less than optimal responses as defined by National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) (NCCN, 2016; Baccarani et al., 2013). In the International Randomized Study of Interferon and STI571 (IRIS) trial, 31% of patients had not achieved complete cytogenetic response (CCyR) by 12 months, and 13% failed to achieve CCyR by 60 months (Druker et al., 2006). Similarly, in the Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) study, by 18 months approximately 45% of patients treated with frontline imatinib had suboptimal response (lack of major molecular response [MMR; defined as *BCR-ABL1* $\leq$ 0.1% standardized to the International Scale (IS)]) and 16% had treatment failure (lack of CCyR) (Hughes et al., 2014a), both defined based on 2009 ELN recommendations (Baccarani et al., 2009). Patients missing NCCN and ELN response milestones (NCCN, 2016; Baccarani et al., 2013) are at increased risk of disease progression and CML-related death (Marin et al., 2012a; Branford et al., 2012; Marin et al., 2012b; Hughes et al., 2014c), highlighting a significant unmet medical need for those patients with suboptimal response to frontline TKI therapy.

Recent data have linked early molecular response (EMR; *BCR-ABL1*^{IS} $\leq$ 10% at 3 or 6 months) to TKI therapy as well as faster rates of *BCR-ABL1* decline with improved long-term clinical outcomes, including higher rates of overall survival (OS) and progression-free survival (PFS) (Marin et al., 2012a; Branford et al., 2012; Marin et al., 2012b; Hughes et al., 2014c; Branford et al., 2014; Hanfstein et al., 2014). On the basis of these data, NCCN and ELN recommendations have begun to incorporate EMR into the definitions of optimal response (Table 1) (NCCN, 2016; Baccarani et al., 2013); however, recommendations differ regarding switching therapy on the basis of EMR. While NCCN guidelines suggest assessing the potential benefits of a change in treatment following EMR failure at 3 months in imatinib-treated patients (NCCN, 2016), the ELN recommends waiting until the 6-month time point before deciding whether to switch treatment due to EMR failure (Baccarani et al., 2013). The long-term impact of switching therapy based on 3- or 6-month response levels remains under investigation, and additional data from prospective studies will help inform clinical decisions on switching therapy based on molecular responses at early time points, such as 3 months. In this review, we summarize current treatment milestones recommended by the NCCN and ELN, discuss several factors that may impact the decision to switch therapy for patients with CML, and review the current status of and data available from switch studies.

2. Treatment goals and monitoring in CML therapy

A main goal of CML-CP treatment with TKI therapy is to prevent disease progression to accelerated phase (AP) or blast crisis (BC) (NCCN, 2016). Current NCCN and ELN treatment guidelines emphasize the importance of achieving key TKI response milestones to reduce progression risk (NCCN, 2016; Baccarani et al., 2013). The NCCN lists hematologic, cytogenetic, and molecular response milestones at specified time points (eg, 3, 6, 12, and 18 months) from TKI treatment initiation, and EMR is considered as a response goal at both 3 months and 6 months of therapy (NCCN, 2016). For patients with *BCR-ABL1*^{IS} > 10% at 3 months, current NCCN guidelines recommend that a switch in therapy be considered along with other options (eg, enrollment in a clinical trial; Fig. 1), depending on the frontline TKI (NCCN, 2016). NCCN recommends that patients with 3-month EMR failure with frontline imatinib therapy be switched to an alternative TKI, receive an increased dose of imatinib (if not a candidate for an alternative TKI), or consider participating in a clinical trial (NCCN, 2016). For patients with 3-month EMR failure with frontline nilotinib or dasatinib therapy, NCCN recommendations are to continue treatment with the same TKI and dose, switch to an alternative TKI (other than imatinib), or consider participating in a clinical trial (NCCN, 2016). The same molecular response milestone, EMR, is given for 6-month assessments as for 3-month assessments, but for patients with *BCR-ABL1*^{IS} > 10% after 6 months of any frontline TKI, the NCCN recommends switching to an alternative TKI (other than imatinib) or enrollment in a clinical trial (NCCN, 2016). Per the NCCN, evaluation of patient adherence, drug interactions, and mutational analysis is recommended prior to treatment switch at 3 or 6 months (NCCN, 2016).

Similarly, current ELN recommendations consider EMR at 3 months to be an optimal treatment response (Baccarani et al., 2013). Patients with treatment failure at 3 months (lack of complete hematologic response [CHR] and/or lack of cytogenetic response) may consider switching therapy per the ELN recommendations; however, the ELN considers 3-month EMR failure a "warning," indicating that more frequent monitoring, but not treatment switch, is recommended (Baccarani et al., 2013). Overall, TKI switch due to EMR failure prior to 6 months is considered investigational per ELN recommendations (Baccarani et al., 2013). Specifically, the ELN cautions that a single molecular response measurement at 3 months may not be sufficient to inform a change in treatment, and recommends that a second time point (ie, 6 months) be used to determine whether switch in therapy is warranted (Baccarani et al., 2013). Of note, some studies have questioned the utility of 6-month molecular response measurements for patients with 3-month EMR failure (Marin et al., 2012a; Neelakantan et al., 2013).

3. Importance of achieving optimal responses on TKI therapy

Despite the increasing availability of effective TKIs, the outlook for patients who progress to AP/BC remains poor—with few treatment options and a median OS of less than 1 year following progression (Larson et al., 2012). This highlights the need to prevent transformation to advanced disease and identify patients with increased risk of progression at the earliest possible point. One important milestone for optimal TKI treatment is EMR. Patients who fail to achieve EMR milestones, such as those listed by the NCCN and ELN, have poorer long-term outcomes, including an increased risk of disease progression and reduced long-term OS (Marin et al., 2012a; Branford et al., 2012; Marin et al., 2012b; Hughes et al., 2014c), than patients who achieve EMR milestones.

Several independent analyses have associated achievement of EMR with higher rates of TKI treatment response and improved OS and PFS. An analysis of patients treated with frontline imatinib at the Hammersmith Hospital demonstrated that patients who achieved *BCR-ABL1*^{IS} $\leq$ 9.84% at 3 months had higher OS at 8 years compared with patients who did not achieve this level of response at 3 months (Marin et al., 2012a). In addition, a landmark analysis of patients in ENESTnd showed that patients with EMR at 3 months treated with nilotinib or imatinib therapy were more likely than patients without 3-month EMR to achieve MMR by 2 years and MR$^{4.5}$ by 4 years, and these patients also had improved rates of OS and PFS at 4 years (Hughes et al., 2014c). Achievement of 3-month EMR was also found to be predictive of improved long-term outcomes in an analysis of patients treated with nilotinib therapy who were resistant to or intolerant of frontline imatinib; in this study, patients with 3-month EMR had a greater likelihood of achieving MMR by 24 months and improved event-free survival (EFS) at 24 months than patients without 3-month EMR (Branford et al., 2012).

In the DASatinib versus Imatinib Study in treatment-Naive CML patients (DASISION) trial, patients who achieved EMR after