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How to treat chronic myeloid leukemia (CML) in older adults☆,☆☆

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ABSTRACT

Chronic myeloid leukemia (CML), a myeloproliferative neoplasm defined by the t(9;22)(q34;q11) chromosomal translocation, primarily affects older adults. Historically, effective treatment options were not available for older CML patients ineligible for curative allogeneic stem cell transplant, and the disease was therefore usually fatal within several years of diagnosis. The development of tyrosine kinase inhibitors (TKIs) that effectively target the constitutively active mutant tyrosine kinase in CML has dramatically improved outcomes for all patients with CML, including older patients. While older patients were underrepresented in prospective trials, TKI therapy can be successfully administered to older adults with CML with excellent efficacy and proven tolerability. TKI selection and monitoring for adverse events should be tailored based on co-morbidities. As with younger patients, life expectancy of older adults with CML now approaches that of age-matched controls. Here we review guidelines for management of older adults with CML.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm defined by the balanced reciprocal translocation t(9;22)(q34;q11) known as the Philadelphia chromosome. This chromosomal rearrangement creates the *BCR-ABL1* fusion gene which produces a constitutively active tyrosine kinase. The impact of this unregulated tyrosine kinase activity is the uncontrolled proliferation of mature and maturing myeloid cells (predominantly granulocytes) which eventually leads to symptomatic hematologic derangements and splenomegaly [1]. CML in the modern era is usually diagnosed in the asymptomatic or minimally symptomatic chronic phase. However, if untreated, chronic phase CML universally progresses to an aggressive, fatal form (accelerated and blast phase CML) in a median of 3–5 years [1–3]. Early therapies for CML such as busulfan, hydroxyurea, and interferon-α were only modestly successful at controlling CML-related symptoms and altering the natural course of the disease [4–6]. Until recently, allogeneic stem cell transplantation was the only highly effective therapy for CML; however, the toxicity of this procedure made it unavailable to older, less fit patients [7–9].

The treatment of CML was transformed in 2001 with Druker et al.'s landmark publication demonstrating that imatinib, the first tyrosine kinase inhibitor (TKI) to successfully inhibit the mutant constitutively active BCR-ABL1 kinase, was a remarkably well-tolerated and effective drug in CML [10]. Subsequent clinical trials and population studies confirmed the dramatic improvement in the length and quality of life in most patients diagnosed with CML in chronic phase treated with imatinib compared to the previous standard of care, interferon-α [11–14]. In subsequent years, more potent second-generation TKIs – nilotinib [15,16], dasatinib [7,18], and bosutinib [19,20] – were developed and approved for both initial and second-line treatment of CML, with ponatinib [21] now approved specifically for patients refractory to or intolerant of initial therapies. Today, patients diagnosed with chronic phase CML who are adherent to TKI therapy are likely to experience near normal life expectancy [14].

CML affects adults of all ages with the Surveillance, Epidemiology, and End Results (SEER) Program in the United States (US) reporting a median age at diagnosis of 67 years [22] while other European registries report a slightly younger median age at diagnosis of approximately 60 years [23,24]. However, the extraordinary efficacy of TKI therapy in CML means that younger patients diagnosed with CML will age on therapy and become older adults with CML. Therefore, most CML patients treated in clinical practice today are older and many suffer from co-morbid health conditions. This contrasts with the young, fit patients included in the prospective trials of TKIs in CML [11,15,17]. Highlighting this point, a study by Rohrbacher and colleagues of a representative region of Germany showed that CML patients in clinical trials were on average

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10 years younger (median age 54.1 years) then those that did not participate (median age, 64.8 years, P = 0.0001) [24].

Others have extensively reviewed general management principals of CML [22,25–27]. Here, we highlight specific aspects CML management that require consideration when caring for older adults. As a guiding principal, older adults should be treated as aggressively as their younger counterparts as TKI therapy is effective and tolerable in this population. However, selection of TKI and monitoring for and management of adverse events requires special attention (Table 1).

2. Tyrosine Kinase Inhibitors Are Effective in Older Adults With CML

The phase 3 IRIS trial comparing imatinib to interferon-α enrolled patients up until age 70, with approximately 20% over age 60 [11]. While the clinical response of older patients was not specifically reported, patients with high risk Sokal and Hasford scores (which both incorporate age) were noted to have excellent response rates. For example, 82% and 69% of patients with intermediate and high Sokal scores treated with imatinib achieved a complete cytogenetic response (CCyR) at 12 months [12]. In the phase 3 DASISION trial comparing dasatinib to imatinib in the frontline, approximately 8% of patients (20 of 259 in the dasatinib arm) were older than 65 years [17]. Response rates were high among those with intermediate and high risk Hasford scores (CCyR rate of 78% at 12 months) with high rates of continued deep remission at longer follow-up [17,28,29]. Finally, the ENESTnd trial comparing upfront nilotinib to imatinib enrolled patients up to age 85 [15]. Among patients with high Sokal risk taking 400 mg of nilotinib twice daily, 63% achieved a CCyR and 32% achieved a major molecular response (MMR) at 12 months, again with high rates of deep and ongoing molecular remissions confirmed after several years of follow-up [15,30,31]. In summary, although prospective clinical trials enrolled few older adults, and those enrolled were likely biased to be more fit than their age-matched counterparts, the limited available prospective data suggests efficacy and tolerability in the older population. Other retrospective data reviewed below confirms this finding.

Beyond the rarefied world of investigational trials which select for fit and motivated patients, population studies have confirmed that TKIs have improved the average life expectancy in CML patients, such that it approaches that of the general population [14]. Importantly, this gain in survival has been confirmed in older adults, both in the US [32] and in Sweden [14].

Recommendation: TKI therapy is effective in older adults with CML and should be offered to all patients immediately after diagnosis.

3. Challenges to Administering TKI Therapy in Older Adults: Drug-Drug Interactions

A unique aspect of safely treating older adults with TKIs is managing the risks associated with polypharmacy. Drug-drug interactions may decrease the efficacy or increase the toxicity associated TKI therapy. Haoula et al. presented a detailed review of the available evidence regarding the pharmacologic interactions between imatinib, dasatinib, and nilotinib and commonly prescribed co-medications (proton pump inhibitors, H2-antagonists, anti-emetics, anti-diabetic drugs, anti-platelet drugs, anticoagulants, anti-hypertensives, antibiotics, and others), as well as drugs that significantly impact the cytochrome P450 system [33]. We refer readers to this publication for its comprehensive reference list and user friendly outline of drug-drug interactions. An important point emphasized by the authors is that many of the described interactions are based on pre-clinical studies with uncertain clinical relevance. Therefore, clinical judgment is required when making decisions about continuing a potentially interacting medication necessary to effectively manage a co-morbid condition (which may be more immediately life-threatening than CML). Closer monitoring for organ toxicity and efficacy can be instituted when continuation or initiation of a drug with a potential interaction is required.

Iurlo et al. studied the real-world impact of polypharmacy (defined as taking 5 or more drugs) in 296 patients followed at Italian hematologic centers who were over 75 years of age and taking imatinib for CML [34]. The authors found that polypharmacy affected approximately one third of patients (36.1%), but there was no impact of polypharmacy on cytogenetic or molecular responses or toxicity. In clinical practice, we recommend a careful review of concomitant medications in patients initiating TKI therapy and at follow-up, particularly when medications have changed. When possible, drugs predicted to significantly interact with the prescribed TKI based on available data should be discontinued or changed [33]. Patients should be reminded to inform his or her hematologist when starting any new medication so appropriate monitoring can be arranged. A geriatrician may be helpful in managing concomitant medications.

Recommendation: Carefully review concomitant medications at initiation of TKI therapy and at every subsequent follow-up visit with attention to new medications. Discontinue medications predicted to have significant interaction with TKI when possible. Consider referral to a geriatrician to assist in management of polypharmacy.

4. Challenges to Administering TKI Therapy in Older Adults: Impact of Patient Co-morbidities for TKI Selection

Four TKIs – imatinib, dasatinib, nilotinib, and bosutinib – are FDA-approved for initial treatment of CML [20,22]. Treatment guidelines recommend that patient co-morbidities be considered when choosing initial therapy, a recommendation of particularly relevance to older patients [22]. Jabbour et al. examined claims databases (commercial and Medicare) to identify the prevalence of co-morbid conditions in patients initiating TKI treatment for CML and found that 41% had at least one co-morbid condition likely to influence TKI selection, with higher prevalence (65%) in Medicare insured patients [35]. Among Medicare-insured patients, 45% had heart disease, 17% had arrhythmia, 24% had diabetes, 25% had lung disease, and 4% had a pleural effusion. Practically speaking, this implies that a significant proportion of older patients may have a medical condition at risk for exacerbation by dasatinib (history of pulmonary disease or pleural effusion) or nilotinib (history of heart disease, arrhythmia, and/or lung disease). Bosutinib, which was just recently FDA-approved in late 2017 for initial therapy, has relatively shorter long-term safety data and is associated with significant gastrointestinal toxicity, specifically diarrhea. Therefore, imatinib will typically be the most appropriate initial TKI for older patients due to its long-term safety and efficacy data and lack of cardiopulmonary side effects, a finding confirmed after long-term follow-up [36–39].

Another reason that imatinib will typically be the most appropriate TKI for older patients is that the importance of achieving a deep remission, which is more likely with a second-generation TKI, will

Table 1
Principles of managing older adults on TKI therapy.

All older adults diagnosed with CML should be considered candidates for TKI therapy.
Imatinib has demonstrated the lowest long-term cardiovascular risk profile and therefore represents the safest treatment for most older adults.
Imatinib will soon be available in generic formulations and therefore will soon represent the most affordable treatment for most older adults.
Patient co-morbidities should be considered when selecting TKI therapy, whether selecting initial therapy or subsequent therapy after resistance or intolerance to initial therapy.
Concomitant medications should be carefully reviewed with efforts to minimize drug-drug interactions, and implement appropriate monitoring plans as necessary.
Financial toxicity should be assessed in older patients on TKIs.

TKI, tyrosine kinase inhibitor.

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