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CHRONIC MYELOID LEUKEMIAS (MJ MAURO AND G SAGLIO, SECTION EDITORS)

The Evolving Landscape of Frontline Therapy in Chronic Phase Chronic Myeloid Leukemia (CML)

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Abstract

Purpose of Review Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by uncontrolled proliferation of mature and maturing granulocytes. The disease is characterized by the presence of translocation t(9;22) leading to the abnormal BCR-ABL fusion. Historically, treatment options included hydroxyurea, busulfan, and interferon-α (IFN-α), with allogeneic stem cell transplant being the only potential curative therapy. More recently, the development of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of CML and turned a once fatal disease into a chronic and manageable disorder. This review aims to discuss the frontline treatment options in chronic-phase CML, provide recommendations for tailoring frontline treatment to the patient, and explore emerging therapies in the field.

Recent Findings The first-generation TKI, imatinib, was FDA approved in 2001 for use in CML. Following the approval and success of imatinib, second- and third-generation TKIs have been developed providing deeper responses, faster responses, and different toxicity profiles. With numerous options available in the frontline setting, choosing the best initial treatment for each individual patient has become a more complex decision.

Summary When choosing a frontline therapy for patients with chronic-phase CML, one should consider disease risk, comorbid conditions, and the goal of therapy.

Keywords Chronic myeloid leukemia · Frontline therapy · Tyrosine kinase inhibitors · Treatment · Adverse effects

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by uncontrolled proliferation of mature and maturing granulocytes. The hallmark of CML is the presence of the translocation t(9;22) which generates an abnormal BCR-ABL fusion also known as the Philadelphia chromosome. The BCR-ABL gene fusion produces BCR-ABL protein, which ultimately leads to constituently active tyrosine kinase activity and associated dysregulated cell signaling. The natural course of the disease includes three distinct phases: a chronic phase (CP), an accelerated phase (AP), and the terminal blast phase (BP). Prior to the invent of the targeted tyrosine kinase inhibitors (TKI), CML was a fatal disease with a 5-year overall survival of 20% in patients over the age of 65 [1].

Historically, treatment regimens for CML included arsenic trioxide and total body or splenic irradiation. After the discovery of chemotherapy in the 1950s, chemotherapeutic agents such as hydroxyurea and busulfan were used for disease control but did not ultimately alter the course of disease [2]. In the late 1970s, allogeneic bone marrow or stem cell transplants emerged as the only potential curative therapy for CML. However, this potential cure came with significant mortality and morbidity [3]. In addition, bone marrow transplantation was only available for young, otherwise healthy patients with a suitable donor. In the 1980s, interferon-α (IFN-α) was developed which was thought to target the Ph-positive clone and found in studies to induce hematologic and cytogenetic remissions and to improve overall survival. Treatment with IFN-α was limited by significant side effects that include "flu-like" symptoms with fevers, chills, myalgias, nausea, vomiting, and diarrhea [4].

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IFN-α and allogeneic transplants remained the standard of care for CML until the emergence of TKIs in 2001.

Imatinib (Gleevec)

Following the discovery of the Philadelphia chromosome and the BCR-ABL fusion gene, scientists sought out to identify ways to target this dysregulated tyrosine kinase. In the early 1990s, Dr. Brian Druker and Dr. Nicholas Lydon discovered a small molecule, STI-571, which targeted and inhibited the BCR-ABL1 tyrosine kinase. STI-571, which was later named imatinib, competes with ATP for the ATP-binding site on the kinase and inhibits phosphorylation and activation of downstream pathways [5].

The initial phase I clinical trial using imatinib enrolled 83 patients who had previously failed therapy with IFN-α. At a dose of ≥ 300 mg daily, imatinib produced complete hematologic responses (CHR) in 98% of patients, major cytogenetic responses (MCyR) in 60%, and complete cytogenetic responses (CCyR) in 41%. Based on pharmacologic studies and the results from the phase I study, a dose of 400 mg daily was ultimately chosen for further investigation [6]. The phase II trials confirmed the efficacy of imatinib in larger groups of patients. Side effects of imatinib included edema (60%), nausea (55%), muscle cramping (49%), rash (32%), and diarrhea (29%). Most of these side effects were grades 1–2 and only 2% of patients discontinued imatinib due to drug-related side effects [7]. The pivotal phase III IRIS trial enrolled 1106 patients with newly diagnosed chronic-phase CML. This study compared imatinib 400 mg daily to the standard of care at the time, IFN-α and low-dose cytarabine. The estimated 18-month MCyR rate was 87.1% in the imatinib group and 34.7% in the IFN-α and low-dose cytarabine arm. The estimated rates of CCyR were 76.2% and 14.5%, respectively. In addition, imatinib was found to improve the rate of freedom from progression to AP or BP CML [8]. Based on the impressive aforementioned data, imatinib was FDA approved in 2001 for Ph + CML in all disease phases. It has revolutionized the treatment of CML and remains a reliable frontline option for CP CML.

Second- and Third-Generation TKIs

Despite the success of imatinib, alternative therapeutic options were needed and ultimately developed for those patients that experienced disease progression while on imatinib, had inadequate responses, or struggled with imatinib tolerance due to various side effects. At the 10-year follow-up of the IRIS trial, 15.9% of patients discontinued imatinib due to unsatisfactory therapeutic effect and an additional 6.9% due to adverse effects. Furthermore, patients with a high Sokal score had inferior survival in comparison to patients with intermediate- or low-risk disease based on the Sokal score. In patients who fail imatinib, attempts at dose escalation to 600 mg daily or 800 mg have been made. However, benefit was only seen in patients who previously had a cytogenetic response [9]. In patients who develop intolerance, dose escalation is not a viable option. Accordingly, newer therapies were needed to fill these gaps.

Dasatinib (Sprycel)

Dasatinib was the first second-generation TKIs developed and was FDA approved in 2006. In vitro, the drug is 325 times more potent inhibiting the wild-type BCR-ABL kinase and was hypothesized to provide a superior clinical response [10]. In the phase I dose-escalation study, patients were enrolled who were intolerant or resistant to imatinib. Dasatinib was associated with high rates of CHR, MCyR, and CCyR. Based on pharmacokinetic data, a dose of 70 mg twice a day was chosen [11]. Several phase II studies confirmed that dasatinib was highly active following imatinib resistance or intolerance. Despite pharmacokinetic data suggesting a twice a day dosing schedule, the phase II START-C study suggested that a 100 mg daily dose may provide similar efficacy with less toxicity [12–14]. A phase III dose-optimization trial studied dasatinib in CP CML at doses of 100 mg daily, 50 mg BID, 140 mg daily, and 70 mg BID. There was no difference in terms of efficacy between the different dosing groups. Compared to the 70 mg twice a day dosing, the 100 mg daily dose had significantly lower rates of pleural effusion, grades 3 to 4 thrombocytopenia, grades 3 to 4 anemia, dose interruption, dose reduction, and treatment discontinuation [15].

The randomized phase III trial phase III DASSION trial compared dasatinib 100 mg daily to imatinib 400 mg daily as frontline therapy for newly diagnosed CP CML. At 12 months, dasatinib versus imatinib was found to have higher rates of CCyR (77% versus 66%, $p = 0.007$) and major molecular response (MMR) (46% versus 28%, $p = < 0.001$). Response rates were achieved faster with dasatinib compared to imatinib and the rate of progression to accelerated or blast crisis phase was lower in dasatinib-treated patients (1.9% versus 3.5%). Thrombocytopenia (grades 3–4 in 18%) and pleural effusions (any grade 17%) were more common with dasatinib while fluid retention and gastrointestinal side effects were more common with imatinib [16]. At the 5-year follow-up of the DASSION study, a higher proportion of dasatinib-treated patients achieved deep molecular responses such as MMR (76%) and $MR^{4.5}$ (42%) compared to imatinib (MMR 64% and $MR^{4.5}$ 33%). Despite this, there was no difference between 5-year overall survival between the groups (91% with dasatinib versus 90% with imatinib). Pulmonary arterial hypertension developed in 5% patients on dasatinib, however, has been thought to be reversible with drug discontinuation [17].

Due to adverse effects encountered in real-world practice with dasatinib, attempts have been made to study lower doses to balance efficacy and tolerability. Naqvi et al. studied the effects of dasatinib 50 mg daily in patients with newly diagnosed CP CML. The longer term follow-up from this study was recently published in 2020. After a minimum of 12 months of follow-up, the rates of CCyR, MMR, $MR^{4.0}$, and $MR^{4.5}$ were 95%, 81%, 55%, and 49%, respectively. In patients with longer follow-up, rates of MMR, $MR^{4.0}$, and $MR^{4.5}$ at 18 months continued to improve at 88%, 74%, and 68%, respectively. The 2-year event-free and overall survival rates were 100%. Treatment was tolerated well overall with lower rates of toxicity compared to what has been described with the 100 mg dose. Twenty-one (25%) of patients required dose interruption with a median time of 13 days. Five patients (6%) developed pleural effusions. Of these patients, 4 underwent dose reduction to 20 mg (1 patient) or 40 mg (3 patients) daily without recurrence of the pleural effusion. Other causes for dose interruption included thrombocytopenia (in 3 patients), gastrointestinal bleeding (in 2 patients), creatinine elevation (in 2 patients), transaminitis (in 2 patients), and unintended pregnancy (in 2 patients). Compared to historical data of imatinib or dasatinib 100 mg, the 50 mg daily dose resulted in more favorable responses with higher rates of CCyR and MMR rates. This difference may be attributed due to more continuous drug exposure and minimal treatment interruptions. This lower dose strategy provides a safe and effective strategy associated with potential cost-savings in frontline CP CML [18].

Nilotinib (Tasigna)

Nilotinib is a second-generation TKI that is 10–30 times more potent in comparison to imatinib with less off-target effects, specifically in targeting PDGFRβ and KIT kinases. It is active against many of the imatinib-resistant mutations, except the T315I mutation [10]. The phase I dose-escalation study enrolled 119 patients with imatinib-resistant CML or Philadelphia chromosome-positive ALL. With a median follow-up of 4.9 moths, 92% patients with CP disease had a CHR and 35% patients obtained a CCyR [19]. Several phase II studies were conducted confirming the clinical safety and efficacy of nilotinib at a dose of 400 mg twice a day [20, 21].

The phase III ENESTnd clinical trial enrolled 846 patients with newly diagnosed CP CML, who were randomized to nilotinib 300 mg BID, nilotinib 400 mg BID, or imatinib 400 mg daily. At a median follow-up of 12 months, the patients who received nilotinib had significantly better rates of MMR (44% for nilotinib 300 mg BID, 43% for nilotinib 400 mg BID, and 22% for imatinib) and CCyR (80% for nilotinib 300 mg BID, 78% for nilotinib 400 mg BID, and 65% for imatinib). Headaches, rashes, alopecia, and pruritus were more common in patients who received nilotinib. Grades 3 or 4 anemia and neutropenia were more common with imatinib; however, grades 3 or 4 thrombocytopenia were slightly more common with nilotinib [22]. The 5-year follow-up was published in 2016, which demonstrated rates of MMR in 77% of patients on nilotinib 300 mg BID, 77.2% on nilotinib 400 mg BID, and 60.4% on imatinib. The frequency of deeper molecular remissions such as $MMR^{4.5}$ was higher in the nilotinib arms compared to the imatinib arm. Treatment with nilotinib also reduced progression to AP or BP CML. Despite these improvements, there was no significant difference in overall survival between the groups. Cardiovascular events (CVEs), such as ischemic heart disease, cerebral vascular events, and peripheral arterial disease, were more common with nilotinib. Grades 3–4 cardiovascular events occurred in 4.7% of patients on nilotinib 300 mg BID and 8.7% of patients on the 400 mg BID dose. Of note, patient's baseline cardiovascular risk scores were predictive of cardiovascular events during therapy [23]. The 10-year follow-up of the ENESTnd trial was recently published which demonstrated cumulative higher rates of MMR, MR^4, and $MR^{4.5}$ with nilotinib versus imatinib. This translated higher rates of estimated TFR eligibility (at 5 and 10 years) than with imatinib. The 10-year overall survival (OS) and progression-free survival (PFS) remain similar between nilotinib and imatinib. Long-term follow-up confirmed similar tends of adverse events on nilotinib. Of note, there was a higher rate of CVEs with nilotinib versus imatinib which continued to increase over time. Cumulative rates of CVEs at the 10-year follow-up were 16.5% with nilotinib 300 mg BID, 23.5% with nilotinib 400 mg BID, and 3.6% with imatinib. Again, baseline Framingham cardiovascular risk scores were predictive of patients' risk of developing a CVE during treatment, raising the importance of aggressive cardiovascular risk factor modification while on treatment with nilotinib [24].

Bosutinib (Bosulif)

Bosutinib is the most recent second-generation TKI to receive FDA approval. It is active against many kinase domain mutations with the exception of T315I and V299L. Unlike the other second-generation TKIs, bosutinib has minimal off-target effects on c-kit and platelet-derived growth factor receptor (PDGFR) which are thought to play a role in several toxicities commonly seen with use of other TKIs [25]. The initial phase I/II clinical trial enrolled 288 patients with imatinib-intolerant or imatinib-resistant CML. The maximal tolerated dose of bosutinib was found to be 500 mg daily. At a median of 24 months, 86% achieved a CHR, 53% had a MCyR, and 41% had a CCyR. Of those who obtained a CCyR, 64% achieved a MMR [26].

The BELA trial was the first phase III randomized control trial of bosutinib in patients with newly diagnosed

Ph + CML. Patients were randomized to bosutinib 500 mg daily versus imatinib 400 mg daily. Treatment with bosutinib demonstrated quicker responses, deeper responses with superior MMR rates, and fewer patients in the bosutinib arm with transformation to AP/BP disease. However, the study showed no significant difference CCyR rate at 12 months, which was the study's primary endpoint. Drug discontinuations due to adverse events were common in the bosutinib arm with 48 patients (19%) having stopped the drug at the initial 12-month analysis. Common adverse events with bosutinib included diarrhea and elevations in liver function tests [27]. Following this, the phase III BFORE trial randomized newly diagnosed CML patients to bosutinib 400 mg daily versus imatinib 400 mg daily. At 12 months, the rate of MMR was significantly higher with bosutinib versus imatinib (47.2% versus 36.9%; $p = 0.02$) as was the CCyR rate (77.2% vs. 66.4, respectively; $p = 0.0075$). Redemonstrated again in this study, patients achieved earlier responses with fewer patients progressing on to AP/BP disease. The most common drug-related toxicities with bosutinib were diarrhea (7.8% with grade ≥ 3), increased ALT (19% with grade ≥ 3), increased AST (9.7% with grade ≥ 3), and thrombocytopenia (13.8% with grade ≥ 3). Cardiac toxicities were rare with bosutinib [28]. The authors of the BFORE trial recently presented the 5-year long-term follow-up data of this study at the 2020 American Society of Hematology Meeting. They demonstrated continued superior efficacy compared to imatinib with regard to rates of MMR, MR^4, and $MR^{4.5}$. There were no differences in terms of 5-year event-free survival (EFS) or OS between the bosutinib and imatinib arms. Safety profiles were consistent with previous reports. The most common long-term adverse events with bosutinib were diarrhea (75%), nausea (37.3%), thrombocytopenia (35.8%), and increased ALT (33.6%). No new safety signals were found [29].

Ponatinib (Iclusig)

Despite the success with the second-generation TKIs, approximately 30–40% of patients do not have an optimal response or lose response to TKI therapy [17, 23, 28]. Until the development of ponatinib, this group of patients had a poor prognosis with limited treatment options available. The T315I BCR-ABL mutation is present in 20% of patients with TKI-resistant disease and confers resistance against all other approved TKIs. Ponatinib was developed as a pan-BCR-ABL inhibitor with activity against all BCR-ABL mutations, including the T315I mutation. The phase I dose-escalation trial enrolled patients who had failed at least 2 prior TKIs. The study demonstrated efficacy and safety of ponatinib in a refractory patient population [30]. The phase II PACE trial included 449 patients with heavily pretreated CML (93% who had received > 2 prior TKIs). At a dose of 45 mg daily, the 12-month MCyR rate was 56%, CCyR rate of 46%, MMR rate of 34%, and 15% of patients achieved a $MMR^{4.5}$. The most common toxicities seen with ponatinib were rash (34%), dry skin (32%), abdominal pain (22%). Hematologic toxicities were common with thrombocytopenia developing in 30% of patients (24% grade ≥ 3), neutropenia in 19% (17.5% grade ≥ 3), and anemia in 13% of patients (12% grade ≥ 3). Notably, an increased rate of arterial thrombotic events was observed in ponatinib-treated patients with 7.1% developing cardiovascular events, 3.6% with cerebrovascular events, and 4.9% with peripheral vascular events [31]. Despite the signal for increased arterial events, ponatinib provides a potential therapeutic option in a patient population with a poor prognosis and no other available treatment options. Based on the success of the phase I and II trials in resistant and T315I-mutated disease, ponatinib was FDA approved in 2012 for CML patients with resistance or intolerance to prior TKIs.

Ponatinib was also studied in newly diagnosed CML patients in the phase III EPIC trial. The trial was terminated early due to concern for increased vascular events. Arterial occlusive events occurred in 7% of patients on ponatinib with 10 (6%) events designated as serious. Despite limited assessment, there were no differences in rates of MMR between the ponatinib and imatinib arms [32]. The efficacy of ponatinib in newly diagnosed CML patients remains to be determined. The long-term follow-up of the PACE trial was reviewed with a focus on arterial occlusive events (AOEs). The 5-year cumulative incidence of AOE on ponatinib was 31% with 26% considered serious events. Patients with > 2 cardiac risk factors at the start of treatment had an increased risk of serious AOEs [33]. The SCORE risk score has been developed to risk stratify and provide personalized prevention strategies to reduce the risk of arterial events while on ponatinib [34].

Management

A majority of patients diagnosed with CML will present in the CP of the disease. Treatment is indicated at diagnosis to prevent progression to the advanced phases. The development of TKIs has revolutionized the treatment for CP CML and has provided patients with safe and effective treatment options. With numerous options available in the frontline setting, choosing the best initial treatment for each individual patient has become a more complex decision.

When choosing a frontline treatment in CP CML, one should consider three important factors: disease risk, goal of therapy, and comorbid conditions. Clinical risk models such as the Sokal score, Hasford (EURO) score, or EUTOS long-term survival (ELTS) score remain important to identify the patients that may be at risk for inferior outcomes and increased risk for disease progression. In the IRIS study,

patients with a high Sokal score had an inferior 10-year OS (68.6%) compared to intermediate-risk (80.3%) or low-risk patients (89.9%). Nilotinib has been associated with improved outcomes compared to imatinib which was more evident in intermediate- and high-risk disease groups [23]. Similar outcomes have been shown with dasatinib and bosutinib [16, 28]. For patients with intermediate- or high-risk disease, second-generation TKIs are generally preferred.

No clinical trial has demonstrated an improvement in overall survival with second-generation TKIs in comparison to imatinib. However, studies have demonstrated more rapid and deeper molecular responses with the second-generation TKIs. This becomes important when the goal of treatment is the ability to achieve and maintain a treatment-free remission (TFR). In younger patients, females interested in family planning, or others who are interested in drug discontinuation, use of a second-generation TKI is appropriate in order to best achieve the optimal criteria for TKI discontinuation.

The selection of an initial TKI should take into consideration the patient's comorbid conditions as well as each drug's unique toxicity profile. Table 1 demonstrates common adverse effects seen with the TKIs. Clinicians have the most experience with imatinib and it carries the safest toxicity profile. However, imatinib can be poorly tolerated due to side effects such as fatigue, muscle cramps, and diarrhea which can significantly impact quality of life [8]. Dasatinib is frequently well tolerated but can be associated with significant adverse effects including pleural effusions, platelet dysfunction, and pulmonary hypertension [17]. Nilotinib is again well tolerated but should be used with caution in patients with underlying cardiovascular or peripheral vascular disease due to the signal for increased rates of cardiovascular, cerebral vascular, and peripheral vascular events. QTc prolongation and pancreatitis have also been seen with nilotinib [23]. Bosutinib appears to have lower rates of cardiovascular and pulmonary effects; however, gastrointestinal effects such as diarrhea are common. Rarely, drug-related liver toxicity was also seen [28]. Accordingly, careful consideration of the patient's medical history is needed to tailor initial therapy [35].

Table 1 Currently available tyrosine kinase inhibitors

	First generation	Second generation			Third generation
	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
FDA approval	CP: 400 mg daily	CP: 100 mg daily AP/BP: 140 mg daily	CP: 300 mg BID AP/BP: 400 mg BID	CP: 400 mg daily AP/BP: 500 mg daily	CP: 45 mg daily AP/BP: 45 mg daily
Approval	First-line	First-line or subsequent lines	First-line or subsequent lines	First-line or subsequent lines	Resistant/intolerant ≥ 2 TKI or T315I mutant
Phase III trials	IRIS [8]	DASISION [15, 16]	ENESTnd [20, 21]	BFORE [25]	PACE [27] ¥
CCyR at 12 mo	69%	Dasatinib: 84% Imatinib: 69%	Nilotinib: 80% Imatinib: 65%	Bosutinib: 77.2% Imatinib: 66.4%	Ponatinib: 46%†
MMR at 12 mo	39%	Dasatinib: 46% Imatinib: 28%	Nilotinib: 44% Imatinib: 22%	Bosutinib: 47.2% Imatinib: 36.9%	Ponatinib: 34%†
Overall survival	89%*	Dasatinib: 91%* Imatinib: 90%*	Nilotinib: 93.7%* Imatinib: 91.7%*	Bosutinib: 99.2%** Imatinib: 97%**	Ponatinib: 73%*
Contraindicated mutations	Numerous	T315I, V299L, G250E, or F317L	T315I, Y253H, E255K/V, F359V/C/L, G250E	T315I, V299L, G250E, or F317L	No common mutations
Adverse effects (all grades)	Edema (60%) Muscle cramps (45%) Nausea (50%) Diarrhea (45%) Fatigue (39%) Headache (37%)	Thrombocytopenia (58%) Pleural effusion (28%) Pulmonary hypertension (5%) Pericardial effusion (3%)	Rash (39%) Headache (32%) Hypertension (10%) Ischemic Heart Disease (3.9%) Cerebrovascular Events (1.4%) Peripheral Artery Disease (2.5%)	Diarrhea (70%) Nausea (35%) Thrombocytopenia (35%) Increased ALT (30.6%) Increased AST (22.8%)	Abdominal pain (33%) Headache (32%) Rash (31%) Constipation (27%) Hypertension (13%) Arterial occlusive events (7%)

CCyR complete cytogenetic response, no Ph-positive metaphases on FISH

MMR major molecular response, BCR-ABL1 (IS) ≤ 0.1%

*5-year overall survival

**2-year overall survival

¥Due to the phase III EPIC trial closing early, the phase II PACE is shown

†Median follow-up of 15 months as 12 months was not reported

Future Directions

Asciminib is a novel TKI which binds at the myristoyl site on the BCR-ABL protein and locks BCR-ABL in an inactive conformation. As it does not bind at the ATP site, it is active against both unmutated BCR-ABL and mutations such as T315I. In a phase 1 clinical trial, asciminib demonstrated safety and efficacy in a heavily pretreated patient population, including those with T315I mutations [36]. The phase III ASCEMBL trial (NCT03106779) is ongoing comparing asciminib 40 mg BID versus bosutinib 500 mg daily in patients with CP CML previously treated with ≥ 2 TKIs. Early efficacy and safety data was recently presented. At a median follow-up time of 14 months, 61.8% of patients remained on asciminib versus 30.3% of patients randomized to bosutinib. The MMR rate at 24 weeks was 25.5% in the asciminib group versus 13.2% with bosutinib. Patients achieved MMR faster on asciminib (12.7 weeks with asciminib versus 14.3 weeks with bosutinib). In addition, deeper responses were achieved on asciminib compared to bosutinib. Grade ≥ 3 adverse events occurred in 50.6% of patients receiving asciminib versus 60.5% in the bosutinib arm. The most common grade ≥ 3 adverse events with asciminib versus bosutinib were thrombocytopenia (17.3% versus 6.6%), neutropenia (14.7% versus 11.8%), diarrhea (0% versus 10.5%), and increased aminotransferase (0.6% versus 14.5%). Two patients receiving asciminib died during the study. One death was related to an ischemic stroke and the other from an arterial embolism. Further studies are needed to fully assess the risk of vascular events with asciminib [37]. Due to the early promising effects of asciminib, a phase II trial (NCT03906292) is ongoing studying asciminib in the frontline setting in newly diagnosed Ph + CML patients.

While the TKIs are effective treatment of CML, they rarely eliminate the CML stem cell. Pre-clinical data demonstrates that Bcl-2 is a key survival factor for early CML progenitor cells [38]. Combination regimens including low-dose dasatinib and venetoclax are currently under investigation (NCT02689440). Venetoclax plus TKI has shown activity in myeloid BP disease [39]. Additional combination regimens such as ruxolitinib and second-generation TKIs are under investigation in hopes of achieving deeper remissions and periods of TFR.

With the therapies currently available, patients with CML have a life expectancy similar to age-matched controls [40]. Researchers and clinicians are focusing on the development of novel TKIs and treatment strategies to minimize toxicity and overcome resistance mutations, while still providing deep responses to allow for periods of TFRs. Financial toxicity remains another important issue in the chronic management of patients with CML.

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Data availability Not applicable.

Code Availability Not applicable.

Declarations

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