Is there a best frontline therapy in chronic myeloid leukemia?

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Abstract

The management of chronic myeloid leukemia in chronic phase (CML-CP) was transfigured with the introduction of imatinib in 2001. Since then, four other tyrosine kinase inhibitors (TKI), dasatinib, nilotinib, bosutinib and most recently asciminib, have garnered approval for frontline management of CML-CP. The second generation TKI (2G-TKI) and asciminib have all been shown to be significantly superior to imatinib in attaining molecular responses, and asciminib possibly superior to 2G-TKI. With limited prospective comparisons between the 2G-TKI and similar survival outcomes with imatinib compared to 2G-TKI, the selection of a TKI for patients with newly diagnosed CML-CP must be individualized to the needs of that specific patient. Important factors to consider when choosing a drug include patient-related factors (age, co-morbidities, lifestyle considerations, quality of life, patient preferences, shared-decision making and whether treatment-free remission is a goal), disease-related factors (risk stratification, transcript type, presence of high-risk gene mutations such as *ASXL1*) and drug-related factors (major molecular response rates with each TKI, adverse events, rates of treatment discontinuation and treatment-free remission rates).

Introduction

After the characterization of the “minute chromosome” described in seven patients with chronic myeloid leukemia (CML)[1] as a reciprocal translocation between chromosomes 9 and 22 (Philadelphia or Ph$^+$ chromosome)[2], the resulting BCR::ABL1 fusion oncoprotein with constitutive activation of the tyrosine kinase was identified.[3-5] Prior to approval of imatinib, patients with CML in chronic phase (CML-CP) had a median survival probability of 3-5 years and, without an allogeneic stem cell transplant, their disease eventually transformed to accelerated and/or blast phase.[6] The remarkable journey of advances in CML, starting with recognition of the oncogenic driver, perfecting methods of detection, and targeting it with ever more potent and selective tyrosine kinase inhibitors (TKI), has inspired the era of genomics and its integration into treatment. As the techniques of detection of the Ph$^+$ chromosome evolved from conventional cytogenetics to fluorescence *in situ* hybridization to quantitative reverse transcriptase polymerase chain reaction, not only did the diagnosis and detection of the disease become more standardized, but also the monitoring and detection of minimal amounts of residual disease that allowed for a change in treatment goals. This resulted in the advancement of the endpoints of CML clinical trials and patient care, from complete hematologic remission to complete cytogenetic remission (CCyR) to deep molecular response (DMR). For both the treating physician and the patient, the goals progressed from symptom control to improvement in overall survival (OS) to achieving a treatment-free remission (TFR) and improved quality of life. With five TKI now approved for frontline therapy, in this review we analyze whether there is a “best” upfront therapy for management of CML.

Introduction of tyrosine kinase inhibitors

Prior to the 1980s, the treatment armamentarium for CML included busulphan and hydroxyurea.[7] During the 1980s and 1990s, stem cell transplantation and interferon-α became treatments of choice.[6] The introduction of imatinib in the 2000s transfigured CML into a malignancy where the life

expectancy approaches that of the general population.[8,9] The age-adjusted mortality rate of patients with CML improved from 0.8 in 1999 to 0.5 in 2020.[10] The treatment armamentarium for frontline therapy has expanded, with imatinib, dasatinib, nilotinib, bosutinib and asciminib currently approved for frontline treatment in many parts of the world. Two other TKI, radotinib and flumatinib, are approved in selected countries but are not discussed in this manuscript.

Current frontline therapies

Imatinib

The pivotal, phase III, IRIS (International Randomized Study of Interferon and STI571) study compared imatinib to the standard of care at that time, i.e. interferon-α and low-dose cytarabine, in patients with CML-CP within 6 months of diagnosis. At 18 months, imatinib at a dose of 400 mg once daily led to a significantly improved CCyR (76.2% *vs*. 14.5%; *P*<0.001) compared to the standard of care.[11] As a result of this dramatic improvement in response rates, 65.6% of the patients randomly assigned to interferon-α and low-dose cytarabine crossed over to imatinib early in the trial (median duration on standard-of-care treatment, 9 months).[12] Due to this cross-over, OS was initially similar between the two arms (97% and 95%).[13-15] However, in a retrospective cross-trial comparison, imatinib was shown to lead to a significantly improved OS compared to interferon-α and low-dose cytarabine.[16]

The 10-year follow-up from IRIS reported an estimated OS rate of 83.3% with imatinib.[12] The 10-year CCyR rate was 92%, major molecular response (MMR) rate was 93% and a 4.5-log reduction in *BCR::ABL1* (MR4.5) was achieved by 63%. Only 38 patients (7%) developed accelerated or blast phase disease, 34 of them within the first 4 years. About 6.9% patients discontinued imatinib therapy due to adverse events and 15.9% because there was no therapeutic effect.[12]

The phase I study of imatinib had not identified a maximally tolerated dose. Thus, some studies explored the use of higher doses of imatinib. Multiple non-randomized studies suggested that higher-dose imatinib (600-800 mg) led to higher CCyR and MMR rates and that these responses could occur faster.[17-20] This led to a randomized phase III study, TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) to evaluate the 12-month rate of MMR with 800 mg *versus* 400 mg of imatinib as initial therapy for CML-CP.[21] Although MMR rates were higher at 3 and 6 months, the 12-month MMR rate was not significantly higher with higher-dose imatinib (MMR, 46% *vs*. 40%; *P*=0.2035; CCyR, 70% *vs*. 66%; *P*=0.3470). The long-term follow-up of the TOPS study showed that attaining MMR at 6, 12 or 18 months led to significantly improved progression-free survival (PFS, defined as time between randomization and death due to any cause or progression to accelerated phase/blast crisis on treatment) and OS underscoring the value of early responses.[22] This is similar to what was shown in IRIS. Conversely, a randomized trial comparing 400 mg to 800 mg imatinib among patients with high-risk Sokal scores did not show a significant difference in CCyR at 1 year (64% *vs*. 58%; *P*=0.435) or MMR at any time (12 months, 49% *vs*. 41%).[23] Imatinib has not been associated with an increased risk of the arterio-occlusive events that have limited the use of some other TKI. Hence, imatinib at a higher dose (600–800 mg) could be considered in select patients when second-generation TKI (2G-TKI) are either not available, too costly compared to generic imatinib, or are not tolerated.

Dasatinib

Dasatinib (Sprycel; Bristol-Myers Squibb), a multitarget (Src family, EphA2, PDGFR, c-Kit) kinase inhibitor of BCR::ABL1 was the first 2G-TKI to be approved in 2006, initially for patients with Ph$^+$ CML resistant or intolerant to imatinib. This approval was based on several phase II studies that, besides showing its efficacy and safety in this setting, established the standard dose as 100 mg daily, which resulted in a better safety profile, particularly lower rates of pleural effusion, compared to the originally approved 70 mg twice daily (BID).[24,25] In October 2010, dasatinib was approved for the treatment of newly diagnosed CML-CP based on results of a randomized phase III study, DASISION (Dasatinib *Versus* Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients) in which dasatinib 100 mg demonstrated superior efficacy compared to 400 mg imatinib at achieving, by 12 months, CCyR (the primary endpoint, 77% *vs*. 66%; *P*=0.007), and MMR (46% *vs*. 28%; *P*<0.0001).[26] In the final 5-year follow-up of the study, 61% and 63% of the dasatinib- and imatinib-treated patients, respectively, were still on their initial study treatment.[27] The 5-year MMR and MR4.5 rates were 76% and 42% *versus* 64% and 33%; *P*=0.0022 and *P*=0.0251, respectively. The estimated 5-year OS (91% and 90%) and event-free survival (85% and 86%) were comparable for both arms.[27]

In DASISION, the frequency of grade 3 or 4 neutropenia was similar (21% *vs*. 20%), but the rate of thrombocytopenia was higher with dasatinib (19% *vs*. 10%).[26] All-grade fluid retention was higher with imatinib (42% *vs*. 19%) but pleural effusion was unique to dasatinib, reported in 26 patients (10%), 2% were grade 1 and 8% were grade 2. In the initial report, the overall rate of discontinuation was 5% and 4% in the dasatinib and imatinib arms, respectively.[26] By the 5-year follow up, 26% patients had experienced pleural effusion and 5% had developed pulmonary hypertension. Arterio-occlusive events were twice as frequent with dasatinib than with imatinib (5% and 2%).[27] Several real-world series with dasatinib have reported pleural effusion rates of ~17-25%.[28-30]

Considering that for other 2G-TKI the standard dose for frontline treatment is lower than that used for second or later lines of therapy, there has been interest in exploring lower doses. Early studies with dasatinib frontline had

shown that by 12 months approximately a third of patients had already required a dose reduction.[31] Recent studies have suggested that dasatinib might be equally effective at lower doses. In a study of 83 patients, dasatinib at a dose of 50 mg induced an early molecular response (i.e., *BCR::ABL1* <10% at 3 months) in 96%.[32] Rates of MMR, a 4-log reduction in *BCR::ABL1* (MR4) and MR4.5 at 12 months were 79%, 71% and 46%, respectively, while pleural effusions occurred in only 6%.[32] Another study used dasatinib 20 mg as the starting dose for patients older than 70 years with an option to increase the dose if optimal response was not achieved but treatment was adequately tolerated.[33] At 12 months, 60% achieved an MMR and 27% an MR4. Using a dynamic approach, Rousselot *et al*. started patients with dasatinib 100 mg daily. Plasma levels were measured after 7-10 days; those with concentrations <3 nM continued at the starting dose, whereas those with concentrations ≥3 nM (28% of all patients) were randomized to continue the standard dose or a dose adjusted through plasma concentrations. The response rate was similar for the three groups, but patients who had higher plasma levels and continued the standard dose had a higher probability of developing pleural effusions (42.8%) compared to those with low plasma concentrations (17.4%) or with therapeutic dose monitoring (13.2%).[34] A recently reported study randomized patients to a starting dose of dasatinib of 100 mg or 70 mg daily. In an early analysis, the rate of MMR at 12 months was 81% with 70 mg and 71% with 100 mg (*P*=NS), with no differences in other efficacy endpoints between the two arms. There was less thrombocytopenia, less neutropenia, and fewer pleural effusions (5% *vs*. 10%) with the lower dose.[35] In DasaHiT (Dasatinib Holiday to Improve Tolerability) trial, the standard 100 mg daily dose was compared to giving a weekend holiday (5 days on, 2 days off). The rates of MMR in frontline (81% *vs*. 79%) and later lines (87% *vs*. 62.5%) of therapy were not inferior. However fewer patients in the 5+2 arm experienced pleural or pericardial effusions (8% *vs*. 16.2%).[36] These studies suggest that lower or intermittent doses or shorter duration of dasatinib might be an option as frontline treatment for some patients with CML-CP. What the right dose is and how to select the proper dose for each patient while weighing risk factors, efficacy and safety such as age and risk scores, remain to be defined.

Nilotinib

In 2010, nilotinib (Tasigna; Novartis Pharmaceuticals) was also approved for frontline treatment of CML-CP. ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients) was a randomized, open-label study that showed significantly better rates of MMR at 12 months with nilotinib at 300 mg or 400 mg BID compared to imatinib 400 mg daily (44% and 43% *vs*. 22%; *P*<0.001).[37] In view of the similar efficacy with 300 mg BID compared to 400 mg BID, the former was approved for frontline therapy while 400 mg BID remained standard for patients with failure of prior TKI. In a 10-year follow-up report, the cumulative rates of MMR and MR4.5 at 10 years were 77.7% and 61% with 300 mg BID, and 79.5% and 61.2% with 400 mg BID nilotinib compared to imatinib (62.5% and 39.2%, respectively).[38] Estimated 10-year rates of TFR eligibility were 48.6% with nilotinib 300 mg BID and 29.7% with imatinib. A plateau was observed in MMR rates by approximately 5 years and for DMR at approximately 7-8 years. The 10-year OS and PFS probabilities were similar across the three arms. These results underscore the fact that there is a ceiling on how many patients can be expected to reach DMR and become eligible for treatment discontinuation with 2G-TKI.

At the 5-year follow-up of ENESTnd, an increased frequency of cardiovascular events was seen with nilotinib compared to imatinib, particularly in the 400 mg BID arm. The risks continued to increase after 5 years and reached 24.8%, 33.4%, and 6.3% for nilotinib 400 mg BID, 300 mg BID and imatinib, respectively. Although the cardiovascular risk was initially not recognized, in retrospect, the dose-correlation of risk of cardiovascular events confirms the preference of 300 mg BID as the proper dose for frontline therapy. There was a correlation with baseline Framingham cardiovascular risk score and the patients' risk of developing cardiovascular events. However, an increase in cardiovascular events was seen even in low-risk patients (300 mg BID, 16.5%; 400 mg BID, 23.5% *vs*.3.6% with imatinib).[39] Hence patients treated with nilotinib (and other TKI) should be assessed for risk factors and comorbidities prior to the start of therapy, comorbidities should be closely monitored and properly managed throughout therapy, and patients should be cautioned about the risk of cardiovascular events. Other than cardiovascular events, most other adverse events were grade 1 or 2 with rash and headache being the most common ones.

Bosutinib

In 2017 bosutinib (Bosulif; Pfizer Labs, New York, NY, USA) was approved for the management of newly diagnosed CML-CP based on results of a randomized trial, BFORE (Bosutinib Trial in First-Line Chronic Myelogenous Leukemia Treatment), which showed bosutinib 400 mg once daily was superior to imatinib 400 mg in achieving the primary endpoint of MMR at 12 months (47.2% *vs*. 36.9%, respectively; *P*=0.02).[40] Prior to BFORE, bosutinib was studied in the newly diagnosed setting in the BELA (Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia) study comparing bosutinib 500 mg daily with imatinib 400 mg daily. The primary endpoint of CCyR at 12 months was not met (70% *vs*.68%, respectively; *P*=0.601).[41] However, the rate of MMR (a secondary endpoint) was significantly higher with bosutinib (41% *vs*.27%; *P*<0.001).[41] An important distinction between the BELA and BFORE trials was the dose of bosutinib 500 mg *vs*. 400 mg. Due to the higher dose, the treatment discontinuation rate in BELA was 29% compared to 22% in BFORE. As with other studies of 2G-TKI, there was no difference in OS or event-free survival.[42]

Bosutinib has been associated with lower rates of hematologic adverse events, particularly neutropenia (due, perhaps, to its lack of activity against c-kit) and decreased musculoskeletal events and edema. In contrast, diarrhea is nearly universal, most frequently grade 1-2 and transient, and elevated transaminases may lead to treatment discontinuation.[43] Bosutinib is perhaps the 2G-TKI with the lowest risk of cardiovascular events, although still conferring a somewhat higher risk compared to imatinib.[44]

Asciminib

The newest TKI to get frontline approval, as of 2024, is asciminib (Scemblix; Novartis Pharmaceuticals). Asciminib is a first-in-class TKI that specifically targets the ABL myristoyl pocket (STAMP inhibitor). It was initially studied in the pivotal ASCEMBL study in patients who had received two or more prior TKI, who showed a superior MMR rate of 24% compared to 13% with bosutinib which led to its initial approval in the third-line setting in 2021.[45] Asciminib was then shown to produce a superior rate of MMR at 48 weeks compared to investigator-selected TKI (69.3% with asciminib *vs*. 40.2% with imatinib [95% confidence interval, 95% CI: 16.9 to 42.2%; *P*<0.001] and 66% *vs*. 57.8% in the 2G-TKI stratum [95% CI: -5.1 to 21.5]).[46] In a recent 96-week update, MMR rates remain higher with asciminib than with investigator-selected TKI.[47] Despite the earliness of the data, there was already an advantage appearing for asciminib in the rates of DMR, reaching over 40% with asciminib.
Asciminib was also reported to have a favorable safety profile. The rate of grade 3 or higher adverse events was lower with asciminib compared to imatinib and 2G-TKI (38% *vs*. 44.4% and 54.9%) and the rate of discontinuation due to adverse events was lower with asciminib as well (4.5% for asciminib, 11.1% for imatinib and 9.8% for 2G-TKI).[46]

Factors in treatment selection

While prospective randomized data comparing the three 2G-TKI, dasatinib, nilotinib and bosutinib are lacking, a study from the Japanese Adult Leukemia Study Group (JALSG) reported similar rates of MR4.5 at 18 months with dasatinib and nilotinib (30.8% and 32.6%; *P*=0.66).[48] In addition, there were no significant differences in early response rates, PFS and OS confirming that dasatinib and nilotinib are both equally effective.[48]
Ponatinib, a third-generation TKI, is not approved for frontline use in CML-CP but it was investigated for this purpose in the EPIC (Evaluation of Ponatinib *versus* Imatinib) study of ponatinib *vs*. imatinib, and in a separate single-arm study. Both studies showed impressive early responses with MMR rates of ~80% within 1 year but were terminated prematurely because of the risk of arterio-occlusive events with ponatinib.[49,50] The OPTIC (Optimizing Ponatinib Treatment in CP-CML) study has optimized ponatinib dosing in later lines of therapy decreasing the risk of arterio-occlusive events.[51] Interim results from an ongoing trial, TIPI (Trial of Imatinib after Ponatinib Induction) with a primary endpoint of TFR at 36 months, showed high early molecular response (97%) and MMR (44% at 6 months) rates.[52] Although ponatinib is unlikely to ever be a frontline option, these studies suggested the potential benefit of improved efficacy with newer inhibitors and introduced the concept of stronger "induction" TKI followed by "maintenance" TKI. How this may translate into possible improvements in TFR rates remains to be determined.
Table 1 summarizes the efficacy of various TKI in the pivotal trials. Importantly, none of the 2G-TKI has been shown to improve OS or PFS compared to imatinib. This is perhaps not unexpected considering the high rates of CCyR with imatinib which lead already to a near-normal life expectancy. The interest in better therapies is mostly aiming to increase the probability of TFR and improve safety and tolerability, particularly related to low-grade, chronic adverse events and quality of life. Attaining early molecular response has been associated with favorable long-term outcomes. In addition, achieving MMR by 12 or 18 months correlates with higher 7-year PFS and OS rates (99% *vs*. 90% in IRIS).[15] Attaining MMR by 12 months is thus considered an optimal response according to National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) guidelines as it predicts for a higher probability of long-term DMR.[53,54] Across pivotal trials, the MMR by 12 months with 2G-TKI was higher (~45%) than with imatinib (~30%). In ASC4FIRST, at 48 weeks, asciminib induced MMR in 68% patients compared to 58% with 2G-TKI and 40% with imatinib.[46] These differences further separated by 96 weeks. Hence, asciminib can lead to faster and deeper responses. The difference between the results for asciminib and 2G-TKI was numerically but not statistically higher, although the study was not powered for this comparison. However, it is clear that all available TKI are good options for frontline therapy. The beneficial properties of each individual TKI can be considered and adapted to each patient's goals and characteristics to select the most appropriate therapy for each patient.

High-risk *versus* low-risk chronic myeloid leukemia: tailoring treatment based on risk stratification

Prognostic scores

Risk scores such as Sokal, Euro or Hasford, and ELTS (European Long-Term Survival) may be considered as a guide to select between imatinib, 2G-TKI and asciminib. The NCCN guidelines recommend imatinib as the first choice for low-risk patients and a 2G-TKI for those with intermediate- or high-risk scores. Some of this may be justified. In the 10-year follow-up of IRIS, patients with a high-risk Sokal score had a worse 10-year OS probability than those with an intermediate- or low-risk score (68.6%,

Table 1. Summary of the results of pivotal trials of available frontline tyrosine kinase inhibitors.

Factors	DASISION		ENESTnd		BFORE		ASC4FIRST		
	DAS	IMA	NIL	IMA	BOS	IMA	ASC	2G-TKI	IMA
Age, years, median (range)	46 (18-84)	49 (18-74)	47 (18-85)	46 (18-80)	52 (18-84)	53 (19-84)	51 (18-86)	43 (18-83)	55 (20-86)
Risk score, %									
Low	33	33	37	37	38	39	61	60	62
Intermediate	48	47	36	36	41	39	28	26	30
High	19	19	28	28	21	21	11	14	8
Major molecular response, %									
3 months	8	0.4	9	1	4.1	1.7	-	-	-
6 months	27	8	33	12	35	18	-	-	-
1 year	46	28	44	22	47	37	68	58	40
2 years	64	46	71	44	61	51	74	57	47
5 years	76	64	77	60	74	66	-	-	-
Molecular response 4, %									
2 years	-	-	39	18	33	26	49	31	24
5 years	-	-	66	42	58	48	-	-	-
Molecular response 4.5, %									
1 year	5	3	4.3	0.4	8.1	3.3	17	13	5
2 years	19	8	25	9	13	11	31	24	12
5 years	42	33	54	31	47	37	-	-	-
Progression to accelerated or blast phase, %									
1 year	1.9	3.5	0.7	3.9	1.6	2.5	0.9	1	2.9
2 years	3.5	5.8	3.2	6.4	2.2	2.6	-	-	-
5 years	4.6	7.3	3.7	7.9	2.2	2.6	-	-	-
Complete cytogenetic response, %									
1 year	83	72	80	65	77	66	-	-	-
2 years	86	82	87	77	82	76	-	-	-
5 years	-	-	-	-	83	77	-	-	-
Overall survival, %									
1 year	97	99	99	99	99	98	99	100	99
2 years	95	95	97	96	99	97	-	-	-
5 years	91	90	94	92	95	95	-	-	-
Progression-free survival, %									
1 year	96	97	99	96	-	-	-	-	-
2 years	94	92	98	95	-	-	-	-	-
5 years	85	86	92	91	93	91	-	-	-

TKI: tyrosine kinase inhibitor; DAS: dasatinib; IMA: imatinib; NIL: nilotinib; BOS: bosutinib; ASC: asciminib; 2G-TKI: second-generation tyrosine kinase inhibitor.

80.3%, and 89.9%, respectively).[12] Patients in the high-risk category by any score do indeed have an increased probability of progression and CML-related death and hence will benefit most from a 2G-TKI or, potentially, an allosteric TKI. For low-risk patients, all five TKI approved for the treatment of newly diagnosed CML-CP, including imatinib, are options. However, all randomized pivotal trials also showed a greater probability of achieving MMR for the low-risk patients with the newer TKI options (2G-TKI over imatinib, and asciminib over imatinib and over all TKI). Thus, although low-risk patients have a better probability of response with imatinib compared to high-risk patients, there is still potential advantages from 2G-TKI or, according to early data, from allosteric TKI which should be considered when making selections for individual patients.

Additional chromosomal abnormalities

Another high-risk feature is the presence of additional chromosomal abnormalities. Many of these abnormalities (particularly the major route ones) are associated with inferior PFS and OS,[55,56] and have been considered a criterion for accelerated phase. Patients with such features at the time of diagnosis have been reported to have an outcome similar to those with chronic phase features, particularly when treated with 2G-TKI.[57]

Genetic and molecular profiling in determining therapy

p190 versus p210 versus rare transcripts. Depending on the breakpoint within the *BCR* and *ABL* genes, different sizes of the *BCR::ABL1* fusion protein can be produced. p210 is more commonly found in CML while p190 is more commonly seen in Ph^+ acute lymphoblastic leukemia (~50-70%) than in CML (1-2%).[58,59] When p190 is seen in CML, it is associated with monocytosis, additional chromosomal abnormalities, increased risk of progression to accelerated or blast phase, and inferior response to TKI.[59-61] Hence, it is suggested that patients with p190 *BCR::ABL1* should be treated with 2G-TKI.[62] Other rare transcripts, such as e19a2 (resulting in protein product p230) and e13a3 or e14a3 may be associated with inferior responses to imatinib and 2G-TKI could be considered.[63,64] Importantly, patients with e13a3 or e14a3 rearrangements (and possibly e19a2) should not be treated with asciminib as these have been shown not to be inhibited by asciminib *in vitro* due to the absence of SH3 residues encoded by exon 2.[65]

Next-generation sequencing. With the adoption of next-generation sequencing in various myeloid malignancies, there is increasing evidence that the presence of mutations in known cancer genes is associated with increased progression to blast phase, inferior response rates, and greater probability of development of *ABL* kinase domain mutations.[66] Mutations in *ASXL1* are associated with inferior response rates and mutations in *RUNX1* have been associated with increased risk of progression to blast phase.[67-69] Testing for *ASXL1* mutations at diagnosis is now included in the NCCN guidelines.[53] Recent studies have shown that the poor outcome associated with mutations in other genes, particularly in *ASXL1*, is not overcome by 2G-TKI or asciminib.[70] An intriguing recent report suggests that a combination of asciminib and an ATP-competitive TKI may overcome the poor prognosis associated with *ASXL1* mutations.[71] These results require confirmation but open a possible option for these patients. For now, however, these patients can be treated with any TKI but monitored closely and perhaps promptly considered for stem cell transplantation if demonstrating early evidence of resistance.

Age, comorbidities/known toxicity, and lifestyle factors

The most important factors when considering frontline TKI include age, co-morbidities at the time of diagnosis, and lifestyle considerations. Despite the median age at diagnosis of CML being reported as 67 years, many patients younger than 65 years are diagnosed with CML each year. Retrospective studies have shown that 2G-TKI are more commonly chosen as frontline therapy in younger patients, perhaps due to fewer co-morbidities and hence better tolerance and lower risk of adverse events.[72,73] Similar to real-world studies, in ASC4FIRST, which required pre-randomization selection by the physician and the patient of the stratum to which the patient would be allocated, patients in the imatinib stratus were older than those in the 2G-TKI stratum.[46] In addition, if male patients are considering fathering children or female patients are considering a pregnancy, age can be an important consideration when deciding treatment.

Co-morbidities and concomitant medications are important to consider when selecting frontline treatment.[74] Cardiovascular risk factors and comorbidities, including hypertension, coronary artery or other arterio-occlusive diseases, and high cardiac risk scores, such as the Framingham risk score, should preclude the use of nilotinib and possibly dasatinib (at least at full dose). Nilotinib can also lead to hyperglycemia (36% all-grade in ENESTnd) and hyperlipidemia as adverse effects, further increasing the risk of arterio-occlusive events.[38] For patients with pre-existing gastrointestinal comorbidities, such as inflammatory bowel disease or irritable bowel syndrome, bosutinib (70% all-grade diarrhea in BFORE) would not be considered the first choice.[40] For patients with pre-existing lung disease, such as chronic obstructive lung disease, or heart failure which predisposes them to pleural effusion, dasatinib may not be ideal. Asciminib was shown in the 96-week update to have a better side-effect profile compared to imatinib and other 2G-TKI in ASC4FIRST, with only 5% patients discontinuing asciminib compared to 10% patients in the 2G-TKI stratum and 11% in the imatinib stratum.[46,47] Asciminib can cause asymptomatic elevations in pancreatic enzymes warranting the monitoring of amylase and lipase after the initiation of asciminib. However, in ASC4FIRST, the rate of lipase elevation was higher with 2G-TKI than with asciminib, suggesting that this is a class effect that merits consideration for all patients.

Arterio-occlusive events are of special interest since some analyses have reported increased metabolic syndrome and higher cardiovascular risk scores in CML patients than in the general population.[75] At 5 years, the rates of cardiovascular, cerebrovascular and peripheral arterial arterio-occlusive events were 5%, 1.4% and 3.6% with nilotinib, 4%, 1% and 0% with dasatinib and 4.9%, 0.7% and 2.2% with bosutinib in each pivotal trial.[27,39,42] All of these rates were higher than those observed with imatinib (overall nilotinib 8% *vs*. imatinib 2%; dasatinib 5% *vs*. imatinib 2%; bosutinib 8% *vs*. imatinib 3%), with the caveat that there are considerable differences on how these events were identified between different studies. At the 96-week analysis of ASC4FIRST, the rate of arterio-occlusive events with asciminib was 2% (N=4) compared to 2.9% (N=3) with 2G-TKI and none with imatinib, even though the patients in the imatinib stratum were older and there were more high-risk Framingham patients in this stratum.[47] Hence, when choosing treatment for patients who are at high risk of arterio-occlusive events, imatinib might be the safest option perhaps followed by asciminib pending further follow-up of ASC4FIRST.

Patients' preferences and quality of life

In addition to severe, life-threatening adverse events, persistent low-grade adverse events can impair a patient's

quality of life and lead to poor adherence and in turn a poor response to therapy. Table 2 compares the rate of discontinuation in the pivotal trials leading to approval of each TKI for frontline therapy in CML-CP. Overall, asciminib has the lowest rate of discontinuation, suggesting better tolerability although the follow-up is still only to 96 weeks. Interim results from ASC4START, a unique study evaluating asciminib *versus* nilotinib with a primary endpoint of time to treatment discontinuation due to adverse events, reported that the primary endpoint was significantly better with asciminib with a hazard ratio of 0.45 (95% CI: 0.25-0.81; *P*=0.004). While 17.3% of patients discontinued nilotinib (11.6% due to adverse events), only 10.9% discontinued asciminib (4.9% due to adverse events).[76] It is, however, important to consider that rules for treatment discontinuation in clinical trials may not mirror what happens outside of clinical trials. In addition, even without treatment discontinuation, tolerability and quality of life may be affected with continued therapy, and these effects are perhaps better appreciated with longer-term therapy.

Another lifestyle factor to keep in mind when considering adherence is schedule of administration. Twice daily dosing and fasting before and after taking the TKI can make dosing difficult for some patients and lead to reduced adherence. In such cases nilotinib might not be optimal. Asciminib can be administered (and is approved) both as a twice daily and once daily dose, always in a fasting state. However, a recent study suggests there might be a better probability of response by administering twice daily than once daily: the 48-week MMR rates were 42% and 35%, respectively.[77] In a study analyzing motivations and behavioral patterns of adherence in CML, Geissler *et al*. found that older age, male sex, manageable side-effect profile, once daily dosing and being well informed by the treating physician were associated with high adherence.[78] This study also showed that less personal payments increased the patients' probability of adhering to their TKI treatment.[78] Other studies have identified a similar correlation between co-payments and adherence.[79,80] With generic imatinib available at the lowest cost (~$35 in US and lower in some other countries), this is an attractive option in patients who are low risk, older, with multiple comorbidities and cannot afford 2G-TKI or allosteric TKI. Dasatinib is also now available in a generic formulation in the USA (and other countries), but the cost of generic dasatinib has not reached the levels of generic imatinib.

Achieving treatment-free remission

TFR is the ultimate goal for a growing majority of patients with CML-CP. The first prospective study evaluating TFR was undertaken by the French CML group enrolling 12 patients in 2004 who maintained polymerase chain reaction negativity for at least 2 years with a 45-month median duration on imatinib.[81] Of the 12 patients, six were able to stay in molecular remission for over 12 months. Promising results from this French study led to the development of the STIM (Stop Imatinib) study in which remission was maintained in 41% patients.[82] Similar results were obtained in the contemporaneous TWISTER trial.[83]

The STOP-2G TKI trial evaluated TFR after treatment with 2G-TKI. TFR rates of 63% and 53% at 12 and 48 months in 30 patients on dasatinib and 30 on nilotinib were reported.[84] Patients who had switched therapy from imatinib to a 2G-TKI due to intolerance had a higher TFR rate compared to patients who had switched due to resistance (60% *vs*. 20% at 5 years).[84] As mentioned earlier, in ENESTnd the cumulative rates of achieving TFR eligibility at 10 years were higher with nilotinib than with imatinib.[38] In the ENESTop study, patients who did not achieve a DMR on imatinib but did so after switching to nilotinib, attempted TFR after staying in MR4.5 for 12 months with an ~50% success rate.[85] The ongoing SUSTRENIM trial is comparing TFR rates with nilotinib *versus* imatinib (with switching to nilotinib in the absence of an optimal response). In an interim analysis, the probability of TFR eligibility was similar in the two arms, although more patients who switched from imatinib to nilotinib accomplished this goal compared to those who stayed on imatinib.[86] TFR after resistance to prior TKI is feasible but the probability of success is generally lower. Multiple other studies have evaluated TFR and rates of successful TFR have been associated with longer duration on TKI, duration of DMR, percentage of blasts in blood at diagnosis and transcript type.[87,88] Since the duration of DMR is associated with TFR success, achieving earlier molecular responses may lead to meeting TFR criteria earlier, minimizing exposure and, with that, possibly risk of

Table 2. Rates of treatment discontinuation by tyrosine kinase inhibitor.

Time	DASISION		ENESTnd		BFORE		ASC4FIRST		
	DAS	IMA	NIL	IMA	BOS	IMA	ASC	2GTKI	IMA
2 years, %	23	25	26	33	29	31	18	30	46
5 years, %	39	37	39	50	40	42	NA	NA	NA
10 years, %	NA	NA	53[a]	48[b]	NA	NA	NA	NA	NA

[a]62% including those who switched to imatinib or increased to nilotinib 400 mg BID (14% for efficacy). [b]65% including those who switched to nilotinib or increased imatinib dose (24% for efficacy). BID: twice daily; TKI: tyrosine kinase inhibitor; DAS: dasatinib; IMA: imatinib; NIL: nilotinib; BOS: bosutinib; ASC: asciminib; 2G-TKI: second-generation tyrosine kinase inhibitor; NA: not available.

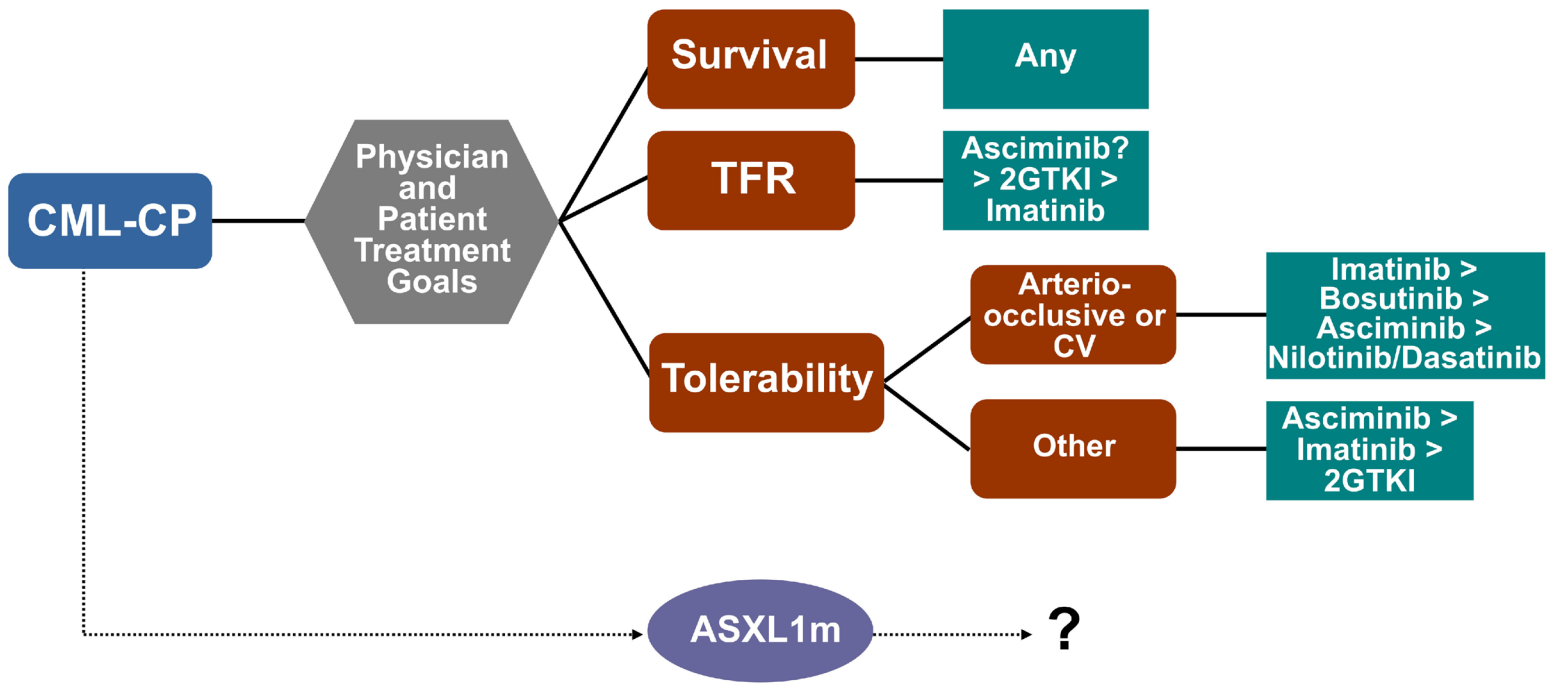

Figure 1. Suggested treatment algorithm using treatment goal as a decision centerpiece when choosing between various frontline tyrosine kinase inhibitor treatment options. If survival is the treatment goal, then any tyrosine kinase inhibitor (TKI) can be used. If treatment-free remission (TFR) is the ultimate goal then a second-generation TKI may be preferred over imatinib. Data on asciminib are lacking; however, with more, faster and deeper molecular remissions, TFR rates can potentially be higher with asciminib. When choosing a TKI based on a patient's comorbidities or tolerability, if the primary concern is arterio-occlusive events, imatinib has the lowest risk. For other adverse events, asciminib has shown improved tolerability compared to other TKI. The impact of non-*ABL1* myeloid mutations such as *ASXL1* on frontline therapy is still being studied. *In some instances availability and/or cost may drive the selection of TKI (uninsured patients, national policies, availability in some parts of the world, etc.) which may override medical decisions. CML-CP: chronic myeloid leukemia in chronic phase; 2GTKI: second-generation tyrosine kinase inhibitor: CV: cardiovascular; m: mutation.

side effects and costs. Hence more potent, better tolerated TKI might be preferred to improve TFR rates.

Taken together, the data suggest that if TFR is the ultimate goal for an individual patient, therapy with options that give the highest probability of DMR and do so earlier may yield the best probability of achieving TFR. In this regard, the ASC4FIRST data are particularly promising for increasing the likelihood of TFR. Although the study is still young, MR4 and MR4.5 rates of 40% and 30%, respectively, at 96 weeks are very encouraging considering that early responses have been predictive of the achievement of later DMR.

Conclusion

In conclusion, there is not one TKI that can be considered the universal best choice for all patients with CML-CP. We are fortunate to have multiple options. The selection of TKI should be individualized (Figure 1) for each patient, taking into account patient-related factors (age, comorbidities, lifestyle considerations, quality of life, the patient's preferences and goals), disease-related factors (risk stratification, transcript type, presence of high-risk gene mutations such as *ASXL1*) and drug-related factors (MMR rates with each TKI, adverse events, rates of treatment discontinuation and TFR rates). Treatment choice should be a shared decision between patients and physicians. A recent survey suggested that such shared decision-making is relatively uncommon in CML.[89] It should become the norm.

Disclosures

AGJ has participated in speakers' bureau for Rigel and Geron; has provided consultancy services for Novartis and Servier; and has been a member of advisory boards for Takeda, Sobi, Servier and Ascentage. JEC has acted as a consultant for Novartis, Pfizer, Sun Pharma, Takeda, Tern Pharma, Enliven, Rigel, Biopath Holdings and Syndax and has received research support from Novartis, Kuro Oncology and CytoAgents. MD has no conflicts of interest to disclose.

Contributions

AGJ wrote the manuscript. MD reviewed the manuscript and extracted data to construct the tables. JEC conceptualized the review and critically reviewed the entire manuscript.

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