

Chronic myeloid leukemia - Section 6

Current treatment approaches in CML

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Take home messages

- Five tyrosine kinase inhibitors are available, the treatment strategy is still challenging.
- Baseline risk, comorbidities, and patient and physician expectations play a pivotal role.
- Treatment-free remission is a new opportunity.

Introduction

The treatment of chronic myeloid leukemia (CML) is mainly based on tyrosine kinase inhibitors (TKIs): imatinib (first-generation TKI), nilotinib, dasatinib, and bosutinib (second-generation TKIs) are approved for front-line treatment; the same TKIs, plus ponatinib (third-generation TKI), are available beyond the first-line in case of resistance or intolerance.^{*1} The choice among different drugs is an opportunity for treating physicians, but this choice is frequently difficult and always controversial.

Imatinib, available as a generic drug in most countries, allows long-term stable response in approximately 50% of patients. Imatinib efficacy is dependent on adequate blood and intracellular levels (the latter refers to *in vitro* data), and emerging BCR-ABL1 mutations are more frequent on imatinib than on second-generation TKIs.^{*1} Surprisingly, all prospective comparisons of second-generation TKIs and imatinib, failed to show relevant overall survival (OS) differences.²⁻⁴ Despite similar OS, a trend for an inferior rate of progression to advanced phases has been observed with second-generation TKIs. However, the excellent long-term survival expectation of CML patients (over 85%, similar to healthy age-matched population) is based not only on frontline treatment, but also on the timely implementation of

salvage therapy in case of resistance or intolerance. Importantly, second-generation TKIs induced higher cumulative rate of deep molecular response (DMR) compared with imatinib.²⁻⁴ A stable DMR is a prerequisite for treatment discontinuation and living without treatment (treatment-free remission [TFR]) is no more an experimental endpoint, being more and more largely implemented in clinical practice.⁵

Current status of the art

The current treatment approach, particularly for first-line treatment, is based on factors additional to survival: age, disease risk, comorbidities, early and late safety, rapidity of response, and patient and physician expectations on TFR.

Overall survival

All available TKIs confer the same survival probabilities at 5 years and beyond. An accurate evaluation of baseline or emerging comorbidities and a long-term management of adverse events are mandatory to confirm the current figures. The great majority of patients on stable response (major molecular response [MMR] or deeper) are expected to maintain their response in the very long-term. Whether the higher rate of DMR with front-line second-generation TKIs is associated with improved long-term survival or not is matter of debate: the “comparator arm” of DMR patients is mainly constituted of stable MMR patients (once upon a time defined “safe heaven”), with very high long-term survival expectations.

CML risk

Three scoring systems, aiming at assessing the long-term outcome of CML patients, are available; Sokal, Euro, and ELTS formulations^{*6} have been developed in patients treated with conventional chemotherapy, interferon and imatinib, respectively. With any treatment, high-risk patients have inferior outcome and higher probability of early progression. The potential advantage of second-generation TKIs front-line over imatinib is more based

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Table 1**Main Characteristics of the Tyrosine Kinase Inhibitors Registered for Chronic Myeloid Leukemia**

	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Standard dose, first line	400 mg OD	300 mg BID	100 mg OD	400 mg OD	NA
Dose, second line	3–400 mg BID	400 mg BID	100 mg OD	500 mg OD	45 mg OD
Plasma half-life, h	~20	~15	~5	~34	~19
Plasma conc., peak	4202 ± 1272	2329 ± 772	133 ± 74	~392	145 ± 73
Plasma conc, through	2062 ± 1334	1923 ± 1233	5.5 ± 1.4	~268	64 ± 29
IC50, Bcr-Abl1	260–679	10–25	0.8–1.8	42	0.5
IC50, PDGFR α	72	75	2.9	3.0	1.1
IC50, cKit	99	209	18	10,000	12
IC50, Src	>1000	>1000	0.1	3.0	5.4
IC50, VEGFR2	10,000	3720	NA	NA	1.5
IC50, BTK	>5000	NA	1.1	2.5	849

All values (plasma concentration and IC50) are expressed as nM.

BID = twice daily, NA = not available, OD = once daily.

on expectations than on evidence: the OS is independent from the front-line treatment (second-generation TKIs or imatinib) in each risk category, but the first-line use of second-generation TKIs induce more rapidly a reduction of disease burden and reduce the probability of progression (Table 1).

Early molecular milestones

Comparing imatinib versus second-generation TKIs, an early molecular response (EMR, <10% BCR-ABL1 transcript at 3 months) is achieved significantly more frequently with second-generation TKIs. Many post hoc analyses showed that EMR is associated with better progression-free survival and OS probabilities, and to higher DMR rates.^{*1} This argument has been proposed to prioritize second-generation with respect to imatinib as better first-line treatment, and to support the early switch to second-generation TKIs in patients failing the 3-month milestone. Published guidelines (NCCN v. 1.2019,^{*7} ESMO 2017,^{*8} and ELN 2013^{*9}) do not recommend a straightforward choice but underline the need of a close monitoring, delaying the treatment optimization in between the 3rd and 6th month on primary treatment. It should not be overlooked the technical limitations of EMR evaluation, due to QPCR variability and to the use of ABL as control gene: the use of GUS as control gene and/or a more frequent (monthly) evaluation of BCR-ABL1 levels during the first months on TKI have been proposed.

Treatment-free remission

TFR is an achievable endpoint.² Treatment discontinuation, followed by a strict monitoring, is clearly attractive for patients and physicians, minimizing the possibility of TKI-related adverse events, improving the long-term safety, and reducing the economic burden. Several studies demonstrated that 40% to 50% of patients in stable DMR (2 years or more) do not relapse after TKI discontinuation. In case of molecular relapse (confirmed loss of MMR), the original TKI rapidly restores the response in the great majority of patients. In randomized phase III trials, the estimated 5-year DMR cumulative rates were higher for second-generation TKIs with respect to imatinib: 51% and 42% of MR^{4,5} for nilotinib and dasatinib, 31% and 33% for imatinib in ENESTnd and DASISION trials, respectively.^{2,3} No direct comparisons of imatinib versus second-generation TKIs with TFR as primary endpoint are available, but, looking at available data, second-generation TKIs seem more promising when TFR is an attractive treatment goal. Nilotinib is the only drug approved for TFR.

Beyond first-line

Treatment of patients failing one or more TKI for resistance or intolerance is complex, because many variables should be considered: the first-line treatment (imatinib or second-generation TKIs), the type (primary or secondary), and the level (hematologic, cytogenetic, or molecular) of resistance, the presence and the type of emergent mutations, the comorbidities (many patients are older than 65 years, especially in western countries), and the severity of adverse events. The available TKIs have different efficacy and quite different safety profiles. Ponatinib¹⁰ has been approved for the treatment of CML patients failing at least 2 TKIs, showing high efficacy, in particular for patients failing treatment with second-generation TKIs (indirect comparisons). No single BCR-ABL1 mutation was able to induce ponatinib resistance, including T315I mutation.^{*11} The high incidence of cardiovascular adverse events with ponatinib 45 mg daily highlighted the importance of patient selection and induced to explore lower dosage regimens.

Future perspectives

An important novelty is asciminib (previously ABL001),^{*12} a new allosteric TKI targeting the myristoyl pocket of the BCR-ABL1 kinase. The efficacy and safety results of the ongoing phase I/II trial (asciminib as monotherapy, or in combination with imatinib, nilotinib, or dasatinib in refractory CML and Ph+ ALL patients), together with the future results of the new trials (asciminib vs bosutinib in CP patients resistant to at least 2 previous TKIs; add-on of asciminib to other TKIs to induce DMR) will clarify the role of this promising drug.

The heterogeneity of CML is relatively low, but CML treatment must be adapted, according to disease and patient characteristics. Comorbidities, tolerability, and long-term safety play a key role, as well as the efficacy. The achievement of TFR is an opportunity for an increasing proportion of patients, emphasizing the need of a physician and patient common plan.

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The most updated guidelines.

Asciminib, the most relevant new drug in CML scenario.