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CHRONIC MYELOID LEUKEMIAS (G SAGLIO, SECTION EDITOR)

Early Management of CML

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Abstract

Purpose of Review The marked improvement in clinical outcomes for patients with chronic myeloid leukaemia (CML) can be solely attributed to the introduction of targeted therapies against the fusion oncoprotein, *BCR-ABL1*. However, patient responses, although generally positive, remain heterogenous. Careful drug selection, ensuring the optimal TKI, is chosen for each patient and involves a complex decision process which incorporates consideration of numerous factors.

Recent Findings For some patients, with disease characteristics that indicate adverse intrinsic disease biology, more potent *BCR-ABL1* inhibition is often appropriate, whereas other patients with major co-morbidities will benefit from a less aggressive approach to avoid life-shortening toxicities. For the vast majority of patients, the long-term goal of therapy will be the achievement of a deep molecular response and subsequent treatment-free remission and this consideration will play a large part in the drug selection process.

Summary We explore early management of CML, from the first presentation through to frontline therapy selection.

Keywords TKI · Deep molecular responses · Drug toxicity · Treatment-free remission

Introduction

Since the introduction of imatinib, the first targeted *BCR-ABL1* inhibitor, newer, more potent tyrosine kinase inhibitors (TKIs) have been vital additions to the therapeutic landscape of chronic phase chronic myeloid leukaemia (CP-CML) management. TKIs bind to the fusion chimeric protein, *BCR-ABL1*, via the ATP-binding site, inhibiting kinase activity and thus leukaemogenesis, through reduction in proliferation, regulation of differentiation, and restoration of the impaired apoptotic pathway [1]. However, despite the excellent treatment options available to newly diagnosed CML patients, optimal TKI selection is not straightforward despite the well-established benefits and risks associated with each individual drug. Upfront treatment selection, assuming availability of imatinib, nilotinib, dasatinib and bosutinib, should ideally entail consideration of multiple clinical and laboratory factors. While the primary purpose of CML therapy is to prevent disease progression, we recommend early determination of the long-term goals of therapy, specifically what priority should be given to achieving deep molecular response (DMR) as a platform for the eventual achievement of treatment-free remission, as it will influence TKI selection. The dramatically improved survival [2] now observed in CP-CML signifies that newly diagnosed patients may be required to endure decades of TKI therapy, mandating optimal upfront drug selection to maximize molecular response and safety outcomes.

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First Presentation

The diagnosis of CML is frequently incidental, with a large proportion of patients identified with asymptomatic leucocytosis on routine investigation. The recommended

baseline investigations are listed in Table 1 [6]. Peripheral blood demonstrates an abundance of mature granulocytes, especially in CP, with a myelocyte peak [7]. Eosinophilia and basophilia are common, while dysplastic features are infreqeunt [7]. Thrombocytosis may be the sole haematological abnormality in rare cases, and CML should be considered as a differential diagnosis to patients with unexplained persistent thrombocytosis, especially in the setting of *JAK2*, *MPL*, and *CALR* negativity. Active questioning and assessment for features of leukostasis, especially when white cell counts exceed 100×10^9/L, should be conducted. Evidence of hyperviscosity affecting pulmonary (dyspnoea), neurological (headache, tinnitus and visual changes) and vascular (including priapism and cardiac ischaemia) systems necessitates urgent cytoreduction via hydroxyurea and/or leukopheresis [6, 8]. Physical examination should focus on evaluation for splenomegaly and documentation of the actual length palpable below the costal margin (important for prognostic scoring models), exclusion of extramedullary leukaemia and sites of leukostasis involvement including fundoscopic evaluation for retinal haemorrhage. While the diagnosis of CML can be confirmed via peripheral blood cytogenetic analysis or *BCR-ABL1* quantitative PCR, we recommend performing a diagnostic bone marrow biopsy to confirm the disease stage as per either the ELN or WHO criteria [3••, 9]. Differentiating between CP, accounting for 90–95% of new diagnoses [7], and the more aggressive accelerated phase (AP) and blast crisis (BC) CML is imperative to ensure appropriate management is instituted. The significance of marrow fibrosis, although previously considered to be a predictor of therapy failure, is unclear [10, 11]. Potential transplant candidates diagnosed with more aggressive disease (AP/BC CML) need to be tissue typed with early consideration of an allograft [4••], although more recent data suggests that not all AP patients necessarily have the same adverse outcomes [12]. Patients with cytogenetic abnormalities as the sole criterion for AP classification can have a more favourable prognosis with TKI therapy than patients categorised as AP due to other features [12].

Table 1 Baseline evaluation recommended in a newly diagnosed CML patient [3••, 4••, 5••]

History
- Comorbidity assessment
Physical examination
- Spleen size—measured, not estimated - Evaluation for extramedullary leukaemia - Evaluation for leukostasis (including fundoscopy) - Vascular assessments including blood pressure and peripheral pulses
Peripheral blood investigations
- Full blood count - Biochemistry including urate, renal and liver function - Fasting lipid studies - Fasting glucose ± HbA1c - Lipase/amylase - Thyroid function tests - Vitamin D - Parathyroid hormone - Hepatitis B serology - *BCR-ABL1* qPCR
Bone marrow biopsy
- Blast count evaluation - Cytogenetic analysis: standard karyotyping or fluorescence in situ hybridization (FISH)
Other investigations
- Chest X-ray - ECG - Tissue typing (if an allogeneic transplant is anticipated or patient is diagnosed in accelerated or blast crisis)
Optional
- Ankle brachial index

Fertility and Family Planning

Fertility and family planning discussions need to occur in female patients with child-bearing potential prior to the commencement of any TKI. Despite the limited data in this setting, TKI exposure during pregnancy is associated with increased rates of miscarriage and foetal malformations [13–15]. We recommend interruption of TKI therapy prior to conception and alternative methods for disease control utilized throughout the pregnancy in female CML patients [16]. The impact of TKIs on male fertility is less clear with conflicting reports on the effect on spermatogenesis and male sex hormones, although the frequency of foetal malformations and stillbirths appears to be no higher than for healthy contemporaries [15, 17]. The general consensus is that TKI therapy does not need to be discontinued in male patients prior to conception [4••]. Referral to fertility specialists may be warranted prior to TKI commencement for patients wishing to explore potential options for fertility preservation.

Current First-Line Therapeutic Landscape

Prior to exploring the various factors important in deciding the optimal TKI for newly diagnosed CML patients, a review of the available first-line options is essential with important molecular and survival measures documented in Table 2.

Imatinib

Imatinib, the first-generation TKI, revolutionized CML management with its introduction. With almost two decades of therapeutic availability, imatinib is the TKI that clinicians have had the longest familiarity with—through the first in-human clinical trials to the current local drug access programs specific to each country. Long-term

Table 2 Molecular responses based upon first line TKI studies

	IRIS[18]		CML IV[19•]		ENESTnd[20•]			DASISION[21•]		BFORE[22•]	
	Cytarabine/ IFN	IM 400 mg	IM 400 mg	IM 800 mg	NIL 300 mg twice daily	NIL 400 mg twice daily	IM 400 mg	DAS 100 mg	IM 400 mg	BOS 400 mg	IM 400 mg
MMR											
- 1 year		27.7%	36.7%	55.6%	55%	51%	27%	46%	28%	47.2%	36.9%
- 2 year					71%	67%	44%	64%	46%		
- 3 year			80.6%	83.2%	73%	70%	53%	67%	55%		
- 4 year		42.5%			76%	73%	56%	73%	60%		
- 5 year		50.3%	86.3%	86.8%	77%	77%	60%	76%	64%		
- 10 year		34.4%	92.2%	89.1%							
MR4.5											
- 1 year		0.7%	4.8%	9.2%	11%	7%	1%	5%	3%	8.1%	3.3%
- 2 year					25%	19%	9%	19%	8%		
- 3 year			34.6%	43.1%	32%	28%	15%	24%	13%		
- 4 year		9.0%			40%	37%	23%	34%	23%		
- 5 year		23.0%	49.4%	58.4%	54%	52%	31%	42%	33%		
- 10 year		23.3%	7.2%	70.6%							
EFS											
- 1 year										96.3%	93.6%
- 5 year					95%	96.9%	92.6%				
- 10 year	56.6%	79.6%									
PFS											
- 5 year					96.5%	98.3%	94.7%	85%	86%		
- 10 year			83%	77%							
OS											
- 5 year					93.7%	96.2%	91.7%	91%	90%		
- 10 year	78.8%	83.3%	83.3%	79%							
Progression to AP/BC											
- 1 year										1.6%	2.5%
- 5 year					3.7%	2.2%	7.9%	4.6%	7.3%		
- 10 year		6.9%									

IFN: Interferon; IM: Imatinib; NIL: Nilotinib; DAS: Dasatinib; BOS: Bosutinib; MMR: Major molecular response; EFS: Event-free survival; PFS: Progression-free survival; OS: Overall survival; AP: Accelerated phase; BC: Blast crisis.

safety and toxicity data from the earliest clinical trials are readily available with published molecular and response measurements. Moreover, with the addition of generic imatinib to the pharmaceutical market in recent years, the declining costs of treatment to the patient and governmental bodies have also improved accessibility.

While imatinib maintains the safest toxicity profile of all TKIs, it is also the least tolerated, with toxicities often impacting on quality of life (QOL) measures [23]. Gastrointestinal events, especially diarrhoea, were reported in almost 30% of patients in the International Randomized study of Interferon and STI571 (IRIS) study, although only 2% were reported to be grade 3–4 severity [24]. Fatigue and muscle cramps have been consistently reported as the main culprits negatively impacting QOL [23–25]. Concerns regarding long-term cardiotoxicity have proved to be largely unfounded with the incidence of grade 3–4 cardiac events in the 10-year follow-up of IRIS only being 7.1% [18]. Reductions in bone mineral density have also been reported in a small population of patients, indicating the importance of close monitoring of bone health [26]. Long-term imatinib therapy is also associated with a reduction in glomerular filtration rate and slight increase in the frequency of chronic renal failure, indicating

the importance of regular assessment of renal function [27, 28]. Apprehension regarding second malignancy risk with imatinib treatment has not materialized as although 11.3% of the imatinib cohort in IRIS [18] developed a second cancer, this may be attributed to the slightly increased malignancy risk associated with CML as opposed to a specific TKI [29, 30].

The pivotal IRIS trial demonstrated the dramatic survival benefit associated with targeted *BCR-ABL1* inhibition by imatinib, later corroborated by the German CML-IV study [18, 19•]. Disease progression was also less likely with imatinib when compared to the control arm of interferon alpha and cytarabine, predominantly occurring early in therapy [24]. The 10-year rates of major molecular response (MMR, equating to a *BCR-ABL1* ≤ 0.1% IS) and MR4.5 (equating to a *BCR-ABL1* ≤ 0.0032% IS) were 93.1% and 63.2%, respectively [18]. However, kinase domain mutations develop in almost 20% of patients, a higher frequency compared to treatment with second-generation TKIs [19•, 20•, 21•]. Additionally almost 30% of imatinib-treated patients will require a TKI switch due to intolerance or resistance, highlighting the need for early optimal treatment selection [18, 19•].

The optimal dose of imatinib has been a contentious issue. The German CML-IV study had five treatment arms, two of which were 400 mg and 800 mg of imatinib [19•]. While the 10-year OS and molecular measurements were largely similar between the two groups, the 800-mg cohort achieved MMR and MR4 (equating to a *BCR-ABL1* ≤ 0.01% IS) more rapidly [19•]. Higher rates of MMR at 12 and 24 months of TKI therapy were demonstrated by the Australian group in patients maintaining 600 mg of imatinib compared to those tolerating < 600 mg daily [31]. In contrast, data from the Tyrosine kinase inhibitor OPtimization and Selectivity (TOPS) trial did not reveal a significant difference in MMR achievement between a daily dose of 400 mg compared to 800 mg of imatinib. Furthermore, higher doses of imatinib have a clear association with an increased incidence of adverse events [25, 32•], especially those impacting quality of life such as gastrointestinal toxicities [23]. Due to the difficulties in maintaining higher doses of imatinib secondary to toxicities together with the lack of proven survival benefit [19•], 400 mg daily of imatinib has become the accepted standard dose [4••].

Nilotinib

Nilotinib, a second-generation TKI, has significantly higher affinity for binding to the kinase domain of *BCR-ABL1* compared to imatinib, leading to increased potency [33]. Although nilotinib, like other second- and third-generation TKIs, can rescue some patients with imatinib-resistant disease, this falls out of the purview of this review and will be explored elsewhere [34–37].

The Evaluating Nilotinib Efficacy and Safety in clinical Trials–Newly Diagnosed (ENESTnd) study, the head-to-head comparison of imatinib 400 mg daily to nilotinib in newly diagnosed CP-CML patients, recently published a 5-year update [20•]. Early molecular response (*BCR-ABL1* ≤ 10% IS at 3 months), a predictor of molecular milestone achievement, was significantly higher with either nilotinib dose [20•]. By 5 years, MMR achievement was 77% with 300 mg twice daily of nilotinib compared with 60% of imatinib-treated patients [20•]. Similarly, 54% of nilotinib-treated patients achieved MR4.5 compared to only 31% of imatinib patients [20•]. Additionally, not only was molecular milestone achievement higher with nilotinib, they were reached more rapidly with early divergence of the cumulative incidence curves [20•]. Transformation risk and *BCR-ABL1* kinase domain mutation development is also significantly lower with nilotinib [20•]. Despite the dramatic molecular benefit observed with nilotinib, the study failed to prove a survival benefit compared to imatinib, perhaps due to the added toxicity burden of nilotinib [20•].

Despite nilotinib being relatively well tolerated, it is associated with serious toxicities which patients need to be aware of prior to frontline selection. A concerning signal for cardiovascular toxicity, including ischaemic heart disease, cerebrovascular events and peripheral arterial disease, emerged on the nilotinib studies. The risk was relative to dose, as 400 mg twice daily of nilotinib (13.4%) had almost double the incidence of events compared with 300 mg twice daily (7.5%) by 5 years [20•]. Only 2.1% of imatinib-treated patients developed similar toxicity [20•]. High Framingham scores at study entry, primarily due to pre-existing risk factors (such as smoking, hypercholesterolemia and hypertension), had a strong association with cardiovascular events, whereas patients deemed low risk had a similar rate of events compared to low-risk patients receiving imatinib [20•]. Other grade 3–4 toxicities observed with both nilotinib doses include hypertension (8.3–10.4%), hypercholesterolemia (26.7–27.6%) and grade 3–4 elevated glucose (6.9–7.2%), requiring regular monitoring to minimize additional cardiovascular events [20•]. QT prolongation and pancreatitis have also been observed with nilotinib. There is no discernible difference in the incidence of second malignancies between nilotinib and imatinib [20•].

Together with the increased toxicity burden associated with the higher dose and in conjunction with the minimal differences in molecular responses observed in the randomised study, 300 mg twice daily of nilotinib is the recommended dose in first-line therapy [4••]. The dosing schedule is twice daily with recommended administration in a fasting state [4••] which can lead to compliance difficulties, emphasizing the importance of adequate patient education prior to drug commencement. The schedule of drug administration may also influence TKI selection for patients in certain settings, such as shift workers who may struggle complying with the strict twice daily regime of nilotinib therapy.

Dasatinib

Dasatinib, providing dual tyrosine kinase inhibition against both *SRC* and *ABL*, has similar responses and outcomes to nilotinib with clear superiority in efficacy compared to imatinib. The landmark trial proving efficacy in upfront treatment was the DASatinib vs. Imatinib Study In Treatment-Naïve CML patients (DASISION), comparing 100 mg dasatinib to 400 mg imatinib. By the end of the 5-year follow-up, dasatinib demonstrated higher rates of achievement of molecular targets including MMR (76% vs. 64%) and MR4.5 (42% vs. 33%) compared to imatinib [21•]. Fewer patients progressed to AP/BC with dasatinib (4.6%) compared to imatinib (7.3%) [21•]. However, like ENESTnd with nilotinib, there was no associated survival benefit observed with dasatinib [21•].

Haematological toxicity is frequently observed with dasatinib, occasionally necessitating treatment interruption. There is a minor risk of bleeding secondary to platelet dysfunction which patients need to be aware of [38]. Cardiovascular events in DASISION were only slightly increased compared with imatinib therapy by 5 years, although more recent data suggests the risk may be similar to nilotinib [21•, 39, 40]. Pulmonary toxicities are the hallmark of dasatinib therapy, manifesting as pleural effusions or the more serious complication of pulmonary hypertension. Up to 28% of patients developed a pleural effusion by 5 years of dasatinib exposure, the incidence linearly increasing with each year of therapy [21•]. The risk appears to be relative to age with 60% of patients ≥ 65 developing an event [21•]. Additionally, elevated dasatinib levels (≥ 3 nmol/L) are associated with an increased risk of effusion development [41]. In comparison, pulmonary hypertension is infrequent, occurring in less than 5% of patients. If detected, however, dasatinib should be ceased [21•]. The pulmonary hypertension generally resolves with drug discontinuation, but one third of patients showed evidence of persistence [42, 43]. Although the standard dose of dasatinib is 100 mg daily, lower doses of dasatinib have been associated with good clinical response. Clinical trials investigating dasatinib dose adjustment according to therapeutic drug monitoring are underway to evaluate the balance between molecular response and drug toxicity [41, 44].

Bosutinib

Restricted availability of bosutinib has limited familiarization compared to the other first-line TKIs but like dasatinib, it is a potent dual *SRC* and *ABL* kinase inhibitor [22•]. The recently published BFORE study, comparing 400 mg daily of bosutinib to 400 mg daily of imatinib, revealed similar efficacy to the other second-generation agents [22•]. Although long-term experience with bosutinib is still accruing, progression to AP/BC is less frequent compared to imatinib [22•, 45]. Molecular milestone achievement by 12 months is comparable to the other second-generation TKIs [22•]. The toxicities frequently observed with both nilotinib and dasatinib, including cardiovascular and pulmonary events, are also less prominent with bosutinib therapy [22•]. Gastrointestinal toxicities, specifically diarrhoea, are more characteristic with grade ≥ 3 diarrhoea developing in almost 8% of patients treated with 400 mg daily of bosutinib in BFORE, frequently resulting in drug interruption [22•].

What Is Old Is Now New—the Reintroduction of Interferon to CML Therapy

Attempts to further improve the molecular responses observed with TKIs have led to a resurgence of interest in interferon, the historical preferred treatment of CML. Combining pegylated interferon with TKI therapy is the focus of a number of ongoing clinical trials. Superior rates of MMR achievement were observed with the addition of pegylated interferon Alfa-2a to imatinib [46]. Preliminary data from combining nilotinib with pegylated interferon is indicative of comparable, if not superior, molecular responses to nilotinib monotherapy [47–49]. Similar early results are reported from dasatinib studies [50]. While the toxicity profile of combination therapy appears to be relatively manageable, the data requires maturation and longer-term follow-up is needed before pegylated interferon can be incorporated into standard practice [46–50].

First-Line Therapy Selection

Goals of Therapy

As the OS of patients diagnosed with CML approaches the general population, CML patients may anticipate decades of TKI exposure for disease control with concurrent accumulation of TKI-associated toxicities. However, select patients are also able to achieve treatment-free remission (TFR) after achievement of a durable DMR. On average, 50–60% of eligible patients attempting TKI discontinuation successfully achieve TFR [51–60]. Although second-generation TKIs have not been proven to increase TFR success to date, earlier achievement of DMR with these agents allows for earlier TFR attempts, potentially greatly shortening the duration of TKI exposure and thus limiting toxicities. Consequently, strategies to maximize early achievement of DMR, definition dependent on institution (MR4 or MR4.5), in addition to maximizing stability of depth of response should be at the forefront of consideration. For females of child-bearing age, timely achievement of stable DMR will allow for TKI discontinuation either as a TFR attempt or temporary interruption, enabling conception and pregnancy and minimizing the need for CML-specific management [16].

Patient Comorbidities

While the effectiveness of TKIs in treatment of CML is indisputable, appropriate treatment selection is warranted to achieve the right balance between toxicity and molecular response. TKIs are generally well tolerated, but as described earlier, each drug has a relatively unique toxicity profile requiring consideration of suitability for each patient prior to selection. While patient comorbidities do not affect achievement of molecular responses or risk of progression, higher scores on the Charleston comorbidity index correlated with inferior OS, even with exclusion of the age-dependent factors [61].

The risk of vascular events is a major concern and should be a key factor when considering optimal therapy for each patient. Epidemiological data has demonstrated that the incidence of major arterial events (per 100/patient-years) was lowest with imatinib (0.1), incidence increasing with the more potent agents—bosutinib (0.4)—dasatinib (1.1) and nilotinib (2.8) [62]. The risk of peripheral arterial occlusions remains highest for nilotinib compared with the other first-line agents [62]. Similarly, nilotinib had an increased rate of ischaemic heart disease with at 1.4/100 patient-years with fewer events observed with the other TKIs (dasatinib 0.6, bosutinib 0.3, imatinib 0.1) [62]. However, other studies suggest that the cardiovascular risk associated with nilotinib and dasatinib is actually similar [39, 40]. Cerebrovascular events were only observed in 0.5% of patients treated with first-line agents [62]. Moreover, upfront use of second-generation TKIs is associated with less cardiovascular risk compared with utility second-line or beyond, perhaps due to shorter treatment duration or due to inherent bias regarding therapy selection [63].

Cardiovascular risk should be evaluated at diagnosis with initiation of appropriate therapies to minimize CV risk [64•]. Risk models such as the Framingham and the systemic coronary risk evaluation (SCORE) have been utilised to predict patient risk of developing cardiovascular toxicity, higher scores correlating with higher risk of cardiovascular events [20•, 65]. Hypertension should be controlled according to local guidelines, and appropriate diabetes therapy should be applied, while hyperlipidemia should be treated with statin therapy where indicated. Statins least likely to interfere with TKI metabolism by CYP3A4 (i.e. rosuvastatin and pravastatin) are preferred [66]. Evidence for primary prophylaxis with aspirin is inconclusive [63] and may actually be detrimental in patients treated with dasatinib due to the slight increase in intrinsic bleeding risk [38, 66]. A harmonious balance between treatment goals, disease risk and cardiovascular risk should be sought. For example, a second-generation TKI would be preferred in patients with low cardiovascular but high CML risk. If TFR is a goal of therapy, then a second-generation TKI may be preferred for early achievement of DMR. If cardiovascular risk is deemed to be high, then avoiding nilotinib and possibly dasatinib would be prudent. Guideline-driven monitoring of cardiovascular risk is recommended for all patients [64•], while appropriate lifestyle changes (such as smoking cessation and establishment of a healthy weight) are strongly advised.

Pleural effusions are a major complication associated with dasatinib, advanced age being the only consistent risk factor associated with development [67]. Preliminary data suggests that elevated dasatinib levels are linked with an increased risk of effusion development with a clinical trial in accrual, investigating dasatinib dose adjustment secondary to therapeutic drug monitoring and incidence of pleural effusions [41, 44]. In the interim, careful patient selection prior to dasatinib commencement is advised. Given the risk of pulmonary hypertension with dasatinib, patients with pre-existing pulmonary hypertension should be considered for an alternate TKI [68]. Due to concomitant platelet dysfunction, dasatinib should be prescribed with caution in patients on anticoagulants due to the risk of haemorrhagic complications [69].

Hepatitis B reactivation has been reported secondary to TKI therapy leading to the recommendation for serological screening prior to TKI commencement [70].

Disease Risk Scores

Risk stratification in CML incorporates simple disease parameters to calculate the risk of CML-related death, OS or cytogenetic response utilizing models including the Sokal, Hasford, EUTOS or ELTS [71–74]. Although the Sokal and the Hasford scores were developed in the pre-TKI era, they remain predictive of molecular response [18, 20•, 22•, 75]. High Sokal scores is associated with poorer 10-year OS rates (68.6%) compared to intermediate (80.3%) or low scores (89.9%) [18]. High Sokal risk patients also have inferior achievement of MMR and stable MR4.5 [76, 77]. Treatment with second-generation TKIs improved molecular responses regardless of risk score compared with imatinib but failed to completely nullify the adverse effect of a high-risk Sokal or Hasford score [20•, 21, 22•]. These results are indicative that more potent *BCR-ABL1* inhibition via second-generation TKIs, while not able to eliminate the adverse prognostic implications of high Sokal or Hasford-risk, still provides significant benefit compared to imatinib therapy. Arguably, their greatest benefit is seen in the high-risk categories.

The EUTOS score, developed and validated in an imatinib-treated cohort, is felt to be a simpler and more refined prognostic model, having removed factors in the prior risk calculators that fail to predict imatinib response [73]. Like the Sokal and Hasford scores, high-risk calculation as per the EUTOS score predicted for inferior MR4 achievement compared to a low-score despite first-line nilotinib therapy [78]. This led to the development of the ELTS score, using the same variables as the Sokal score with different weighting, to improve long-term survival prediction, specifically for CML-related death

[74]. Recently, a comparative analysis has shown that the Sokal score overestimates the number of high-risk patients compared to the ELTS leading to inaccuracy in long-term survival prediction [79•, 80]. However, only the Sokal and Hasford scores are incorporated into the current NCCN guidelines although the EUTOS score is included in the 2013 ELN recommendations [3••, 4••]. Regardless of which score is utilized, all of these scoring systems will provide risk discrimination and improved TKI selection can then follow although the ELTS score is probably more accurate in the TKI era.

Cytogenetic Abnormalities

Additional chromosomal abnormalities (ACAs) in the Ph+ clone at diagnosis are present in about 5% of patients with increasing incidence in the more aggressive phases of disease [81–83]. Identification of major route ACAs (defined as a second Ph+, trisomy 8, isochromosome 17q or trisomy 19) heralds an inferior survival rate while foreshadowing progression to AP/BC [81]. Recognition of major route ACAs from the German CML IV and Italian studies indicated slower MMR achievement with inferior OS and PFS, despite upfront imatinib therapy [81, 82]. However, more recent data suggests that ACAs, irrespective of major route abnormalities, do not predict for inferior molecular or survival outcomes, although these findings may be confounded by treatment with a second-generation TKI [84]. ACAs remain an indicator of poor prognosis in AP/BC CML [83, 84]. To date, there is no clarity as to whether a second-generation TKI is truly beneficial in this scenario although it remains our standard practice.

Transcript Type

The most common transcripts identified in patients are the e13a2 (b2a2) or e14a2 (b3a2); any other transcripts, termed 'atypical', are infrequently observed (less than 2% of cases) [85]. Early studies demonstrated that the e14a2 transcript was associated with better cytogenetic responses [86]. This data was corroborated by other studies while also demonstrating more rapid achievement of MMR and DMR with either the e14a2 or both transcripts compared with e13a2 alone in additional to improved OS and PFS [85, 87]. In contrast, German data demonstrated that while inferior cumulative molecular responses are associated with e13a2 transcripts, there was no significant impact on OS [88]. While the impact of transcript type on survival is uncertain, more recent data has emerged suggesting that patients with the e13a2 transcript who achieve a deep molecular response and attempt to achieve TFR are less likely to enter a successful TFR [89, 90]. At this stage, the impact of the transcript type on response and outcome is not sufficiently clarified to be included in frontline treatment consideration.

The First Conversation

Initiating a dialogue with patients is mandatory to ensure that they are aware of all the available options, the potential

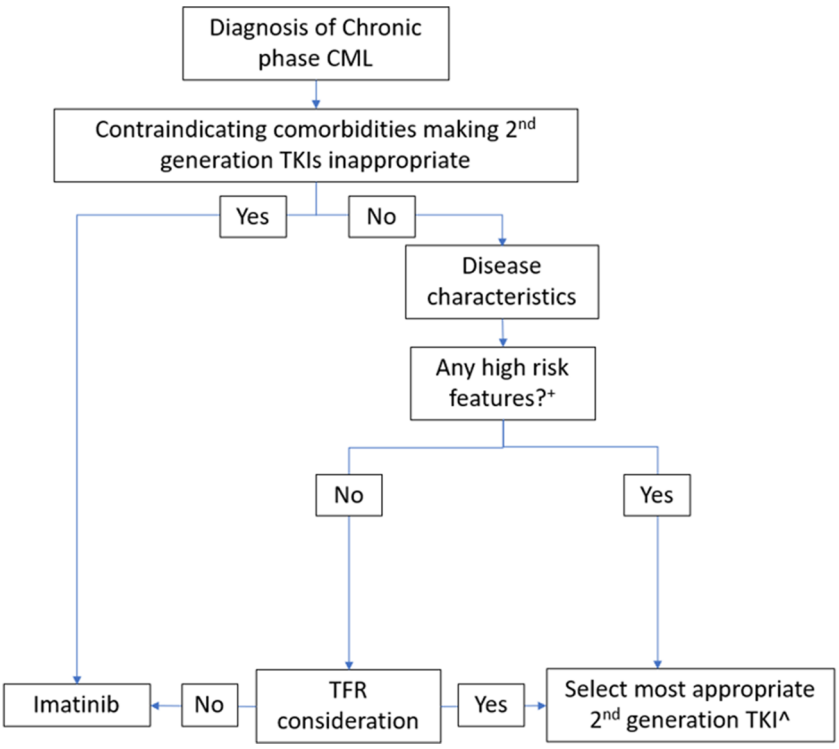

Fig. 1 Decision tree for TKI selection. + high score on risk model (Sokal, Hasford, EUTOS, ELTS) and/or and additional cytogenetic abnormality. ^ Suggest avoid nilotinib in patients with high cardiac risk scores by Framingham or SCORE models

advantages of second-generation TKIs in terms of response, but also understand the common toxicities associated with each drug to inform drug selection (Fig. 1). Issues that need to be addressed in younger patients include fertility and family planning. In all patients, but particularly in older patients, comorbidities must be identified and considered, because they will often lead to the physician and patient favouring one TKI above others. The importance of drug adherence as well as compliance with monitoring requirements must be clearly outlined. The goals of therapy should be introduced including the longer-term goals of deep molecular response and TFR. The potential to eventually stop therapy rather than commit to lifelong therapy is very attractive for many patients and will likely influence frontline therapy selection.

TKI Adherence

Good TKI adherence is vital to achieve molecular milestones [91], and as such, clinicians should ensure that patients are appropriately educated regarding the importance of drug adherence. Suboptimal responses are often associated with poor compliance with the prescribed TKI [91, 92]. Addressing patient concerns regarding dosing schedules, drug toxicity and concomitant medications may assist with improving compliance [93]. Strategies to improve inadvertent non-compliance should be encouraged including electronic reminders, mobile phone applications or dose administration aids [94]. Tackling deliberate drug non-adherence requires directed discussion for potential factors influencing non-compliance while reinforcing the hazards of poor disease control [94].

Conclusion

The goals of therapy have shifted from a sole focus on prevention of disease progression to toxicity minimization and achieving a deep molecular response as a platform for future attempts at drug discontinuation. We have presented an overview of the various first-line TKI options with disease characteristics and considerations that we anticipate will inform drug selection in the haematology clinic. Early discussion of goals of therapy will enable TKI selection to encompass long-term plans, while the focus for some patients will remain on disease control and toxicity prevention. Individualizing CML therapy by tailoring TKI selection to each patient's comorbidities, disease biology and expectations will ideally maximize outcomes, walking the fine line between optimal molecular response and minimal toxicity.

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Compliance with Ethical Standards

Conflict of Interest N.S. received honoraria from Novartis and Bristol-Myers Squibb and travel and accommodation expenses from Novartis, Gilead, Amgen, and Janssen. T.P.H. holds a consultancy role in and has received research funding and honoraria from Novartis, Bristol-Myers Squibb, and Ariad.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Quintás-Cardama A, Cortes J. Molecular biology of bcr-abl1–positive chronic myeloid leukemia. Blood. 2009;113(8):1619–30. https://doi.org/10.1182/blood-2008-03-144790.
2. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TML. Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. J Clin Oncol. 2016;34(24):2851–7. https://doi.org/10.1200/JCO.2015.66.2866.
3.•• Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122. https://doi.org/10.1182/blood-2013-05-501569. **Current international guidelines regarding CML management**.
4.•• Radich JP, Deininger M, Abboud CN, Altman JK, Berman E, Bhatia R, et al. Chronic Myeloid Leukemia, Version 1.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2018;16(9):1108–35. https://doi.org/10.6004/jnccn.2018.0071. **Current international guidelines regarding CML management**.
5.•• Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv41–51. https://doi.org/10.1093/annonc/mdx219. **Current international guidelines regarding CML management**.
6. Thompson PA, Kantarjian HM, Cortes JE. Diagnosis and Treatment of Chronic Myeloid Leukemia in 2015. Mayo Clin Proc. 2015;90(10):1440–54. https://doi.org/10.1016/j.mayocp.2015.08.010.
7. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th edition ed. World Health Organization Classification of Tumours. France: International Agency for Research on Cancer; 2008.
8. Aqui N, O'Doherty U. Leukocytapheresis for the treatment of hyperleukocytosis secondary to acute leukemia. Hematology. 2014;2014(1):457–60. https://doi.org/10.1182/asheducation-2014.1.457.

9. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405. https://doi.org/10.1182/blood-2016-03-643544.
10. Buesche G, Ganser A, Schlegelberger B, von Neuhoff N, Gadzicki D, Hecker H, et al. Marrow fibrosis and its relevance during imatinib treatment of chronic myeloid leukemia. Leukemia. 2007;21(12):2420–7 http://www.nature.com/leu/journal/v21/n12/suppinfo/2404917s1.html.
11. Kantarjian HM, Bueso-Ramos CE, Talpaz M, O'Brien S, Giles F, Rios MB, et al. The degree of bone marrow fibrosis in chronic myelogenous leukemia is not a prognostic factor with imatinib mesylate therapy. Leuk Lymphoma. 2005;46(7):993–7. https://doi.org/10.1080/10428190500097581.
12. Ohanian M, Kantarjian HM, Quintas-Cardama A, Jabbour E, Abruzzo L, Verstovsek S, et al. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. Clin Lymphoma Myeloma Leuk. 2014;14(2):155–62.e1. https://doi.org/10.1016/j.clml.2013.08.008.
13. Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, et al. The effects of imatinib on pregnancy outcome. Blood. 2008;111(12):5505–8. https://doi.org/10.1182/blood-2007-10-114900.
14. Ault P, Kantarjian H, O'Brien S, Faderl S, Beran M, Rios MB, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol. 2006;24(7):1204–8. https://doi.org/10.1200/jco.2005.04.6557.
15. Cortes JE, Abruzzese E, Chelysheva E, Guha M, Wallis N, Apperley JF. The impact of dasatinib on pregnancy outcomes. Am J Hematol. 2015;90(12):1111–5. https://doi.org/10.1002/ajh.24186.
16. Berman E, Druker BJ, Burwick R. Chronic myelogenous leukemia: pregnancy in the era of stopping tyrosine kinase inhibitor therapy. J Clin Oncol. 2018;36(12):1250–6. https://doi.org/10.1200/JCO.2017.77.2574.
17. Yassin MA, Soliman AT, Elawa AS, El-Ayoubi HR, Desanctis V. Effects of Tyrosine Kinase Inhibitors On Spermatogenesis and Pituitary Gonadal Axis in Males with Chronic Myeloid Leukemia. Blood. 2012;120(Suppl 1):Abstract 1688.
18. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med. 2017;376(10):917–27. https://doi.org/10.1056/NEJMoa1609324.
19.• Hehlmann R, Lauseker M, Saußele S, Pfirrmann M, Krause S, Kolb HJ, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. Leukemia. 2017;31:2398–406. https://doi.org/10.1038/leu.2017.253. **The 10-year update on CML IV**.
20.• Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30(5):1044–54. https://doi.org/10.1038/leu.2016.5. **The 5-year update on ENESTnd**.
21.• Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. J Clin Oncol. 2016. https://doi.org/10.1200/jco.2015.64.8899. **The 5-year update on DASISION**.
22.• Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim D-W, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE Trial. J Clin Oncol. 2017;36(3):231–7. https://doi.org/10.1200/JCO.2017.74.7162. **The 5-year update on BFORE**.
23. Efficace F, Baccarani M, Breccia M, Alimena G, Rosti G, Cottone F, et al. Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. Blood. 2011;118(17):4554–60. https://doi.org/10.1182/blood-2011-04-347575.
24. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348. https://doi.org/10.1056/NEJMoa022457.
25. Hehlmann R, Lauseker M, Jung-Munkwitz S, Leitner A, Müller MC, Pletsch N, et al. Tolerability-Adapted Imatinib 800 mg/d Versus 400 mg/d Versus 400 mg/d Plus Interferon-α in Newly Diagnosed Chronic Myeloid Leukemia. J Clin Oncol. 2011;29(12):1634–42. https://doi.org/10.1200/jco.2010.32.0598.
26. Berman E, Nicolaides M, Maki RG, Fleisher M, Chanel S, Scheu K, et al. Altered bone and mineral metabolism in patients receiving imatinib mesylate. N Engl J Med. 2006;354(19):2006–13. https://doi.org/10.1056/NEJMoa051140.
27. Yilmaz M, Lahoti A, O'Brien S, Nogueras-Gonzalez GM, Burger J, Ferrajoli A, et al. Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. Cancer. 2015;121(21):3894–904. https://doi.org/10.1002/cncr.29587.
28. Sakurai M, Mori T, Karigane D, Kasahara H, Tozawa K, Matsuki E, et al. Long-Term Treatment with Imatinib Is Associated with Decreased Estimated Glomerular Filtration Rate and Hemoglobin Level in Patients with Chronic Myelogenous Leukemia. Blood. 2016;128(Suppl 1):Abstract 1888.
29. Miranda MB, Lauseker M, Kraus MP, Proetel U, Hanfstein B, Fabarius A, et al. Secondary malignancies in chronic myeloid leukemia patients after imatinib-based treatment: long-term observation in CML Study IV. Leukemia. 2016;30:1255. https://doi.org/10.1038/leu.2016.20 https://www.nature.com/articles/leu201620#supplementary-information.
30. Gunnarsson N, Stenke L, Höglund M, Sandin F, Björkholm M, Dreimane A, et al. Second malignancies following treatment of chronic myeloid leukaemia in the tyrosine kinase inhibitor era. Br J Haematol. 2015;169(5):683–8. https://doi.org/10.1111/bjh.13346.
31. Hughes TP, Branford S, White DL, Reynolds J, Koelmeyer R, Seymour JF, et al. Impact of early dose intensity on cytogenetic and molecular responses in chronic- phase CML patients receiving 600 mg/day of imatinib as initial therapy. Blood. 2008;112(10):3965–73. https://doi.org/10.1182/blood-2008-06-161737.
32.• Baccarani M, Druker BJ, Branford S, Kim D-W, Pane F, Mongay L, et al. Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: final update from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study. Int J Hematol. 2014;99(5):616–24. https://doi.org/10.1007/s12185-014-1566-2. **Addresses the question of optimal imatinib dosing**.
33. Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, Palandri F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome–positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood. 2007;110(10):3540–6. https://doi.org/10.1182/blood-2007-03-080689.
34. Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassmann B, et al. Nilotinib in Imatinib-Resistant CML and Philadelphia Chromosome–Positive ALL. N Engl J Med. 2006;354(24):2542–51. https://doi.org/10.1056/NEJMoa055104.
35. Cortes J, Kim DW, Raffoux E, Martinelli G, Ritchie E, Roy L, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant

patients with chronic myeloid leukemia in blast phase. Leukemia. 2008;22(12):2176–83.
36. Khoury HJ, Cortes JE, Kantarjian HM, Gambacorti-Passerini C, Baccarani M, Kim D-W, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012;119(15):3403–12. https://doi.org/10.1182/blood-2011-11-390120.
37. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013;369(19):1783–96. https://doi.org/10.1056/NEJMoa1306494.
38. Quintas-Cardama A, Han X, Kantarjian H, Cortes J. Tyrosine kinase inhibitor-induced platelet dysfunction in patients with chronic myeloid leukemia. Blood. 2009;114. https://doi.org/10.1182/blood-2008-09-180604.
39. Dahlen T, Edgren G, Lambe M, Hoglund M, Bjorkholm M, Sandin F, et al. Cardiovascular events associated with use of tyrosine kinase inhibitors in chronic myeloid leukemia: a population-based cohort study. Ann Intern Med. 2016;165(3):161–6. https://doi.org/10.7326/m15-2306.
40. Douxfils J, Haguet H, Mullier F, Chatelain C, Graux C, Dogne JM. Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival: a systematic review and meta-analysis. JAMA Oncology. 2016;2(5):625–32. https://doi.org/10.1001/jamaoncol.2015.5932.
41. Rousselot P, Mollica L, Etienne G, Bouchet S, Guerci A, Nicolini FE, et al. Pharmacologic monitoring of dasatinib as first line therapy in newly diagnosed chronic phase chronic myelogenous leukemia (CP-CML) identifies patients at higher risk of pleural effusion: a sub-analysis of the OPTIM-Dasatinib Trial. Blood. 2012;120(21): Abstract 3770.
42. Weatherald J, Chaumais M-C, Savale L, Jaïs X, Seferian A, Canuet M, et al. Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. Eur Respir J. 2017;50(1):1700217. https://doi.org/10.1183/13993003.00217-2017.
43. Shah NP, Wallis N, Farber HW, Mauro MJ, Wolf RA, Mattei D, et al. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. Am J Hematol. 2015;90(11):1060–4. https://doi.org/10.1002/ajh.24174.
44. The DIRECT study: individualised dasatinib dosing for elderly patients with chronic myelogenous leukaemia [database on the Internet]. ALLG. 2016. Accessed: 29/05/2019.
45. Cortes JE, Kim DW, Kantarjian HM, Brummendorf TH, Dyagil I, Griskevicius L. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol. 2012;30. https://doi.org/10.1200/jco.2011.38.7522.
46. Preudhomme C, Guilhot J, Nicolini FE, Guerci-Bresler A, Rigal-Huguet F, Maloisel F, et al. Imatinib plus peginterferon Alfa-2a in chronic myeloid leukemia. N Engl J Med. 2010;363(26):2511–21. https://doi.org/10.1056/NEJMoa1004095.
47. Yeung DT, Grigg AP, Shanmuganathan N, Cunningham I, Shortt J, Rowling P, et al. Combination of nilotinib and pegylated interferon Alfa-2b results in high molecular response rates in chronic phase CML: interim results of the ALLG CML 11 Pinnacle Study. Blood. 2018;132(Suppl 1):Abstract 459. https://doi.org/10.1182/blood-2018-99-110569.
48. Hochhaus A, Saussele S, Baerlocher GM, Brümmendorf TH, Burchert A, La Rosée P, et al. Nilotinib vs nilotinib plus pegylated interferon-alpha2b induction and nilotinib or pegylated interferon-alpha2b maintenance therapy for newly diagnosed BCR-ABL+ chronic myeloid leukemia patients in chronic phase: interim analysis of the Tiger (CML V)-Study. Blood. 2018;132(Suppl 1): Abstract 460.
49. Nicolini FE, Etienne G, Dubruille V, Roy L, Huguet F, Legros L, et al. Nilotinib and peginterferon alfa-2a for newly diagnosed chronic-phase chronic myeloid leukaemia (NiloPeg): a multicentre, non-randomised, open-label phase 2 study. Lancet Haematol. 2015;2(1):e37–46. https://doi.org/10.1016/S2352-3026(14)00027-1.
50. Hjorth-Hansen H, Stentoft J, Richter J, Koskenvesa P, Höglund M, Dreimane A, et al. Safety and efficacy of the combination of pegylated interferon-α2b and dasatinib in newly diagnosed chronic-phase chronic myeloid leukemia patients. Leukemia. 2016;30:1853. https://doi.org/10.1038/leu.2016.121 https://www.nature.com/articles/leu2016121#supplementary-information.
51. Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerci-Bresler A, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. Blood. 2017;129(7):846–54. https://doi.org/10.1182/blood-2016-09-742205.
52. Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol. 2010;11(11):1029–35. https://doi.org/10.1016/s1470-2045(10)70233-3.
53. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol. 2018;19(6):747–57. https://doi.org/10.1016/S1470-2045(18)30192-X.
54. Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Yeung DT, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. Blood. 2013;122(4):515–22. https://doi.org/10.1182/blood-2013-02-483750.
55. Lee S-E, Choi SY, Song H-Y, Kim S-H, Choi M-Y, Park JS, et al. Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: the KID study. Haematologica. 2016;101(6):717–23. https://doi.org/10.3324/haematol.2015.139899.
56. Imagawa J, Tanaka H, Okada M, Nakamae H, Hino M, Murai K, et al. Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial): a multicentre phase 2 trial. Lancet Haematol. 2015;2(12):e528–35. https://doi.org/10.1016/s2352-3026(15)00196-9.
57. Etienne G, Guilhot J, Rea D, Rigal-Huguet F, Nicolini F, Charbonnier A, et al. Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia. J Clin Oncol. 2017;35(3):298–305. https://doi.org/10.1200/jco.2016.68.2914.
58. Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. J Clin Oncol. 2014;32(5):424–30. https://doi.org/10.1200/jco.2012.48.5797.
59. Mahon F, Boquimpani C, Kim D, et al. Treatment-free remission after second-line nilotinib treatment in patients with chronic myeloid leukemia in chronic phase: results from a single-group, phase 2, open-label study. Ann Intern Med. 2018;168(7):461–70. https://doi.org/10.7326/M17-1094.
60. Kumagai T, Nakaseko C, Nishiwaki K, Yoshida C, Ohashi K, Takezako N, et al. Dasatinib cessation after deep molecular response exceeding 2 years and natural killer cell transition during dasatinib consolidation. Cancer Sci. 2018;109(1):182–92. https://doi.org/10.1111/cas.13430.

61. Saussele S, Krauss MP, Hehlmann R, Lauseker M, Proetel U, Kalmanti L, et al. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. Blood. 2015;126(1):42–9. https://doi.org/10.1182/blood-2015-01-617993.
62. Chai-Adisaksopha C, Lam W, Hillis C. Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. Leuk Lymphoma. 2016;57(6):1300–10. https://doi.org/10.3109/10428194.2015.1091929.
63. Caocci G, Mulas O, Annunziata M, Luciano L, Bonifacio M, Orlandi EM, et al. Cardiovascular toxicity in patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors in the real-life practice: identification of risk factors and the role of prophylaxis. Am J Hematol. 2018;93(7):E159–e61. https://doi.org/10.1002/ajh.25102.
64.• Ross DM, Arthur C, Burbury K, Ko BS, Mills AK, Shortt J, et al. Chronic myeloid leukaemia and tyrosine kinase inhibitor therapy: assessment and management of cardiovascular risk factors. Intern Med J. 2018;48(Suppl 2):5–13. https://doi.org/10.1111/imj.13716. **Review paper addressing cardiovascular health in CML patients**.
65. Breccia M, Molica M, Zacheo I, Serrao A, Alimena G. Application of systematic coronary risk evaluation chart to identify chronic myeloid leukemia patients at risk of cardiovascular diseases during nilotinib treatment. Ann Hematol. 2015;94(3):393–7. https://doi.org/10.1007/s00277-014-2231-9.
66. Haouala A, Widmer N, Duchosal MA, Montemurro M, Buclin T, Decosterd LA. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. Blood. 2011;117(8):e75–87. https://doi.org/10.1182/blood-2010-07-294330.
67. Hughes TP, Laneuville P, Rousselot P, Snyder DS, Rea D, Shah NP, et al. Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. Haematologica. 2019;104(1):93–101. https://doi.org/10.3324/haematol.2018.188987.
68. Ozgur Yurttas N, Eskazan AE. Dasatinib-induced pulmonary arterial hypertension. Br J Clin Pharmacol. 2018;84(5):835–45. https://doi.org/10.1111/bcp.13508.
69. Fox LC, Cummins KD, Costello B, Yeung D, Cleary R, Forsyth C, et al. The incidence and natural history of dasatinib complications in the treatment of chronic myeloid leukemia. Blood Adv. 2017;1(13):802–11. https://doi.org/10.1182/bloodadvances.2016003889.
70. Chang C-S, Tsai C-Y, Yan S-L. Hepatitis B reactivation in patients receiving targeted therapies. Hematology. 2017;22(10):592–8. https://doi.org/10.1080/10245332.2017.1321882.
71. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood. 1984;63(4):789–99.
72. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, et al. A New Prognostic Score for Survival of Patients With Chronic Myeloid Leukemia Treated With Interferon Alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst. 1998;90(11):850–9. https://doi.org/10.1093/jnci/90.11.850.
73. Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood. 2011;118(3):686–92. https://doi.org/10.1182/blood-2010-12-319038.
74. Pfirrmann M, Baccarani M, Saussele S, Guilhot J, Cervantes F, Ossenkoppele G, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia. 2016;30(1):48–56. https://doi.org/10.1038/leu.2015.261.
75. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. N Engl J Med. 2010;362(24):2260–70. https://doi.org/10.1056/NEJMoa1002315.
76. Branford S, Yeung DT, Ross DM, Prime JA, Field CR, Altamura HK, et al. Early molecular response and female sex strongly predict stable undetectable BCR-ABL1, the criteria for imatinib discontinuation in patients with CML. Blood. 2013;121(19):3818–24. https://doi.org/10.1182/blood-2012-10-462291.
77. Branford S, Yeung DT, Ross DM, Parker WT, Braley J, Seymour JF, et al. The Adverse Effect of High Sokal Risk for First Line Imatinib Treated Patients Is Overcome By a Rapid Rate of BCR-ABL Decline Measured As Early As 1 Month of Treatment. Blood. 2014;124(21):816.
78. Hochhaus A, Rosti G, Cross NC, Steegmann JL, le Coutre P, Ossenkoppele G, et al. Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study. Leukemia. 2016;30(1):57–64. https://doi.org/10.1038/leu.2015.270.
79.• Pfirrmann M, Baccarani M, Saussele S, Turkina A, Faber E, Steegmann JL et al., editors. The EUTOS long-term survival (ELTS) score is superior to the Sokal score for prognosis of survival probabilities of patients with chronic-phase chronic myeloid leukaemia. Oral presenation at the 23rd Annual Congress of the European Hematology Association; 2018; Stockholm, Sweden. **Potential new scoring model developed in the TKI era**.
80. Molica M, Canichella M, Alunni Fegatelli D, Colafigli G, Massaro F, Latagliata R, et al. The Eutos long-term survival score accurately predicts the risk of death in chronic myeloid leukaemia patients treated outside of clinical trials. Am J Hematol. 2017;92(12):E661–E4. https://doi.org/10.1002/ajh.24913.
81. Fabarius A, Leitner A, Hochhaus A, Müller MC, Hanfstein B, Haferlach C, et al. Impact of ACA at diagnosis on prognosis of CML: long-term observation from 1151 patients of the randomized CML Study IV. Blood. 2011;118(26):6760–8. https://doi.org/10.1182/blood-2011-08-373902.
82. Luatti S, Castagnetti F, Marzocchi G, Baldazzi C, Gugliotta G, Iacobucci I, et al. Additional chromosomal abnormalities in Philadelphia-positive clone: adverse prognostic influence on frontline imatinib therapy: a GIMEMA Working Party on CML analysis. Blood. 2012;120(4):761–7. https://doi.org/10.1182/blood-2011-10-384651.
83. Krishna Chandran R, Geetha N, Sakthivel KM, Suresh Kumar R, Jagathnath Krishna KMN, Sreedharan H. Impact of additional chromosomal aberrations on the disease progression of chronic myelogenous leukemia. Front Oncol. 2019;9(88). https://doi.org/10.3389/fonc.2019.00088.
84. Alhuraiji A, Kantarjian H, Boddu P, Ravandi F, Borthakur G, DiNardo C, et al. Prognostic significance of additional chromosomal abnormalities at the time of diagnosis in patients with chronic myeloid leukemia treated with frontline tyrosine kinase inhibitors. Am J Hematol. 2018;93(1):84–90. https://doi.org/10.1002/ajh.24943.
85. Jain P, Kantarjian H, Patel KP, Gonzalez GN, Luthra R, Shamanna RK, et al. Impact of BCR-ABL transcript type on outcome in patients with chronic-phase CML treated with tyrosine kinase inhibitors. Blood. 2016;127(10):1269–75. https://doi.org/10.1182/blood-2015-10-674242.
86. Lucas CM, Harris RJ, Giannoudis A, Davies A, Knight K, Watmough SJ, et al. Chronic myeloid leukemia patients with the e13a2 BCR-ABL fusion transcript have inferior responses to imatinib compared to patients with the e14a2 transcript. Haematologica. 2009;94(10):1362–7. https://doi.org/10.3324/haematol.2009.009134.
87. Castagnetti F, Gugliotta G, Breccia M, Iurlo A, Levato L, Albano F, et al. The BCR-ABL1 transcript type influences response and outcome in Philadelphia chromosome-positive chronic myeloid

leukemia patients treated frontline with imatinib. Am J Hematol. 2017;92(8):797–805. https://doi.org/10.1002/ajh.24774.

88. Hanfstein B, Lauseker M, Hehlmann R, Saussele S, Erben P, Dietz C, et al. Distinct characteristics of e13a2 versus e14a2 BCR-ABL1 driven chronic myeloid leukemia under first-line therapy with imatinib. Haematologica. 2014;99(9):1441–7. https://doi.org/10.3324/haematol.2013.096537.
89. Claudiani S, Apperley JF, Gale RP, Clark R, Szydlo R, Deplano S, et al. E14a2 BCR-ABL1 transcript is associated with a higher rate of treatment-free remission in individuals with chronic myeloid leukemia after stopping tyrosine kinase inhibitor therapy. Haematologica. 2017;102(8):e297–e9. https://doi.org/10.3324/haematol.2017.168740.
90. Shanmuganathan N, Branford S, Yong ASM, Hiwase DK, Yeung DT, Ross DM, et al. The e13a2 BCR-ABL1 transcript is associated with higher rates of molecular recurrence after treatment-free remission attempts: retrospective analysis of the adelaide cohort. Blood. 2018;132(Suppl 1):Abstract 1731. https://doi.org/10.1182/blood-2018-99-111083.
91. Marin D, Bazeos A, Mahon F-X, Eliasson L, Milojkovic D, Bua M, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol. 2010;28(14):2381–8. https://doi.org/10.1200/jco.2009.26.3087.
92. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachee P, Berneman Z, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood. 2009;113(22):5401–11. https://doi.org/10.1182/blood-2008-12-196543.
93. Jabbour E, Saglio G, Radich J, Kantarjian H. Adherence to BCR-ABL inhibitors: issues for CML therapy. Clin Lymphoma Myeloma Leuk. 2012;12(4):223–9. https://doi.org/10.1016/j.clml.2012.04.002.
94. Usherwood T. Encouraging adherence to long-term medication. Aust Prescr. 2017;40:147–50.