Leukemia (2016) **30**, 1648–1671

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REVIEW

European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia

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Most reports on chronic myeloid leukaemia (CML) treatment with tyrosine kinase inhibitors (TKIs) focus on efficacy, particularly on molecular response and outcome. In contrast, adverse events (AEs) are often reported as infrequent, minor, tolerable and manageable, but they are increasingly important as therapy is potentially lifelong and multiple TKIs are available. For this reason, the European LeukemiaNet panel for CML management recommendations presents an exhaustive and critical summary of AEs emerging during CML treatment, to assist their understanding, management and prevention. There are five major conclusions. First, the main purpose of CML treatment is the antileukemic effect. Suboptimal management of AEs must not compromise this first objective. Second, most patients will have AEs, usually early, mostly mild to moderate, and which will resolve spontaneously or are easily controlled by simple means. Third, reduction or interruption of treatment must only be done if optimal management of the AE cannot be accomplished in other ways, and frequent monitoring is needed to detect resolution of the AE as early as possible. Fourth, attention must be given to comorbidities and drug interactions, and to new events unrelated to TKIs that are inevitable during such a prolonged treatment. Fifth, some TKI-related AEs have emerged which were not predicted or detected in earlier studies, maybe because of suboptimal attention to or absence from the preclinical data. Overall, imatinib has demonstrated a good long-term safety profile, though recent findings suggest underestimation of symptom severity by physicians. Second and third generation TKIs have shown higher response rates, but have been associated with unexpected problems, some of which could be irreversible. We hope these recommendations will help to minimise adverse events, and we believe that an optimal management of them will be rewarded by better TKI compliance and thus better CML outcomes, together with better quality of life.

Leukemia (2016) **30,** 1648–1671; doi:10.1038/leu.2016.104

INTRODUCTION

Although successful pharmacologic treatment of chronic myeloid leukaemia (CML) is nowadays likely to result in near-normal life expectancy, at least a quarter of patients will change TKI at least once during their life, because of either inadequate response or intolerance.[1–11] The clinical imperative for continuous daily treatment over many years is burdened by the accompanying long-standing adverse effects (AEs) and a resultant decreased quality of life. The attention given by the scientific community to AEs has grown over recent years, but our understanding remains poor. We have no knowledge of why only some (and not all) patients develop particular AEs, and this might be related to many factors, including polymorphisms in genes that affect TKI movement and metabolism.[12] More generally, publications about prevention and management of TKI AEs are scarce. Although this problem has been addressed by the Council of Europe several years ago,[13] the dissemination and implementation of these recommendations has been suboptimal.[14]

In view of these considerations, the European LeukemiaNet working party on CML asked authors JLS and REC to convene a panel of members who had previously published and/or expressed an interest in AEs. Panel members were asked to review available data in their field of interest and to make recommendations for when certain TKI should be optimally used or avoided. The present publication represents a consensus document from email correspondence and a series of meetings held during 2014 and 2015.

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Received 29 February 2016; accepted 18 April 2016; accepted article preview online 28 April 2016; advance online publication, 3 June 2016

General considerations and limitations of these recommendations

In CML, we have a somewhat simpler landscape than for many other diseases, partly because of the fastidiousness devoted to AEs in TKI studies and the several resultant publications.[15–18] This could be ascribed to regulatory issues, more commitment from the pharmaceutical industry, and growing interest from the haematologist and other health providers. However, current recommendations have several limitations. The most important is the scarcity of evidence for managing specific complications. In addition, the ease of monitoring some laboratory parameters (for example, blood counts or biochemical alterations in liver or renal function), and if abnormal the protocolised requirement to stop/change TKI therapy, could have underestimated the true magnitude of some TKI-related AEs. In contrast, the difficulty of monitoring other systems (for example, endothelium, the nervous system) may account for the severity of some AEs, especially if presenting after many years of TKI treatment. Finally, long-term information on AEs is more available on imatinib than on other TKIs regarding type, frequency, time of onset and severity of AEs. Long-term observations on AEs exist only for imatinib, and we have learned that a delayed presentation could be possible for any AE.[7]

The prevention of AEs of TKI treatment of CML has been addressed only marginally in randomized trials. Two reasons account for this: first, because it is not the objective of these kind of trials, and second, because in pivotal randomized trials, the spectrum of AEs is still being discovered and with longer follow-up, unforeseen late AEs are revealed. Also, this topic cannot be properly addressed in retrospective studies. The information on the kinetics of appearance of AEs is scarce. Development of AEs can be determined by type of TKI, dosage, schedule, disease phase, concomitant medications and body size.

Our present recommendations comprise three types of information. First, the kinetics of appearance of AEs, in order to inform the reader when to be more cautious. Second, the conditions before or concurrent with TKI treatment that predispose to TKI toxicity. Here it is important to note that, while it is sensible to treat comorbidities optimally (for example, the control of hyperlipidemia) or to change food or lifestyle, there are only very scarce data on whether this mitigates the incidence or severity of AEs. Third, the hypotheses on pathogenesis that the authors have offered in their studies. In the absence of evidence for prevention of AEs, our recommendations are based on the application of *ars medica*, reflecting the opinion given by the authors of system-specific sections and the opinion of the panel reviewers and members.

General approach to the management of AEs

Early and prompt recognition is crucial for optimal management, without unduly compromising treatment continuity. First of all, patient education on potential AEs and their time course is vital, together with pre-emptive treatment to reduce AE risk (for example, loperamide to pre-empt bosutinib-associated diarrhoea). Most of the study protocols have used the National Cancer Institute common toxicity criteria (NCI-CTC) for classifying the severity of AEs, and there are similarities in management strategies across different studies.[1,2,5,19–23] It is worth noting that the NCI-CTC criteria are not always precise enough to quantitate the severity of AEs.

However, the success of these strategies has not been studied in depth. Aspects such as reversibility, frequency of relapses and severity are known only for a limited number of AEs. Our general approach for managing AEs is summarised as follows, depending on the grade of severity:

Grade 1 AE. No change in TKI therapy or dose is needed, though the AE may require specific treatment.

Grade 2 AE. Withholding the TKI until the grade falls to <2 is the preferred approach. However, it may be reasonable to initially continue the TKI for a week with appropriate treatment of the AE where practical, and then if there is no resolution, to withhold the TKI until toxicity grade is <2, with weekly monitoring. In the case of two or three episodes, we recommend dose reduction to the next lower level.

Grade 3 AE. Withholding the TKI until the grade falls to <3 is the recommended approach, and then resuming at the next lower level. Another reasonable option is to withhold the drug until severity falls to <2, and resume at the same dose. If there is no resolution within 4 weeks, then discontinue the TKI, and switch to another when appropriate. In the case of a third episode of grade 3, discontinuation and switching is the best option.

Grade 4 AE. Stop the TKI and switch to another TKI when appropriate. A cautionary comment is pertinent here. In all studies of TKIs, particularly in company-sponsored registration studies, toxicity was sometimes reported to be 'manageable', meaning that balancing dose interruption, dose reduction and some symptomatic treatment, it was possible to keep most patients on treatment with that TKI. The term 'manageable' has sense when it is not possible for some reason to switch to another TKI. But in all other cases the concept of 'manageable' should be revised, and the pros and cons of continuing the same TKI, with dose interruption and reduction, should be balanced against the pros and cons of switching.

In addition, we have used the following terminology:

'Not recommended' means that it is wise to consider a different TKI and/or strategy, unless there is a compelling clinical reason not to do so.

'Not advisable' means that it is most unwise to pursue this strategy, and it is very unlikely that there will be a clinical scenario in which this does not apply.

In practice, these recommendations cannot be dogmatic, and must be informed by many variables such as disease phase, numbers of prior treatment lines, and TKI and stem cell transplantation availability. Specific measures are recommended for special situations, and these will be addressed in the following system-specific sections.

SPECIFIC SYSTEMS

Vascular AEs

Vascular events leading to ischaemic heart disease (IHD), ischaemic cerebrovascular events (ICVE) or peripheral arterial occlusive disease (PAOD) have become an emerging new type of toxicity in CML patients treated with ponatinib or nilotinib.[24] Pooled data from multiple trials indicate the importance of dose intensity of ponatinib for the occurrence of vascular adverse events[25] which also includes—in contrast to nilotinib—an increased risk for venous thrombosis.[26] Vascular events from ponatinib therefore seem to be more common and qualitatively different from those seen with nilotinib and sequential therapy with these two agents may confer the highest risk.[27] The available data do not indicate an elevated risk of arterial events in patients treated with imatinib, bosutinib or dasatinib in any of the phase 3 trials with these agents.[4,7,9,22,28–30]

Peripheral arterial occlusive disease

Incidence and severity: Although we have no data from direct comparisons between second generation (2G) TKIs, the data coming from randomized trials between these vs imatinib suggest that the excess risk of peripheral arterial occlusive disease (PAOD) appears to be highest with ponatinib, then with nilotinib, and almost negligible with the rest.[3,23,29,31–52] The actual increment of risk is not known, because the trials were not designed to assess

this point, and vascular risk factors were not properly assessed before or during the treatment (Table 1).

Predisposing factors and kinetics: Both with ponatinib and nilotinib, higher doses seem to be associated with more risk.[3,23,31] In addition, patients developing PAOD frequently (though not always) have pre-existing cardiovascular risk factors.[3,32,33,53,54] Although the vast majority of documented cases of PAOD occurred within the first 48 months of therapy, some have been seen as early as 4 months, or as late as 5 years.

Preventive measures: As PAOD may be irreversible, prevention and early detection is important. The cardiovascular risk score before and while on therapy with TKIs should be documented based on national or international guidelines[55] and should include palpation of peripheral pulses. We strongly recommend performing either the ankle–brachial index (ABI) or duplex ultrasonography to assess asymptomatic PAOD in all newly diagnosed patients with CML aged over 65 years[56] and in younger patients in the presence of cardiovascular risk factors or symptoms suggestive of claudication. We recommend to obtain baseline parameters of fasting glucose, HbA1c, lipids (cholesterol, low- and high-density lipoprotein (LDL and HDL) and triglycerides), and creatinine, and to repeat these parameters every 6–12 months when a therapeutic regimen including ponatinib or nilotinib is chosen. The frequency of repeat monitoring will depend on the baseline results; we advise to repeat ABI (or duplex ultrasonography) every 6–12 months in patients under treatment with ponatinib or nilotinib, if necessary under the guidance of a vascular surgeon or analogous specialist. Diabetic patients need a more meticulous approach. Statins or low-dose aspirin should only be given if there is a classical cardiovascular indication.

Ischaemic heart and cerebrovascular disease. The presently published data on IHD or ICVE in TKI recipients are scarcer. As both IHD and ICVE have been observed at similar frequencies in patients receiving any of the currently available first-line drugs (imatinib, nilotinib, dasatinib), a recommendation to exclude any of these drugs for the first-line treatment of patients with a history of IHD or ICVE cannot currently be made. However, given the similar pathogenesis of PAOD, IHD and ICVE, haematologists prescribing ponatinib or nilotinib must be aware of the higher cardiovascular toxicity profiles of these drugs and they must be used with caution.

Choice of TKI depending on cardiovascular risk factors. There is no absolute contraindication for using any given TKI if comorbidities are considered. In more advanced disease, the balance between efficacy and toxicity alters and this may modify the choice of TKI. The more advanced the disease, the more important is efficacy as the main variable when choosing TKI. In first-line treatment of chronic phase CML in patients at very high risk of cardiovascular disease, imatinib or dasatinib are preferred options. In such patients, nilotinib is not recommended, and should be indicated only after careful consideration of risk factors, severity and expected benefit of CML treatment. In low or moderate cardiovascular risk patients, any TKI can be considered. In patients with known PAOD before TKI therapy, a widely used staging system is the Rutherford classification[57] which defines mild, moderate and severe forms of PAOD. In any Rutherford stage, ponatinib is not advisable, and nilotinib is not advisable if prior PAOD is severe. However, in patients with only mild to moderate preexisting PAOD, nilotinib may be prescribed with caution and after balancing the individual risk profile of alternative TKIs. In all cases, correction of all the cardiovascular risk factors is recommended; although there is no evidence that doing so mitigates or diminishes the vascular risk of ponatinib or nilotinib. In any case, TKI therapy cannot be delayed.

Management of vascular problems. Management recommendations regarding arterial events should be considered provisional. They are driven by both the potentially irreversible nature of arterial damage[58] (and thus the need to prevent this complication), and also by the present and foreseeable lack of data from prospective clinical trials on how to manage vascular issues. We suggest taking into consideration the status of response, the BCR-ABL1 mutation status (for example, the presence of the T315I mutation) and the grade and history of PAOD as well as information on previous cardiovascular disease.

Management of PAOD emerging on TKI treatment. Optimal management of newly emerging PAOD while on TKI therapy is affected by the depth of response and severity of PAOD. For the purpose of the different treatment strategies suggested here, we define severe PAOD as any type of disease that requires medical and interventional treatment. With regard to depth of response, we here define a stable deep molecular response as MR^4 (BCR-ABL1 $\leqslant$0.01% on the international scale, IS) or better response for at least 18 months. This stratification is based on the fact that most of the presently ongoing or future discontinuation trials are using MR^4 or $MR^{4,5}$ (BCR-ABL1 $\leqslant$0.0032% IS) as entry criteria.

In patients with emergent mild PAOD while on ponatinib or nilotinib, switching to an alternative TKI is recommended, based on the patient's response and comorbidities. If PAOD is moderate or severe, switching should be done without delay. In addition, medical and invasive management of PAOD in these patients should follow local guidelines. Since there are no data indicating an elevated risk of PAOD in CML patients receiving imatinib, dasatinib or bosutinib, we at present do not recommend any specific modification of TKI therapy in patients developing PAOD on these TKI. In these patients PAOD should be exclusively managed according to local recommendations.

Management recommendations for emergent IHD and ICVE. In patients in whom IHD or ICVE occur while on any TKI, optimal care of the cardio- or cerebrovascular AE must be provided. Baseline and follow-up electrocardiogram (ECG) and baseline echocardiography are advised, and a switch to an alternative TKI may be considered if the presently administered TKI is suspected as causal.

Cardiological adverse events

Cardiac function. Despite an initial report of *in vitro* imatinib-induced damage to cardiac myocytes,[59] several clinical studies covering several thousand patients have been unable to demonstrate an excess incidence of cardiomyopathy in TKI recipients with either CML or gastrointestinal stromal tumours (GIST) which are also amenable to TKI treatment. Clinical trials are listed in Table 2.[60–68] So far, clinical studies with nilotinib and dasatinib also do not reveal direct cardiotoxic effects.[3,37,60,69,70] Ponatinib has a black box warning because of an 8% reported incidence of heart failure.

Cardiac rhythm alterations. A summary of the effect of TKIs on QT interval was published in 2013.[70] TKIs have the potential to prolong the QT interval of the ECG, through inhibition of the hERG subunit of the potassium channel, although *in vivo* effects have been predominantly reported with imatinib and nilotinib.[71] The exception seems to be ponatinib, which inhibited hERG at concentrations above 1 μM, substantially in excess of the steady-state maximal concentrations observed in patients treated at the clinical dose of 45 mg.[72] An update of data of TKIs within clinical studies[73–76] is given in Table 3. The results of a QT study in healthy

Table 1. Arterial problems in patients treated with TKIs

Reference Study *design*	N	*Treatment*	*Follow-up*	*Cardiovascular event*	*IHD*	*ICVE*	*PAOD*	*Other*	*Median time to event (range)*
Aichberger *et al.*[53] retrospective cohort analysis (single centre)	24	Nilotinib	24 months	6 (25%)	1 (4%)	NR	4 (16.7%)	1 (4%)	11 (10–39) months
Tefferi *et al.*[38] case report	2	Nilotinib	NR	NR	NR	NR	2	NR	NR
le Coutre *et al.*[39] retrospective cohort analysis (multicentric)	179	Nilotinib	NR	NR	NR	NR	11 (6.2%)	NR	26 (4–53) months
Quintas-Cardama *et al.*[40] retrospective cohort analysis (single centre)	233	Nilotinib	NR	NR	NR	1 (0.4%)	3 (1.3%)	1 (0.4%)	NR
Labussiere-Wallet *et al.*[41] prospective cohort screening (single centre)	54	Nilotinib	NR	NR	1 (1.9%)	2 (3.7%)	4 (7.4%)	NR	31 (7–53) months
Giles *et al.*[32] retrospective cohort analysis (multicentric, pooled trials)	556	Nilotinib	NR	NR	NR	NR	7 (1.2%)	NR	NR
	1301	Imatinib	NR	NR	NR	NR	2 (0.2%)	NR	NR
	533	Interferon	NR	NR	NR	NR	3 (0.6%)	NR	NR
Kim *et al.*[33] retrospective cohort analysis (multicentric)/prospective cohort screening (single centre)	66	Nilotinib	NR	NR	NR	NR	7 (10.6%)	NR	40 (21–56) months
	54	Imatinib	NR	NR	NR	NR	1 (1.9%)	NR	NR
Levato *et al.*[42] retrospective cohort analysis (single centre)	27	Nilotinib	NR	NR	1 (3.7%)	1 (3.7%)	2 (7.4%)	NR	24 (7–34) months
Giles *et al.* (ENEST1st)[43] prospective phase IIIb (multicentric)	819	Nilotinib	NR	NR	31 (3.8%)	4 (0.5%)	13 (1.6%)	NR	NR
Jeon *et al.*[44] prospective cohort screening (single centre)	88	Nilotinib	NR	NR	NR	NR	3 (3.4%)	NR	NR
le Coutre *et al.*[45] retrospective cohort analysis (multicentric, pooled trials)	2705	Dasatinib	NR	NR	NR	NR	6 (0.2%)	NR	20 (2–53) months
Cortes *et al.* (PACE)[23] prospective phase II (multicentric)	449	Ponatinib	3 years	99 (22%)	52 (12%)	37 (8%)	37 (8%)	NR	NR
Larson *et al.* (ENESTnd)[46] prospective phase III (multicentric)	279	Nilotinib 300 mg BID	72 months	28 (10%)	14 (5%)	4 (1.4%)	12 (4.3%)	4 (1.4%)	30 (6–78) months
	277	Nilotinib 400 mg BID		44 (15.9%)	18 (10.1%)	9 (3.2%)	9 (3.2%)	3 (1.1%)	36 (6–90) months
	280	Imatinib 400 mg QD		7 (2.5%)	6 (2.1%)	1 (0.4%)	0	0	42 (6–78) months
Gugliotta *et al.* (GIMEMA)[47] prospective phase II (multicentric)	215	Nilotinib	57 months	13 (6%)	3 (1.4%)	NR	4 (1.9%)	NR	37 months
Gora-Tybor *et al.*[54] retrospective cohort analysis (multicentric)	50	Dasatinib	28 months	2 (4%)	1 (2%)	1 (2%)	0	0	20 (19–22) months
	55	Nilotinib		6 (11%)	2 (3.6%)	1 (1.8%)	1 (1.8%)	2 (3.6%)	15 (6–69) months
Hadzijusufovic *et al.*[48] retrospective cohort analysis (single centre)	36	Nilotinib	44 months	NR	NR	NR	16 (44.4%)	NR	NR
Fossard *et al.*[49] prospective cohort analysis (multicentric)	114	Nilotinib	NR	21 (18.5%)	NR	NR	NR	NR	47 (8–82) months
Gilbert *et al.*[50] retrospective cohort analysis (single centre)	183	Nilotinib	NR	20 (10.9%)	9 (5%)	4 (2%)	7 (4%)	NR	NR
Rea *et al.*[51] retrospective cohort analysis (single centre)	57	Nilotinib	47 months	13 (23%)	3 (5%)	2 (4%)	8 (14%)	NR	28 (9–50) months
Cortes *et al.* (DASISION)[52] prospective phase III (multicentric)	259	Dasatinib	60 months	12 (5%)	10 (3.9%)	2 (0.7%)	0	NR	NR
Hochhaus *et al.*[36] prospective cohort analysis (multicentric)	1089	Nilotinib 600	24 months	65 (6%)	37 (3.4%)	9 (0.8%)	21 (1.9%)	NR	NR
Hochhaus *et al.*[37] prospective cohort analysis (multicentric)	279	Nilotinib 600	60 months	21 (7.5%)	11 (3.9%)	4 (1.4%)	7 (2.5%)	NR	NR
Hochhaus *et al.*[37] prospective cohort analysis (multicentric)	277	Nilotinib 800	60 months	37 (13.4%)	24 (8.7%)	9 (3.2%)	7 (2.5%)	NR	NR
Hochhaus *et al.*[37] prospective cohort analysis (multicentric)	280	Imatinib 400	60 months	6 (2.1%)	5 (1.8%)	1 (0.4%)	0	NR	NR

Abbreviations: IHD, ischaemic heart disease; ICVE, ischaemic cerebrovascular event; PAOD, peripheral arterial occlusive disease; NR, not reported.

Table 2. Cardiac adverse events in CML patients treated with TKIs

CML	*Study design*	*Method*	*Result*	*Conclusion*
Rosti *et al.*[60]	Retrospective; 833 patients 296 patients in late CP (LCP) and 537 patients in early CP (ECP) 400 mg or 800 mg imatinib; median FU 64 (LCP) and 18 months (ECP)	Estimation of cardiac deaths and cardiac severe adverse events (SAEs)	77 Deaths have been recorded, 68 in the group of 296 LCP patients (22.9%) and 9 in the group of 537 ECP patients (1.6%). Three were recorded and confirmed	Overall cardiac mortality rate of 0.3%
Atallah *et al.*[61]	Retrospective 1276 patients, median FU 5 years	Eligibility criteria excluded patients with cardiac problems (for example, patients with classes III and IV according to the NYHAC); routine examinations	22 Patients (1.8%) having symptoms attributed to CHF. 18 Patients had previous medical conditions predisposing them to cardiac disease	CHF in connection with imatinib use was reasonably unambiguous in only 7 of the 1276 patients reviewed (0.5%)
Hatfield *et al.*[62]	Retrospective Novartis clinical database of six trials, 2,327 patients including advanced CML ($n = 553$), and CML in CP ($n = 1442$), GIST ($n = 147$), or a variety of rare malignant diseases ($n = 185$)	Adverse events and serious adverse events were recorded by investigators in all trials	12 Cases of CHF (0.5%) were considered as incident cases (with no previous history of CHF or left ventricular dysfunction)	Incidence of CHF is 0.2% per year across all trials
Gambacorti-Passerini *et al.*[63]	Retrospective 103 patients, median age 51, median FU 48 months	Annual electrocardiogram and echocardiographic examinations	3 Deaths non-CML-related, 2 sudden deaths. No case of CHF developed	No significant drop in mean ejection fraction values
Estabragh *et al.*[64]	Prospective evaluation; 59 CML patients median FU 3.4 years	Echocardiography and MUGA scanning		No evidence of myocardial deterioration
Marcolino *et al.*[68]	Retrospective 90 CML patients for a median FU of 3.3 years	Clinical evaluation, electrocardiography, echocardiography, brain natriuretic peptide (BNP) and troponin I measurements	Mean ejection fraction 68%, Median BNP level 9.6 pg/ml. 2 Patients with either an elevated BNP or a depressed ejection fraction	Imatinib-related cardiotoxicity is an uncommon event even during long-term treatment
Marcolino *et al.*[66]	Prospective; 12 CML patients	Electrocardiographic abnormalities, echocardiographic measurements and BNP levels	Median ejection fraction at baseline 67% vs 68% under FU (median intra-patient change 0.5%). Median BNP levels were 8.3 vs 7.3 pg	It is probably safe to perform cardiac monitoring on an annual basis
Atallah *et al.*[67]	Retrospective 1276 patients enroled, median age 70 years Median time on imatinib 162 days	Review of all reported serious adverse events of cardiac adverse events	22 (1.7%) were identified as having symptoms that could be attributed to systolic heart failure, 8 (0.6%) were considered possibly or probably related to imatinib	Imatinib therapy as a causal factor of CHF is uncommon
Ribeiro *et al.*[65]	Prospective, 103 CML on imatinib and 57 MPN not treated with imatinib	BNP levels and echocardiographic measurements for imatinib and control groups	4 Patients in the imatinib group presented a BNP level > 100 pg/ml, one of them with depressed LVEF	No statistical difference

Abbreviations: BNP, brain natriuretic peptide; CHF, congestive heart failure; ECP, early chronic phase; FU, follow-up; LCP, late chronic phase; MUGA, multigated acquisition scan; NYHAC, New York Heart Association Criteria.

Table 3. Data for QTc prolongation for TKIs

TKI	*Studies*	*Increase of QT interval*	*Result absolute value*	*Conclusion*
Imatinib	ENESTnd imatinib 400 mg ($n=280$)[3]		>480 ms: 0.7% >500 ms: 0.4%	Symptomatic prolongation in 2.5%
Nilotinib	2101 CP and AP[a]	>30 ms: 29.4% >60 ms: 1.3%	>450 ms: 10.2% >480 ms: 1.1% >500 ms: 0.5%	No episode of torsade de pointes
Nilotinib	ENESTnd, nilotinib 300 mg ($n=279$)[3]		>480 or 500 ms: 0%	Symptomatic prolongation in 1.8%
Bosutinib	Healthy adult subjects[73] and BELA trial[74]	No subjects had change from baseline >30 ms	No subjects had QTcB, QTcF, QTcI or QTcN >450 ms.	No clinically relevant PK/PD relationship was observed between bosutinib concentrations and QTc BELA: no data provided
Ponatinib	Phase 1 trial, AP24534-07-101[75]	On 30 mg dosage: decrease of QT On 45 mg dosages: Increase of 3.3 ms		Low risk of QT prolongation
Dasatinib	2440 patients[a,76]	Maximum mean Changes in QTcF (90% upper bound CI) from baseline ranged from 7.0 to 13.4 ms.	>500 ms: 1%	

Abbreviations: AP, accelerated phase; CP, chronic phase. [a]Information taken from investigator brochure.

volunteers have demonstrated a relationship between nilotinib serum concentration and QTcF interval prolongation. Up to now no torsade de point cases were reported with nilotinib but some sudden deaths occurred within clinical trials potentially associated to this effect, and this led to a transient box warning in the United States.

Prevention of cardiac problems

Cardiac function monitoring: Currently, there is no need to monitor heart function during imatinib therapy. For dasatinib, nilotinib and bosutinib, caution is necessary, as reports on cardiac toxicity may arise. Echocardiography has a low power for detecting subclinical toxicity, but brain natriuretic peptide has excellent negative predictive value for left ventricular dysfunction and a normal value can be informative in clinical practice.[77] Monitoring of cardiac function is mandatory for ponatinib (see above).

ECG monitoring: It is sensible to recommend an ECG before initiating any TKI therapy, because most of the TKIs affect the QT interval, and there is a high individual variability of changes in QTc. In case of QTc prolongation of >440 ms or when ponatinib is used, frequent monitoring is recommended, and this should be sustained at 3–6 monthly intervals if there is a prolongation of >30 ms from baseline. In the case of prolongation of >50 ms from baseline or QTc >500 ms, treatment cessation and cardiological advice are recommended. As concomitant administration of strong CYP3A4 inhibitors significantly increases the serum concentration of TKIs, appropriate management of concomitant medications is essential.

Nilotinib should be avoided in the long QT syndrome, or where there are concomitant drugs that prolong the QT interval. Hypokalaemia or hypomagnesaemia should be corrected prior to nilotinib use and these electrolytes should be monitored periodically. An ECG should be obtained to monitor QTc at baseline, then 7 days after start, after dose increase and periodically. Food should be avoided 2 h before and 1 h after dosing. Nilotinib should not be given to patients with risk of arrhythmias.

Management of cardiac adverse events

Management of rhythm disturbances and QTc prolongation: The development of arrhythmias should prompt the interruption of the TKI and consultation with a cardiologist. In the case of nilotinib, it must be stopped permanently.

Emergent QTc prolongation should prompt a review of potential TKI interactions and measurement of electrolytes. In the case of QTc >440 ms or prolongation of >30 ms from baseline, strict monitoring is recommended (at least weekly). In the case of QTc >500 ms or prolongation of >50 ms from baseline, temporary treatment cessation is recommended, followed by weekly ECG and TKI resumption when QTc ⩽450 ms in two consecutive ECGs. In the case of nilotinib treatment, resumption at a lower dose is recommended once the QTc falls in this way, without subsequent re-escalation.

Other cardiac problems and hypertension: Other cardiac problems should be managed following the aforementioned general rules of non-haematological toxicity. Peripheral oedema could be a sign of cardiac dysfunction, and treatment must be aetiologically based. However, in most cases fluid retention is not associated with cardiac dysfunction, and is normally manageable and reversible with diuretics. Arterial hypertension must be actively treated, especially in recipients of ponatinib, which has been associated with hypertension in 9% of recipients by 12 months, being severe in 2%. In all cases, early detection and management of hypertension according to local/national guidelines is important.

Pulmonary adverse problems

Pleural effusion

Incidence and severity: The risk of effusions exists with all the TKIs currently approved for first-line CML treatment (imatinib, dasatinib and nilotinib), but is much higher with dasatinib. Common symptoms of effusions include significant dry cough, fatigue, chest pain and dyspnoea[78,79] With imatinib treatment very few cases have been reported, usually associated with pericardial effusions or associated with advanced phases and doses of imatinib above 400 mg daily.[80] The risk of pleural effusion with nilotinib in first line is also very low.[3] With dasatinib, in patients resistant to imatinib, the incidence of reported pleural effusions ranges from 14 to 39%, higher in more advanced phases.[81–84] The frequency appears to be related to the dose, both in advanced phase[85,86] and in chronic phase.[87] In the DASISION trial, at 5 years of follow-up the incidence was 28% as compared with <1% with imatinib.[69] The risk of appearance of pleural

effusion in dasatinib treated patients does not seem to decrease with time.[88] Besides, recurrence of pleural effusion occurs in roughly 70% of the cases. However, most of the pleural effusions are mild or moderate, with grade 3/4 reported in 4%[19] and low rates of dasatinib discontinuation due to this side effect during the first year.[83] In patients treated with bosutinib in second line, pleural effusions were detected in 4% by 2 years.[21]

Kinetics: Pleural effusion needs long-term attention. In second-line treatment with dasatinib, the median time to appearance is 5–11 months,[89,90] but it can be delayed until 3 years.[91] In first-line use, the median time to pleural effusion was 10 months, and most effusions (89%) occurred more than 8 weeks into treatment;[88] although the risk diminishes with time, pleural effusion can occur throughout treatment.[35]

Predisposing conditions: In second-line use, previous or concomitant cardiac disease and hypertension seem to be the most common predisposing conditions.[78,79] Also, twice daily scheduling,[78] advanced phases, hypercholesterolaemia, a previous history of auto-immune disorders and skin rashes experienced during imatinib therapy have been identified as risk factors.[79] Older age is also associated with pleural effusion,[89] and in patients older than 60 years, the presence of concomitant pulmonary disease, the initial daily dose of dasatinib (140 mg vs 100 mg),[90] and a higher comorbidity index[92] were associated with pleural effusion. As well as knowing the situations that increase the risk of pleural effusion, patients and doctors must be vigilant in the presence of cough, dyspnoea or chest pain, and these symptoms should prompt a chest X-ray.

Management of pleural effusions: Management of dasatinib-related pleural effusions includes treatment suspension or reduction of the dose, with or without steroids and diuretics. In rare instances, usually of grade 3–4, more invasive measures such as thoracocentesis are necessary to resolve the effusion.[19,78,89] Pleural effusions are potentially reversible after discontinuation of dasatinib and the administration of steroids and diuretics. They can also be recurrent. Whereas after resolution of the first episode, the drug could be resumed at the same dose, in the case of a second episode it is advisable to reduce the dose to the next lower level (for example, 80 mg from 100 mg/day). In the case of further relapses, either stepwise lowering the dose down to 50 mg/day or switching to another TKI are reasonable options. If the relapse is symptomatic, even if during the first occurrence of an effusion, switching is the preferred option. A regimen of 5 days on, 2 days off is under investigation.[93]

Pleural effusions emerging on second-line bosutinib therapy may also occur; a similar management approach to that taken with dasatinib seems to be reasonable.

Pulmonary arterial hypertension

Incidence and severity: Pulmonary arterial hypertension (PAH) has been reported with the use of dasatinib[94–97] at an estimated incidence of 0.45% and a median delay between drug initiation and PAH diagnosis of 34 months (range 8–48 months). At PAH diagnosis, most patients had severe clinical, functional and haemodynamic signs of failure, some of them requiring vasoactive drugs and management in the intensive care unit.[97] Clinical and functional improvements were usually observed after discontinuing dasatinib; however, the majority of patients failed to demonstrate complete haemodynamic recovery and two patients died at follow-up.[97]

Prevention and management: The presence of dyspnoea and syncope not explained by pleural effusion should prompt the suspicion of PAH. Although rare, it is potentially fatal. Prompt withdrawal of dasatinib may totally or partially reverse PAH, but pharmacologic treatment may be needed,[94,95] and referral to a suitable specialist is mandatory.

Pneumonitis. Pneumonitis is a quite rare complication, and it has been described mostly with imatinib[98,99] and in Asian countries. It can be reversible[100] or not.[101] Both hypersensitivity pneumonitis[102] and eosinophilic types have been described. In second-line therapy with dasatinib 70 mg twice daily, 17% developed lung parenchyma changes with either ground glass or alveolar opacities or septal thickening.[103] The treatment for imatinib-induced pneumonitis is to discontinue the medication and administer glucocorticoids. Although there are a few cases of successful retrial with imatinib,[101] switching to nilotinib or bosutinib are the preferred options if the pneumonitis is not mild.

Hepatobiliary AEs

A comprehensive meta-analysis of 12 published studies suggested that there is a significant overall increase in the odds of developing high-grade (grade 3 or above) hepatotoxicity with the use of TKIs in cancer compared with the control arms.[104] In pre-approval clinical trials of TKIs, hepatotoxicity manifested itself as low-grade increases in serum alanine (ALT) and/or aspartate transaminases (AST) in 25–35% of patients and as high-grade (grade 3 or above) increases in these transaminases in ~2%. As shown in Tables 4, 5a and b, the incidences of both all-grade and high-grade transaminase increases vary widely between agents and the potential for serious hepatotoxicity with ponatinib is believed to be sufficiently high as to require a boxed label warning[1,2,5,21,22,46,105–107]

Table 4 presents a summary of kinetics in principal (registration) clinical trials of hepatotoxicity. In the majority of cases, the time to onset of increased ALT and AST is 2–8 weeks after initiating therapy. Exceptionally, however, it may be delayed as in a few cases following treatment with imatinib. The median time to onset of ALT or AST elevation following ponatinib was 46 days (range 1–334 days).[108]

There have been few reports of hepatic failure with some TKIs and in general, fatalities from TKI-induced hepatotoxicity are rare, reported so far with imatinib and ponatinib. In most patients, lesions showed necrotic hepatitis associated with a non-specific inflammatory infiltrate; patients with fulminant hepatitis had a massive viral hepatitis-like necrosis compatible with an inflammatory idiosyncratic mechanism.[109–115]

Hyperbilirubinaemia is the most frequent laboratory AE observed with nilotinib, but in most cases does not represent true hepatotoxicity. Pharmacogenetic analysis demonstrated that genotypic differences may account for an increased risk of hyperbilirubinaemia in some nilotinib-treated patients.[116]

Prevention. Imatinib is metabolised by cytochrome P450, especially CYP3A4 and (where functional) CYP3A5. Therefore, an increase in toxic metabolites may occur where there is concomitant use of enzymatic inducers like alcohol[117] or therapeutic agents such as roxythromycin.[114] Nilotinib and to a lesser extent other TKIs have the potential to inhibit UDP glucuronosyltransferase A1 (UGT1A1) and this may contribute to TKI-related unconjugated hyperbilirubinaemia. This must be taken into account in patients with Gilbert's syndrome, in whom this bilirubin transporter is congenitally impaired. When acetaminophen (paracetamol) glucuronidation is impaired, the risk of acetaminophen hepatotoxicity is higher. Caution is also advised when using imatinib and acetaminophen concomitantly.[118]

Management. Management of TKI-induced hepatotoxicity should be in line with general principles. In the case of grade 3 toxicity, we prefer to withhold therapy until grade <2, and then

Table 4. Liver toxicity (Shah *et al.*, modified)[108]

Drug	*Major indication*	*Incidence of ALAT/ASAT elevations (%)*[a]		*Latency to onset of hepatic injury*	*Cases of hepatitis or hepatic failure*	*Fatal cases of hepatic failure*
		All grade	*Grade 3-4*			
Imatinib	CML ALL HS GIST	6–12	3–6	Median 12–77 days	Yes	Yes
Dasatinib	CML ALL	50	1–9	No information	No	No
Nilotinib	CML	35–62	1–4	No information	Yes	No
Bosutinib	CML	20	4–9	Median 30-33 days	Yes	No
Ponatinib	CML ALL	56	8	Within 1 week	Yes	Yes

Abbreviations: ALAT, alanine aminotransferase; ALL, acute lymphoblastic leukaemia; ASAT, aspartate aminotransferase; CML, chronic myeloid leukaemia; GIST, Gastointestinal stromal tumours; HS, Hypereosinophilic syndrome. Side effects, grading according to NCI-CTC (Common Terminology Criteria for Adverse Events of the National Cancer Institute). [a]Values shown are best estimates computed from pre-approval of European Union Medicines Agency. European public assessment reports assessment history and product information (http://www.emea.europa.eu/ema/index.jsp?curl = pages/medicines/landing/epar_searc.jsp&mid = WC0b01ac058001d124) and US Food and Drug Administration. Product reviews and labels (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). Regulatory reviews and labels of the TKI concerned from data across a number of trials and indications when appropriate.

resume at a lower dose, or to switch to another TKI. In the face of grade 4 toxicity, switching to another TKI is mandatory.

After discontinuation of imatinib for hepatotoxicity, liver function typically resolves fully with normalisation of liver tests in 7 weeks (range 2 – 20 weeks). However, fatal liver injury has occurred in some patients, especially in those treated by acetaminophen or with hepatitis B virus infection. In several published cases, early administration of glucocorticoid therapy (prednisone or methyl-prednisolone) resulted in rapid and complete hepatic recovery[119] and in a few case reports they have enabled the re-introduction of imatinib in patients who develop recurrent hepatotoxicity, usually at reduced doses. Steroids used in these case reports included oral prednisone 25–30 mg daily tapered over 5–8 months. In potentially fatal hepatic cases liver transplantation has been needed.[120]

Cross-intolerance. Available data on cross-intolerance of hepatotoxicity to other TKI are scarce. In patients treated previously with imatinib, with grades 3–4 or persistent grade 2 liver toxicity, none developed this degree of liver toxicity with subsequent nilotinib therapy.[109,121] Nilotinib was used without liver toxicity in a patient undergoing liver transplantation for fulminant liver failure associated with imatinib.[120] Dasatinib has been safely used after a patient receiving imatinib and developing liver toxicity was successfully treated with glucocorticoids.[122]

Endocrine and metabolic abnormalities

Hyperglycaemia and glucose metabolism

Incidence and severity: In patients resistant or intolerant to imatinib and treated with nilotinib, grade 3–4 hyperglycaemia has been reported in 12% of chronic phase and 6.7% of accelerated phase CML patients enroled in phase II studies.[123,124] In the ENACT trial, hyperglycaemia occurred after 7 days from start of nilotinib, with a median duration of 21 days.[125] In first-line treatment, randomised studies have shown that the incidence of grade 3–4 hyperglycaemia with nilotinib is about 6, vs 0% with imatinib.[3] In diabetic patients treated with nilotinib, 31% changed antidiabetic treatment and 60% developed grade 3–4 hyperglycaemia, but none developed ketoacidosis, hyperosmolar events or cardiovascular complications.[126] In normoglycaemic patients, excluding patients with diabetes at baseline, 20.1% developed diabetes by 3 years vs 8.9% with imatinib. In the whole series of patients, none had discontinued due to this side effect and $< 2\%$ were started with antidiabetic drugs.[127] In contrast, dasatinib has been shown to reduce fasting glucose.[128,129]

Prevention of glucose alterations: Hyperglycaemia during nilotinib therapy is frequently observed in the first 2–3 weeks of administration and also the hypoglycaemic effect of dasatinib has been described as an early event.[123–129] Diabetic patients receiving TKIs may need their diabetes monitored more frequently in case their antidiabetic treatment needs adjustment. Patients with type II controlled diabetes or pre-diabetes may receive nilotinib or other available TKIs but with strict monitoring of fasting glucose and glycosylated haemoglobin and review of therapy by an appropriate specialist. In the case of persistent fasting glucose level higher than 126 mg/dl (7.0 mmol/l) or a glycosylated haemoglobin level higher than 6.5%, a temporary reduction or discontinuation and specialist referral are recommended.

Management of diabetes mellitus: General recommendations apply to the treatment of diabetes emergent during TKI, with special attention when the patient is receiving nilotinib. It is worth noting that diabetic patients treated with nilotinib as first line developed hyperglycaemia almost constantly, half of them of grade 3–4, but no major complications related to diabetes (for example, hyperosmolar coma, ketoacidosis, hospitalisation) were detected, and 74% of patients did not change antidiabetic treatment. Though follow-up was short, none of the patients developed a cardiovascular complication.[126]

Effects on lipid metabolism

Incidence and severity: In the ENESTnd trial of first line therapy,[130] nilotinib is associated with hypercholesterolaemia in 22% of patients, compared with 3% of imatinib recipients; indeed, imatinib may reduce the total level of cholesterol and tryglycerides.[131–133] There were no cases of hypercholesterolaemia grade 3–4 in either arm.[130] In a recent small study, the median increase of LDL-cholesterol after nilotinib treatment was 33 mg/dl at 3 months. The median decrease of triglycerides was of the same magnitude in the same period.[134] In phase I trial of ponatinib in

Table 5a. Liver toxicity of TKI used as first-line therapy (imatinib, nilotinib, bosutinib and dasatinib)

Source	*IRIS*					
TKI, dosage (*n*)	Imatinib 400 mg QD (*N* = 553)					
Median duration, months	At 18 months[1]		Year 1–2	Year 3–4	>4 Years	By 5 years[46]
AE Grade	All grades		Grade 3/4	Grade ¾	Grade 3/4	Grade 3/4
Elevated ALT	43.2%		5.1%	5%	< 1%	0%
Elevated AST						5%

Source	*ENESTnd*[2]				*BELA*[22]				*DASISION*[5]			
TKI, dosage (*n*)	Nilotinib 300 mg twice daily (*n* = 279)		Nilotinib 400 mg twice daily (*n* = 277)		Imatinib 400 mg daily (*n* = 280)		Bosutinib 500 mg daily (*n* = 248)		Imatinib 400 mg daily (*n* = 251)		Dasatinib 100 mg daily (*n* = 258)		Imatinib 400 mg daily (*n* = 258)	
Median duration, months	14		14				14				24			
AE grade	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grade	Grade 3/4	All grades	Grade 3/4
Elevated ALAT	66%	4%	73%	9%	20%	2%	69%	22%	29%	3%	—	0.5%	—	2%
Elevated ASAT	40%	1%	48%	3%	23%	1%	56%	11%	27%	3%	—	0.5%	—	1%
Elevated total Bilirubin	53%	4%	62%	8%	10%	< 1%	—	—	—	—	—	—	—	—

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase. Side effects, grading according to NCI-CTC (Common Terminology Criteria for Adverse Events of the National Cancer Institute).

resistant disease, hypertriglyceridaemia was reported in 12% of patients at all grades, but none of the patients experienced a grade 3/4 event.[135] No evidence of impaired lipid metabolism with dasatinib or bosutinib have been reported up to now.

Prevention and management: An increased cholesterol level with nilotinib has been reported as an early effect,[134] and has been associated with PAOD.[53,134,136] It is therefore suggested to test the lipid profile at baseline and during the course of treatment, and in the event of persistent hypercholesterolaemia (higher than 240 mg/dl (6.2 mmol/l), considered high risk according to American Association of Clinical Endocrinologists (AACE) guidelines), to add an appropriate statin in line with regional/national guidelines.

Phosphate and calcium metabolism

Incidence and severity: Hypophosphataemia was first described with imatinib, with an early onset in younger patients treated with higher doses.[137] As a consequence of hypophosphataemia, a reduced serum calcium level and increased renal phosphate excretion with increased serum levels of parathyroid hormone have been reported.[138] In the long-term, 50% of adults developed decreased bone mineral density.[139] In the first-line trials ENESTnd and DASISION, hypophosphataemia (mostly mild) was seen in 49% and 25% of patients treated with imatinib, respectively, and in 33% and 7% of those treated with nilotinib or dasatinib.[2,5,130] Hypocalcaemia is less common than hypophosphataemia.

Prevention and management: The serum phosphate and calcium level should be tested before and during treatment with imatinib and nilotinib every month for the first 3 months and then every 3–6 months thereafter. Prompt correction of hypophosphataemia and hypocalcaemia may be necessary if clinically indicated. Hypovitaminosis D must be corrected. Long-standing hypophosphataemia and hyperparathyroidism are indications for bone densitometry.[139]

Other endocrine abnormalities. In patients treated with imatinib, nilotinib and dasatinib, thyroid abnormalities were detected in 25%, 55% and 70% of patients, respectively.[140] Hypothyroidism is more common than hyperactivity, and it responds to hormone supplementation.[140] Gynaecomastia has been reported in 6% patients with imatinib, mostly associated with diminution of testosterone levels[141] and dasatinib.[142]

Haematological adverse events: myelosuppression

General comments. Myelosuppression developing during TKI treatment of CML is very common. It is due to the combined effect of the suppression of the leukaemic clone and the inhibition of non-leukaemic haematopoiesis, which is greatly reduced at CML diagnosis.[143] After TKI-induced reduction of leukaemic haematopoiesis, normal stem and progenitor cells need time to recover from pre-existing suppression by the malignant clone and to re-populate the bone marrow.

This interpretation is supported by several observations: first, myelosuppression is almost always limited to the first weeks or months of treatment. Second, the incidence of grade 3 or 4 myelosuppression is predominant at the initiation of treatment and decreases substantially with longer exposures to any TKI. Third, haematological side effects of TKIs are (mostly) dose-dependent, reversible on treatment cessation or dose reduction, and affect all three lineages to a variable degree.[15,16,144,145] Thus, myelosuppression is an expression of efficacy rather than a true toxicity, and it is rare once a remission has been achieved.

Nevertheless, haematological toxicity is important because it is the major cause of treatment discontinuation/interruption and

dose reduction, since a patient with chronic phase CML cannot be put at risk of dying from infection or bleeding[144–147] Thus, the management of cytopenias lies mainly in tight monitoring of blood counts.

Incidence of myelosuppression

Limitations of this analysis: Many papers have reported the haematological toxicity of TKIs, in different disease phases (chronic phase or advanced disease), in different lines of therapy and at

Table 5b. Liver toxicity of TKI used in CML as second-line therapy

Source	*CAMN107A2101*[105]		*CA180034*[106]		*3160A4-200-WW*[21]		*3160A4-200-WW*[107]	
TKI dosage (*n*)	Nilotinib 400 mg twice daily (*n* = 321)		Dasatinib100 mg daily (*n* = 165)		Bosutinib 500 mg daily (*n* = 286)		Bosutinib 500 mg daily (*n* = 118)	
Median duration, months	24		22		25		9	
Treatment line	Second line		Second line		Second line		Third/fourth line	
AE grade	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Elevated ALAT	69%	4%	—	—	22%	9%	15%	6%
Elevated ASAT	55%	3%	—	—	19%	4%	8%	3%
Elevated total Bilirubin	72%	7%	—	—	—	—	—	—

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase. Side effects, grading according to NCI-CTC (Common Terminology Criteria for Adverse Events of the National Cancer Institute).

Table 6. Myelosuppression in CML patients treated with TKIs

Reference	*Treatment*	*Toxicity*	*Number of patients*	*Number of patients (%) with grade 3/4 toxicity*
1,2,4,6,22,155–157,159	First line, imatinib 400 mg daily	Anaemia	2232	109 (4.9%)
		Thrombocytopenia	2232	227 (10.2%)
		Neutropenia	1911	330 (17.3%)
6,148,151,154,157	First line, imatinib 400 mg twice daily	Anaemia	946	59 (6.2%)
		Thrombocytopenia	946	152 (16.1%)
		Neutropenia	442	152 (34.4%)
2,159	First line, nilotinib 300 mg twice daily	Anaemia	412	14 (3.4%)
		Thrombocytopenia	412	62 (15.0%)
		Neutropenia	412	61 (14.8%
2,159	First line, nilotinib 400 mg twice daily	Anaemia	413	12 (2.9%)
		Thrombocytopenia	413	42 (10.2%)
		Neutropenia	413	38 (9.2%)
4,156,158	First line, dasatinib, 100 mg daily	Anaemia	442	51 (11.5%)
		Thrombocytopenia	442	77 (17.4%)
		Neutropenia	442	86 (19.4%)
22	First line, bosutinib 500 mg daily	Anaemia	248	15 (6.0%)
		Thrombocytopenia	248	35 (14.1%)
		Neutropenia	248	27 (10.8%)
105,124,149	Second line, nilotinib 400 mg twice daily	Anaemia	321	35 (10.9%)
		Thrombocytopenia	1743	409 (23.5%)
		Neutropenia	1743	299 (17.2%)
87	Second line dasatinib 100 mg daily	Anaemia	166	16 (9.6%)
		Thrombocytopenia	166	37 (22.3%)
		Neutropenia	166	55 (33.1%)
84,87,150	Second line, dasatinib 70 mg twice daily or 140 mg daily	Anaemia	717	138 (19.2%)
		Thrombocytopenia	818	386 (47.2%)
		Neutropenia	818	376 (45.8%)
29	Second line, bosutinib 500 mg daily	Anaemia	288	40 (13.9%)
		Thrombocytopenia	288	69 (23.9%)
		Neutropenia	288	49 (17.0%)
107	Third line, bosutinib 500 mg daily	Anaemia	118	9 (7.6%)
		Thrombocytopenia	118	30 (25.4%)
		Neutropenia	118	22 (18.6%)
23	Third line, ponatinib 45 mg daily	Anaemia	270	16 (5.9%)
		Thrombocytopenia	270	86 (31.8%)
		Neutropenia	270	38 (17.8%)

Side effects, grading according to NCI-CTC (Common Terminology Criteria for Adverse Events of the National Cancer Institute).

Table 7. Myelosuppression in the main randomized trials in first line

		Neutropenia		*Thrombocytopenia*		*Anemia*	
		All grades (%)	*Grade ¾ (%)*	*All grades (%)*	*Grade 3/4 (%)*	*All grades (%)*	*Grade 3/4 (%)*
ENESTND[2]	Nilotinib 300 mg twice daily	43	12	48	10	38	3
	Imatinib 400 mg daily	68	20	56	9	47	5
DASISION[4]	Dasatinib 100 mg daily	65	21	70	19	90	10
	Imatinib 400 mg daily	52	20	62	10	84	7
BELA[22]	Bosutinib 500 mg daily	28	11	66	14	80	6
	Imatinib 400 mg daily	54	24	62	14	84	7

Side effects, grading according to NCI-CTC (Common Terminology Criteria for Adverse Events of the National Cancer Institute).

different doses. In chronic phase, while there are first-line studies comparing imatinib with other TKIs, there are no comparison studies between individual 2G TKI. This also applies for studies in second and subsequent lines. In advanced phases, data are scarce, and myelosuppression, though more common in chronic phase, is difficult to interpret because it is very common in these phases *per se*.

Regrettably, haematologic toxicity has always been reported as a percentage of patients with grade 1/2 and with grade 3/4 toxicity, which is not very useful, since grade 1 is irrelevant, while sustained grade 2 can be more important than occasional grade 3. The reported incidence of all grades of toxicities varies over such a wide range, from 2 to 90%, thus data on the incidence of all grades of toxicities are difficult to interpret.

Available data: In chronic phase patients, data on haematologic toxicity are available in at least 20 company-sponsored and 10 investigator-sponsored studies, reporting on a total of 8417 patients.[1–6,11,19,20,22,23,29,84,87,105,124,148–159] There are variations of up to threefold in the reported incidence of grade 3/4 toxicities, so we have pooled together the data from different studies, in order to offer a comprehensive overview of haematologic toxicities (Table 6). Results of randomised trials in first line comparing imatinib with other TKIs are given in Table 7.

Myelosuppression of grade 3 or 4, leading to transient (rarely permanent) treatment discontinuation, was more frequent in patients with resistant disease, where the reservoir of normal haematopoietic progenitors may be diminished. Neutropenia is most frequent, followed by thrombocytopenia and anaemia. Clinical features associated with a greater risk of myelosuppression include an increased percentage of bone marrow blasts and a lower haemoglobin level. In second- and third-line therapy, the incidence of grade 3/4 anaemia ranged between 5.9% (ponatinib 45 mg daily) and 19.2% (dasatinib 70 mg twice daily or 140 mg once daily), that of grade 3/4 thrombocytopenia between 23.5% (nilotinib 400 mg twice daily) and 47.2% (dasatinib 70 mg twice daily or 140 mg once daily), and that of grade 3/4 neutropenia between 17.0% (bosutinib 500 mg once daily) and 45.8% (dasatinib 70 mg twice daily or 140 mg once daily).

In first-line therapy, we can conclude that imatinib 400 mg once daily induces more neutropenia than nilotinib (at either 300 or 400 mg each twice daily) or bosutinib 500 mg once daily, and slightly less than dasatinib 100 mg daily. A differential effect between TKIs on other lines is less clear, although imatinib appears to induce slightly less thrombocytopenia and anaemia than dasatinib. The data listed in Table 6 should be considered with caution and cannot be compared with a classic chi-squared test. However, it appears that dasatinib may have greater haematologic toxicity, and its toxicity is dose- and schedule-related, as also shown in prospective studies.[87]

Other variables associated with cytopenias: In contrast to observations in GIST, in chronic phase CML the haematological toxicity of imatinib is likely to be dose-related, and has been shown to be related to plasma drug concentration.[160] Interestingly, with nilotinib in first line, neutropenia is more frequent at a dose of 300 mg twice daily than at the higher dose of 400 mg twice daily, maybe because patients receiving 400 mg twice daily underwent dose reduction or discontinuation more frequently because of other AEs.[2,3] The haematologic toxicity of imatinib does not appear to be higher in patients aged more than 65 years.[161]

Kinetics of cytopenias: Haematological toxicity is almost always limited to the first weeks or months of treatment but late cytopenias have also been observed. In chronic phase patients, the peak incidence of myelosuppression is within the first 4–6 weeks after starting TKI treatment: the decline of platelets generally occurs 1–2 weeks later than the decline in neutrophil count. The incidence of grade 3 or 4 cytopenias is highest at the initiation of treatment and decreases substantially with longer exposures to any TKI.[15,16,144,145] In fact, the increment of the incidence of cytopenias beyond the first year of therapy is in the range of 1–2 percentage points, and this is valid for imatinib, nilotinib, dasatinib and bosutinib.[2–4,22,29,74,162]

Consequences of cytopenias. Haematologic toxicity may cause infection and bleeding, which can be fatal. The causes of death in chronic phase are not identified in all reports. Mortality figures for deaths due to sepsis/haemorrhage should be regarded as approximate, because some deaths may have occurred after progression, and also because in most studies the follow-up was short.

Infections: In first-line therapy, deaths due to infection after dasatinib or imatinib were 1.9% and 0.4%,[1,3,4,11,22,30,106] whereas they were 0% with nilotinib,[3,152,153] and bosutinib.[22] In second- and third-line therapy, deaths due to infection after dasatinib and nilotinib were reported in 1% and 0.07%, respectively.[105,124,149] In contrast no deaths due to infection were reported with bosutinib[23,29,107] or ponatinib.[23]

Dasatinib is more frequently associated with death from sepsis than other TKIs, and this is also true at 100 mg once daily.[4,5,87] It is worth noting that dasatinib inhibits proinflammatory functions of mature human neutrophils,[163] and all TKIs have a potential immunosuppressive effect (reviewed in refs 15,144,146,147).

Bleeding: In the IRIS study it was reported that the incidence of bleeding at any grade was 20%, both with imatinib and in the interferon plus ara-C arm. The incidence of severe bleeding was almost nil. In other first line studies, deaths due to bleeding after imatinib were 0.4%.[1,3,4,11,22,30,106] In contrast, there were no deaths

with dasatinib,[5] nilotinib,[3,152,153] or bosutinib.[22] In second line therapy, clinically relevant dasatinib-related bleeding has been associated with thrombocytopenia and advanced phases,[164] with an incidence of 25%, severe in 3%.[19] With bosutinib, the corresponding figures are 5 and 1%, respectively.[21] In the case of ponatinib, bleeding has been seen in 11%, and most bleeding episodes were not directly related to the drug.[165]

In second- and third-line treatment, deaths due to bleeding after dasatinib and nilotinib were reported in 0.9%,[87,106,150] and 0.8% of patients, respectively,[105,124,149] whereas it was 0.4% with bosutinib[23,29,107] and 0% with ponatinib.[23] It must be taken into account that dasatinib,[164,166,167] and to a lesser extent imatinib[167] and ponatinib,[168] induce platelet dysfunction.

Long-term effects: The long-term consequences of cytopenias are not well known. In patients previously treated with interferon, neutropenia developing during the first 3 months of TKI therapy was associated with lower progression-free survival.[169] Patients treated with imatinib who developed anaemia and other manifestations of myelosuppression were found to have a significantly worse outcome than those with isolated anaemia.[170]

Monitoring. In chronic phase, during the first 4–6 weeks, blood counts should be monitored weekly. Later and in absence of relevant (grade 2–4) cytopenias, the frequency can be reduced to every 2 weeks or monthly until month 3, depending on the stability of blood counts. After month 3, monitoring every 3 months is advised. More frequent monitoring is advised for patients with advanced disease, especially because the dose intensity is pivotal for optimal response.

Management of myelosuppression. A general principle in the management of TKI-induced myelosuppression is to balance the risks and the benefits according to the aggressiveness of CML. Moreover, the incidence of severe cytopenias varies depending on the TKI used. Consequently, recommendations for managing myelosuppression are slightly different for different TKIs in chronic phase vs advanced phases. Table 8 reports suggestions to manage severe cytopenias according to the prescribing information and study protocols.

Management in chronic phase: For all TKIs in chronic phase patients, in the case of grade 3 or 4 cytopenias, the drug must be withheld at the first episode. In the case of recurrence and depending on the duration of the first episode of cytopenia, the drug must be restarted at a lower dose, but once a stable response has been achieved, re-escalation to the target dose should be considered. With recurrent grade 3–4 cytopenias, especially in first-line chronic phase, switching to an alternative TKI

Table 8. Management of cytopenias

TKI	*Setting and starting dose*	*Hematopoietic toxicity*	*Dose adjustments for neutropenia and thrombocytopenia*
Imatinib	CP, 400 mg daily	ANC $<1.0\times10^9$/l and/or platelets $<50\times10^9$/l	(1) Stop imatinib until ANC $>1.5\times10^9$/l and platelets $>75\times10^9$/l > resume starting dose (2) Recurrence: repeat step 1 and resume at the reduced dose of 300 mg daily
	AP and BP, 600 mg daily	ANC $<0.5\times10^9$/l and/or platelets $<10\times10^9$/l	(1) Check if neutropenia is related to leukaemia (marrow aspiration or biopsy) (2) If UNRELATED, reduce imatinib to 400 mg daily (3) If cytopenia persists >2 weeks, reduce to 300 mg daily If cytopenia persists for >4 weeks and is still unrelated to leukaemia, stop imatinib until ANC $\geqslant1\times10^9$/l and platelets $\geqslant20\times10^9$/l and resume at 300 mg daily
Nilotinib	CP, frontline, 300 mg twice daily CP, second line, or AP, 400 mg twice daily	ANC $<1.0\times10^9$/l and/or platelets $<50\times10^9$/l	(1) Stop nilotinib until ANC $>1.0\times10^9$/l and platelets $>50\times10^9$/l > resume starting dose (2) If blood counts remain low for >2 weeks, resume at 400 mg daily
Dasatinib	CP, 100 mg daily	ANC $<0.5\times10^9$/l and/or platelets $<50\times10^9$/l	(1) Stop dasatinib until ANC $>1.0\times10^9$/l and platelets $>50\times10^9$/l > resume the original starting dose (2) If platelets $<25\times10^9$/l and/or recurrence of ANC $<0.5\times10^9$/l, repeat step 1 and resume dasatinib at a reduced dose of 80 mg once daily for the second episode. For third episode, further reduce to 50 mg daily (newly diagnosed patients) or discontinue dasatinib (for patients resistant or intolerant to prior therapy including imatinib)
Dasatinib	AP, BP and Ph+ ALL, 140 mg daily	ANC $<0.5\times10^9$/l and/or platelets $<10\times10^9$/l	(1) Check if neutropenia is related to leukaemia (marrow aspiration or biopsy) (2) If UNRELATED to leukaemia, stop dasatinib until ANC $\geqslant1.0\times10^9$/l and platelets $\geqslant20\times10^9$/l and resume the original dose (3) If recurrence of cytopenia, repeat step 1 and resume dasatinib at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode) (4) If cytopenia is related to leukaemia, consider dose escalation to 180 mg once daily
Bosutinib	CP, AP, BP CML, 500 mg daily	ANC $<1.0\times10^9$/l and/or platelets $<50\times10^9$/l	(1) Withhold bosutinib until ANC $\geqslant1.0\times10^9$/l and platelets $\geqslant50\times10^9$/l (2) Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for >2 weeks, reduce dose by 100 mg and resume treatment (3) If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment Doses <300 mg/day have not been evaluated
Ponatinib	CML, CP, AP and BP or Ph+ ALL, 45 mg daily	ANC $<1.0\times10^9$/l and/or platelets $<50\times10^9$/l	(1) First episode: stop ponatinib until ANC $>1.5\times10^9$/l and platelets $>75\times10^9$/l and resume at 45 mg daily (2) Second episode: stop ponatinib until ANC $>1.5\times10^9$/l and platelets $>75\times10^9$/l and resume at 30 mg daily (3) Third episode: stop ponatinib until ANC $>1.5\times10^9$/l and platelets $>75\times10^9$/l and resume at 15 mg daily

Abbreviations: ALL, acute lymphoblastic leukaemia; ANC, absolute neutrophil count; AP, accelerated phase; BP, blastic phase; CML, chronic myeloid leukaemia; CP, chronic phase.

Table 9. Incidence of gastrointestinal AEs and pancreatitis

Drug/Side effects in %	*Nausea*	*Abdominal pain*	*Vomiting*	*Dyspepsia*	*Diarrhoea*	*Constipation*	*Pancreatitis*
Imatinib							
Trial: O´Brien *et al.*[1]							
Design: randomized trial, newly diagnosed CML CP patients							
Planned dose: 400 mg daily. $N=551$							
All grades	43.7	27.7	16.9	16.2	32.8	8.5	NR
Grades 3 and 4	0.7	2.4	1.5	0	1.8	0.7	NR
Trial: Druker *et al.*[174]							
Design: follow-up of IRIS							
Planned dose: 400 mg daily. $N=382$							
All grades	50	37	NR	NR	45	NR	NR
Trial: Deininger *et al.*[175]							
Design: randomized trial, newly diagnosed CML CP patients							
Planned doses: 400 vs 800 mg daily. $N=145$							
All grades, 400 vs 800 mg	50 vs 58	NR	15 vs 28	Anorexia: 15 vs 22	39 vs 56	NR	NR
Grades 3 and 4, 400 mg vs 800 mg	3 vs 3	NR	1 vs 0	0 vs 0	1 vs 6	NR	NR
Nilotinib							
Trial: Kantarjian *et al.*[105]							
Design: single-arm phase 2 trial, imatinib resistant or intolerant CP CML patients							
Planned dose: 400 mg twice daily. $N=321$							
All grades	25	NR	13	NR	12	13	47[a]
Grades 3 and 4	<1	NR	<1	NR	2	<1	18[a]
Trial: Saglio *et al.*[2]							
Design: randomized trial, 3 arms, newly diagnosed CML CP patients, imatinib vs nilotinib in two dose regimens							
Planned doses: 300 mg ($N=282$) or 400 mg twice daily ($N=281$)							
All grades, 300 mg vs 400 mg	11 vs 19	NR	5 vs 9	NR	8 vs 6	NR	24 vs 29[a] 15 vs 18[b]
Grades 3 and 4, 300 mg vs 400 mg	<1 vs 1	NR	0 vs 1	NR	1 vs 0	NR	6 vs 6[a] <1 vs 1[b]
Dasatinib							
Trial: Kantarjian *et al.*[4]							
Design: randomized trial, newly diagnosed CML CP patients, imatinib vs dasatinib							
Planned dose: 100 mg once daily ($N=258$)							
All grades	8	NR	5	NR	17	NR	NR
Grades 3 and 4	0	NR	0	NR	<1	NR	NR
Trial: Shah *et al.*[106]							
Design: randomized trial, CML CP patients with resistance, suboptimal response or intolerance to imatinib							
Planned doses: 100 mg once daily vs 50 mg twice daily vs 140 mg once daily vs 70 mg twice daily ($N=670$)							
All grades, 100 mg once daily vs 50 mg twice daily vs 140 mg once daily vs 70 mg twice daily	18 vs 20 vs 24 vs 29	12 vs 12 vs 13 vs 10	7 vs 10 vs 10 vs 13	5 vs 3 vs 10 vs 7	25 vs 31 vs 29 vs 27	9 vs 10 vs 3 vs 2	NR
Grades 3 and 4, 100 mg once daily vs 50 mg twice daily vs 140 mg once daily vs 70 mg twice daily	1 vs 1 vs 1 vs 1	1 vs 0 vs 1 vs 1	1 vs 1 vs 1 vs 0	0 vs 0 vs 0 vs 0	1 vs 2 vs 4 vs 4	1 vs 0 vs 0 vs 0	NR
Bosutinib							
Trial: Khoury *et al.*[107]							
Design: phase 2 study in CML CP patients after imatinib and dasatinib and/or nilotinib failure							
Planned doses: 500 mg once daily ($N=118$)							
All grades	43	15 (upper abdominal pain 13%)	32	NR	81	NR	24[c]
Grades 3 and 4	0	0	1	NR	8	NR	7[c]
Trial: Cortes *et al.*[22]							
Design: randomized trial, newly diagnosed CML CP patients, imatinib vs bosutinib							
Planned doses: 500 mg once daily ($N=248$)							
All grades	31	11 (+ upper abdominal pain 12%)	32	NR	68	NR	38[a]
Grades 3 and 4	1	1 (upper abdominal pain 0%)	3	NR	11	NR	9[a]

Table 9. (Continued)

Drug/Side effects in %	*Nausea*	*Abdominal pain*	*Vomiting*	*Dyspepsia*	*Diarrhoea*	*Constipation*	*Pancreatitis*
Ponatinib							
Trial: Cortes *et al.*[135]							
Design: phase 2 trial in Ph+ leukaemias (six different cohorts of CML and Ph+ ALL)							
Planned doses: 45 mg once daily ($N = 449$)							
All grades	3–19 in different cohorts	10–27 in different cohorts	NR	NR	NR	5–20 in different cohorts	0–8 in different cohorts[d]
Grades 3 and 4	0 to < 1 in different cohorts	2–7 in different cohorts	NR	NR	NR	0–3 in different cohorts	0–6 in different cohorts[d]

Abbreviations: ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; CP, chronic phase; NR, not reported. Side effects, grading according to NCI-CTC (Common Terminology Criteria for Adverse Events of the National Cancer Institute). [a]Reported as elevated lipase. [b]Reported as elevated amylase. [c]Reported as elevated lipase, and reported to be present in 6% of cases at baseline. [d]Increased lipase of any grade reported separately in 9–21% patients in different cohorts (21% in the largest cohort, CP CML, $n = 270$), and of grade 3–4 in 6–13% patients in different cohorts (10% in the largest cohort, CP CML, $n = 270$).

may be considered, though the chance of similar problems on an alternative TKI is high.

Management in advanced phase: In patients with advanced phase disease, the management of severe myelosuppression (Table 8) follows the general concept of keeping a higher dose intensity than for chronic phase. In the face of a persistent cytopenia, a bone marrow examination may be useful in order to differentiate persistence of leukaemia from hypocellularity, especially if the patient is treated with imatinib or dasatinib. It is unclear whether continuing TKI treatment, despite myelosuppression, improves the response rate or simply results in greater morbidity (infectious and/or bleeding complications). Advanced phase CML poses highly variable haematological and clinical situations, and therefore the TKI dose management should be optimised based on the individual characteristics of each case.
Use of growth factors: The incidence of severe infections during the course of TKI treatment is low. Prolonged therapy-induced myelosuppression may, however, increase the risk of severe infection. G-CSF and erythropoietic agents can be used transiently to facilitate neutrophil or haemoglobin recovery. The concomitant use of G-CSF[171,172] or erythropoietic agents[170] with TKIs is effective and does not appear to be associated with lower response or TKI failure.

Febrile neutropenia: If the patient is in chronic phase and receiving TKI as first line, in the case of grade 3, withhold therapy, treat infection appropriately, and resume at a lower dose when the grade resolves to < 3. The same strategy is recommended for grade 4, except that G-CSF should be considered together with a switch to another TKI when the grade resolves to < 3. If the patient is in second line or in advanced phase, and switching options to another TKI are limited, then a stepwise lowering of the dose is warranted.

Prevention and management of bleeding: Dasatinib,[164,166,167] and to a lesser extent imatinib[167] and ponatinib[168] induce platelet dysfunction. Antiplatelet therapy must be used carefully in the presence of TKIs, especially when dasatinib is used as second line,[19] or with ponatinib.[165] In addition, adjustment of warfarin or acenocoumarol is recommended, because imatinib may increase their serum levels.

Cross-intolerance: Nilotinib, at a dose of 400 mg twice daily[121] and dasatinib at various doses have been used as second-line treatment for haematological intolerance to imatinib,[173] which represents a combination of toxicity and of resistance to imatinib itself. Recurring grade 3–4 cytopenias after switching seem to be more common with dasatinib (86%) than with nilotinib (55%), but discontinuation due to recurrence of haematological toxicity is similar (16% vs 23%).

Gastrointestinal problems

Incidence and severity. Gastrointestinal side effects are frequently reported toxicities of TKIs. Table 9 summarises published data from large trials.[1,2,105,174,175] For imatinib and nilotinib, the most frequent side effects are nausea, diarrhoea, abdominal pain and vomiting; dyspepsia and constipation are less frequent. In the vast majority of patients, the side effects are of grades 1 and 2 only. The gastrointestinal tolerability of dasatinib is generally good.[4] Diarrhoea was the reason for dose interruption in 1–3% of patients, and diarrhoea or dyspepsia each were the reasons for dose reductions in 0–2% of patients.[106]

Gastrointestinal problems are similar with bosutinib, with the exception of diarrhoea, which is more frequent and annoying. It starts typically in the first 4 weeks, with a median of 1.5–3 days, and the median duration is 2–7 days. Grades 3–4 are seen in 8–11%. Of those who experienced diarrhoea, 21% and 8% of patients required dose interruptions and reductions, respectively. Per protocol, it was recommended that at the first sign of diarrhoea, medications such as diphenoxylate/atropine or loperamide should be used as needed, which effectively controlled diarrhoea in most instances; such concomitant medication was required in 67% of patients. Discontinuation because of diarrhoea was rare.[22,107] For ponatinib, gastrointestinal toxicity is usually not a major issue; some patients report nausea, abdominal pain or constipation.[23,135]

Kinetics and prevention. Most gastrointestinal problems occur during the first month of therapy, and preventive measures are therefore most appropriate at this time. However, one must take into account that, for example, bosutinib-related diarrhoea may appear as late as 18 months after starting TKI.[22] In patients treated with imatinib for least for 3 years, only 72% and 57% of patients were free of nausea and diarrhoea respectively,[176] even though these cluster in the first year.[22,35]

Few data are available about preventive measures. To avoid or mitigate nausea and vomiting, imatinib should be taken with food and administered with the largest meal of the day. Another management strategy involves splitting the dose and taking them with separate meals. Alternatively, some patients prefer to take the TKI at bedtime to avoid the burden of nausea during waking hours.

Management: Mild and transient nausea, vomiting and diarrhoea do not require therapy other than symptomatic relief and diet modification, unless they interfere with quality of life. For more severe cases, antiemetic and antidiarrhoeal medication should be utilised, and attention must be paid to drug interactions and hydration,[177] and the general rules of toxicity management should be applied. In the case of bosutinib, we recommend to start with medications such as diphenoxylate/atropine or loperamide at the first sign of diarrhoea.[74] In the case of abdominal pain, gastric and pancreatic problems must be ruled out. Proton-pump inhibitors may be helpful, though their dosing should be separated from dasatinib intake by 12 h.

Gastrointestinal bleeding: Gastrointestinal bleeding may be more frequent in patients receiving dasatinib especially in second line, with a frequency of 17% across all phases. Basic coagulation studies were normal in 97% of patients. Sixty-three percent of episodes occurred with platelet counts $\leqslant 100 \times 10^9$/l, and thrombocytopenia and advanced phase CML were independent risk factors for bleeding.[164] In chronic phase, in second line it occurred in 2–5% of patients.[106] In first line, it has not been reported.[178] Management should include investigations to find the source of bleeding, coagulation studies and interruption of the drug. Switching TKI may be necessary especially in the case of dasatinib, and probably of ponatinib.

Pancreatic problems

Incidence and severity. It is important to note that lipase or amylase elevations may occur in the absence of evidence of pancreatitis,[179] and with all TKIs, although clinical awareness should be high in patients treated with nilotinib and ponatinib. In patients treated with nilotinib, lipase elevations have been reported with a frequency of 29–47%, with grade 3–4 elevations ranging between 6 and 18%, being higher in second line. Pancreatitis has been rare, between 0.9%[180] and 2%.[2] In patients treated with ponatinib in chronic phase, in second line or further, lipase elevations were recorded in 20% of the patients (10% grade 3–4).[23] Pancreatitis occurred in 7%, tended to appear early (median time to onset of 14 days, 69% of cases occurred in the first month and 17% in the second month) and was reversible (most cases resolved within 1 week). All patients with pancreatitis resumed treatment with ponatinib, and three patients had recurrent events (multiple events occurred in one patient). Only one patient discontinued treatment because of pancreatitis.[23]

Management. Suspicion of pancreatitis is always a call for action, and the advice of an appropriate gastroenterologist or surgeon may be needed. If the patient is asymptomatic but with grade 3 lipase/amylase elevation, withholding therapy and resuming at a lower dose when the grade is < 2 is the recommended approach. If full recovery takes more than 4 weeks, therapy should be stopped. In the case of symptoms, CT scan is recommended, and if it is positive or the pancreatitis is grade 3, stopping nilotinib is mandatory, whereas in the case of ponatinib (which is normally used when other options are ineffective or contraindicated), withholding therapy and resuming at a lower dose could be reasonable. Stopping therapy is mandatory for pancreatitis grade 4, irrespective of whether the concurrent TKI is thought to be causal.

Cutaneous problems

Incidence and severity

Imatinib: Skin AEs are common with imatinib and occur in 7–89% of patients across different series.[181–186] In particular, in a large series of 532 chronic phase patients the frequency was 32%, described mostly as skin eruption.[187] In advanced phase patients, skin AEs occurred in 23% of cases.[188] They appear predominantly during the first 3–4 weeks of treatment[181] The severity is dose-dependent with a rate of 7% of skin events in patients receiving standard dose of imatinib (400 mg daily) compared with a variable rate between 20 and 88% in patients treated with higher doses of imatinib.[181–185] The manifestations are extremely heterogeneous. Most common manifestations include peripheral oedema, maculopapular erythematous rash, papulosquamous eruptions and pigmentary changes. Most rashes are easily manageable and self-limiting.[30] Hypopigmentation,[189,190] which can be generalised or patchy,[191] may include greying of hair[192] and is reversible after discontinuation.[193] Less-common manifestations are skin fragility,[194] dermatofibromas[195] and exacerbations of porphyria cutanea tarda.[196] Photosensitivity and neutrophilic dermatosis are rare.[186]

Nilotinib: Although fluid retention is seen with nilotinib treatment, with a frequency of 17% in first line in the first 3 years,[3,197] periorbital oedema is relatively uncommon, and oedema is less apparent than with imatinib. A rash is roughly twice as common with nilotinib as with imatinib in first line,[3,197] and its incidence appears to be lower in second line.[180] It is usually localised to the trunk, face and scalp.[198] Other side effects are pruritus (24%), dry skin (10%) and rarely alopecia (6%).[149,180,199] Sweet's syndrome is uncommon.[200]

Dasatinib: The frequency of peripheral fluid retention is similar in first line (19%)[201,202] and second line (26%)[150] and lower than with imatinib.[201,202] A rash has been described in 11% in first line,[201,202] in 18% by 36 months[150,203] and 33% by 6 years.[19] A recent meta-analysis has shown that the incidence of rash is lower with dasatinib than with nilotinib.[198]

Bosutinib: Fluid retention has been described in 15% of the patients in second line[21] and in less than 10% in first line.[22,29] A rash has been described in 43% (6% of grade 3–4 severity), when used in patients resistant/intolerant to imatinib in second line.[21] In first-line use, 20% of patients experienced a skin rash in the first year, but only 1% as grade 3–4.[22,29]

Ponatinib: Overall, the incidence of a rash was 34% in the PACE trial and 32% in the phase I trial, being of grade 3–4 severity in 3–4%.[23,135] It has been reported as an early event, without evidence of tardive side effects.

Conditions that facilitate skin adverse events: Most cutaneous AEs are probably due to a direct drug effect. Several conditions may contribute to the occurrence of skin adverse events that require particular attention. Cardiovascular diseases, older age and higher doses predispose to oedema. Rash is more frequent with higher doses, drugs that have CYP3A4 interactions, dehydration and salty food, sunburn and skin contusions.[181,183,185]

Management. The severity of cutaneous side effects is dose-related, but most of them are mild to moderate and self-limiting. A dermatologist may be required to direct treatment. Mild to moderate AEs can be managed with topical therapies (lotions or glucocorticoids), systemic therapies with antihistamines or short courses of systemic steroids. Severe cases always require interruption or temporary reduction of TKI. Rare cases of very severe skin reactions require the permanent withdrawal of the causative TKI.[181,185,204–206]

In case of temporary discontinuation, weekly monitoring and prednisone (1 mg/kg daily) should be started with gradual reintroduction of the TKI at a reduced dose. Often, the skin rash does not recur when the same TKI is restarted, particularly with a reduced dose.[207] If, in spite of all the supportive measures, the skin reaction does not resolve, the patient should be deemed

intolerant to that particular TKI, and a switch to other TKIs should be evaluated. Patients who develop a rash on imatinib do not appear to experience a recurrence on dasatinib or other TKIs.[173] If no other options are available to control the CML, treatment with the offending TKI may be continued with concomitant oral steroid, despite the persistence of skin reaction.

Immunological alterations and infections

Incidence and severity. All TKIs have a potential immunosuppressive effect (reviewed in refs 15,144,146,147). *In vitro* studies have shown that imatinib, dasatinib and nilotinib have inhibitory effects on T-cell proliferation and activation.[208] The *in vitro* effects of dasatinib have been found to be more profound, probably due to more potent off-target inhibition and a broader kinase target spectrum.[209] With imatinib, infection by opportunistic agents and viruses does not appear to be a major problem.[210] In a series of 771 patients across all disease phases treated with imatinib, the incidence was low (2%), and only 1 with varicella.[211] Hepatitis B reactivation has been described during imatinib treatment.[212] Reactivation of pulmonary tuberculosis while on imatinib has been reported.[213] Two cases of granulomatous lymphadenitis have also been described.[214] However, one out of four elderly patients treated with imatinib developed infections.[215]

With regard to 2G TKIs, for chronic phase recipients of second-line nilotinib, infection was one of the most common AEs, but of mild nature.[216] Febrile neutropenia has been a common AE in advanced phase patients treated in second line with nilotinib.[217] Dasatinib at higher doses, in second line, has been associated with an ~50% incidence of infections when used in BCR-ABL1 positive acute leukaemia,[218] or with previous ara-C or rapamycin,[219] or with other antineoplastic agents or glucocorticoids.[218] Infections have not been frequently associated with ponatinib in second or later lines.[23] In large phase II/III clinical studies with dasatinib,[220] nilotinib[197] or bosutinib[74] in first line, no significantly increased rates of infections have been reported in comparison with imatinib.

Therefore, in spite of the immunosuppressive *in vitro* effects of TKIs, the incidence of infections seems to be slightly augmented in second line, advanced phases and elderly people. In first line, there is no significant difference between imatinib and other TKIs, although the incidence with dasatinib appears to be higher, also at 100 mg once daily.[4,5,87]

Prevention and management. Attention is most needed in elderly patients treated with imatinib,[215] patients treated with dasatinib, and in the presence of neutropenia (see above). Responses to vaccination against influenza and pneumococcus are blunted in TKI treated patients.[221] Concomitant use of antiviral agents should be recommended on TKI therapy for prevention of hepatitis B virus reactivation.[222] A watchful attitude is recommended in patients with previous tuberculosis. In patients treated with dasatinib, cytomegalovirus reactivation should be considered in the presence of large granular lymphocytosis (LGL)[223,224] or colitis.[225,226]

Dasatinib and lymphocytosis. In dasatinib-treated CML and Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) patients, an oscillating LGL has been observed. This phenomenon has not been described with other TKIs, and its incidence in second line is roughly 50%.[227,228] The time of appearance is typically at 4–5 months on therapy.[227,228] This LGL is caused for the most part by rapid mobilisation of cytotoxic CD8+ T cells and NK cells into the blood 1–2 h after intake of dasatinib.[229] The actual incidence of LGL in first-line dasatinib therapy is not known, although in the DASISION trial the cumulative 2-year probability of a lymphocytosis was 26% (vs 6% with imatinib).[230] Lymphocytosis (total or LGL) seems to be more frequent in patients with pleural effusions,[230,231] colitis[232] or better responses.[227,231,233] In some cases, cytomegalovirus reactivation has been associated with LGL.[223,225]

Musculoskeletal effects

Incidence and severity. Under this heading, we have included such AEs as muscle and bone pain, arthralgia, myalgia and muscle cramps. In the IRIS trial, whereas muscle pain, myalgia and arthralgia were less frequent with imatinib than with interferon plus ara-C, it was the opposite with muscle cramps (38% vs 11%).[1] When imatinib was compared with dasatinib in first-line therapy, the incidence of myalgia was more frequent with imatinib (1st year: 34.5% vs 19.8%).[178] However the incidence of myalgia appears roughly the same with nilotinib and imatinib, whereas muscle cramps are more frequent with imatinib (24% vs 7%).[2] Grade 3–4 muscle pain is reported in $<2\%$ of cases. However, muscle cramps are disturbing, and they interfere with quality of life.[234] Their pathogenesis is unknown, although they have been linked with low adjusted calcium levels.[235]

Prevention and treatment. Other than symptomatic relief, there is no definitive treatment. Serum electrolyte levels should be monitored and corrected, if necessary. Some patients find relief with the use of beverages containing quinine.

Ocular adverse events

Incidence and severity. A spectrum of ophthalmological side effects has been reported on TKI therapy, predominantly minor and self-limiting. Despite shared inhibition of signalling pathways between the TKIs, the bulk of ocular side effects lie with imatinib. Periorbital oedema is the most frequent ocular side-effect associated with imatinib[236] and can occur in up to 70% of treated patients,[237] probably through the inhibition of platelet-derived growth factor receptor.[238] Epiphora (excessive watering of the eye) occurs in roughly 20% of patients,[238] as a result of conjunctival chemosis.[236] Conjunctival haemorrhage has been reported in 11% of patients, in the absence of cytopenias or bleeding diathesis.[239] Rare and reversible imatinib-induced optic disc oedema and optic nerve dysfunction, and neuritis have been described.[240,241]

With nilotinib, there is a paucity of published data. Ocular side effects ($\geqslant$1/100 to $<$1/10) associated with nilotinib include periorbital oedema, eye pruritus and dryness including xerophthalmia. Uncommonly, visual impairment, conjunctival haemorrhage and eye irritation occur. Papilloedema and optic neuritis have not been reported.[242] The literature on dasatinib-induced ophthalmological toxicity is absent, but common documented side effects include eye dryness, visual disturbance and reduction in acuity. Uncommonly ($\geqslant$1/1000 to $<$1/100), photophobia and excess lacrimation have been reported.[243] No ocular side effects have been reported with bosutinib therapy.[244] Although there are no published references to ponatinib-related ophthalmological AEs, common reported eye disorders have included blurring of vision, eye dryness and periorbital oedema. Reports of ocular arterial thrombosis/occlusion on ponatinib therapy are uncommon, as are retinal vein thrombosis or occlusion.[245]

Prevention and management. Loss of visual acuity should prompt examination for imatinib-induced optic disc oedema,[240] or optic nerve dysfunction and neuritis,[241] rare but serious conditions that are reversible after TKI discontinuation or additional systemic steroid therapy.[240,241]

Diuretic therapy has limited benefit in periorbital oedema, and its management includes dose modification and ultimately changing to an alternative TKI as necessary.[236] Surgical debulking has been described but is rarely appropriate.[246] Epiphora may respond to diuretics and steroids.[236] Conjunctival haemorrhage is

normally self-limiting, and disturbing cases sometimes respond to topical steroids.[239]

Gynaecologic adverse events

Incidence and severity. In non-clinical animal studies, fertility does not appear to be influenced by imatinib or nilotinib.[242,247] However, formal clinical studies examining fertility and gametogenesis have not been undertaken. On the basis of non-clinical findings, bosutinib has the potential to impair reproductive function and fertility in humans. The effect of dasatinib and ponatinib on fertility is as yet unknown.[242–245,247] During imatinib therapy, menorrhagia and irregular menstrual cycle are reported as uncommon, but in practice are often under-reported; therefore their true incidence is probably higher. More unusual side effects include haemorrhagic corpus luteum/haemorrhagic ovarian cyst. Dasatinib has also been associated infrequently with irregular menstruation, but no effects on the menstrual cycle appear to have been described with nilotinib and bosutinib.[242] Limited bleeding episodes on ponatinib have been noted and menorrhagia has not been described in the absence of other haemostatic challenges.[165]

Prevention and management. The most important advice to women of childbearing potential receiving any of the TKIs is to use effective contraception during all TKI treatment due to documented teratogenicity, and to avoid breast feeding.[248]

Neurological adverse events

Incidence and severity. Headache is a very common neurological AE associated with the use of all TKIs. Caution is required with respect to a causal relationship between headache and TKI usage, given the high frequency of headache in the general population and the wide variation of observed frequencies across different clinical trials. As an example, in newly diagnosed chronic phase patients treated with imatinib at 400 mg daily, headache was reported in 31%[1] 23%[2] 10%[178] and 8%.[22] In newly diagnosed chronic phase patients treated with nilotinib twice daily, dasatinib at 100 mg daily or bosutinib at 500 mg daily, headache was observed in 39%,[2] 12%,[22] and 10%[178] of the cases, respectively. With ponatinib 45 mg daily in second or later lines, headache was reported in 23% of chronic phase patients but few cases were considered as drug-related.[23] Unfortunately, descriptive features of headache such as episodic or chronic nature, duration and type are lacking.

Other TKI AEs affecting the nervous system are less frequent and must be distinguished from other causes of neurological disorders (including those induced by other drugs). Peripheral neuropathy has been described during treatment with all TKIs and is considered as uncommon (frequency $\geqslant$1/1000 to $<$1/100) to common (frequency $\geqslant$1/100 to $<$1/10).[152,158,249–253] Establishment of a causal relationship between peripheral neuropathy and the use of TKIs is limited to a few case reports in patients treated with imatinib, as well as description of clinical features.[254,255] Peripheral neuropathy is an important diagnosis as it affects quality of life and can lead to significant disability. In addition, dose decrease or TKI discontinuation may lead to significant improvement.[254,255] Most of the neuropathies diagnosed in CML patients could be ascribed to concomitant or previous ailments (diabetes, interferon-associated autoimmune phenomena and so on). Memory impairment may occur in patients treated with imatinib, dasatinib and nilotinib.[158,249–251] Its exact frequency is difficult to estimate based on the available data. Whether memory impairment may also arise in bosutinib- or ponatinib-treated patients is unknown.

Other rare neurologic complications such as cranial nerve palsy, optic neuritis and optic disc oedema[240,241,255] may be associated with the use of imatinib or dasatinib and their frequency cannot be estimated from the available data. Cerebral oedema has been reported in an isolated case report in an imatinib-treated patient.[256] Cerebral ischaemic events associated with the use of ponatinib or nilotinib are discussed in the vascular section. Intracranial bleeding is restricted to patients with thrombocytopenia and advanced phase CML.

Prevention and management. Headache, which is quite common in the general population, is a common AE in TKI recipients. Hypertension must be ruled out, especially in the case of ponatinib. In the case of peripheral neuropathy, most cases have other causes than TKI treatment. If TKI seems to be causal, dose decrease or TKI discontinuation may lead to significant improvement.[254,255]

Renal adverse events

Incidence and severity. Initially, renal failure on account of imatinib was reported as a rare event, shown to occur in $<$1% patients in the dose-escalating studies of chronic phase and blast crisis CML.[257,258] Similarly, the Novartis Oncology Medical information website (www.oncologymedicalservices.com) reported renal function abnormalities in 1.6% of 1234 CML patients, and there were no reports of renal failure among the 553 newly diagnosed CML patients treated with imatinib in the IRIS trial, with up to 6 years of follow-up.

It is now clear that imatinib therapy can rarely be associated with potentially irreversible acute renal injury, and long-term treatment may cause a clinically relevant decrease in the estimated glomerular filtration rate. In 105 patients receiving imatinib after prior interferon, 7% developed acute kidney injury, the mean decrease of glomerular filtration rate was 2.77 ml/min per 1.73 m^2 per year and 12% of patients developed chronic renal failure.[259] In other cases, renal failure linked to imatinib is often reversible,[260,261] although haemodialysis is sometimes needed.[262] Thrombotic thrombocytopenic purpura,[263] acute tubular necrosis,[262] tubular vacuolisation[264] and partial Fanconi syndrome[265] have all been reported following imatinib therapy.

Renal failure was not described in the dasatinib phase I–III trials.[83,84,266,267] However, renal failure has been reported with dasatinib administration,[268] and switching to nilotinib in blast crisis has reversed acute kidney injury with maintenance of stable renal function.[81,269,270] Rarely dasatinib has been reported to induce thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome either through an auto-immune mechanism or by direct endothelial toxicity/acute tubular necrosis,[270] salvageable by renal transplantation.[269,271]

None of the nilotinib-treated patients in the phase I and II studies for CML or Ph+ ALL developed renal failure, although tumour lysis syndrome remains a possibility.[272] Nilotinib has been reported to be beneficial for renal dysfunction[273] through the dissipation of fibrosis in chronic kidney disease. Increases in serum creatinine and renal failure ($<$5%) have been observed with bosutinib.[244]

Prevention and management. In the first few days of treatment, attention to tumour lysis syndrome is mandatory with all TKIs. In the chronic setting, monitoring serum creatinine is needed in patients treated with imatinib, and less stringently, with dasatinib and bosutinib. There is no need in patients treated with nilotinib, and it is uncertain with ponatinib. In renal insufficiency (ranging from renal dysfunction to dialysis) a maximum imatinib starting dose of 400 mg is recommended. No clinical studies have been conducted with dasatinib, nilotinib or ponatinib in patients with decreased renal function ($>$3 times the upper limit of the normal range), but the minimal or absent renal clearance of these two drugs makes dose adjustment unnecessary for renal insufficiency. Dasatinib administration in renal impairment has not led to worsening of renal function.[274] Nilotinib can be safely

administered in patients receiving haemodialysis.[275] With bosutinib caution is recommended due to observed increases in serum creatinine and renal failure ($<5\%$).[244] Caution is recommended when administering ponatinib to patients with an estimated creatinine clearance of <50 ml/min, or end-stage renal disease.[245]

CONCLUSIONS

In summary, and despite the reservations mentioned in the introduction, a number of things have been learnt in the recent past. First, the main objective of CML treatment is the antileukaemic effect and thus the minimisation of disease-related mortality. Suboptimal management of AEs must not compromise this first objective. Second, most patients will have AEs,[7] usually early after treatment initiation, mostly mild to moderate in intensity, and which will resolve spontaneously or are easily controlled by simple means. Third, reduction or interruption of treatment must only be done if optimal management of the AE cannot be anticipated or accomplished. Dose reduction or interruption must be kept to a minimum, and frequent patient monitoring may be helpful in this regard, in order to detect resolution of the AE as early as possible. Fourth, strict attention must be given to comorbidities and drug interactions, and new events unrelated to TKI are inevitable during such a prolonged (lifelong) treatment; these new events may modify the choice of TKI. Fifth, some TKI-related AEs have emerged that were not predicted or detected in earlier studies, maybe because of suboptimal attention to or absence from the preclinical data. Overall, imatinib has demonstrated a good long-term safety profile, though recent findings suggest underestimation of symptom severity by physicians.[276] Second and third generation TKIs may have higher response rates, but have been associated with unexpected lung and vascular problems, which could be irreversible. We hope these recommendations will help to minimise adverse events, and we believe that an optimal management of them will be rewarded by better outcomes, and better quality of life.

CONFLICT OF INTEREST

Authors declare the following relationships with pharmaceutical companies: Amgen-receipt of honoraria (GR); Ariad—receipt of honoraria: (JLS, MB, MaB, VG-G, DWK, HJK, PLC, DM, DR, GR and SS) and research funding (JLS, LFC, VG-G, AH, DWK, PLC and GR); Bristol–Myers–Squibb—receipt of honoraria (JLS, MB, MaB, LFC, VG-G, AH, DWK, HJK, PLC, DM, KP, DR, GR, SS, RH and REC), research funding (JLS, LFC, VG-G, DWK, JM, KP, GR, SS and REC) and nonfinancial support (JM); MSD- research support (AH); Novartis—receipt of honoraria (JLS, MB, MaB, LFC, VG-G, DWK, HJK, PLC, DM, KP, DR, GR, SS and REC), research funding (JLS, LFC, VG-G, AH, DWK, JM, KP, GR, SS, RH and REC) and nonfinancial support (JM); ILYANG—receipt of honoraria (DWK) and research funding (DWK); Pfizer-receipt of honoraria (JLS, MB, MaB, LFC, VG-G, DWK, HJK, PLC, DM, KP, DR, GR, SS and REC) and research funding (JLS, LFC, VG-G, AH, DWK, KP, GR and REC); Roche—receipt of honoraria (GR); Sanofi-receipt of honoraria (REC) and research funding (REC); Teva—receipt of honoraria (HJK).

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