

REVIEW

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

JL Steegmann¹, M Baccarani², M Breccia³, LF Casado⁴, V García-Gutiérrez⁵, A Hochhaus⁶, D-W Kim⁷, TD Kim⁸, HJ Khoury⁹, P Le Coutre⁸, J Mayer¹⁰, D Milojkovic¹¹, K Porkka^{12,13}, D Rea¹⁴, G Rosti², S Saussele¹⁵, R Hehlmann¹⁶ and RE Clark¹⁷

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.

¹Servicio de Hematología y Grupo 44 IIS-IP, Hospital Universitario de la Princesa, Madrid, Spain; ²Department of Hematology and Oncology 'L. and A. Seràgnoli', St Orsola University Hospital, Bologna, Italy; ³Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy; ⁴Servicio de Hematología, Hospital Virgen de la Salud, Toledo, Spain; ⁵Servicio Hematología y Hemoterapia, Hospital Universitario Ramón y Cajal, Madrid, Spain; ⁶Hematology/Oncology, Universitätsklinikum Jena, Jena, Germany; ⁷Seoul St Mary's Hospital, Leukemia Research Institute, The Catholic University of Korea, Seoul, South Korea; ⁸Medizinische Klinik mit Schwerpunkt Onkologie und Hämatologie, Campus Charité Mitte, Charité—Universitätsmedizin Berlin, Berlin, Germany; ⁹Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA; ¹⁰Department of Internal Medicine, Hematology and Oncology, Masaryk University Hospital Brno, Brno, Czech Republic; ¹¹Department of Haematology Imperial College, Hammersmith Hospital, London, UK; ¹²Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; ¹³Hematology Research Unit, University of Helsinki, Helsinki, Finland; ¹⁴Service d'Hématologie Adulte, Hôpital Saint-Louis, APHP, Paris, France; ¹⁵III. Med. Klinik Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany; ¹⁶Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany and ¹⁷Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK. Correspondence: Dr JL Steegmann, Servicio de Hematología y Grupo 44 IIS-IP, Hospital de la Princesa, Diego de León 62, Madrid 28006, Spain.

E-mail: jlsteegmann.hlpr@salud.madrid.org or jlsteegmann@gmail.com

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 events²⁵ 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 guidelines⁵⁵ 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 years⁵⁶ 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 classification⁵⁷ 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 damage⁵⁸ (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 MR⁴ (BCR-ABL1 $\leq 0.01\%$ 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 MR⁴ or MR^{4.5} (BCR-ABL1 $\leq 0.0032\%$ 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 <i>et al.</i> 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 <i>et al.</i> ³⁸ case report	2	Nilotinib	NR	NR	NR	NR	2	NR	NR
le Coutre <i>et al.</i> ³⁹ retrospective cohort analysis (multicentric)	179	Nilotinib	NR	NR	NR	NR	11 (6.2%)	NR	26 (4–53) months
Quintas-Cardama <i>et al.</i> ⁴⁰ retrospective cohort analysis (single centre)	233	Nilotinib	NR	NR	NR	1 (0.4%)	3 (1.3%)	1 (0.4%)	NR
Labussiere-Wallet <i>et al.</i> 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 <i>et al.</i> ³² retrospective cohort analysis (multicentric, pooled trials)	556	Nilotinib	NR	NR	NR	NR	7 (1.2%)	NR	NR
Kim <i>et al.</i> ³³ retrospective cohort analysis (multicentric)/prospective cohort screening (single centre)	1301 533 66	Imatinib Interferon Nilotinib	NR NR NR	NR NR NR	NR NR NR	NR NR NR	2 (0.2%) 3 (0.6%) 7 (10.6%)	NR NR NR	NR NR 40 (21–56) months
Levato <i>et al.</i> ⁴² retrospective cohort analysis (single centre)	54 27	Imatinib Nilotinib	NR NR	NR NR	NR 1 (3.7%)	NR 1 (3.7%)	1 (1.9%) 2 (7.4%)	NR NR	NR 24 (7–34) months
Giles <i>et al.</i> (ENEST1 st) ⁴³ prospective phase IIb (multicentric)	819	Nilotinib	NR	NR	31 (3.8%)	4 (0.5%)	13 (1.6%)	NR	NR
Jeon <i>et al.</i> ⁴⁴ prospective cohort screening (single centre)	88	Nilotinib	NR	NR	NR	NR	3 (3.4%)	NR	NR
le Coutre <i>et al.</i> ⁴⁵ retrospective cohort analysis (multicentric, pooled trials)	2705	Dasatinib	NR	NR	NR	NR	6 (0.2%)	NR	20 (2–53) months
Cortes <i>et al.</i> (PACE) ²³ prospective phase II (multicentric)	449	Ponatinib	3 years	99 (22%)	52 (12%)	37 (8%)	37 (8%)	NR	NR
Larson <i>et al.</i> (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
Gugliotta <i>et al.</i> (GIMEMA) ⁴⁷ prospective phase II (multicentric)	277 280 215	Nilotinib 400 mg BID Imatinib 400 mg QD Nilotinib	57 months	44 (15.9%) 7 (2.5%) 13 (6%)	18 (10.1%) 6 (2.1%) 3 (1.4%)	9 (3.2%) 1 (0.4%) NR	9 (3.2%) 0 4 (1.9%)	3 (1.1%) 0 NR	36 (6–90) months 42 (6–78) months 37 months
Gora-Tybor <i>et al.</i> ⁵⁴ retrospective cohort analysis (multicentric)	50	Dasatinib	28 months	2 (4%)	1 (2%)	1 (2%)	0	0	20 (19–22) months
Hadziusufovic <i>et al.</i> ⁴⁸ retrospective cohort analysis (single centre)	55 36	Nilotinib Nilotinib	44 months	6 (11%) NR	2 (3.6%) NR	1 (1.8%) NR	1 (1.8%) 16 (44.4%)	2 (3.6%) NR	15 (6–69) months NR
Fossard <i>et al.</i> ⁴⁹ prospective cohort analysis (multicentric)	114	Nilotinib	NR	21 (18.5%)	NR	NR	NR	NR	47 (8–82) months
Gilbert <i>et al.</i> ⁵⁰ retrospective cohort analysis (single centre)	183	Nilotinib	NR	20 (10.9%)	9 (5%)	4 (2%)	7 (4%)	NR	NR
Rea <i>et al.</i> ⁵¹ retrospective cohort analysis (single centre)	57	Nilotinib	47 months	13 (23%)	3 (5%)	2 (4%)	8 (14%)	NR	28 (9–50) months
Cortes <i>et al.</i> (DASISION) ⁵² prospective phase III (multicentric)	259	Dasatinib	60 months	12 (5%)	10 (3.9%)	2 (0.7%)	0	NR	NR
Hochhaus <i>et al.</i> ³⁶ prospective cohort analysis (multicentric)	1089	Nilotinib 600	24 months	65 (6%)	37 (3.4%)	9 (0.8%)	21 (1.9%)	NR	NR
Hochhaus <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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%).	Overall cardiac mortality rate of 0.3%
Atallah <i>et al.</i> 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	Three were recorded and confirmed 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ⁶⁴	Prospective evaluation; 59 CML patients median FU 3.4 years	Echocardiography and MUGA scanning		No evidence of myocardial deterioration
Marcolino <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ⁶⁷	Retrospective 1276 patients enrolled, 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 <i>et al.</i> 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 (<i>n</i> = 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 (<i>n</i> = 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. ^aInformation 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 index⁹² 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 thoracentesis 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 reversible¹⁰⁰ or not.¹⁰¹ Both hypersensitivity pneumonitis¹⁰² 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 retreatment 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 alcohol¹¹⁷ 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, Gastrointestinal stromal tumours; HS, Hypereosinophilic syndrome. Side effects, grading according to NCI-CTC (Common Terminology Criteria for Adverse Events of the National Cancer Institute). ^aValues 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_search.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 recovery¹¹⁹ 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 enrolled 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 triglycerides.^{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)	By 5 years ⁴⁶
Median duration, months		> 4 Years	Grade 3/4
AE Grade		Grade 3/4	0%
Elevated ALT		Grade 3/4	5%
Elevated AST		Grade 3/4	5%
Source		ENESTnd ²	
TKI, dosage (n)		Nilotinib 300 mg twice daily (n = 279)	Nilotinib 400 mg twice daily (n = 277)
Median duration, months		All grades	All grades
AE grade		Grade 3/4	Grade 3/4
Elevated ALAT		4%	9%
Elevated ASAT		66%	73%
Elevated total Bilirubin		40%	48%
		53%	62%
Source		BELA ²²	
TKI, dosage (n)		Bosutinib 500 mg daily (n = 248)	Imatinib 400 mg daily (n = 251)
Median duration, months		All grades	All grades
AE grade		Grade 3/4	Grade 3/4
Elevated ALAT		69%	29%
Elevated ASAT		56%	27%
Elevated total Bilirubin		—	—
Source		DASISION ⁵	
TKI, dosage (n)		Dasatinib 100 mg daily (n = 258)	Imatinib 400 mg daily (n = 258)
Median duration, months		All grades	All grades
AE grade		Grade 3/4	Grade 3/4
Elevated ALAT		—	—
Elevated ASAT		—	—
Elevated total Bilirubin		—	—

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 levels¹⁴¹ 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)		Dasatinib 100 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 3/4 (%)	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 imatinib¹⁶⁷ 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 AP and BP, 600 mg daily	ANC < $1.0 \times 10^9/l$ and/or platelets < $50 \times 10^9/l$ ANC < $0.5 \times 10^9/l$ and/or platelets < $10 \times 10^9/l$	(1) Stop imatinib until ANC > $1.5 \times 10^9/l$ and platelets > $75 \times 10^9/l$ > resume starting dose (2) Recurrence: repeat step 1 and resume at the reduced dose of 300 mg daily (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 $\geq 1 \times 10^9/l$ and platelets $\geq 20 \times 10^9/l$ and resume at 300 mg daily
Nilotinib	CP, frontline, 300 mg twice daily CP, second line, or AP, 400 mg twice daily	ANC < $1.0 \times 10^9/l$ and/or platelets < $50 \times 10^9/l$	(1) Stop nilotinib until ANC > $1.0 \times 10^9/l$ and platelets > $50 \times 10^9/l$ > resume starting dose (2) If blood counts remain low for > 2 weeks, resume at 400 mg daily
Dasatinib	CP, 100 mg daily	ANC < $0.5 \times 10^9/l$ and/or platelets < $50 \times 10^9/l$	(1) Stop dasatinib until ANC > $1.0 \times 10^9/l$ and platelets > $50 \times 10^9/l$ > resume the original starting dose (2) If platelets < $25 \times 10^9/l$ and/or recurrence of ANC < $0.5 \times 10^9/l$, 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 < $0.5 \times 10^9/l$ and/or platelets < $10 \times 10^9/l$	(1) Check if neutropenia is related to leukaemia (marrow aspiration or biopsy) (2) If UNRELATED to leukaemia, stop dasatinib until ANC $\geq 1.0 \times 10^9/l$ and platelets $\geq 20 \times 10^9/l$ 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 < $1.0 \times 10^9/l$ and/or platelets < $50 \times 10^9/l$	(1) Withhold bosutinib until ANC $\geq 1.0 \times 10^9/l$ and platelets $\geq 50 \times 10^9/l$ (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 < $1.0 \times 10^9/l$ and/or platelets < $50 \times 10^9/l$	(1) First episode: stop ponatinib until ANC > $1.5 \times 10^9/l$ and platelets > $75 \times 10^9/l$ and resume at 45 mg daily (2) Second episode: stop ponatinib until ANC > $1.5 \times 10^9/l$ and platelets > $75 \times 10^9/l$ and resume at 30 mg daily (3) Third episode: stop ponatinib until ANC > $1.5 \times 10^9/l$ and platelets > $75 \times 10^9/l$ 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 <i>et al.</i> ¹							
Design: randomized trial, newly diagnosed CML CP patients							
Planned dose: 400 mg daily. <i>N</i> = 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 <i>et al.</i> ¹⁷⁴							
Design: follow-up of IRIS							
Planned dose: 400 mg daily. <i>N</i> = 382							
All grades	50	37	NR	NR	45	NR	NR
Trial: Deininger <i>et al.</i> ¹⁷⁵							
Design: randomized trial, newly diagnosed CML CP patients							
Planned doses: 400 vs 800 mg daily. <i>N</i> = 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 <i>et al.</i> ¹⁰⁵							
Design: single-arm phase 2 trial, imatinib resistant or intolerant CP CML patients							
Planned dose: 400 mg twice daily. <i>N</i> = 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 <i>et al.</i> ²							
Design: randomized trial, 3 arms, newly diagnosed CML CP patients, imatinib vs nilotinib in two dose regimens							
Planned doses: 300 mg (<i>N</i> = 282) or 400 mg twice daily (<i>N</i> = 281)							
All grades, 300 mg vs 400 mg	11 vs 19	NR	5 vs 9	NR	8 vs 6	NR	24 vs 29 ^a
Grades 3 and 4, 300 mg vs 400 mg	< 1 vs 1	NR	0 vs 1	NR	1 vs 0	NR	15 vs 18 ^b 6 vs 6 ^a < 1 vs 1 ^b
Dasatinib							
Trial: Kantarjian <i>et al.</i> ⁴							
Design: randomized trial, newly diagnosed CML CP patients, imatinib vs dasatinib							
Planned dose: 100 mg once daily (<i>N</i> = 258)							
All grades	8	NR	5	NR	17	NR	NR
Grades 3 and 4	0	NR	0	NR	< 1	NR	NR
Trial: Shah <i>et al.</i> 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 (<i>N</i> = 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 <i>et al.</i> ¹⁰⁷							
Design: phase 2 study in CML CP patients after imatinib and dasatinib and/or nilotinib failure							
Planned doses: 500 mg once daily (<i>N</i> = 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 <i>et al.</i> ²²							
Design: randomized trial, newly diagnosed CML CP patients, imatinib vs bosutinib							
Planned doses: 500 mg once daily (<i>N</i> = 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 <i>et al.</i> 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). ^aReported as elevated lipase. ^bReported as elevated amylase. ^cReported as elevated lipase, and reported to be present in 6% of cases at baseline. ^dIncreased 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 agents¹⁷⁰ 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 imatinib¹⁶⁷ and ponatinib¹⁶⁸ 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 daily¹²¹ 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 $\leq 100 \times 10^9/l$, 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 hair¹⁹² and is reversible after discontinuation.¹⁹³ Less-common manifestations are skin fragility,¹⁹⁴ dermatofibromas¹⁹⁵ 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 line²¹ 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 nilotinib¹⁹⁷ or bosutinib⁷⁴ 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} colitis²³² 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 imatinib²³⁶ 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 ($\geq 1/100$ 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 ($\geq 1/1000$ 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 $\geq 1/1000$ to $< 1/100$) to common (frequency $\geq 1/100$ 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 m² 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 vacuolisation²⁶⁴ and partial Fanconi syndrome²⁶⁵ 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 dysfunction²⁷³ 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).

REFERENCES

- O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F *et al*. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003; **348**: 994–1004.
- Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C *et al*. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010; **362**: 2251–2259.
- Larson RA, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW *et al*. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia* 2012; **26**: 2197–2203.
- Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M *et al*. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2010; **362**: 2260–2270.
- Kantarjian HM, Shah NP, Cortes JE, Baccarani M, Agarwal MB, Undurraga MS *et al*. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood* 2012; **119**: 1123–1129.
- Hehlmann R, Lauseker M, Jung-Munkwitz S, Leitner A, Muller MC, Pletsch N *et al*. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-alpha in newly diagnosed chronic myeloid leukemia. *J Clin Oncol* 2011; **29**: 1634–1642.
- Kalmanti L, Saussele S, Lauseker M, Muller MC, Dietz CT, Heinrich L *et al*. Safety and efficacy of imatinib in CML over a period of 10 years: data from the randomized CML-study IV. *Leukemia* 2015; **29**: 1123–1132.
- Castagnetti F, Gugliotta G, Breccia M, Specchia G, Intermesoli T, Capucci A *et al*. Frontline treatment with imatinib mesylate in chronic myeloid leukemia patients in early chronic phase: a very long-term analysis by the GIMEMA CML Working Party. *Blood* 2013; **122**: 258.
- Gambacorti-Passerini C, Antolini L, Mahon FX, Guilhot F, Deininger M, Fava C *et al*. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. *J Natl Cancer Inst* 2011; **103**: 553–561.
- Casado LF, Garcia-Gutierrez JV, Massague I, Giraldo P, Perez-Encinas M, de Paz R *et al*. Switching to second-generation tyrosine kinase inhibitor improves the response and outcome of frontline imatinib-treated patients with chronic myeloid leukemia with more than 10% of BCR-ABL/ABL ratio at 3 months. *Cancer Med* 2015; **4**: 995–1002.
- Deininger M, O'Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP *et al*. International randomized study of interferon and ST1571 (IRIS) 8-year follow-up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with imatinib. *Blood* 2009; **114**: 462.
- Giannoudis A, Wang L, Jorgensen AL, Xinarianos G, Davies A, Pushpakom S *et al*. The hOCT1 SNPs, M420del and M408V alter imatinib uptake and M420del modifies clinical outcome in imatinib-treated chronic myeloid leukemia. *Blood* 2013; **121**: 628–637.
- Perneger T. The Council of Europe recommendation Rec(2006)7 on management of patient safety and prevention of adverse events in health care. *Int J Qual Health Care* 2008; **20**: 305–307.
- Perneger T. The Council of Europe recommendation Rec(2006)7 on management of patient safety and prevention of adverse events in health care. *Int J Qual Health Care* 2008; **20**: 305–307.
- Steegmann JL, Cervantes F, le Coutre P, Porkka K, Saglio G. Off-target effects of BCR-ABL1 inhibitors and their potential long-term implications in patients with chronic myeloid leukemia. *Leuk Lymphoma* 2012; **53**: 2351–2361.
- Rosti G, Castagnetti F, Gugliotta G, Palandri F, Baccarani M. Physician's guide to the clinical management of adverse events on nilotinib therapy for the treatment of CML. *Cancer Treat Rev* 2012; **38**: 241–248.
- Breccia M, Alimena G. Occurrence and current management of side effects in chronic myeloid leukemia patients treated frontline with tyrosine kinase inhibitors. *Leuk Res* 2013; **37**: 713–720.
- Rea D. Management of adverse events associated with tyrosine kinase inhibitors in chronic myeloid leukemia. *Ann Hematol* 2015; **94**(Suppl 2): S149–S158.
- Shah NP, Guilhot F, Cortes JE, Schiffer CA, le Coutre P, Brummendorf TH *et al*. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of phase 3 study. *Blood* 2014; **123**: 2317–2324.
- Giles FJ, le Coutre PD, Pinilla-Ibarz J, Larson RA, Gattermann N, Ottmann OG *et al*. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. *Leukemia* 2013; **27**: 107–112.
- Cortes JE, Kantarjian HM, Brummendorf TH, Kim DW, Turkina AG, Shen ZX *et al*. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood* 2011; **118**: 4567–4576.
- Cortes JE, Kim DW, Kantarjian HM, Brummendorf TH, Dyagil I, Grisevicius L *et al*. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. *J Clin Oncol* 2012; **30**: 3486–3492.
- Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C *et al*. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013; **369**: 1783–1796.
- Valent P, Hadzijušufovic E, Scherthaner G, Wolf D, Rea D, le Coutre P. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. *Blood* 2014; **125**: 901–906.
- Knickerbocker R, Dorer DJ, Haluska FG, Baccarani M, Cortes JE, Hochhaus A *et al*. Impact of dose intensity of ponatinib on selected adverse events: multivariate analyses from a pooled population of clinical trial patients. *Blood* 2014; **124**: 4546.

- 26 Cortes JE, Kim D-W, Pinilla-Ibarz J, Le Coutre P, Paquette R, Chuah C *et al.* Long-term follow-up of ponatinib efficacy and safety in the phase 2 PACE trial. *Blood* 2014; **124**: 3135.
- 27 Mayer K, Gielen GH, Willinek W, Muller MC, Wolf D. Fatal progressive cerebral ischemia in CML under third-line treatment with ponatinib. *Leukemia* 2014; **28**: 976–977.
- 28 Cortes JE, Saglio G, Baccarani M, Kantarjian HM, Mayer J, Boqué C *et al.* Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056). *Blood* 2014; **124**: 152.
- 29 Gambacorti-Passerini C, Cortes JE, Lipton JH, Dmoszynska A, Wong RS, Rossiev V *et al.* Safety of bosutinib versus imatinib in the phase 3 BELA trial in newly diagnosed chronic phase chronic myeloid leukemia. *Am J Hematol* 2014; **89**: 947–953.
- 30 Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L *et al.* Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia* 2009; **23**: 1054–1061.
- 31 Lipton J, Chuah C, Guerci-Bresler A, Rosti G, Simpson D, Assouline S *et al.* Epic: A phase 3 trial of ponatinib compared with imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CP-CML). *Blood* 2014; **124**: 519.
- 32 Giles FJ, Mauro MJ, Hong F, Ortmann CE, McNeill C, Woodman RC *et al.* Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia* 2013; **27**: 1310–1315.
- 33 Kim TD, Rea D, Schwarz M, Grille P, Nicolini FE, Rosti G *et al.* Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia* 2013; **27**: 1316–1321.
- 34 Cortes J, Mauro M, Steegmann JL, Saglio G, Malhotra R, Ukrepec JA *et al.* Cardiovascular and pulmonary adverse events in patients treated with BCR-ABL inhibitors: data from the FDA adverse event reporting system. *Am J Hematol* 2015; **90**: E66–E72.
- 35 Cortes JE, Hochhaus A, Kim DW, Shah NP, Mayer J, Rowlings P *et al.* Four-year (Yr) follow-up of patients (Pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) receiving dasatinib or imatinib: efficacy based on early response. *Blood* 2013; **122**: 653.
- 36 Hochhaus A, Rosti G, Cross NC, Steegmann JL, le Coutre P, Ossenkoppele G *et al.* Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study. *Leukemia* 2016; **30**: 57–64.
- 37 Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S *et al.* Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia* 2016; **30**: 1044–1054.
- 38 Tefferi A, Letendre L. Nilotinib treatment-associated peripheral artery disease and sudden death: yet another reason to stick to imatinib as front-line therapy for chronic myelogenous leukemia. *Am J Hematol* 2011; **86**: 610–611.
- 39 Le Coutre P, Rea D, Abruzzese E, Dombret H, Trawinska MM, Herndlhofer S *et al.* Severe peripheral arterial disease during nilotinib therapy. *J Natl Cancer Inst* 2011; **103**: 1347–1348.
- 40 Quintas-Cardama A, Kantarjian H, Cortes J. Nilotinib-associated vascular events. *Clin Lymphoma Myeloma Leuk* 2012; **12**: 337–340.
- 41 Labussière-Wallet H, Guillermin Y, Etienne M, Barale A-C, Serrier C, Tigaud I *et al.* Analysis of clinical arterial and metabolic parameters in chronic phase CML patients on nilotinib in a single center cohort. *Blood* 2012; **120**: 3756.
- 42 Levato L, Cantaffa R, Kropp MG, Magro D, Piro E, Molica S. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in chronic myeloid leukemia: a single institution study. *Eur J Haematol* 2013; **90**: 531–532.
- 43 Giles F, Baccarani M, Brummendorf TH, Hellmann A, Mahon F-X, Rosti G *et al.* Deep molecular responses in patients with newly diagnosed chronic myeloid leukemia receiving nilotinib as assessed within the EUTOS laboratory network in the ENEST1st study. *Blood* 2013; **122**: 4030.
- 44 Jeon YW, Lee SE, Choi S-Y, Kim S-H, Park J-E, Jeon H-R *et al.* Peripheral arterial occlusive disease (PAOD) in chronic phase chronic myeloid leukemia patients treated with nilotinib. *Blood* 2013; **122**: 4018.
- 45 le Coutre PD, Hughes TP, Mahon F-X, Kim D-W, Steegmann JL, Shah NP *et al.* Peripheral arterial occlusive disease (PAOD) in patients (Pts) receiving dasatinib: experience across multiple clinical trials. *Blood* 2013; **122**: 1489.
- 46 Larson RA, Kim DW, Issaragrisil S, le Coutre P, Dorlhiac Llacer PE, Etienne G *et al.* Efficacy and safety of nilotinib (NIL) vs imatinib (IM) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): long-term follow-up (f/u) of ENESTnd. *Blood* 2014; **124**: 4541.
- 47 Gugliotta G, Castagnetti F, Breccia M. Five-year outcome of 215 newly diagnosed chronic myeloid leukemia patients treated frontline with nilotinib-based regimens: a gimema cml working party analysis. *Blood* 2014; **124**: 3141.
- 48 Hadzijušević E, Albrecht-Schgoer K, Huber K, Grebien F, Eisenwort G, Schgoer W *et al.* Further evaluation of pro-atherogenic and anti-angiogenic effects of nilotinib in mice and in patients with Ph-Chromosome+ CML. *Blood* 2014; **124**: 1800.
- 49 Fossard G, Blond E, Giraudier S, Morisset S, Ruby J, Escoffre-Barbe M *et al.* Hyperhomocysteinemia and high doses of nilotinib favour cardio-vascular events in chronic phase chronic myelogenous leukemia (CML) patients. *Blood* 2014; **124**: 3136.
- 50 Gilbert J, Deplano S, Szydło R, Palanicawandar R, Gerrard G, Foroni L *et al.* Incidence of vascular thrombotic events in 183 consecutive patients treated with nilotinib: a single centre experience. *Blood* 2014; **124**: 3147.
- 51 Rea D, Mirault T, Raffoux E, Boissel N, Andreoli AL, Rousselot P *et al.* Usefulness of the 2012 European CVD risk assessment model to identify patients at high risk of cardiovascular events during nilotinib therapy in chronic myeloid leukemia. *Leukemia* 2015; **29**: 1206–1209.
- 52 Cortes JE, Saglio G, Baccarani M, Kantarjian HM, Mayer J, Boqué C *et al.* Final study results of the phase 3 dasatinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) trial (DASISION, CA180-056). *Blood* 2014; **124**: 152.
- 53 Aichberger KJ, Herndlhofer S, Schernthaner GH, Schillinger M, Mitterbauer-Hohendanner G, Sillaber C *et al.* Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *Am J Hematol* 2011; **86**: 533–539.
- 54 Gora-Tybor J, Medras E, Calbecka M, Kolkowska-Lesniak A, Ponikowska-Szyba E, Robak T *et al.* Real-life comparison of severe vascular events and other non-hematological complications in chronic myeloid leukemia patients undergoing second line nilotinib or dasatinib treatment. *Leuk Lymphoma* 2015; **7**: 1–19.
- 55 Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M *et al.* European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012; **33**: 1635–1701.
- 56 Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss L *et al.* Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **61**: 1555–1570.
- 57 Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S *et al.* Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997; **26**: 517–538.
- 58 Mirault T, Rea D, Azarine A, Messas E. Rapid onset of peripheral artery disease in a chronic myeloid leukemia patient without prior arterial disorder: direct relationship with nilotinib exposure and clinical outcome. *Eur J Haematol* 2015; **94**: 363–367.
- 59 Kerkela R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C *et al.* Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006; **12**: 908–916.
- 60 Rosti G, Martinelli G, Baccarani M. In reply to 'Cardiotoxicity of the cancer therapeutic agent imatinib mesylate'. *Nat Med* 2007; **13**: 15.
- 61 Atallah E, Kantarjian H, Cortes J. In reply to 'Cardiotoxicity of the cancer therapeutic agent imatinib mesylate'. *Nat Med* 2007; **13**: 14.
- 62 Hatfield A, Owen S, Pilot PR. In reply to 'Cardiotoxicity of the cancer therapeutic agent imatinib mesylate'. *Nat Med* 2007; **13**: 13.
- 63 Gambacorti-Passerini C, Tornaghi L, Franceschino A, Piazza R, Corneo G, Pogliani E. In reply to 'Cardiotoxicity of the cancer therapeutic agent imatinib mesylate'. *Nat Med* 2007; **13**: 13–14.
- 64 Estabragh ZR, Knight K, Watmough SJ, Lane S, Vinjamuri S, Hart G *et al.* A prospective evaluation of cardiac function in patients with chronic myeloid leukaemia treated with imatinib. *Leuk Res* 2011; **35**: 49–51.
- 65 Ribeiro AL, Marcolino MS, Bittencourt HN, Barbosa MM, Nunes Mdo C, Xavier VF *et al.* An evaluation of the cardiotoxicity of imatinib mesylate. *Leuk Res* 2008; **32**: 1809–1814.
- 66 Marcolino MS, Ribeiro AL, Clementino NC, Nunes Mdo C, Barbosa MM, Silva MH *et al.* The use of imatinib mesylate has no adverse effects on the heart function. Results of a pilot study in patients with chronic myeloid leukemia. *Leuk Res* 2011; **35**: 317–322.
- 67 Atallah E, Durand JB, Kantarjian H, Cortes J. Congestive heart failure is a rare event in patients receiving imatinib therapy. *Blood* 2007; **110**: 1233–1237.
- 68 Marcolino MS, Boersma E, Clementino NC, Nunes Mdo C, Barbosa MM, Silva MH *et al.* The duration of the use of imatinib mesylate is only weakly related to elevated BNP levels in chronic myeloid leukaemia patients. *Hematol Oncol* 2011; **29**: 124–130.
- 69 Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boque C *et al.* Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year

- follow-up from a randomized phase 3 trial (DASISION). *Blood* 2014; **123**: 494–500.
- 70 Shah DR, Shah RR, Morganroth J. Tyrosine kinase inhibitors: their on-target toxicities as potential indicators of efficacy. *Drug Safety* 2013; **36**: 413–426.
- 71 Kloth JS, Pagani A, Verboom MC, Malovini A, Napolitano C, Kruit WH et al. Incidence and relevance of QTc-interval prolongation caused by tyrosine kinase inhibitors. *Br J Cancer* 2015; **112**: 1011–1016.
- 72 Sonnichsen D, Dorer DJ, Cortes J, Talpaz M, Deininger MW, Shah NP et al. Analysis of the potential effect of ponatinib on the QTc interval in patients with refractory hematological malignancies. *Cancer Chemother Pharmacol* 2013; **71**: 1599–1607.
- 73 Abbas R, Hug BA, Leister C, Gaaloul ME, Chalon S, Sonnichsen D. A phase I ascending single-dose study of the safety, tolerability, and pharmacokinetics of bosutinib (SKI-606) in healthy adult subjects. *Cancer Chemother Pharmacol* 2012; **69**: 221–227.
- 74 Brummendorf TH, Cortes JE, de Souza CA, Guilhot F, Duvillie L, Pavlov D et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. *Br J Haematol* 2015; **1**: 69–81.
- 75 Sonnichsen D, Dorer DJ, Cortes J, Talpaz M, Deininger MW, Shah NP et al. Analysis of the potential effect of ponatinib on the QTc interval in patients with refractory hematological malignancies. *Cancer Chemother Pharmacol* 2013; **71**: 1599–1607.
- 76 Johnson FM, Agrawal S, Burris H, Rosen L, Dhillon N, Hong D et al. Phase 1 pharmacokinetic and drug-interaction study of dasatinib in patients with advanced solid tumors. *Cancer* 2010; **116**: 1582–1591.
- 77 Orphanos GS, Ioannidis GN, Ardavanis AG. Cardiotoxicity induced by tyrosine kinase inhibitors. *Acta Oncol* 2009; **48**: 964–970.
- 78 Quintas-Cardama A, Kantarjian H, O'Brien S, Borthakur G, Bruzzi J, Munden R et al. Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. *J Clin Oncol* 2007; **25**: 3908–3914.
- 79 de Lavallade H, Punjalingam S, Milojkovic D, Bua M, Khorashad JS, Gabriel IH et al. Pleural effusions in patients with chronic myeloid leukaemia treated with dasatinib may have an immune-mediated pathogenesis. *Br J Haematol* 2008; **141**: 745–747.
- 80 Breccia M, D'Elia GM, D'Andrea M, Latagliata R, Alimena G. Pleural-pericardic effusion as uncommon complication in CML patients treated with Imatinib. *Eur J Haematol* 2005; **74**: 89–90.
- 81 Brave M, Goodman V, Kaminskas E, Farrell A, Timmer W, Pope S et al. Sprycel for chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. *Clin Cancer Res* 2008; **14**: 352–359.
- 82 Pavlu J, Marin D. Dasatinib and chronic myeloid leukemia: two-year follow-up in eight clinical trials. *Clin Lymphoma Myeloma* 2009; **9**: 417–424.
- 83 Hochhaus A, Kantarjian HM, Baccarani M, Lipton JH, Apperley JF, Druker BJ et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007; **109**: 2303–2309.
- 84 Kantarjian H, Pasquini R, Hamerschlak N, Rousselot P, Holowiecki J, Jootar S et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: a randomized phase 2 trial. *Blood* 2007; **109**: 5143–5150.
- 85 Apperley JF, Cortes JE, Kim DW, Roy L, Roboz GJ, Rosti G et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. *J Clin Oncol* 2009; **27**: 3472–3479.
- 86 Saglio G, Hochhaus A, Goh YT, Masszi T, Pasquini R, Maloisel F et al. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. *Cancer* 2010; **116**: 3852–3861.
- 87 Shah NP, Kantarjian HM, Kim DW, Rea D, Dorlhiac-Llacer PE, Milone JH et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. *J Clin Oncol* 2008; **26**: 3204–3212.
- 88 Porkka K, Baccarani M, Cortes J, Hochhaus A, Kantarjian H, Shah N et al. Pleural effusion in patients with chronic-phase chronic myeloid leukemia (CML-CP) who received first-line dasatinib in the DASISION trial: patient characteristics, management, and outcomes. 16th Congress of the EHA. *Haematologica* 2011; **692**.
- 89 Porkka K, Khoury HJ, Paquette RL, Matloub Y, Sinha R, Cortes JE. Dasatinib 100 mg once daily minimizes the occurrence of pleural effusion in patients with chronic myeloid leukemia in chronic phase and efficacy is unaffected in patients who develop pleural effusion. *Cancer* 2010; **116**: 377–386.
- 90 Latagliata R, Breccia M, Fava C, Stagno F, Tribelli M, Luciano L et al. Incidence, risk factors and management of pleural effusions during dasatinib treatment in unselected elderly patients with chronic myelogenous leukaemia. *Hematol Oncol* 2013; **31**: 363–369.
- 91 Kim D, Goh HG, Kim SH, Cho BS, Kim DW. Long-term pattern of pleural effusion from chronic myeloid leukemia patients in second-line dasatinib therapy. *Int J Hematol* 2011; **94**: 361–371.
- 92 Breccia M, Latagliata R, Stagno F, Luciano L, Gozzini A, Castagnetti F et al. Charlson comorbidity index and adult comorbidity evaluation-27 scores might predict treatment compliance and development of pleural effusions in elderly patients with chronic myeloid leukemia treated with second-line dasatinib. *Haematologica* 2011; **96**: 1457–1461.
- 93 La Rosee P, Martiat P, Leitner A, Klag T, Muller MC, Erben P et al. Improved tolerability by a modified intermittent treatment schedule of dasatinib for patients with chronic myeloid leukemia resistant or intolerant to imatinib. *Ann Hematol* 2013; **92**: 1345–1350.
- 94 Rasheed W, Flaim B, Seymour JF. Reversible severe pulmonary hypertension secondary to dasatinib in a patient with chronic myeloid leukemia. *Leuk Res* 2009; **33**: 861–864.
- 95 Mattei D, Feola M, Orzan F, Mordini N, Rapezzi D, Gallamini A. Reversible dasatinib-induced pulmonary arterial hypertension and right ventricle failure in a previously allografted CML patient. *Bone Marrow Transplant* 2009; **43**: 967–968.
- 96 Dumitrescu D, Seck C, ten Freyhaus H, Gerhardt F, Erdmann E, Rosenkranz S. Fully reversible pulmonary arterial hypertension associated with dasatinib treatment for chronic myeloid leukaemia. *Eur Respir J* 2011; **38**: 218–220.
- 97 Montani D, Bergot E, Gunther S, Savale L, Bergeron A, Bourdin A et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation* 2012; **125**: 2128–2137.
- 98 Bergeron A, Bergot E, Vilela G, Ades L, Devergie A, Esperou H et al. Hypersensitivity pneumonitis related to imatinib mesylate. *J Clin Oncol* 2002; **20**: 4271–4272.
- 99 Ma CX, Hobday TJ, Jett JR. Imatinib mesylate-induced interstitial pneumonitis. *Mayo Clin Proc* 2003; **78**: 1578–1579.
- 100 Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol* 2005; **79**: 80–81.
- 101 Go SW, Kim BK, Lee SH, Kim TJ, Huh JY, Lee JM et al. Successful rechallenge with imatinib in a patient with chronic myeloid leukemia who previously experienced imatinib mesylate induced pneumonitis. *Tuberc Respir Dis* 2013; **75**: 256–259.
- 102 Tamura M, Saraya T, Fujiwara M, Hiraoka S, Yokoyama T, Yano K et al. High-resolution computed tomography findings for patients with drug-induced pulmonary toxicity, with special reference to hypersensitivity pneumonitis-like patterns in gemcitabine-induced cases. *Oncologist* 2013; **18**: 454–459.
- 103 Bergeron A, Rea D, Levy V, Picard C, Meignin V, Tamburini J et al. Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: a case series. *Am J Respir Crit Care Med* 2007; **176**: 814–818.
- 104 Teo YL, Ho HK, Chan A. Risk of tyrosine kinase inhibitors-induced hepatotoxicity in cancer patients: a meta-analysis. *Cancer Treat Rev* 2013; **39**: 199–206.
- 105 Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, Gattermann N et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. *Blood* 2011; **117**: 1141–1145.
- 106 Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PE, Enrico A et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. *Haematologica* 2010; **95**: 232–240.
- 107 Khoury HJ, Cortes JE, Kantarjian HM, Gambacorti-Passerini C, Baccarani M, Kim DW et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood* 2012; **119**: 3403–3412.
- 108 Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. *Drug Safety* 2013; **36**: 491–503.
- 109 Spataro V. Nilotinib in a patient with postnecrotic liver cirrhosis related to imatinib. *J Clin Oncol* 2011; **29**: e50–e52.
- 110 Tonyali O, Coskun U, Yildiz R, Karakan T, Demirci U, Akyurek N et al. Imatinib mesylate-induced acute liver failure in a patient with gastrointestinal stromal tumors. *Med Oncol* 2010; **27**: 768–773.
- 111 Lin NU, Sarantopoulos S, Stone JR, Galinsky I, Stone RM, Deangelo DJ et al. Fatal hepatic necrosis following imatinib mesylate therapy. *Blood* 2003; **102**: 3455–3456.
- 112 Kikuchi S, Muroi K, Takahashi S, Kawano-Yamamoto C, Takatoku M, Miyazato A et al. Severe hepatitis and complete molecular response caused by imatinib mesylate: possible association of its serum concentration with clinical outcomes. *Leuk Lymphoma* 2004; **45**: 2349–2351.
- 113 Cross TJ, Bagot C, Portmann B, Wendon J, Gillett D. Imatinib mesylate as a cause of acute liver failure. *Am J Hematol* 2006; **81**: 189–192.

- 114 James C, Trouette H, Marit G, Cony-Makhoul P, Mahon FX. Histological features of acute hepatitis after imatinib mesylate treatment. *Leukemia* 2003; **17**: 978–979.
- 115 Ohyashiki K, Kuriyama Y, Nakajima A, Tauchi T, Ito Y, Miyazawa H *et al*. Imatinib mesylate-induced hepato-toxicity in chronic myeloid leukemia demonstrated focal necrosis resembling acute viral hepatitis. *Leukemia* 2002; **16**: 2160–2161.
- 116 Singer JB, Shou Y, Giles F, Kantarjian HM, Hsu Y, Robeva AS *et al*. UGT1A1 promoter polymorphism increases risk of nilotinib-induced hyperbilirubinemia. *Leukemia* 2007; **21**: 2311–2315.
- 117 Ayoub WS, Geller SA, Tran T, Martin P, Vierling JM, Poordad FF. Imatinib (Gleevec)-induced hepatotoxicity. *J Clin Gastroenterol* 2005; **39**: 75–77.
- 118 Ridruejo E, Cacchione R, Villamil AG, Marciano S, Gadano AC, Mando OG. Imatinib-induced fatal acute liver failure. *World J Gastroenterol* 2007; **13**: 6608–6111.
- 119 Ferrero D, Pogliani EM, Rege-Cambrin G, Fava C, Mattioli G, Dellacasa C *et al*. Corticosteroids can reverse severe imatinib-induced hepatotoxicity. *Haematologica* 2006; **91** (6 Suppl): ECR27.
- 120 Perini GF, Santos FP, Funke V, Ruiz J, Neto BH, Hamerschlag N. Nilotinib post-liver transplantation for acute hepatic failure related to imatinib. *Leuk Res* 2009; **33**: e234–e235.
- 121 Cortes JE, Hochhaus A, le Coutre PD, Rosti G, Pinilla-Ibarz J, Jabbour E *et al*. Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib. *Blood* 2011; **117**: 5600–5606.
- 122 Harbaum L, Marx A, Goekkkurt E, Schafhausen P, Atanackovic D. Treatment with dasatinib for chronic myeloid leukemia following imatinib-induced hepatotoxicity. *Int J Hematol* 2014; **99**: 91–94.
- 123 Breccia M, Muscaritoli M, Gentilini F, Latagliata R, Carosino I, Rossi Fanelli F *et al*. Impaired fasting glucose level as metabolic side effect of nilotinib in non-diabetic chronic myeloid leukemia patients resistant to imatinib. *Leuk Res* 2007; **31**: 1770–1772.
- 124 Nicolini FE, Turkina A, Shen ZX, Gallagher N, Jootar S, Powell BL *et al*. Expanding nilotinib access in clinical trials (ENACT): an open-label, multicenter study of oral nilotinib in adult patients with imatinib-resistant or imatinib-intolerant Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase. *Cancer* 2012; **118**: 118–126.
- 125 le Coutre P, Giles FJ, Hochhaus A, Martinelli G, Wang J, Passos V *et al*. Analysis of glucose profiles in imatinib-resistant or intolerant chronic myelogenous leukemia (CML) patients (pts) treated with nilotinib: lack of correlation between glucose levels and nilotinib efficacy. *Blood* 2007; **110**: 4588.
- 126 Saglio G, Larson RA, Hughes TP, Issaragrisil S, Turkina AG, Marin D *et al*. Efficacy and safety of nilotinib in chronic phase (CP) chronic myeloid leukemia (CML) patients (Pts) with type 2 diabetes in the ENESTnd trial. *Blood* 2010; **116**: 3430.
- 127 Rea D, Gautier JF, Breccia M, Saglio G, Hughes TP, Kantarjian HM *et al*. Incidence of Hyperglycemia by 3 Years in Patients (Pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Nilotinib (NIL) or Imatinib (IM) in ENESTnd. *Blood* 2012; **120**: 1686.
- 128 Breccia M, Muscaritoli M, Cannella L, Stefanizzi C, Frustaci A, Alimena G. Fasting glucose improvement under dasatinib treatment in an accelerated phase chronic myeloid leukemia patient unresponsive to imatinib and nilotinib. *Leuk Res* 2008; **32**: 1626–1628.
- 129 Agostino NM, Chinchilli VM, Lynch CJ, Koszyk-Szewczyk A, Gingrich R, Sivik J *et al*. Effect of the tyrosine kinase inhibitors (sunitinib, sorafenib, dasatinib, and imatinib) on blood glucose levels in diabetic and nondiabetic patients in general clinical practice. *J Oncol Pharm Pract* 2011; **17**: 197–202.
- 130 Larson R, le Coutre P, Reiffers J, Hughes TP, Saglio G, Edrich P *et al*. Comparison of nilotinib and imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd beyond one year. *ASCO Meeting Abstracts* 2008; **26**(15_suppl): 6501.
- 131 Gottardi M, Manzato E, Gherlinzoni F. Imatinib and hyperlipidemia. *N Engl J Med* 2005; **353**: 2722–2723.
- 132 Franceschino A, Tornaghi L, Benemacher V, Assouline S, Gambacorti-Passerini C. Alterations in creatine kinase, phosphate and lipid values in patients with chronic myeloid leukemia during treatment with imatinib. *Haematologica* 2008; **93**: 317–318.
- 133 Gologan R, Constantinescu G, Georgescu D, Ostroveanu D, Vasilache D, Dobrea C *et al*. Hypolipemiant besides antileukemic effect of imatinib mesylate. *Leuk Res* 2009; **33**: 1285–1287.
- 134 Rea D, Mirault T, Cluzeau T, Gautier JF, Guilhot F, Dombret H *et al*. Early onset hypercholesterolemia induced by the second generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. *Haematologica* 2014; **99**: 1197–1203.
- 135 Cortes JE, Kantarjian H, Shah NP, Bixby D, Mauro MJ, Flinn I *et al*. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med* 2012; **367**: 2075–2088.
- 136 Hiwase DK, Yeung DT, Carne L. Hypercholesterolemia in imatinib intolerant/resistant CML-CP patients treated with nilotinib: a retrospective analysis. *Blood* 2013; **122**: 1503.
- 137 Berman E, Nicolaides M, Maki RG, Fleisher M, Chanel S, Scheu K *et al*. Altered bone and mineral metabolism in patients receiving imatinib mesylate. *N Engl J Med* 2006; **354**: 2006–2013.
- 138 Osorio S, Noblejas AG, Duran A, Steegmann JL. Imatinib mesylate induces hypophosphatemia in patients with chronic myeloid leukemia in late chronic phase, and this effect is associated with response. *Am J Hematol* 2007; **82**: 394–395.
- 139 Berman E, Girotra M, Cheng C, Chanel S, Maki R, Shelat M *et al*. Effect of long term imatinib on bone in adults with chronic myelogenous leukemia and gastrointestinal stromal tumors. *Leuk Res* 2013; **37**: 790–794.
- 140 Kim TD, Schwarz M, Nogai H, Grille P, Westermann J, Plockinger U *et al*. Thyroid dysfunction caused by second-generation tyrosine kinase inhibitors in Philadelphia chromosome-positive chronic myeloid leukemia. *Thyroid* 2010; **20**: 1209–1214.
- 141 Gambacorti-Passerini C, Tornaghi L, Cavagnini F, Rossi P, Pecori-Giraldi F, Mariani L *et al*. Gynaecomastia in men with chronic myeloid leukaemia after imatinib. *Lancet* 2003; **361**: 1954–1956.
- 142 Caocci G, Atzeni S, Orru N, Azzena L, Martorana L, Littera R *et al*. Gynecomastia in a male after dasatinib treatment for chronic myeloid leukemia. *Leukemia* 2008; **22**: 2127–2128.
- 143 Sneed TB, Kantarjian HM, Talpaz M, O'Brien S, Rios MB, Bekele BN *et al*. The significance of myelosuppression during therapy with imatinib mesylate in patients with chronic myelogenous leukemia in chronic phase. *Cancer* 2004; **100**: 116–121.
- 144 Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF *et al*. European LeukemiaNet recommendations for the management of chronic myeloid leukemia. *Blood* 2013; **122**: 872–884.
- 145 NCCN. Chronic Myelogenous leukemia. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) version 3.2013. Available at http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
- 146 Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F *et al*. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2006; **108**: 1809–1820.
- 147 Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J *et al*. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol* 2009; **27**: 6041–6051.
- 148 Kantarjian H, Talpaz M, O'Brien S, Garcia-Manero G, Verstovsek S, Giles F *et al*. High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome-positive chronic phase chronic myeloid leukemia. *Blood* 2004; **103**: 2873–2878.
- 149 Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, Palandri F *et al*. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007; **110**: 3540–3546.
- 150 Hochhaus A, Baccarani M, Deininger M, Apperley JF, Lipton JH, Goldberg SL *et al*. Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. *Leukemia* 2008; **22**: 1200–1206.
- 151 Cortes JE, Kantarjian HM, Goldberg SL, Powell BL, Giles FJ, Wetzler M *et al*. High-dose imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: high rates of rapid cytogenetic and molecular responses. *J Clin Oncol* 2009; **27**: 4754–4759.
- 152 Cortes JE, Jones D, O'Brien S, Jabbour E, Konopleva M, Ferrajoli A *et al*. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol* 2010; **28**: 392–397.
- 153 Rosti G, Palandri F, Castagnetti F, Breccia M, Levato L, Gugliotta G *et al*. Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. *Blood* 2009; **114**: 4933–4938.
- 154 Castagnetti F, Palandri F, Amabile M, Testoni N, Luatti S, Soverini S *et al*. Results of high-dose imatinib mesylate in intermediate Sokal risk chronic myeloid leukemia patients in early chronic phase: a phase 2 trial of the GIMEMA CML Working Party. *Blood* 2009; **113**: 3428–3434.
- 155 Preudhomme C, Guilhot J, Nicolini FE, Guerci-Bresler A, Rigal-Huguet F, Maloisel F *et al*. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. *N Engl J Med* 2010; **363**: 2511–2521.
- 156 Radich JP, Kopecky KJ, Appelbaum FR, Kamel-Reid S, Stock W, Malnassy G *et al*. A randomized trial of dasatinib 100 mg vs imatinib 400 mg in newly diagnosed chronic phase chronic myeloid leukemia. *Blood* 2012; **120**: 3898–3905.
- 157 Baccarani M, Druker BJ, Branford S, Kim DW, Pane F, Mongay L *et al*. Long-term response to imatinib is not affected by the initial dose in patients with

- Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: final update from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study. *Int J Hematol* 2014; **99**: 616–624.
- 158 Cortes JE, Jones D, O'Brien S, Jabbour E, Ravandi F, Koller C et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol* 2010; **28**: 398–404.
- 159 Wang J, Shen ZX, Saglio G, Jin J, Huang H, Hu Y et al. Phase 3 study of nilotinib vs imatinib in Chinese patients with newly diagnosed chronic myeloid leukemia in chronic phase: ENESTchina. *Blood* 2015; **125**: 2771–2778.
- 160 Guilhot F, Hughes TP, Cortes J, Druker BJ, Baccarani M, Gathmann I et al. Plasma exposure of imatinib and its correlation with clinical response in the Tyrosine Kinase Inhibitor Optimization and Selectivity Trial. *Haematologica* 2012; **97**: 731–738.
- 161 Proetel U, Pletsch N, Lauseker M, Muller MC, Hanfstein B, Krause SW et al. Older patients with chronic myeloid leukemia (≥ 65 years) profit more from higher imatinib doses than younger patients: a subanalysis of the randomized CML-Study IV. *Ann Hematol* 2014; **93**: 1167–1176.
- 162 Cortes J, Hochhaus A, Kim DW, Shah NP, Mayer J, Rowings P et al. Four-year (Yr) follow-up of patients (Pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) receiving dasatinib or imatinib: efficacy based on early response. *Blood* 2013; **122**: 653.
- 163 Futosi K, Nemeth T, Pick R, Vantus T, Walzog B, Mocsai A. Dasatinib inhibits proinflammatory functions of mature human neutrophils. *Blood* 2012; **119**: 4981–4991.
- 164 Quintas-Cardama A, Kantarjian H, Ravandi F, O'Brien S, Thomas D, Vidal-Senmache G et al. Bleeding diathesis in patients with chronic myelogenous leukemia receiving dasatinib therapy. *Cancer* 2009; **115**: 2482–2490.
- 165 Nazha A, Romo CG, Kantarjian H, Cortes J. The clinical impact of ponatinib on the risk of bleeding in patients with chronic myeloid leukemia. *Haematologica* 2013; **98**: e131.
- 166 Gratacap MP, Martin V, Valera MC, Allart S, Garcia C, Sie P et al. The new tyrosine-kinase inhibitor and anticancer drug dasatinib reversibly affects platelet activation *in vitro* and *in vivo*. *Blood* 2009; **114**: 1884–1892.
- 167 Quintas-Cardama A, Han X, Kantarjian H, Cortes J. Tyrosine kinase inhibitor-induced platelet dysfunction in patients with chronic myeloid leukemia. *Blood* 2009; **114**: 261–263.
- 168 Neelakantan P, Marin D, Laffan M, Goldman J, Apperley J, Milojkovic D. Platelet dysfunction associated with ponatinib, a new pan BCR-ABL inhibitor with efficacy for chronic myeloid leukemia resistant to multiple tyrosine kinase inhibitor therapy. *Haematologica* 2012; **97**: 1444.
- 169 Marin D, Markt S, Bua M, Szydlo RM, Franceschino A, Nathan I et al. Prognostic factors for patients with chronic myeloid leukaemia in chronic phase treated with imatinib mesylate after failure of interferon alfa. *Leukemia* 2003; **17**: 1448–1453.
- 170 Cortes J, O'Brien S, Quintas A, Giles F, Shan J, Rios MB et al. Erythropoietin is effective in improving the anemia induced by imatinib mesylate therapy in patients with chronic myeloid leukemia in chronic phase. *Cancer* 2004; **100**: 2396–2402.
- 171 Gallipoli P, Pellicano F, Morrison H, Laidlaw K, Allan EK, Bhatia R et al. Autocrine TNF-alpha production supports CML stem and progenitor cell survival and enhances their proliferation. *Blood* 2013; **122**: 3335–3339.
- 172 Jorgensen HG, Copland M, Holyoake TL. Granulocyte-colony-stimulating factor (Filgrastim) may overcome imatinib-induced neutropenia in patients with chronic-phase myelogenous leukemia. *Cancer* 2005; **103**: 210–211.
- 173 Khoury HJ, Goldberg SL, Mauro MJ. Dasatinib lack of cross intolerance to imatinib in patients (pts) with chronic myelogenous leukemia chronic phase (CML-CP) intolerant to imatinib: a retrospective analysis of safety. *ASCO Meeting Abstracts* 2008; **26**(15_suppl): 7015.
- 174 Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006; **355**: 2408–2417.
- 175 Deininger MW, Kopecky KJ, Radich JP, Kamel-Reid S, Stock W, Paietta E et al. Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: results of SWOG S0325, an intergroup randomized PHASE II trial in newly diagnosed chronic phase chronic myeloid leukaemia. *Br J Haematol* 2014; **164**: 223–232.
- 176 Efficace F, Baccarani M, Breccia M, Alimena G, Rosti G, Cottone F et al. Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. *Blood* 2011; **118**: 4554–4560.
- 177 Joensuu H, Trent JC, Reichardt P. Practical management of tyrosine kinase inhibitor-associated side effects in GIST. *Cancer Treat Rev* 2011; **37**: 75–88.
- 178 Kantarjian H, Shah NP, Hochhaus A, Cortes JE, Shah S, Ayala M et al. Dasatinib compared to imatinib (IM) in patients (pts) with newly diagnosed chronic-phase chronic myelogenous leukemia in chronic phase (CML-CP): Twelve-month efficacy and safety from the phase III DASISION study. *ASCO Meeting Abstracts* 2010; **28**(18_suppl): 6500.
- 179 Palandri F, Castagnetti F, Soverini S, Poerio A, Gugliotta G, Luatti S et al. Pancreatic enzyme elevation in chronic myeloid leukemia patients treated with nilotinib after imatinib failure. *Haematologica* 2009; **94**: 1758–1761.
- 180 Nicolini FE, Masszi T, Shen Z, Gallagher NJ, Jootar S, Powell BL et al. Expanding Nilotinib Access in Clinical Trials (ENACT), an open-label multicenter study of oral nilotinib in adult patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase or blast crisis. *Leuk Lymphoma* 2012; **53**: 907–914.
- 181 Brazzelli V, Grasso V, Borroni G. Imatinib, dasatinib and nilotinib: a review of adverse cutaneous reactions with emphasis on our clinical experience. *J Eur Acad Dermatol Venereol* 2013; **27**: 1471–1480.
- 182 Cortes JE, Baccarani M, Guilhot F, Druker BJ, Branford S, Kim DW et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. *J Clin Oncol* 2010; **28**: 424–430.
- 183 Valeyrie L, Bastuji-Garin S, Revuz J, Bachot N, Wechsler J, Berthaud P et al. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol* 2003; **48**: 201–206.
- 184 Drummond A, Micallef-Eyraud P, Douglas WS, Hay I, Holyoake TL, Drummond MW. A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Glivec). *Br J Haematol* 2003; **120**: 911–913.
- 185 Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. *Dermatol Ther* 2011; **24**: 386–395.
- 186 Scheinfeld N. Imatinib mesylate and dermatology part 2: a review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol* 2006; **5**: 228–231.
- 187 Hensley ML, Ford JM. Imatinib treatment: specific issues related to safety, fertility, and pregnancy. *Semin Hematol* 2003; **40** (2 Suppl 2): 21–25.
- 188 Breccia M, Carosino I, Russo E, Morano SG, Latagliata R, Alimena G. Early and tardive skin adverse events in chronic myeloid leukaemia patients treated with imatinib. *Eur J Haematol* 2005; **74**: 121–123.
- 189 Leong KW, Lee TC, Goh AS. Imatinib mesylate causes hypopigmentation in the skin. *Cancer* 2004; **100**: 2486–2487, author reply 2487–2488.
- 190 Llamas-Velasco M, Fraga J, Kutzner H, Steegmann JL, Garcia-Diez A, Requena L. Hypopigmented macules secondary to imatinib for the treatment of chronic myeloid leukemia: a histopathologic and immunohistochemical study. *J Cutan Pathol* 2014; **41**: 417–426.
- 191 Brazzelli V, Prestinari F, Barbagallo T, Rona C, Orlandi E, Passamonti F et al. A long-term time course of colorimetric assessment of the effects of imatinib mesylate on skin pigmentation: a study of five patients. *J Eur Acad Dermatol Venereol* 2007; **21**: 384–387.
- 192 Etienne G, Cony-Makhoul P, Mahon FX. Imatinib mesylate and gray hair. *N Engl J Med* 2002; **347**: 446.
- 193 Mariani S, Abruzzese E, Basciani S, Fiore D, Persichetti A, Watanabe M et al. Reversible hair depigmentation in a patient treated with imatinib. *Leuk Res* 2011; **35**: e64–e66.
- 194 Gambacorti-Passerini C, Piazza R. Choosing the right TKI for chronic myeloid leukemia: when the truth lies in "long-term" safety and efficacy. *Am J Hematol* 2011; **86**: 531–532.
- 195 Llamas-Velasco M, Fraga J, Solano-Lopez GE, Steegmann JL, Garcia Diez A, Requena L. Multiple eruptive dermatofibromas related to imatinib treatment. *J Eur Acad Dermatol Venereol* 2014; **28**: 979–981.
- 196 Breccia M, Latagliata R, Carosino I, Mandelli F, Alimena G. Reactivation of porphyria cutanea tarda as a possible side effect of Imatinib at high dosage in chronic myeloid leukemia. *Leukemia* 2004; **18**: 182.
- 197 Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *Lancet Oncol* 2011; **12**: 841–851.
- 198 Drucker AM, Wu S, Busam KJ, Berman E, Amitay-Laish I, Lacouture ME. Rash with the multitargeted kinase inhibitors nilotinib and dasatinib: meta-analysis and clinical characterization. *Eur J Haematol* 2013; **90**: 142–150.
- 199 Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassmann B et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006; **354**: 2542–2551.
- 200 Kaune KM, Baumgart M, Gesk S, Mitteldorf C, Baesecke J, Glass B et al. Bullous sweet syndrome in a patient with t(9;22)(q34;q11)-positive chronic myeloid leukemia treated with the tyrosine kinase inhibitor nilotinib: interphase cytogenetic detection of BCR-ABL-positive lesional cells. *Arch Dermatol* 2008; **144**: 361–364.

- 201 Ogura M, Nakamae H, Fujisawa S, Ishizawa K, Taniwaki M, Utsunomiya A et al. Dasatinib compared with imatinib in newly diagnosed chronic myelogenous leukemia in chronic phase (CML-CP): results of Japanese Subset Analysis In DASISION Trial. *ASH Annual Meeting Abstracts* 2010; **116**: 4484.
- 202 Saglio G, Hochhaus A, Cortes JE, Kantarjian H, Baccarani M, Bradley-Garelik MB et al. Safety and efficacy of dasatinib versus imatinib by baseline cardiovascular comorbidity in patients with chronic myeloid leukemia in chronic phase (CML-CP): analysis of the DASISION Trial. *ASH Annual Meeting Abstracts* 2010; **116**: 2286.
- 203 Breccia M, Alimena G. Activity and safety of dasatinib as second-line treatment or in newly diagnosed chronic phase chronic myeloid leukemia patients. *Bio-Drugs* 2011; **25**: 147–157.
- 204 Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 2003; **21**: 1637–1647.
- 205 Rule SA, O'Brien SG, Crossman LC. Managing cutaneous reactions to imatinib therapy. *Blood* 2002; **100**: 3434–3435.
- 206 Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994; **331**: 1272–1285.
- 207 Khoury HJ, Guilhot F, Hughes TP, Kim DW, Cortes JE. Dasatinib treatment for Philadelphia chromosome-positive leukemias: practical considerations. *Cancer* 2009; **115**: 1381–1394.
- 208 Seggewiss R, Price DA, Purbhoo MA. Immunomodulatory effects of imatinib and second-generation tyrosine kinase inhibitors on T cells and dendritic cells: an update. *Cytotherapy* 2008; **10**: 633–641.
- 209 Salih J, Hilpert J, Placke T, Grunebach F, Steinle A, Salih HR et al. The BCR/ABL-inhibitors imatinib, nilotinib and dasatinib differentially affect NK cell reactivity. *Int J Cancer* 2010; **127**: 2119–2128.
- 210 Breccia M, Girmenia C, Latagliata R, Loggisci G, Santopietro M, Federico V et al. Low incidence rate of opportunistic and viral infections during imatinib treatment in chronic myeloid leukemia patients in early and late chronic phase. *Mediterr J Hematol Infect Dis* 2011; **3**: e2011021.
- 211 Mattiuzzi GN, Cortes JE, Talpaz M, Reuben J, Rios MB, Shan J et al. Development of Varicella-Zoster virus infection in patients with chronic myelogenous leukemia treated with imatinib mesylate. *Clin Cancer Res* 2003; **9**: 976–980.
- 212 Lakhani S, Davidson L, Priebe DA, Sherker AH. Reactivation of chronic hepatitis B infection related to imatinib mesylate therapy. *Hepatol Int* 2008; **2**: 498–499.
- 213 Daniels JM, Vonk-Noordegraaf A, Janssen JJ, Postmus PE, van Altena R. Tuberculosis complicating imatinib treatment for chronic myeloid leukaemia. *Eur Respir J* 2009; **33**: 670–672.
- 214 Agaimy A, Brueckl V, Schmidt D, Krieg S, Ullrich E, Meidenbauer N. Tuberculous and non-tuberculous granulomatous lymphadenitis in patients receiving imatinib mesylate (gleivec) for metastatic gastrointestinal stromal tumor. *Case Rep Oncol* 2013; **6**: 134–142.
- 215 Sanchez-Guijo FM, Duran S, Galende J, Boque C, Nieto JB, Balanzat J et al. Evaluation of tolerability and efficacy of imatinib mesylate in elderly patients with chronic phase CML: ELDERGLI study. *Leuk Res* 2011; **35**: 1184–1187.
- 216 Koren-Michowitz M, le Coutre P, Duyster J, Scheid C, Panayiotidis P, Prejzner W et al. Activity and tolerability of nilotinib: a retrospective multicenter analysis of chronic myeloid leukemia patients who are imatinib resistant or intolerant. *Cancer* 2010; **116**: 4564–4572.
- 217 Hazarika M, Jiang X, Liu Q, Lee SL, Ramchandani R, Garnett C et al. Tassigna for chronic and accelerated phase Philadelphia chromosome-positive chronic myelogenous leukemia resistant to or intolerant of imatinib. *Clin Cancer Res* 2008; **14**: 5325–5331.
- 218 Rodriguez GH, Ahmed SI, Al-akhrass F, Rallapalli V, Safdar A. Characteristics of, and risk factors for, infections in patients with cancer treated with dasatinib and a brief review of other complications. *Leuk Lymphoma* 2012; **53**: 1530–1535.
- 219 Sillaber C, Herrmann H, Bennett K, Rix U, Baumgartner C, Bohm A et al. Immunosuppression and atypical infections in CML patients treated with dasatinib at 140 mg daily. *Eur J Clin Invest* 2009; **39**: 1098–1109.
- 220 Kantarjian H, Shah NP, Cortes JE, Baccarani M, Bradley-Garelik MB, Zhu C et al. Dasatinib or imatinib (IM) in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): two-year follow-up from DASISION. *ASCO Meeting Abstracts* 2011; **29**(15_suppl): 6510.
- 221 de Lavallade H, Khoder A, Hart M, Sarvaria A, Sekine T, Alsuliman A et al. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. *Blood* 2013; **122**: 227–238.
- 222 Kim S-H, Kim HJ, Kwak J-Y, Kim JS, Mun Y-C, Park JS et al. Hepatitis B virus reactivation in chronic myeloid leukemia treated with various tyrosine kinase inhibitors: multicenter, retrospective study. *Blood* 2012; **120**: 3738.
- 223 Kreutzman A, Ladell K, Koehel C, Gostick E, Ekblom M, Stenke L et al. Expansion of highly differentiated CD8+ T-cells or NK-cells in patients treated with dasatinib is associated with cytomegalovirus reactivation. *Leukemia* 2011; **25**: 1587–1597.
- 224 Tanaka H, Nakashima S, Usuda M. Rapid and sustained increase of large granular lymphocytes and rare cytomegalovirus reactivation during dasatinib treatment in chronic myelogenous leukemia patients. *Int J Hematol* 2012; **96**: 308–319.
- 225 Mustjoki S, Ekblom M, Arstila TP, Dybedal I, Epling-Burnette PK, Guilhot F et al. Clonal expansion of T/NK-cells during tyrosine kinase inhibitor dasatinib therapy. *Leukemia* 2009; **23**: 1398–1405.
- 226 Sunami Y, Sato E, Ichikawa K, Yasuda H, Komatsu N. Hemorrhagic colitis caused by dasatinib following cytomegalovirus enterocolitis in a patient with chronic myelogenous leukemia in the second chronic phase. *Rinsho Ketsueki* 2011; **52**: 282–286.
- 227 Kim DH, Kamel-Reid S, Chang H, Sutherland R, Jung CW, Kim HJ et al. Natural killer or natural killer/T cell lineage large granular lymphocytosis associated with dasatinib therapy for Philadelphia chromosome positive leukemia. *Haematologica* 2009; **94**: 135–139.
- 228 Lee SJ, Jung CW, Kim DY, Lee KH, Sohn SK, Kwak JY et al. Retrospective multi-center study on the development of peripheral lymphocytosis following second-line dasatinib therapy for chronic myeloid leukemia. *Am J Hematol* 2011; **86**: 346–350.
- 229 Mustjoki S, Auvinen K, Kreutzman A, Rousselot P, Hernesniemi S, Melo T et al. Rapid mobilization of cytotoxic lymphocytes induced by dasatinib therapy. *Leukemia* 2013; **27**: 914–924.
- 230 Cortes J, Saglio G, le Coutre PD, Porkka K, Mustjoki S, Mohamed H et al. The association of dasatinib-induced lymphocytosis with treatment outcome in patients with chronic myeloid leukemia (CML). *Blood* 2013; **122**: 2741.
- 231 Nagata Y, Ohashi K, Fukuda S, Kamata N, Akiyama H, Sakamaki H. Clinical features of dasatinib-induced large granular lymphocytosis and pleural effusion. *Int J Hematol* 2010; **91**: 799–807.
- 232 Paydas S. Dasatinib, large granular lymphocytosis, and pleural effusion: useful or adverse effect? *Crit Rev Oncol Hematol* 2014; **89**: 242–247.
- 233 Schiffer C, Cortes J, Saglio G, le Coutre P, Guilhot F, Chen A et al. Lymphocytosis following first-line treatment for cml in chronic phase with dasatinib is associated with improved responses: a comparison with imatinib. *Blood* 2010; **116**: 358.
- 234 Efficace F, Breccia M, Saussele S, Kossak-Roth U, Cardoni A, Caocci G et al. Which health-related quality of life aspects are important to patients with chronic myeloid leukemia receiving targeted therapies and to health care professionals? GIMEMA and EORTC Quality of Life Group. *Ann Hematol* 2012; **91**: 1371–1381.
- 235 Zekri JM, Robinson MH, Woll PJ. Relative hypocalcaemia and muscle cramps in patients receiving imatinib for gastrointestinal stromal tumour. *Sarcoma* 2006; **2006**: 48948.
- 236 Dogan SS, Esmaili B. Ocular side effects associated with imatinib mesylate and perifosfor for gastrointestinal stromal tumor. *Hematol Oncol Clin North Am* 2009; **23**: 109–114, ix.
- 237 Ho WL, Wong H, Yau T. The ophthalmological complications of targeted agents in cancer therapy: what do we need to know as ophthalmologists? *Acta Ophthalmol* 2013; **91**: 604–609.
- 238 Esmaili B, Diba R, Ahmadi MA, Saadati HG, Faustina MM, Shepler TR et al. Periorbital oedema and epiphora as ocular side effects of imatinib mesylate (Gleevec). *Eye* 2004; **18**: 760–762.
- 239 Radaelli F, Vener C, Ripamonti F, Iurlo A, Colombi M, Artoni A et al. Conjunctival hemorrhagic events associated with imatinib mesylate. *Int J Hematol* 2007; **86**: 390–393.
- 240 Kwon SI, Lee DH, Kim YJ. Optic disc edema as a possible complication of Imatinib mesylate (Gleevec). *Jpn J Ophthalmol* 2008; **52**: 331–333.
- 241 Govind Babu K, Attili VS, Bapsy PP, Anupama G. Imatinib-induced optic neuritis in a patient of chronic myeloid leukemia. *Int Ophthalmol* 2007; **27**: 43–44.
- 242 eMC TeMC. Tassigna SPC. Datapharm Communications Limited; 2015. Available at <http://www.medicines.org.uk/emc/medicine/24089>.
- 243 eMC TeMC. Sprycel SPC. Datapharm Communications Limited; 2015. Available at <http://www.medicines.org.uk/emc/medicine/26080>.
- 244 eMC TeMC. Bosulif SPC. Datapharm Communications Limited; 2015. Available at <http://www.medicines.org.uk/emc/print-document?documentId=27795>.
- 245 eMC TeMC. Iclusig SPC. Datapharm Communications limited; 2015. Available at <http://www.medicines.org.uk/emc/medicine/28145>.
- 246 McClelland CM, Harocopos GJ, Custer PL. Periorbital edema secondary to imatinib mesylate. *Clin Ophthalmol* 2010; **4**: 427–431.
- 247 eMC TeMC. Gleevec SPC. Datapharm Communications Limited; 2015. Available at <http://www.medicines.org.uk/emc/medicine/15014>.
- 248 Milojkovic D, Apperley JF. How I treat leukemia during pregnancy. *Blood* 2014; **123**: 974–984.
- 249 EMEA. Gleevec: EPAR Product Information EMEA: London, UK, 2015.
- 250 EMEA. Tassigna: EPAR product Information EMEA: London, UK, 2015.
- 251 EMEA. Sprycel. Product Information EMEA: London, UK, 2015.

- 252 EMEA. *Bosulif. EPAR Product Information* EMEA: London, UK, 2015.
- 253 EMEA. *Iclusig: EPAR Product Information* EMEA: London, UK, 2015.
- 254 Ross DM. Peripheral neuropathy on imatinib treatment for chronic myeloid leukaemia: suspected adverse drug interaction with amlodipine. *Intern Med J* 2009; **39**: 708.
- 255 Chakupurakal G, Etti RJ, Murray JA. Peripheral neuropathy as an adverse effect of imatinib therapy. *J Clin Pathol* 2011; **64**: 456.
- 256 Ebnoether M, Stentoft J, Ford J, Buhl L, Gratwohl A. Cerebral oedema as a possible complication of treatment with imatinib. *Lancet* 2002; **359**: 1751–1752.
- 257 Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM *et al*. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001; **344**: 1038–1042.
- 258 Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM *et al*. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; **344**: 1031–1037.
- 259 Marcolino MS, Boersma E, Clementino NC, Macedo AV, Marx-Neto AD, Silva MH *et al*. Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients. *Ann Oncol* 2011; **22**: 2073–2079.
- 260 Kitiyakara C, Atichartakarn V. Renal failure associated with a specific inhibitor of BCR-ABL tyrosine kinase, STI 571. *Nephrol Dial Transplant* 2002; **17**: 685–687.
- 261 Gafter-Gvili A, Ram R, Gafter U, Shpilberg O, Raanani P. Renal failure associated with tyrosine kinase inhibitors—case report and review of the literature. *Leuk Res* 2010; **34**: 123–127.
- 262 Pou M, Saval N, Vera M, Saurina A, Sole M, Cervantes F *et al*. Acute renal failure secondary to imatinib mesylate treatment in chronic myeloid leukemia. *Leuk Lymphoma* 2003; **44**: 1239–1241.
- 263 Al Aly Z, Philoctete Ashley JM, Gellens ME, Gonzalez EA. Thrombotic thrombocytopenic purpura in a patient treated with imatinib mesylate: true association or mere coincidence? *Am J Kidney Dis* 2005; **45**: 762–768.
- 264 Foringer JR, Verani RR, Tjia VM, Finkel KW, Samuels JA, Guntupalli JS. Acute renal failure secondary to imatinib mesylate treatment in prostate cancer. *Ann Pharmacother* 2005; **39**: 2136–2138.
- 265 Francois H, Coppo P, Hayman JP, Fouqueray B, Mougnot B, Ronco P. Partial fanconi syndrome induced by imatinib therapy: a novel cause of urinary phosphate loss. *Am J Kidney Dis* 2008; **51**: 298–301.
- 266 Talpaz M, Shah NP, Kantarjian H, Donato N, Nicoll J, Paquette R *et al*. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006; **354**: 2531–2541.
- 267 Guilhot F, Apperley J, Kim DW, Bullorsky EO, Baccarani M, Roboz GJ *et al*. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood* 2007; **109**: 4143–4150.
- 268 Holstein SA, Stokes JB, Hohl RJ. Renal failure and recovery associated with second-generation Bcr-Abl kinase inhibitors in imatinib-resistant chronic myelogenous leukemia. *Leuk Res* 2009; **33**: 344–347.
- 269 Kaiafa G, Kakaletsis N, Savopoulos C, Perifanis V, Giannouli A, Papadopoulos N *et al*. Simultaneous manifestation of pleural effusion and acute renal failure associated with dasatinib: a case report. *J Clin Pharm Ther* 2014; **39**: 102–105.
- 270 Ozkurt S, Temiz G, Acikalin MF, Soydan M. Acute renal failure under dasatinib therapy. *Ren Fail* 2010; **32**: 147–149.
- 271 Martino S, Daguindau E, Ferrand C, Bamoulied J, Hayette S, Nicolini FE *et al*. A successful renal transplantation for renal failure after dasatinib-induced thrombotic thrombocytopenic purpura in a patient with imatinib-resistant chronic myelogenous leukaemia on nilotinib. *Leuk Res Rep* 2013; **2**: 29–31.
- 272 Sonmez M, Ovali E, Omay SB. Tumor lysis syndrome during treatment with AMN107 (Nilotinib) in a patient with chronic myelogenous leukemia accelerated phase. *J Clin Pharm Ther* 2008; **33**: 91–92.
- 273 Iyoda M, Shibata T, Hirai Y, Kuno Y, Akizawa T. Nilotinib attenuates renal injury and prolongs survival in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**: 1486–1496.
- 274 Sonmez M, Cobanoglu U, Ovali E, Omay SB. Use of dasatinib in the patient with Philadelphia chromosome-positive acute lymphoblastic leukaemia with resistance to imatinib and renal failure. *J Clin Pharm Ther* 2008; **33**: 329–330.
- 275 Onaka T, Takahashi N, Miura M, Yonezawa A, Imada K, Sawada K. Pharmacokinetics of nilotinib in imatinib-resistant/intolerant chronic myeloid leukemia patients on hemodialysis for chronic renal failure. *Am J Hematol* 2012; **87**: 451.
- 276 Efficace F, Breccia M, Francesco LC. Patient-reported outcomes in acute leukemia: a roadmap for future research. *Eur J Haematol* 2014; **93**: 86–87.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>