

Expert Opinion on the Treatment of Refractory Chronic Phase Chronic Myeloid Leukaemia

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The development and clinical availability of second-generation tyrosine kinase inhibitors (TKIs) for the treatment of patients who discontinue imatinib therapy has further improved the outlook for patients with chronic phase chronic myeloid leukaemia (CP-CML). There is, however, uncertainty surrounding how best to treat patients after failing second-generation TKIs. A three-section questionnaire was devised by chronic myeloid leukaemia experts to address questions surrounding this issue. Responses were received from 14 out of 34 experts (41.2%). Generally, a reasonable consensus was found among the responses for most issues. There was a complete consensus that ponatinib was suitable for all patients carrying the T315I mutation regardless of the molecular response to prior treatment. There was also complete consensus that allografting is appropriate in any patient who has had blast crises and is back in a second chronic phase. More recommendations for third-line treatment of CP-CML patients are necessary.

Keywords

Chronic phase chronic myeloid leukaemia, tyrosine kinase inhibitors, allogeneic haematopoietic stem cell transplantation

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The treatment of patients with chronic phase chronic myeloid leukaemia (CP-CML) has changed dramatically with the advent of the first BCR-ABL tyrosine kinase inhibitor (TKI) imatinib (Gleevec®, Novartis Pharmaceutical Corporation, New Jersey, US) in the 1990s.^{1,2} Multiple studies demonstrated the efficacy and acceptable tolerability of imatinib 400 mg daily.^{3,4} Despite the good cytogenetic and molecular response rates, some patients show primary resistance (refractoriness) or relapse after an initial response (secondary or acquired resistance).^{5,6} Adverse events occurred mainly within the first 2 years of treatment initiation and symptoms appeared to be mild or moderate in most instances, but with other treatment options available even low-grade toxicities are less acceptable and lead to discontinuation. Definitions of haematological, cytogenetic and molecular response have been previously described.⁷ Resistance in this setting has been defined as treatment with imatinib ≥ 600 mg/d (for ≥ 3 months) with disease progression ($\geq 50\%$ increase in white blood cells), or no haematological response after 4 weeks, or patients receiving < 600 mg/d with mutations at any of the following ABL amino acids: L248, G250, Q252, Y253, E255, T315, F317, H396.⁷ Dasatinib (Sprycel®, Bristol-Myers Squibb, New Jersey, US) and nilotinib (Tasigna®, Novartis, New Jersey, US), two second-generation TKIs initially launched for use as second-line therapies in 2006/2007, were approved for first line use in 2010. Treatment with dasatinib or nilotinib in recommended doses of 100 mg daily or 400 mg twice daily resulted in significantly higher cytogenetic and molecular response rates compared to imatinib 400 mg daily but there was no progression-free survival (PFS) or overall survival (OS) benefit. With the success of TKIs the earlier gold standard of allogeneic haematopoietic stem-cell transplantation (allo-HSCT) is reserved for later-line patients failing to achieve adequate responses.

Second-line treatment

In second-line, dasatinib and nilotinib have been recommended for treatment of CP-CML patients with resistance/intolerance to imatinib. In addition, bosutinib (Bosulif®; Pfizer, New York, US) received a conditional marketing authorisation in 2013 that is valid throughout the European Union (see *Table 1*),^{8–10} for the treatment of adult chronic myeloid leukaemia (CML) patients in all phases.^{11,12} Despite some good responses to second-line TKI therapy, approximately half of patients treated with dasatinib 100 mg daily or nilotinib 400 mg twice daily develop resistance or intolerance^{8,13,14} and discontinue therapy.

Third-line treatment

Patients who fail to respond to second-line therapy generally receive third-line therapy with another TKI,^{10,15–20} and identifying patients most likely to benefit from third-line TKI therapy represents an important unmet need. A cohort of 26 patients with CP-CML who had failed imatinib and a second-line TKI was analysed to identify prognostic factors for response and outcomes.²¹ For the achievement of complete cytogenetic responses on third-line therapy, prior cytogenetic response with imatinib or a second-line therapy were the only independent predictors. For OS, younger age and the demonstration of a cytogenetic response on second-line therapy were the only independent predictors. The authors highlighted the need to be able to select more accurately

Table 1: Efficacy summary for dasatinib, nilotinib, bosutinib and ponatinib in patients with chronic phase chronic myeloid leukaemia with resistance/intolerance to at least one tyrosine kinase inhibitor

Study	Line of therapy	Proportion (%) of patients receiving therapy	Cumulative CHR	Cumulative CCyR	Cumulative MMR	PFS	OS
Dasatinib 100 mg (n=167)							
Shah et al. (2010) ⁴³ (2-year minimum follow-up)	2nd	91.4% treated	92% by 2-year follow-up	50% by 2-year follow-up	37%* by 2-year follow-up	80% at 2 years	91% at 2 years
Shah et al. (2011) ⁴⁴ (4-year minimum follow-up)	2nd	37% remained on treatment				66% at 4 years	82% at 4 years
Shah et al. (2014) ⁴⁵ (6-year minimum follow-up)	2nd	28% remained on treatment			43% by 6-year follow-up	49% at 6 years	71% at 6 years
Nilotinib 400 mg twice daily (n=321)							
Phase III, dose optimisation study Kantarjian et al. (2011) ¹³ (2-year minimum follow-up)	2nd	39% remained on treatment		44% by 2-year follow-up	28%† by 2-year follow-up	64% at 2 years	87% at 2 years
Giles et al. (2013) ⁹ (4-year minimum follow-up)	2nd	31% were treated for at least 48 months		45% by 4-year follow-up	–	57% at 4 years	78% at 4 years
Bosutinib 500 mg daily (n=288)							
Phase II, Cortes et al. (2011) ⁴⁶ (2-year median follow-up)	2nd		86%	41%	45%‡	79% at 2 years	92% at 2 years
Ponatinib 45 mg daily (n=267)							
Cortes et al. (2013) ³⁹ (15-month, median follow-up)	3rd and 4th	49% remained on treatment	94% by 15-month median follow-up	46% by 15-month median follow-up	34% by 15-month median follow-up	80% at 1 year	94% at 1 year

CCyR = complete cytogenetic response; CHR = complete haematologic response; MMR = major molecular response; OS = overall survival; PFS = progression-free survival. No published randomised or observational head to head trials of these tyrosine kinase inhibitors are available. Data are derived from studies of considerable heterogeneity in terms of demographics, baseline characteristics, study design, and definition and reporting of end points. *Among 154 patients with at least one molecular assessment on study; †Among 294 patients with molecular assessment post-baseline; ‡Excluding patients enrolled in countries (China, India, Russia and South Africa) in which molecular response was not assessed. Information sourced from Khoury and Bixby (2014).⁴⁷

Table 2: European LeukemiaNet recommendations for chronic phase treatment³⁶

First Line
Imatinib or nilotinib or dasatinib HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+)
Second line, intolerance to the first TKI
Anyone of the other TKIs approved first line (imatinib, nilotinib, dasatinib)
Second line, failure of imatinib first line
Dasatinib or nilotinib or bosutinib or ponatinib HLA type patients and siblings
Second line, failure of nilotinib first line
Dasatinib or bosutinib or ponatinib HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Second line, failure of dasatinib first line
Nilotinib or bosutinib or ponatinib HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Third line, failure of and/or intolerance to two TKIs
Anyone of the remaining TKIs; alloSCT recommended in all eligible patients
Any line, T3151 mutation
Ponatinib HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT

alloSCT = allogeneic stem cell transplantation; CCA/Ph+ = clonal chromosome abnormalities in Philadelphia-positive cells; HLA = human leukocyte antigen; TKI = tyrosine kinase inhibitor. Reproduced with permission from Baccarani et al, *Blood* (2013).³⁷

the patients who would be likely to benefit from third-line TKI therapy. It should be noted however, that the small size of the cohort used may have been inadequate to identify independent risk factors. Median failure-free survival of CP-CML patients receiving third-line therapy is 20 months and this falls to 3–5 months in those with advanced disease.²²

In a phase I/II study of 118 patients with CP-CML who had been pre-treated with imatinib followed by dasatinib and/or nilotinib, major cytogenetic response was attained by 32% of patients, with a median follow-up of 28.5 months.¹⁰ After a 48-month follow-up, major cytogenetic response was newly attained or maintained from baseline by 33% and 7% of patients, respectively.²⁰ Treatment with dasatinib or nilotinib in patients with CML (n=25) previously treated with imatinib and a second TKI were evaluated in a single centre study.¹⁹ Of the patients with CP-CML (n=18), 89% achieved a complete haematological response, 13% achieved a complete cytogenetic response and 24% achieved a major molecular response. Fifty-six per cent of CP patients lost haematological response with a median of 23 months. In other studies of CP-CML patients who received nilotinib or dasatinib as third-line, responses to treatment were reported and although these were not generally durable, such treatment did appear able to prolong OS in some patients.^{18,22} The comparative efficacy and optimal sequencing of TKIs as third-line therapies requires prospective evaluation in randomised studies.

Allo-HSCT may be an effective option for treating CP-CML after failure of at least two TKIs.²³ In a prospective, randomised study in 669 patients with newly diagnosed CML, 427 were considered eligible for HSCT and were randomised according to the availability of a matched family donor between primary HSCT (166 patients) and best available drug treatment (261 patients). Survival probabilities were not significantly different between the two groups. Patients with a low transplant risk showed

improved survival compared with those with high risk ($p < 0.001$) transplant and non-high-risk disease.²⁴ This suggests that HSCT remains a valid option in patients at low transplant risk who have failed TKI treatment. Indeed, progress in transplantation has been made but despite this allo-HSCT is associated with 25–30% mortality.²⁵ Further, allo-HSCT is only an option for patients with a good performance status and a suitable stem cell donor. However, no TKI was specifically recommended in the National Comprehensive Cancer Network (NCCN) guidelines for CML treatment after first- and second-line TKI failure and it was noted that newer pharmacological treatments were needed to provide additional options for patients in the third-line therapy setting.

Sub-analysis of the phase I/II study of once-daily bosutinib 500 mg included 118 patients with CP-CML who had been pre-treated with imatinib followed by dasatinib and/or nilotinib, with a median follow-up of 28.5 months.¹⁰ Major cytogenetic response was attained by 32% of patients and a complete cytogenetic response by 24%. Complete haematological response was either achieved or maintained in 73%. Kaplan–Meir-estimated PFS was 73% and estimated OS was 84%. Efficacy was also demonstrated at 48-month follow-up.²⁰ Non-haematological treatment-emergent adverse events at 48 months included (all grades; grade 3/4): diarrhoea (83%; 9%), nausea (48%; 1%) and vomiting (38%; 1%); haematologic toxicities included: thrombocytopenia (39%; 26%), neutropenia (21%; 16%) and anaemia (20%; 7%).

Ponatinib (Iclusig®; Ariad Pharmaceuticals, Massachusetts, US) is a novel kinase inhibitor that includes a triple carbon-carbon bond. This bond extends from the purine scaffold and allows the molecule to bind to the ATP-binding pocket without steric hindrance from the bulky isoleucine residue at position 315 of the BCR-ABL mutant T315I.^{26–28} Ponatinib has been shown to be effective *in vitro* and *in vivo* against all clinically relevant BCR-ABL mutations, including the T315I gate keeper mutation,²⁸ a mutation for which no other currently licensed TKI is effective.²⁹ The 12-month data of the PACE (Ponatinib Ph+ ALL and CML Evaluation) pivotal phase II trial showed sustained benefit of ponatinib treatment in heavily pre-treated CML patients. Among the 267 CP-CML patients, 55% had achieved the primary endpoint of a major cytogenetic response (50% of resistant/intolerant patients and 70% with T315I mutation).²⁷ Based on these results, ponatinib was fast-tracked by the US Food and Drug Administration (FDA) in December 2012 for treatment in patients who could not tolerate therapy with first-line agents or whose disease progressed despite first-line therapy. More recently, with 4 years of follow-up of the PACE trial, ponatinib has been shown to continue to provide benefit to CP-CML patients.³⁰

Among the 267 patients with CP-CML from the 2 years follow-up of the PACE trial, 25% (67 patients) had vascular occlusive events, 7% (20 patients) had cardiovascular serious adverse events, 7% (18 patients) had cerebrovascular serious adverse events and 5% (14 patients) had peripheral vascular serious adverse events.³¹ The median time to onset for arterial thrombotic events among the CP-CML patients was 281 (8–952) days. Investigation is underway to identify the mechanisms underlying the vascular toxicity reported with this drug and to explore dose reductions and/or delays required to manage adverse events. The risk of vascular occlusive events may be dose related.³² An integrated dose intensity analysis found that for vascular occlusion, after adjusting for covariates, overall dose intensity is highly statistically significant with an odds ratio of approximately 1.6 for each 15 mg dose increase.³² A dose reduction would therefore be predicted to reduce the risk of vascular occlusive events. The current package insert states that treatment with ponatinib should be reserved for patients carrying the T315I mutation

Table 3: Section 1 of questionnaire – discussion of the effects of pre-treatment

Question	Consensus response
1. How do you see the frequency of T315I according to real-world data versus trial data?	There may be a higher frequency of T315I in trial data versus real world; however, this is the most common mutation in both settings. Emergence of T315I is more common in Ph+ acute lymphocytic leukaemia
2. What resistance pathways have been observed in your practice?	About 50% are related to kinase domain mutations. There are many other mechanisms that can play a role in tyrosine kinase inhibitor resistance, Axl and src kinase for instance
3. What is your experience on cross-intolerance with previously used TKIs?	In general, cross-tolerance with other tyrosine kinase inhibitors is rare and is usually associated with a poor response. However, a subgroup of patients will tend to develop side effects. Cross-intolerance is seen in patients but these adverse events are rarely grade 3–4 so dose reduction of the tyrosine kinase inhibitor can usually solve the problem. Cross-tolerance is more common with haematological toxicity
4. Discuss optimising management of a patient with compliance issues.	Use regular real-time quantitative reverse transcriptase polymerase chain reaction analysis to recognise poor compliance and the need to motivate better compliance. Good assessment and management of possible adverse events is needed to maximise compliance. Reminders by mobile phone, apps, alarms etc. Appropriate patient education is vital, using chronic myeloid leukaemia nurse appointments as follow-up and an opportunity for discussing reasons for any non-compliance, providing emotional support and for reiterating important issues such as critical reminders and symptom control

or who are resistant to dasatinib or nilotinib; intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate.³³

In the systematic review of TKIs in CP-CML patients who are resistant/intolerant to ≥ 1 prior 2GTKI (bosutinib, dasatinib and nilotinib), the estimated probability of achieving a complete cytogenetic response was 60% for ponatinib compared with 22–26% for the other TKIs. The probability estimated for ponatinib in achieving a higher response rate than the other TKI treatments was 99% for the complete cytogenetic response and 97% for a major cytogenetic response.³⁴ Safety was not compared in this analysis, however.

Guidelines/recommendations on refractory chronic phase chronic myeloid leukaemia management

Guidelines/recommendations for the management of CML patients have been issued by the NCCN (version 1.2016), the European Society of Medical Oncology (ESMO)³⁵ and the European LeukaemiaNet (ELN).³⁶ All these organisations have established definitions for haematological, cytogenetic (based on metaphase cytogenetic preparations) and molecular (based on BCR/ABL transcript levels) responses and timelines for achieving various levels of these responses. These evidence-based ‘milestones’ allow close monitoring of the outcome of patients on TKI therapy. Detailed recommendations for treatment of CP-CML patients in first-, second- and third-line from the ELN are

Table 4: Section 2 of questionnaire – treatment options after failing second-generation tyrosine kinase inhibitors

Question	Consensus response
Addition of second-generation TKI	
1. What is your experience with sequencing of second-generation TKIs?	Sequencing is carried out due to intolerance in most cases, some for lack of response according to ELN guidelines. It is rare, however, to achieve improved response when switching from one second-generation TKI to another for resistance, although switching is often useful in setting of intolerance. Exceptions would be specific mutations and where toxicity limits exposure to a specific second-generation TKI
2. Is it necessary to consider mutations below the detection limit (dormant mutations) for the next treatment decision?	No convincing data available yet to support considering this in clinical practice and independent studies are needed
3. What is your experience with bosutinib in regard to efficacy/safety/treatment duration/dosing with up to 500 mg/day?	Bosutinib is a suitable drug for patients with intolerance to the other second-generation TKIs. Some tolerance issues mentioned, for example diarrhoea at higher doses (500 mg). It was also pointed out that experience with bosutinib is limited at present
When is ponatinib the right option?	
1. Ponatinib is the correct option for any patient who develops a T315I mutation regardless of their molecular response	12/12 respondents answered True. One commented that they would have lost molecular response to be even evaluated for mutations
2. Ponatinib is suitable for any patient who has treatment failure on frontline imatinib	11/12 respondents answered False
3. Ponatinib is suitable for any patient who has treatment failure on frontline nilotinib or dasatinib	7/12 respondents answered False
4. Ponatinib is suitable for any patient who fails two lines of TKI therapy	8/12 respondents answered True
5. Ponatinib is suitable for any patient with advanced phase disease who fails to respond to current TKI therapy	10/12 respondents answered True
6. Ponatinib is suitable for any patient who has failed to respond or is intolerant to two lines of TKI therapy	7/12 respondents answered True
Role of allografting	
1. Allografting is the right option after ponatinib has failed	8/12 respondents answered True
2. Allografting should be conducted before trying ponatinib in younger patients who are at low risk for the adverse effects of an allograft	7/12 respondents answered False
3. Allografting is appropriate in any patient who has had blast crisis and is back in a second chronic phase	11/11 respondents answered True*

ELN = European LeukaemiaNet; TKI = tyrosine kinase inhibitor. *One respondent did not select True or False for this question.

summarised in Table 2. Two elements are in common to all these guidelines/recommendations:

- It is possible to change therapy of imatinib refractory CP-CML patients in second-line or later to an alternate approved TKI (nilotinib, dasatinib or bosutinib).
- HSCT should be considered in case of failure of two TKIs.

A significant difference in the guidelines from the NCCN versus those by the ELN is that not achieving the 10% level at 3 months constitutes a 'warning' according to the ELN recommendations, whereas the NCCN takes a stricter approach and defines this as 'failure' mandating a change in treatment.

Purpose

The aim of this current paper was to explore the level of consensus, or otherwise, regarding treatment of refractory CP-CML through use of a questionnaire distributed to CML experts across Europe.

Expert opinion questionnaire

Methods

A three-section questionnaire was devised by CML experts in August 2015 to address the following questions:

- What are the effects of pre-treatment?
- What are the treatment options after failing second-generation TKIs?
- How do patients present after failing second-generation TKIs?

CML experts were identified through consultation with the lead authors and the members of the *European Oncology & Haematology* editorial board. The questionnaire was formatted as an editable PDF and provided to 34 experts by email from September to November 2015, with follow-ups by email as appropriate. To gain a greater number of responses, the questionnaire was then re-sent to a second subset of experts who had not responded in February 2016 (n=9). The questionnaire responses were summarised so the results could be presented in succinct tabular format.

Results

Responses were received from 14 (41.2%) of the persons requested. Two additional questionnaires were incomplete. The geographical distribution of the respondents was: Italy (5), Germany (2), Turkey (1), Spain (1), Netherlands (1), France (2), Russia (1) and Australia (1). The consensus responses of the three sections of the questionnaire are presented in Tables 3–6.

In general, there was a range of opinion on all three areas of question posed. In particular, opinion was divided on the following:

- whether ponatinib is suitable for any patient who has treatment failure on frontline nilotinib or dasatinib (42% agreed with the statement);
- whether ponatinib is suitable for any patient who has failed to respond or is intolerant to two lines of TKIs (67% agreed); and
- whether allografting should be conducted before trying ponatinib in

Table 5: Section 3 of questionnaire – how do patients present after failing second-generation tyrosine kinase inhibitors?

Question	Consensus response
1. Does bosutinib have a role in third- or fourth-line therapy?	Limited role but may be useful in cases where tolerance has hindered the treatment and optimal dosing has not been used at least for one of prior treatments
2. In what clinical circumstances would you select bosutinib rather than ponatinib?	When there is intolerance to previous TKIs; in patients who are at high risk of cardiovascular events and have been resistant to ≥ 2 previous TKIs and have no mutations
3. How do you approach the patient who has progressed to AP or BC on current TKI therapy?	Appropriate approach is to use another TKI as a bridge to advancing to allotransplant. (1) If advanced disease was observed under 400 mg IM, increasing the IM dose can be an option (not done very frequently nowadays); (2) switching to 140 mg dasatinib or dose escalation of dasatinib (100 \geq 140 mg) if the patient does not carry T315I; (3) nilotinib 800 mg daily can be an alternative; (4) if the patient has a T315I mutation, ponatinib is the choice; (5) AML or ALL like conventional chemotherapy can be added to TKI treatment if the performance status of the patient is OK; (6) allo-HSCT can always be an option, and if the patient is young and fit, allografting can be a reasonable treatment modality if donor is available and a second chronic phase is achieved
4. Does the young patient who has developed a mutation have a prospect of long-term control on TKI therapy or should they always be considered for an allograft?	It depends on the phase of disease when the mutation was detected (chronic phase, yes; blast phase, no). A single mutation able to be handled with a second-generation TKI is not an indication for transplant. So on the whole, normal ELN guidelines should be followed. The alternatives are to continue with the appropriate TKI (if it works) or to give TKI as a bridging therapy and then try for allo-HSCT whenever the patient is ready. These choices should be discussed with every individual patient. These patients can sometimes be well controlled in the long term (and even achieve treatment-free remission) if they receive an appropriate TKI

ALL = acute lymphoblastic leukaemia; allo-HSCT = allogeneic haematopoietic stem cell transplantation; AML = acute myeloid leukaemia; AP = accelerated phase; BC = blastic crisis; IM = imatinib; ELN = European LeukaemiaNet; TKI = tyrosine kinase inhibitor.

younger patients who are at low risk for the adverse effects of an allograft (42% agreed).

The two questions for which there was a 100% response of 'true' were: whether ponatinib was the drug of first choice for any patient who develops a T315I mutation, regardless of their molecular response; and whether allografting is appropriate in any patient who has had blast crises and is back in a second chronic phase. There was also a strong consensus that ponatinib is not suitable for any patient who has treatment failure on frontline imatinib. With 11/12 responses 'false' to the question: 'Ponatinib is suitable for any patient who has treatment failure on frontline imatinib.' For all the other questions there was a variety of opinions (see *Table 4*).

Discussion

In this survey, it was highlighted that there may be a higher frequency of the T315I mutation in trial data compared with real-world data. The frequency reported, ranging from around 10–27%, may differ because of the various methods and schedules used for mutation testing.³⁷ For example, in the DASISION trial, mutation testing was performed at time of disease progression, treatment failure or end of treatment.³⁸ In the ENESTnd trial, mutation testing was carried out in all patients at baseline (exclusion criteria), and in patients with no baseline mutations, mutation analysis was performed when patients experienced either lack of response or loss of response. And in the PACE trial, the number of T315I mutations accumulated (64/270, 24%) due to efficacy of ponatinib in this setting.³⁹

Ponatinib should not be offered immediately after imatinib, indeed, there is no evidence in support of this and strong agreement on this stance emerged from the questionnaire responses. The only exception are patients who are failing imatinib treatment due to emergence of T315I mutation.

The consensus amongst the experts on the use of ponatinib in any CML patient who was tested positive for the T315I mutation needs to be supplemented with data generated in a retrospective observational study. Transplant is the only cure for resistant- and accelerated-phase CML, and more investigation is needed in this setting for outcomes in those

with T315I positive CML. Pooled data from the phase II PACE trial and the European Bone Marrow Transplant registry were used to indirectly compare OS between T315I positive CML patients treated with ponatinib and allogeneic stem cell transplantation (alloSCT). Results showed that CML patients in chronic phase demonstrated significantly longer OS versus CP-CML patients in the alloSCT group: median OS had not been reached in the ponatinib group (hazard ratio [HR] [95% confidence interval (CI)] 0.37 [0.16–0.84]) and was 103.3 in the SCT group ($p=0.013$). In contrast, there was no significant difference in median OS between the two treatment groups in patients with CML in accelerated phase (HR [95% CI] 0.90 [0.20–4.10]; $p=0.889$) and OS was significantly shorter in patients in blast phase who had received ponatinib versus alloSCT (HR [95% CI], 2.29 [1.08–4.82]; $p=0.030$). According to these data ponatinib may be a promising alternative for patients with T315I positive CP-CML, but offers no survival advantage for patients in advanced phase of CML.

The response on whether it is necessary to consider dormant mutations for treatment decision-making was that there are inadequate supporting data. Recent data suggested that some mutations may persist at undetectable levels for years after changing therapy and can be reselected, leading to subsequent TKI resistance.^{40,41} Further, detection of these mutations following imatinib resistance has been recommended to guide subsequent therapy selection. If an inappropriate therapy is selected there is a high risk of treatment failure accompanied by clonal expansion of the resistant mutant.⁴²

All approved BCR-ABL TKIs are effective therapies in CML but are associated with distinct safety profiles, which are not covered in this article. In order to make more tailored treatment decisions clinicians must remain vigilant, recognise low-grade adverse events, and proactively manage adverse events over the long term, considering dose reduction to reduce adverse events and toxicity. In addition, patients are called upon to assess and report subtle changes that might affect their quality of life.

Conclusion

This survey is in no way intended to represent the current state of the art for patients with resistant or refractory disease as it is subject to a number of limitations related to the selection of questions, the knowledge

and experience of the experts involved, the willingness to reply in detail, and more. Not all selected experts contributed to the survey so that the response does not represent a broad consensus of opinion but provides a selective snapshot of current opinions. However, this survey

with highly discordant opinions on treatment and management of these patients demonstrates the high need for generating more mature data and for more intensive exchange on peer-to-peer level to increase the consensus level across the community. □

- Okuda K, Matulonis U, Salgia R, et al., Factor independence of human myeloid leukemia cell lines is associated with increased phosphorylation of the proto-oncogene Raf-1, *Experimental Hematology*, 1994;22:1111-7.
- Jemal A, Siegel R, Xu J, et al., Cancer statistics, 2010, *CA: a cancer journal for clinicians*, 2010;60:277-300.
- de Lavalade H, Apperly JF, Khorashad JS, et al., Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis, *J Clin Oncol*, 2008;26:3358-63.
- O'Brien SG, Deininger MW, Imatinib in patients with newly diagnosed chronic-phase chronic myeloid leukemia, *Semin Hematol*, 2003;40(2 Suppl 2):26-30.
- Weisberg E, Manley PW, Cowan-Jacob SW, et al., Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant chronic myeloid leukaemia, *Nat Rev Cancer*, 2007;7:345-56.
- Ramirez P, DiPersio JF, Therapy options in imatinib failures, *The Oncologist*, 2008;13:424-34.
- Kantarjian HM, Giles F, Gattermann N, 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;110:3540-6.
- Hochhaus A, Baccarani M, Deininger M, et al., Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib, *Leukemia*, 2008;22:1200-6.
- Giles FJ, le Coutre PD, Pinilla-Ibarz J, 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;27:107-12.
- Khoury HJ, Cortes JE, Kantarjian HM, et al., Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure, *Blood*, 2012;119:3403-12.
- Hanaiz Z, Unkrig C, Enzmann H, et al., The European medicines agency review of bosutinib for the treatment of adult patients with chronic myelogenous leukemia: summary of the scientific assessment of the committee for medicinal products for human use, *The Oncologist*, 2014;19:421-5.
- Jabbour E, Kantarjian HM, O'Brien S, et al., Front-line therapy with second-generation tyrosine kinase inhibitors in patients with early chronic phase chronic myeloid leukemia: what is the optimal response?, *J Clin Oncol*, 2011;29:4260-5.
- Kantarjian HM, Giles FJ, Bhalla KN, 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;117:1141-5.
- Kantarjian H, Pasquini R, Levy V, et al., Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R), *Cancer*, 2009;115:4136-47.
- Quintas-Cardama A, Kantarjian H, Jones D, et al., Dasatinib (BMS-354825) is active in Philadelphia chromosome-positive chronic myelogenous leukemia after imatinib and nilotinib (AMN107) therapy failure, *Blood*, 2007;109:497-9.
- Nicolini EE, Alimena G, Ali AJ, et al., Expanding nilotinib access in clinical trials (ENACT) study in adult patients (PTSD with imatinib-resistant or -intolerant chronic myeloid leukemia (CML): Subgroup analysis of patients who failed prior dasatinib therapy, *Haematologica*, 2009;94(S2):257.
- Giles FJ, Abruzzese E, Rosti G, et al., Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy, *Leukemia*, 2010;24:1299-301.
- Russo Rossi A, Breccia M, Abruzzese E, et al., Outcome of 82 chronic myeloid leukemia patients treated with nilotinib or dasatinib after failure of two prior tyrosine kinase inhibitors, *Haematologica*, 2013;98:399-403.
- Ribeiro BF, Miranda EC, Albuquerque DM, et al., Treatment with dasatinib or nilotinib in chronic myeloid leukemia patients who failed to respond to two previously administered tyrosine kinase inhibitors—a single center experience, *Clinics (Sao Paulo, Brazil)*, 2015;70:550-5.
- Gambacorti-Passerini C, Khoury HJ, Kantarjian HM, et al., Bosutinib AS Third-Line Therapy in Patients (Pts) with Chronic Phase Chronic Myeloid Leukemia (CP CML) Following Failure with Imatinib Plus Dasatinib and/or Nilotinib: 48-Month Update of a Phase 1/2 Study, *Blood*, 2014;124:4559.
- Ibrahim AR, Paliompeis C, Bua M, et al., Efficacy of tyrosine kinase inhibitors (TKIs) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy, *Blood*, 2010;116:5497-500.
- Garg RJ, Kantarjian H, O'Brien S, et al., The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up, *Blood*, 2009;114:4361-8.
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. Version 1.2016. Available at: www.nccn.org/professionals/physician_gls/pdf/cml.pdf (accessed 2 September 2016).
- Gratwohl A, Pfeirrmann M, Zander A, et al., Long-term outcome of patients with newly diagnosed chronic myeloid leukemia: a randomized comparison of stem cell transplantation with drug treatment, *Leukemia*, 2016;30:562-9.
- Pavlu J, Szydlo RM, Goldman JM, et al., Three decades of transplantation for chronic myeloid leukemia: what have we learned?, *Blood*, 2011;117:755-63.
- Goldman JM, Ponatinib for chronic myeloid leukemia, *New Eng J Med*, 2012;367:2148-9.
- Cortes JE, Kantarjian H, Shah NP, et al., Ponatinib in refractory Philadelphia chromosome-positive leukemias, *New Eng J Med*, 2012;367:2075-88.
- O'Hare T, Shakespeare WC, Zhu X, et al., AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance, *Cancer Cell*, 2009;16:401-12.
- Redaelli S, Piazza R, Rostagno R, et al., Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants, *J Clin Oncol*, 2009;27:469-71.
- Hochhaus A, Cortes JE, Kim D-W, et al., Efficacy and Safety of Ponatinib in CP-CML Patients By Number of Prior Tyrosine Kinase Inhibitors: 4-Year Follow-up of the Phase 2 PACE Trial, *Blood*, 2015;126:4025.
- Kantarjian HM, Kim D-W, Pinilla-Ibarz J, et al., On behalf of the PACE Study Group. Ponatinib in Patients with Philadelphia Chromosome-Positive Leukemias Resistant or Intolerant to Dasatinib or Nilotinib, or With the T315I Mutation: Longer-term Follow-up of the PACE Trial. 50th American Society of Clinical Oncology (ASCO). Chicago, IL, USA, 2014.
- European Medicines Agency. Assessment report: Ponatinib 2014. Available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002695/WC500183099.pdf (accessed 22 June 2016).
- Ponatinib Full Prescribing Information. 2013. Available at: www.iclusigrems.com/packaged/pdf/P1.pdf (accessed 30 January 2017).
- Lipton JH, Bryden P, Sidhu MK, et al., Comparative efficacy of tyrosine kinase inhibitor treatments in the third-line setting, for chronic-phase chronic myelogenous leukemia after failure of second-generation tyrosine kinase inhibitors, *Leuk Res*, 2014;39:58-64.
- Baccarani M, Pileri S, Steegmann JL, et al., Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Ann Oncol*, 2012;23 Suppl 7:ii72-7.
- Baccarani M, Deininger MW, Rosti G, et al., European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013, *Blood*, 2013;122:872-84.
- Soverini S, Branford S, Nicolini FE, et al., Implications of BCR-ABL1 kinase domain-mediated resistance in chronic myeloid leukemia, *Leuk Res*, 2014;38:10-20.
- Cortes JE, Saglio C, Kantarjian HM, et al., Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients Trial, *J Clin Oncol*, 2016;34:2333-40.
- Cortes JE, Kim DW, Pinilla-Ibarz J, et al., A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias, *N Engl J Med*, 2013;369:1783-96.
- Quintas-Cardama A, Grgurevic S, Rozovski U, et al., Detection of dormant chronic myeloid leukemia clones in the bone marrow of patients in complete molecular remission, *Clin Lymphoma Myeloma Leuk*, 2013;13:681-5.
- Parker WT, Yeoman AL, Jamison BA, et al., BCR-ABL1 kinase domain mutations may persist at very low levels for many years and lead to subsequent TKI resistance, *Br J Cancer*, 2013;109:1593-8.
- Parker WT, Lawrence RM, Ho M, et al., Sensitive detection of BCR-ABL1 mutations in patients with chronic myeloid leukemia after imatinib resistance is predictive of outcome during subsequent therapy, *J Clin Oncol*, 2011;29:4250-9.
- Shah NP, Kim DW, Kantarjian H, 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;95:232-40.
- Shah NP, Cortes JE, Schiffer CA, Five-year follow-up of patients with imatinib-resistant or -intolerant chronic-phase chronic myeloid leukemia (CML-CP) receiving dasatinib, *J Clin Oncol*, 2011;29(Suppl 1):Abstract 65512.
- Shah NP, Guilhot F, Cortes JE, et al., Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study, *Blood*, 2014;123:2317-24.
- Cortes JE, Kantarjian HM, Brummendorf TH, 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;118:4567-76.
- Khoury HJ, Bixby DL, Outcomes of chronic-phase chronic myeloid leukemia beyond first-line therapy, *Leukemia & Lymphoma*, 2014;1:1-9.

APPENDIX

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