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Review article

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MANAGEMENT OF PONATINIB DOSING IN CHRONIC MYELOID LEUKEMIA PATIENTS

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Ponatinib (Iclusig®, Takeda/Incyte) is a third-generation highly-potent-pan-inhibitor of tyrosine kinases, active in all single resistance ABL kinase mutations including the T315l mutation. It is approved to treat of chronic myeloid leukemia (CML) in every phase of disease-resistant or intolerant to second-generation tyrosine kinase inhibitors (2GTKIs) and for whom imatinib is not clinically appropriate as well as for patients with T315I mutation. The drug is also indicated for Ph+ acute lymphoblastic leukemia (ALL). The approved starting dose for ponatinib is 45 mg once daily. Available data revealed ponatinib dose-dependent increased risk of cardiovascular toxicity. There is still no consensus about the optimal, initial dose of ponatinib and its management during therapy. It is crucial to start treatment with the risk-adjusted dose and assess the benefit-risk profile of ponatinib dosing. Evaluation of dosing modification should be considered during treatment, mainly if toxicity occurs. Our study summarizes current knowledge and recommendations about the choice of starting dose of ponatinib and management of ponatinib dosing during the treatment.

Key words: *ponatinib, tyrosine kinase inhibitor, chronic myeloid leukemia, dosing management, cardiovascular adverse events, drug toxicity, arterial occlusive events*

INTRODUCTION

Tyrosine kinase inhibitors (TKIs) have transformed outcomes in chronic myeloid leukemia (CML). Patients who respond to imatinib have a life expectancy comparable with that of the global population; however, up to 40% of patients discontinue imatinib during long-term therapy due to resistance or intolerance (1). *Fig. 1* summarizes the mechanisms of resistance to TKIs used for CML treatment (2-5). Interestingly there is an increasing body of literature suggesting the role of microenvironment niches regulation in the development of drug resistance, including cell adhesion-mediated drug resistance (6). These mechanisms could be a target for novel therapies, but so far, the second and third-generation TKIs are indicated in these situations (*Fig. 2*); however, their use is frequently complicated by significant toxicity limiting the effectiveness of therapy. Therefore, research focusing on developing a possible alternative and less toxic anti-leukemic treatment, such as investigating the role of autophagy and apoptosis modulation of human leukemia cells by the wine polyphenol resveratrol, is very needed could supplement the current treatment (7).

European LeukemiaNet (ELN) guidelines cannot formalize acceptable responses to the third, fourth, or fifth-line of CML treatment. It is accepted that *BCR-ABL1* transcript level >1% or a cytogenetic response less than complete (Ph+ >0%) are insufficient for optimal survival. Allogeneic stem cell transplantation (allo-SCT) should be considered in case of suboptimal response to two or more TKIs (8). Ponatinib (Ponatinib®, Takeda/Incyte) is a third-generation highly-potent-pan-inhibitor of tyrosine kinases, active in all single resistance ABL kinase mutations, including the T315l mutation (9, 10). Ponatinib was designed with a carbon-carbon triple bond to target the T315I point mutation within the kinase domain (KD) of *BCR-ABL1* (11, 12). It is the only approved TKI with clinically relevant activity against the T315I mutation to date. This mutation occurs in up to 20% of resistant patients with CML and confers resistance to all other TKIs (imatinib, nilotinib, dasatinib, and bosutinib) (13). Only the single ATP-binding site mutation T315M has been identified to confer resistance to ponatinib (14).

In a retrospective comparison between the data from the European Bone Marrow Transplant Registry and the Ponatinib Ph+ ALL and CML Evaluation (PACE) clinical trial, ponatinib treatment of patients with CP-CML and T315I mutation was associated with significantly longer overall survival (OS) than allo-SCT (15). Therefore, ponatinib may be an alternative, especially in older patients unsuitable for allo-SCT. In December 2012, ponatinib gained accelerated approval by the US Food and Drug Administration (FDA) in adult CML patients in chronic, accelerated, or blast phase or with Ph+ ALL with T3165I mutation or to all whom no other TKI is indicated (16). EMA approved ponatinib in adult CML patients in chronic, accelerated, or blast phase or with Ph+ ALL being resistant or intolerant to dasatinib, nilotinib, and for whom imatinib is not clinically appropriate, as well as for patients with T315I mutation (17). According to ELN 2020 guidelines, ponatinib is preferred in patients with resistance to a 2GTKI, including patients without specific mutations, rather than an alternative 2GTKI unless cardiovascular risk factors preclude its use (8). The Evaluation of Ponatinib versus Imatinib in Chronic Myeloid Leukemia (EPIC) phase 3 trial study conducted in newly diagnosed patients with CP-CML after dosing reduction

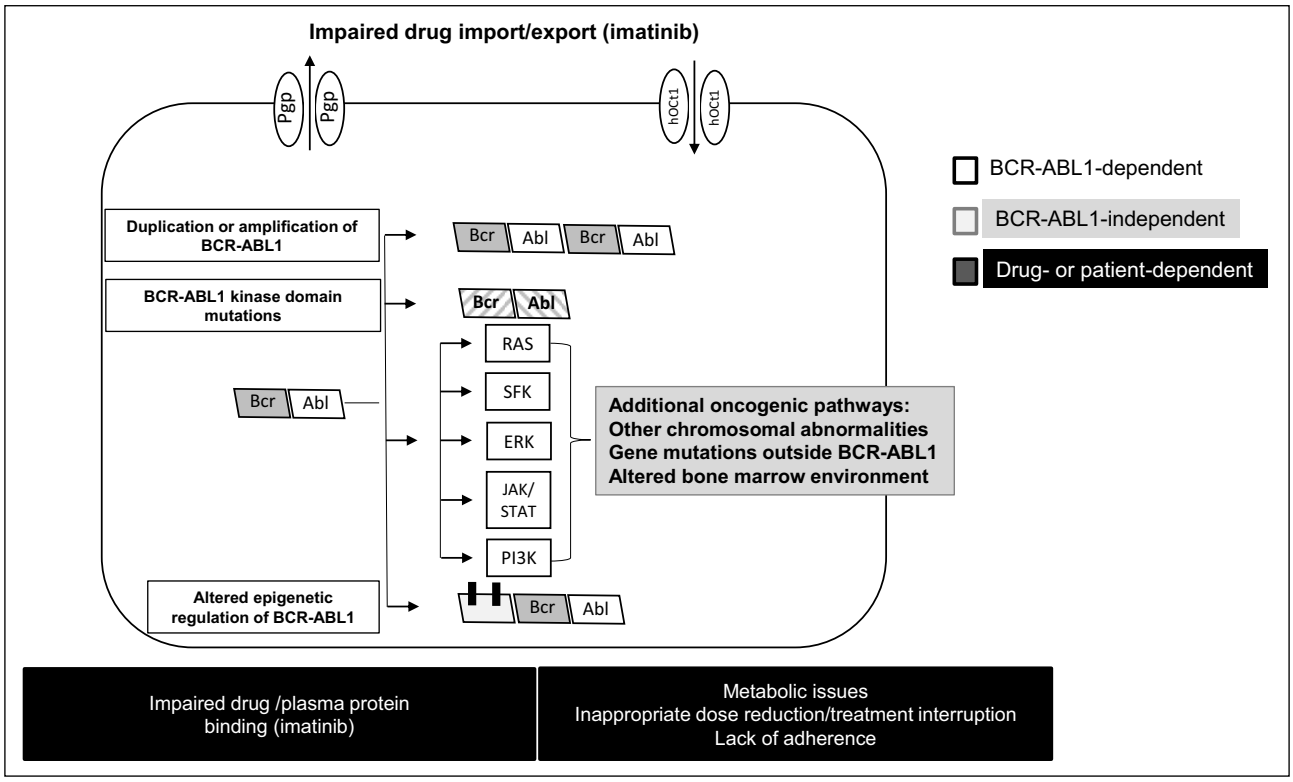

Fig. 1. Mechanisms of resistance to tyrosine kinase inhibitors used for chronic myeloid leukemia (CML) treatment (adapted from ref. (2-5).

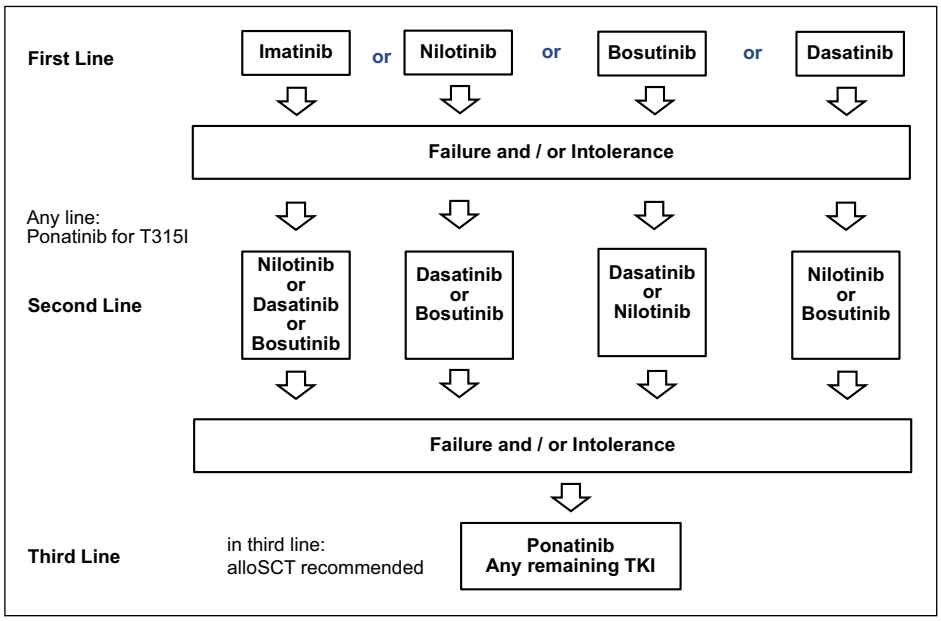

Fig. 2. The algorithm of chronic myeloid leukemia treatment with tyrosine kinase inhibitors.

recommended by FDA in October 2013 was terminated early in June 2014 due to the increased rate of cardiovascular thrombotic events observed in patients receiving ponatinib in different trials. Since then, many investigators have analyzed baseline characteristics of patient candidates for ponatinib, especially cardiovascular profile, to describe general management recommendations in this setting. There is, however, still no consensus about the optimal initial dose of ponatinib and its management during therapy. This publication aims to discuss current recommendations of ponatinib initial dosing and describe the dose management in the course of CML therapy.

CARDIOVASCULAR TOXICITY OF PONATINIB

Mechanisms of ponatinib-induced vascular toxicity

In vitro studies showed that ponatinib treatment increases endothelial cells (ECs) dysfunction and apoptosis, both associated with a higher rate of vascular adverse events (VAE) (18). In cultured human aortic ECs (HAECs) treated with ponatinib, an increase in nuclear factor NF-κB/p65 phosphorylation and NF-κB activity, inflammatory gene expression, cell permeability, and cell apoptosis was found.

Ponatinib also diminished expression of ERK5 responsive genes such as Kruppel-like factor 2/4 (*klf2/4*) and *eNOS*. Additionally, ERK5 SUMOylation, which counteracts its transcriptional activity, is increased by ponatinib shifting ECs to an inflammatory phenotype and disrupting vascular homeostasis (19). Ponatinib was also proved to induce apoptosis, reduce migration, inhibit tube formation of human umbilical vein ECs (HUVECs), and harmed endothelial progenitor cell (EPC) function (20). *In vitro* studies showed that ponatinib dose-dependently induced apoptosis in human coronary artery ECs (HCAEC) (21). In another study, an increased expression of nitrotyrosine and caspase 3 in the adventitia of mice treated with either 15 or 3 mg/kg of ponatinib was observed, suggesting their role in the apoptosis (22). Furthermore, an increased nicotinamide adenine dinucleotide phosphate oxidase-derived reactive oxygen species (ROS) was associated with the adventitia's vessel apoptosis (23). In addition, ponatinib was found to inhibit the proliferation of HUVEC and HMEC-1. Ponatinib also inhibits fetal bovine serum-induced phosphorylation of the VEGF receptor KDR and phosphorylation of MER and insulin receptors, which play a role in angiogenesis, vascular homeostasis, and vessel protection. Application of ponatinib on C57BL/6 mice aortic rings (100 nM, overnight) enhanced norepinephrine-induced vasoconstriction and inhibited acetylcholine-mediated vasodilatation. These drug effects were blocked by inhibition of nitric oxide (NO) or cyclooxygenase (COX), suggesting that ponatinib promotes the generation of vasoconstricting prostanoids (24). Further experiments showed that ponatinib inhibited VEGF-induced VEGFR2 phosphorylation and its downstream signaling pathways, including Akt/eNOS/NO pathway and MAPK pathways (ERK and p38MAPK). These results suggest that inhibition of VEGF signaling at its receptor level and downstream pathways might likely be responsible for the anti-angiogenic activity of ponatinib (25). Another explanation of ponatinib vascular toxicity might be its promotion of a pro-thrombotic state. Ponatinib enhances the mRNA expression of coagulation factors of both the intrinsic and extrinsic pathways in gene expression analysis. Accordingly, ponatinib increased plasma concentrations of FVII (26). Additionally, *in vivo* and *ex vivo* experiments showed that platelets in ponatinib-treated mice were hyperreactive to Collagen-rich peptide (CRP) and thrombin, leading to their extensive activation (22).

Evidence of ponatinib-related cardiovascular adverse events

In the final 5-year follow-up of the PACE trial (n = 449), the cumulative incidence of arterial occlusive events (AOEs), including cardiovascular, cerebrovascular, and peripheral vascular ones, was 25% overall and 31% in patients with chronic phase (CP)-CML. Overall, 13% (59 of 449) of patients had cardiovascular adverse events (CAEs), and 10% (44 of 449) had serious CAEs. In the CP-CML subgroup, 16% (42 of 270) had CAEs, and 12% (33 of 270) had serious CAEs (25). The analysis showed that patients with a higher risk in cardiovascular risk score developed cardiovascular disorder (CVD) more often - with the highest relative risk 2.2 (95% confidence interval, 1.5 – 3.3) for patients with ≥ two risk factors - than those with lower risk or without cardiac comorbidities. Most patients treated with ponatinib who developed CVD tended to have additional CV risk factors. Further post hoc analysis showed that the frequency of AOEs was 32%, 26%, 28%, and 42%, respectively, by an increasing number of prior TKIs used (22). Ponatinib dose reductions (to 30 mg or 15 mg) were suggested in this study by FDA and implemented in October 2013 to reduce the risk of cardiovascular, cerebrovascular, and peripheral arterial occlusive events and venous thromboembolism (27). Four-year results of the PACE study showed the incidence of AOE 8% (6/75) among all dose-reduced patients without a prior AOEs on trial (20). In the EPIC trial, eleven (7%) of 154 patients receiving ponatinib had AOEs; AOEs were designated as serious in 10 (6%) of 154 patients on ponatinib (28).

The frequency of CAEs related to ponatinib in the real world is currently lower than reported in phase 1 trials. Onyee *et al*. examined the survival outcomes and associated toxicities in 78 consecutive ponatinib-treated patients with CML. Eighteen patients (23.1%) experienced some form of CAEs, with the most common being arrhythmia (9%) and hypertension (7.7%), whereas three patients experienced a myocardial infarction (3.8%) (29). Till 2014, most of those patients started ponatinib at the dose of 45 mg daily. According to the author, lower starting dose, more frequent dose reduction, and increased cardio-oncology referral were possibly critical contributing factors to reducing CAEs after 2014. This study proved that ponatinib is highly effective, and dose adjustments and increasing awareness of the cardiotoxicities associated with ponatinib may help maximize its benefits.

THE EFFICACY AND SAFETY OF PONATINIB DOSE REDUCTIONS

The starting dose of 45 mg once daily was established in a phase 1 study (9) and then approved by FDA and EMA. However, pharmacodynamic studies showed that at doses of ≥ 30 mg/d, ponatinib trough plasma concentration > 40 nM was achieved and was sufficient to inhibit all *BCR-ABL1* mutants tested in preclinical studies (9). Furthermore, it was found that the daily dose of 15 mg induced at least a 50% reduction of *CRKL* phosphorylation (a surrogate of *BCR/ABL1* activity) in 32 out of 34 (94%) patients, including 8 of 10 patients (80%) with the T315I mutation. The relationship between ponatinib dose and the number and severity of vascular adverse events was suggested by the report from pooled multivariate analysis of phase 1 dose-escalating study (30), phase 2 PACE trial (31), and phase 3 EPIC trial (28). It has been shown that with each reduction of ponatinib dose by 15 mg daily, the risk of arterial occlusive events is decreased by 33% (32). Based on the pharmacokinetic analysis and preliminary data showing advantages of ponatinib dose reductions in terms of safety while maintaining its efficacy, some recommendations have been made (*Table 1*). In this view, patients with a low level of resistance or intolerant to previous treatment with imatinib or 2GTKIs seem to benefit from starting ponatinib at lower doses. The efficacy and toxicity of a starting ponatinib dose of 15 mg/d, 30 mg/d, and 45 mg/d are currently under investigation in the prospective, open-label phase 2 OPTIC (Optimizing Ponatinib Treatment In CML) trial (NCT02467270) (33, 34). The dose of ponatinib is reduced to 15 mg/d in this trial upon achievement of 1% *BCR-ABL1*^{IS} or less. The interim analysis of the OPTIC trial showed that an initial dose of ponatinib of 45 mg/d might induce higher response rates, especially in resistant to 2GTKI patients with T315I or other ABL-kinase domain mutation, but suggest that this dose may increase the incidence of CAEs. The rates of any AOEs/serious AOEs in patients receiving initially 45 mg/d, 30 mg/d, and 15 mg/d were 5%/2%, 4%/3%, and 1%/0%, respectively. The reduction to ≤ 1% *BCR-ABL1*^{IS} level by 12 months (primary endpoint)/AOEs were observed in 23.3%/1.1% of patients with starting dose 15 mg/d, in 33.3%/4.3% of patients with starting dose 30 mg/d in whom the dose was reduced then to 15 mg/d, and in 47.3%/5.3% of patients with starting dose 45 mg/d in whom the dose was reduced to 15 mg/d after reaching the primary

Table 1. Recommendations of ponatinib dose modifications according to European Leukemia Net (ELN) experts and selected clinical trials protocols (formulated by The Clinical Trial Steering Committees). PACE trial, Ponatinib Ph+ ALL and CML Evaluation trial; OPTIC trial, Optimizing Ponatinib Treatment in CML trial.

PACE trial	For chronic-phase chronic myeloid leukemia (CML) patients with at least a major cytogenetic response, a decrease to 15 mg/day was recommended. For chronic-phase CML patients without a major cytogenetic response and for patients with accelerated- and blast-phase CML, a decrease to 30 mg/day was recommended.
ELN recommendations 2020	The panel advises starting at a lower dose (30 mg or 15 mg daily) for patients with lesser degrees of resistance or multiple intolerances, especially those with an increased cardiovascular risk profile. The dose is increased only if needed. The panel recommends starting with 45 mg daily only in patients with T315I, compound mutations, or progression to an advanced phase. Preliminary data suggest that if a complete cytogenetic response (CCyR) or major molecular response (MMR) is achieved, the daily dose can be decreased to 15 mg daily, followed by careful monitoring of disease and toxicity.
OPTIC trial	Dose reduction to 15 mg/d upon achievement of ≤ BCR-ABL1IS. For patients with 12 months of follow-up, 38.7%, 27.4%, and 26.5% of patients receiving 45, 30, and 15 mg/day starting dose respectively achieved a ≤ 1% BCR-ABL1IS response (primary endpoint). Responses achieved at starting dose of 45 or 30 mg/day was maintained despite the dose reduction to 15 mg/day.

endpoint (n = 9) (33, 34). The rate of serious AEs and AOEs in the cohort of patients receiving 45 mg/d within the OPTIC IA trial were lower than in the PACE trial (31.2% vs. 63.4%) and (5.4% vs. 20.2%), respectively (35). These results suggest that the efficacy of ponatinib is still preserved after even a prompt dose reduction to 15 mg/d after achieving the level of *BCR-ABL1*^{IS} ≤ 1% and could importantly reduce the number and severity of arterial occlusive events. The real-life data on the safety and tolerability of lower initial doses of ponatinib confirm the results of clinical trials showing that in patients intolerant or with a low level of resistance to 2GTKI, the lower initial dose of ponatinib could be the optimal strategy. It might reduce the number and severity of treatment-emergent AOEs and maintain clinical response (36-44).

PONATINIB INITIAL DOSE RECOMMENDATIONS

The 2020 ELN recommendations established criteria for an optimal response during treatment with tyrosine kinase inhibitors, including ponatinib. Monitoring of molecular response by IS at 3, 6, 12 months (milestones) determine if the treatment should be continued (optimal response), changed (failure/resistance), or carefully considered for continuation or change (warning) (*Table 2*) (8). The 2020 ELN recommendations define a group of CML patients in the chronic phase eligible for ponatinib as intolerant or resistant to 2GTKI. Additionally, following the registration, ponatinib should be offered to patients whom no other TKI (including imatinib) is indicated. Patient age, comorbidities, and cardiovascular risk factors are necessary variables that should be considered when selecting the optimal therapy in addition to clinical response to previous TKI treatment. According to ELN, a reduced starting dose, 30 mg or 15 mg once daily, is recommended for patients with a lower degree of resistance or intolerance (that constitutes most CML-CP patients), especially if they have cardiovascular risk factors. The presence of the T315I mutation, compound mutations, or progression to acceleration or blastic phase indicates the 45 mg once daily starting dose (8). In the accelerated phase of chronic myeloid leukemia (AP-CML), blast phase chronic myeloid leukemia (BP-CML), or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) initial dose: 45 mg orally once a day is recommended. According to the risk-benefit profile, several real-life data studies concerning ponatinib dosing in CP-CML patients have been published (26-44). Castagnetti *et al*. created an algorithm for treating CML patients in CP after analyzing real-life data studies. The definitions of optimal response, warning response, or failure was defined in this publication according to the ELN 2020 recommendations (*Table 2*). The authors suggest that the first clinical question before starting treatment with ponatinib should reveal the reason for switching to ponatinib (45).

In the case of failure, or the presence of T315I or compound mutations, the starting dose should be 45 mg daily. If the reason for switching to ponatinib is a warning, the starting dose should be 30 mg daily. In intolerance to 2GTKIs, the crucial point is the assessment of response to previous treatment.

Patients without optimal response should commence therapy with ponatinib at the same dose as resistant patients, while those with an optimal response can initiate treatment with 15 mg/d of ponatinib. The exception should be made for all patients with high or very high cardiovascular risk according to European Society of Cardiology guidelines (SCORE ≥ 5) (*Table 3*) (46). Patients still in the chronic phase should start therapy with 30 mg/d or 15 mg/d, regardless of the reason for the switch to ponatinib (including 'failure' patients). We suggest a slightly modified algorithm for selecting the initial dose of ponatinib in CML patients (*Fig. 3*). Molica *et al*. published a study- review of the optimal use of ponatinib in patients with CP-CML. They concluded that results of clinical trials and real-life experiences documented in patients with CP-CML, even if starting dose was low (30 mg or 15 mg), were suggesting that ponatinib induced or maintained an major molecular response (MMR) or deep molecular response (DMR) with a potential decreased incidence of cardiovascular events. The author concluded that the initial ponatinib dose of 30 or 15 mg daily should always be considered to reduce potential drug-related risks and be recommended for patients who already achieved an MMR and developed an essential intolerance to previously used TKIs. Particular consideration should be reserved for patients who developed a

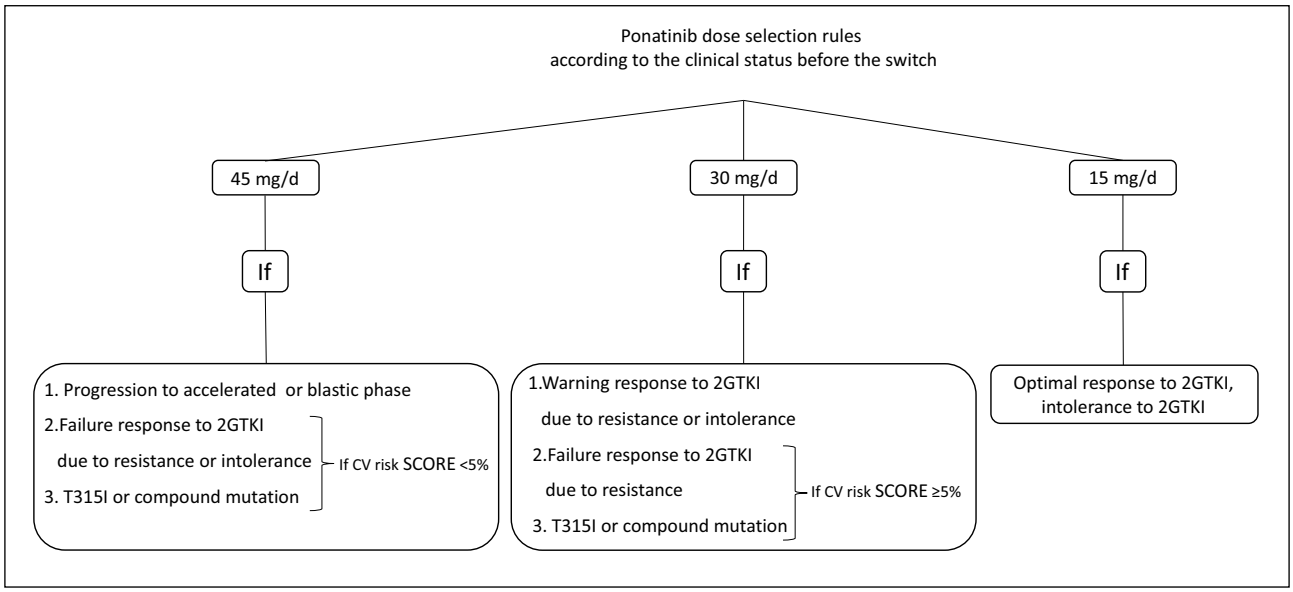

Fig. 3. Ponatinib dose selection rules in the treatment of chronic myeloid leukemia.

thrombotic event with other prior TKIs. Ponatinib at a low dose should be given to these patients only if all other TKIs have already been used (47). German expert consensus panel on ponatinib recommends starting 30 mg/day in CML patients in chronic phase, without ABL-KD mutations, resistant to only one TKI, with good response status, intolerant to TKI despite good response, and having increased cardiovascular risk (48).

DOSE REDUCTION DURING THERAPY WITH PONATINIB

In the PACE trial and according to the FDA and EMA recommendations, a reduced dose of ponatinib could be considered in patients who achieved at least a major cytogenetic response (MCyR) (EMA, FDA). However, in the OPTIC trial, the dose is reduced upon achievement of ≤ 1% *BCR/ABL1*^{IS} corresponding to complete cytogenetic response (CCyR). It is generally agreed that the MMR is considered as a 'safe haven' for patients treated with TKIs since the incidence of disease progression in this condition is extremely low. Therefore we suggest differently from the PACE and OPTIC studies and opinion recently published by Castagnetti *et al*. in patients who commenced ponatinib with 45 mg/d to reduce the dose to 30 mg/d upon achievement of CCyR, and further to 15 mg/d upon achievement of MMR, and for those who started therapy with 30 mg/d to reduce the dose to 15 mg/d upon achievement of MMR. The importance of early dynamics and rapid reduction of BCR/ABL1 transcript level during therapy with TKI is well established. There is a difference of almost three months between the median times to achievement of CCyR and MMR (2.9 months and 5.5 months, respectively) in the PACE trial. As the fastest reduction in BCR/ABL1 level may be of particular importance in a population of patient resistant or intolerant to previously administered TKIs still, without optimal response (*Fig. 3*), the administration of ponatinib in the most effective dose for a short time, and thus the least exposing patients to AEs seems to be the optimal treatment strategy. In the population mentioned above, the decision of reducing the dose of ponatinib must be considered very carefully after conducting a risk-benefit analysis on a case-by-case basis taking into account the risk factors, the quality of achieved response, and total exposure to ponatinib. According to 2020 ELN recommendations, the leading physician should emphasize restricted control of hypertension, hyperlipidemia, diabetes and advise patients to quit smoking to reduce the risk of AOEs. The benefit of prophylactic acetylsalicylic acid or anticoagulation is uncertain.

In conclusion, we state that the cardiovascular and liver toxicity of ponatinib analysis resulted in issuing by the FDA of the warning box related to this drug. The initial dose of ponatinib and dose modifications during the treatment is debated since no standardized guidelines recommend specific treatment strategies. Evidence shows that a lower than approved starting dose (45 mg/d) of ponatinib is effective and that selected patients could benefit from this dose modification. Each patient needs a personalized treatment strategy. The initial dose of ponatinib should be chosen after a thorough analysis of previous response, the cause of switch to ponatinib, and present comorbidities, including calculation of cardiovascular risk. Planned reduction of ponatinib dose during the therapy could reduce the risk of several complications (particularly within the cardiovascular system); however, it requires assessing the response dynamics to the initial dose and toxicity observed during treatment.

Conflict of interests: Tomasz Sacha: Roche, Novartis, Bristol-Myers Squibb, Pfizer, Angelini Pharma; Honoraria, Speakers Bureau. Elzbieta Szczepanek: Angelini Pharma; Honoraria.

REFERENCES

1. Deininger M, O'Brien SG, Guilhot F, *et al*. International Randomized Study of Interferon vs. STI571 (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 (CML-CP) Treated with Imatinib. *Blood* 2009; ASH Abstract: 1126.
2. Bixby D, Talpaz M. Mechanisms of resistance to tyrosine kinase inhibitors in chronic myeloid leukemia and recent therapeutic strategies to overcome resistance. *Hematology Am Soc Hematol Educ Program* 2009: 461-476. doi: 10.1182/asheducation-2009.1.461
3. Apperley JF. Part I: Mechanisms of resistance to imatinib in chronic myeloid leukaemia. *Lancet Oncol* 2007; 8: 1018-1029.

4. Hochhaus A, Ernst T, Eigendorff E, La Rosee P. Causes of resistance and treatment choices of second- and third-line treatment in chronic myelogenous leukemia patients. *Ann Hematol* 2015; 94 (Suppl. 2): S133-S140.
5. Eiring AM, Deininger MW. Individualizing kinase-targeted cancer therapy: the paradigm of chronic myeloid leukemia. *Genome Biol* 2014; 15: 461. doi.org/10.1186/s13059-014-0461-8
6. Takeda T, Tsubaki M, Genno S, *et al*. CD49d and CD49e induce cell adhesion-mediated drug resistance through the nuclear factor-kappaB pathway in Burkitt lymphoma. *J Physiol Pharmacol* 2020; 71: 467-478.
7. Siedlecka-Kroplewska K, Wozniak M, Kmiec Z. The wine polyphenol resveratrol modulates autophagy and induces apoptosis in MOLT-4 and HL-60 human leukemia cells. *J Physiol Pharmacol* 2019; 70: 825-838.
8. Hochhaus A, Baccarani M, Silver RT, *et al*. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia* 2020; 34: 966-984.
9. Cortes JE, Kantarjian H, Shah NP, *et al*. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med* 2012; 367: 2075-2088.
10. 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: 401-412.
11. Huang WS, Metcalf CA, Sundaramoorthi R, *et al*. Discovery of 3-[2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl]-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl) phenyl}benzamide (AP24534), a potent, orally active pan-inhibitor of breakpoint cluster region-abelson (BCR-ABL) kinase including the T315I gatekeeper mutant. *J Med Chem* 2010; 53: 4701-4719.
12. Zhou T, Commodore L, Huang WS, *et al*. Structural mechanism of the Pan-BCRABL inhibitor ponatinib (AP24534): lessons for overcoming kinase inhibitor resistance. *Chem Biol Drug Des* 2011; 77: 1-11.
13. Miller GD, Bruno BJ, Lim CS. Resistant mutations in CML and Ph^{+}ALL - role of ponatinib. *Biologics* 2014; 8: 243-254.
14. Deininger MW, Hodgson JG, Shah NP, *et al*. Compound mutations in BCR-ABL1 are not major drivers of primary or secondary resistance to ponatinib in CP-CML patients. *Blood* 2016; 127: 703-712.
15. Nicolini FE, Basak GW, Kim DW, *et al*. Overall survival with ponatinib versus allogeneic stem cell transplantation in Philadelphia chromosome-positive leukemias with the T315I mutation. *Cancer* 2017; 123: 2875-2880.
16. U.S. Food and Drug Administration. Ponatinib® (Ponatinib) tablets for oral use. Prescribing Information. Available at: https://www.accessdata.fda.gov/ drugsatfda_docs/label/ 2016/203469s022lbl.pdf (accessed 28 September 2020).
17. European Medicines Agency. Ponatinib (Ponatinib). Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/ product-information/ponatinib-epar-product-information_en.pdf (accessed 28 2020).
18. Hadzijusufovic E, Albrecht-Schgoer K, Huber K, *et al*. Nilotinib-induced vasculopathy: identification of vascular endothelial cells as a primary target site. *Leukemia* 2017; 31: 2388-2397.
19. Paez-Mayorga J, Chen AL, Kotla S, *et al*. Ponatinib activates an inflammatory response in endothelial cells via ERK5 SUMOylation. *Front Cardiovasc Med* 2018; 5: 125. doi: 10.3389/fcvm.2018.00125
20. Gover-Proaktor A, Granot G, Shapira S, *et al*. Ponatinib reduces viability, migration, and functionality of human endothelial cells. *Leuk Lymphoma* 2017; 58: 1455-1467.
21. Ai N, Chong CM, Chen W, *et al.* Ponatinib exerts anti-angiogenic effects in the zebrafish and human umbilical vein endothelial cells via blocking VEGFR signaling pathway. *Oncotarget* 2018; 9: 31958-31970.
22. Merkulova A, Mitchell SC, Stavrou EX, *et al*. Ponatinib treatment promotes arterial thrombosis and hyperactive platelets. *Blood Adv* 2019; 3: 2312-2316.
23. Meijles DN, Pagano PJ. Nox and inflammation in the vascular adventitia. *Hypertension* 2016; 67: 14-19.
24. Pouwer MG, Pieterman EJ, Verschuren L, *et al*. The BCR-ABL1 inhibitors imatinib and ponatinib decrease plasma cholesterol and atherosclerosis, and nilotinib and ponatinib activate coagulation in a translational mouse model. *Front Cardiovasc Med* 2018; 5: 55. doi: 10.3389/fcvm.2018.00055
25. Cortes JE, Kim DW, Pinilla-Ibarz J, *et al*. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood* 2018; 132: 393-404.
26. 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. doi: 10.1182/blood.V126.23.4025.4025
27. Cortes JE, Pinilla-Ibarz J, Le Coutre PD, *et al*. 4-year results of the ponatinib phase II PACE trial in patients (pts) with heavily pretreated leukemia. *J Clin Oncol* 2016; 34 (15): abstract 7013.
28. Lipton JH, Chuah C, Guerci-Bresler A, *et al*. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukemia: an international, randomised, open-label, phase 3 trial. *Lancet Oncol* 2016; 17: 612-621.
29. Onyee C, Chetasi T, Leidy I, *et al*. Side-effects profile and outcomes of ponatinib in the treatment of chronic myeloid leukemia. *Blood Adv* 2020; 4: 530-538.
30. Cortes J, Radich J, Mauro MJ. Clinical roundtable monograph: emerging treatment options for TKI-resistant chronic myelogenous leukemia. *Clin Adv Hematol Oncol* 2012; 10 (Suppl. 19): 1-16.
31. 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: 1783-1796.
32. Dorer DJ, Knickerbocker RK, Baccarani M, *et al*. Impact of dose intensity of ponatinib on selected adverse events: Multivariate analyses from a pooled population of clinical trial patients. *Leuk Res* 2016; 48: 84-91.
33. Cortes JE, Apperley F, Hochhaus A, *et al*. Outcome by mutation status and line of treatment in optic, a dose-ranging study of 3 starting doses of ponatinib in patients with CP-CML. 62nd American Society of Hematology Annual Meeting and Exposition 2020; December 5-8: abstract 48.
34. Cortes JE, Lomaia E, Turkina A, *et al*. Interim analysis (IA) of OPTIC: a dose-ranging study of three ponatinib starting doses. *J Clin Oncol* 2020; abstract 7502. doi: 10.1200/ JCO.2020.38.15_suppl.7502
35. Kantarjian HM, Deininger MW, Abruzzese E, *et al*. Efficacy and safety of ponatinib (pon) in patients with chronic-phase chronic myeloid leukemia (CP-CML) who failed one or more second generation (2G) tyrosine kinase inhibitors (TKIs): analyses based on PACE and OPTIC. 62nd American Society of Hematology Annual Meeting and Exposition 2020; December 5-8: abstract 647.
36. Mauro M, McGarry L, Inguilizian A, Moulin R. d, Huang H. A chart review of lower dosing of ponatinib in patients with chronic myeloid leukemia (CML): preliminary findings. 4th Annual Meeting of the Society of Hematologic Oncology. *Clin Lymphoma Myeloma Leuk* 2017; 16 (Suppl. 2): S57-S58.

37. Binotto G, Castagnetti F, Gugliotta G, *et al*. Ponatinib 15 mg daily, combining efficacy and tolerability. A retrospective survey in Italy. (2018). 23rd European Hematology Association Congress 2018; abstract: PS1122.
38. Breccia M, Abruzzese E, Castagnetti F, *et al*. Ponatinib as second-line treatment in chronic phase chronic myeloid leukemia patients in real-life practice. *Ann Hematol* 2018; 97: 1577-1580.
39. Heiblig M, Rea D, Chretien ML, *et al*. Ponatinib evaluation and safety in real-life chronic myelogenous leukemia patients failing more than two tyrosine kinase inhibitors: the PEARL observational study. *Exp Hematol* 2018; 67: 41-48.
40. Iurlo A, Annunziata M, Albano F, *et al*. Multicenter, prospective and retrospective observational cohort study of ponatinib in patients with CML in Italy: interim analysis of the OITI trial. *Blood* 2019; 134: 1652. doi.org/10.1182/blood-2019-126098
41. Iurlo A, Cattaneo D, Malato A, *et al*. Low dose ponatinib is a good option in chronic myeloid leukemia patients intolerant to previous TKIs. *Am J Hematol* 2020; 95: E260-E263. doi: 10.1002/ajh.25908
42. Chan O, Talati C, Isenalumhe L, *et al*. Side effects profile and outcomes of ponatinib in the treatment of chronic myeloid leukemia. *Blood Adv* 2020; 4: 530-538.
43. Iurlo A, Cattaneo D, Orofino N, Bucelli C, Molica M, Breccia M. Low-dose ponatinib in intolerant chronic myeloid leukemia patients: a safe and effective option. *Clin Drug Investig* 2018; 38: 475-476.
44. Santoro M, Accurso V, Mancuso S, *et al*. Management of ponatinib in patients with chronic myeloid leukemia with cardiovascular risk factors. *Chemotherapy* 2019; 64: 205-209.
45. Castagnetti F, Pane F, Rosti G, Saglio G, Breccia M. Dosing strategies for improving the risk-benefit profile of ponatinib in patients with chronic myeloid leukemia in chronic phase. *Front Oncol* 2020; 1642005. doi: 10.3389/fonc.2021.64200
46. Piepoli MF, Hoes AW, Agewall S, *et al*. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315-2381.
47. Molica M, Scalzulli E, Colafigli G, Foa R, Breccia M. Insights into the optimal use of ponatinib in patients with chronic phase chronic myeloid leukaemia. *Ther Adv Hematol* 2019; 10: 2040620719826444. doi:10.1177/2040620719826444
48. Saussele S, Haverkamp W, Lang F, *et al*. Ponatinib in the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute leukemia: recommendations of a German Expert Consensus Panel with Focus on Cardiovascular Management. *Acta Haematol* 2020; 143: 217-231.

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