European LeukemiaNet 2020 Recommendations for Treating Chronic Myeloid Leukaemia: Implications for Ponatinib

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Abstract

The fourth iteration of the European LeukemiaNet (ELN) recommendations for treating chronic myeloid leukaemia (CML) were published in early 2020.[1] This update of the 2013 version[2] is a result of new developments and research, which have led to dramatic changes in the therapeutic landscape of CML.

This article provides an overview of the CML recommendations that are relevant for the third-generation tyrosine kinase inhibitor (TKI) ponatinib (Iclusig®).[3] The authors state that in second-generation TKI-resistant patients without specific mutations, ponatinib is preferred over another second-generation TKI, unless cardiovascular risk factors preclude its use.[4,5]

SUMMARY OF 2020 RECOMMENDATIONS ON PONATINIB

Ponatinib is indicated for the treatment of adults with chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib, are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or have the *T315I* mutation.[3] Ponatinib is not approved for paediatric use.

The recommendations state that in cases of resistance to the initial second-generation tyrosine kinase inhibitor (TKI), given either as first- or second-line therapy, it is unlikely that the patient will achieve a durable response to an alternative second-generation TKI. The 2020 updated European LeukemiaNet (ELN) guidance therefore recommends that patients who are resistant to a second-generation TKI and do not have specific mutations should be treated with ponatinib instead of another second-generation TKI, unless cardiovascular risk factors preclude its use. An experimental agent should also be considered, and the patient should be assessed for allogeneic stem cell transplantation. The 2020 recommendations, similar to the previous 2013 guidance, recommend ponatinib for patients with the *T315I BCR-ABL1* resistance mutation, as it is currently the only TKI with activity against this mutation.

Table 1: Milestones for treating chronic myeloid leukaemia expressed as *BCR-ABL1* on the International Scale (IS).

	Optimal	Warning	Failure
Baseline	Not applicable	High-risk ACA, high-risk ELTS score	Not applicable
3 months	≤10.0%	>10.0%	>10.0% if confirmed within 1–3 months
6 months	≤1.0%	>1.0–10.0%	>10.0%
12 months	≤0.1%	>0.1–1.0%	>1.0%
Any time	≤0.1%	>0.1–1.0%, loss of ≤0.1% major molecular response	>1.0%, resistance mutations, high-risk ACA

Definitions of response applicable to first- and second-line treatment.

A change of treatment may be considered if a major molecular response is not reached by 36–48 months.

ACA: additional chromosome abnormalities in Philadelphia chromosome-positive cells; ELTS: European Treatment and Outcome Study (EUTOS) long-term survival score.

Adapted from Hochhaus et al.[1]

Table 2: Recommended tyrosine kinase inhibitors in case of *BCR-ABL1* resistance mutations.

Mutation	Recommended tyrosine kinase inhibitor(s)
T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, bosutinib,* or ponatinib
V299L	Nilotinib or ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib,* or ponatinib

*There are limited data available regarding mutations associated with clinical resistance to bosutinib *in vivo*. Some *in vitro* data suggest that the *E255K* and, to a lesser extent, the *E255V* mutation might be poorly sensitive to bosutinib.

Adapted from Hochhaus et al.[1]

The approved starting dose of ponatinib is 45 mg once daily, regardless of the CML phase or line of treatment.[3] This is reflected in the ELN guidelines, which do not suggest a different dosage of ponatinib accordingly to disease phase or line of treatment. However, in the new edition of the recommendations, the panel advises starting at 30 mg or 15 mg daily for patients with a low degree of resistance or multiple intolerances, especially those with an increased cardiovascular risk profile. According to the updated panel recommendations, patients with the *T315I* mutation, compound mutations, or progression to an advanced phase should start with ponatinib 45 mg once daily. Data from preliminary studies indicate that the daily dose can be reduced to 15 mg daily if complete cytogenetic remission or major molecular response is achieved. Disease and toxicity should be closely monitored.

Patients who do not respond to ponatinib after 3 months are likely at high risk of progression and the panel advises that they should undergo assessment for allogeneic stem cell transplantation.

CARDIOVASCULAR RISK

Thought should be given to cardiovascular risk when considering use of ponatinib because prior or current arterial disease may be a

contraindication to ponatinib treatment in the second- or third-line. Of all the TKI, ponatinib carries the highest risk of developing an arterial occlusion event.

Numerous steps can be taken to facilitate the use of ponatinib in patients with increased cardiovascular risk. The 2020 ELN recommendations advise to start ponatinib at a reduced dose (30 mg or 15 mg daily); control hypertension, hyperlipidaemia, and diabetes; and cease smoking. The benefit of prophylactic aspirin or anticoagulation is unclear.

IDENTIFYING FAILURE EARLY

Molecular response should be assessed using the International Scale (IS) as the ratio of *BCR-ABL1* transcripts to *ABL1* transcripts and stated as *BCR-ABL1* %. Monitoring milestones at 3, 6, and 12 months are used to decide whether the current treatment should be continued (optimal response); carefully considered for continuation or change, depending on patients' characteristics, comorbidities, and tolerance (warning); or changed (failure/resistance) (Table 1). Treatment has failed when BCR-ABL1 at 3 months is greater than 10%.

Where there is failure/resistance, a change of TKI is mandatory and *BCR-ABL1* kinase domain mutations should be assessed using next-generation sequencing. The TKI selection should then be guided by the profile of *BCR-ABL1* kinase domain mutations, especially if the *T315I* mutation is detected, as only ponatinib is an effective treatment (Table 2).

CONCLUSION

Ponatinib is the preferred option after resistance to one second-generation TKI, unless cardiovascular risk factors preclude its use, and is the only TKI with activity against the *T315I* mutation.

References

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