Comment on Cortes et al, page 2042

Taming the gatekeeper: ponatinib dose holds the key

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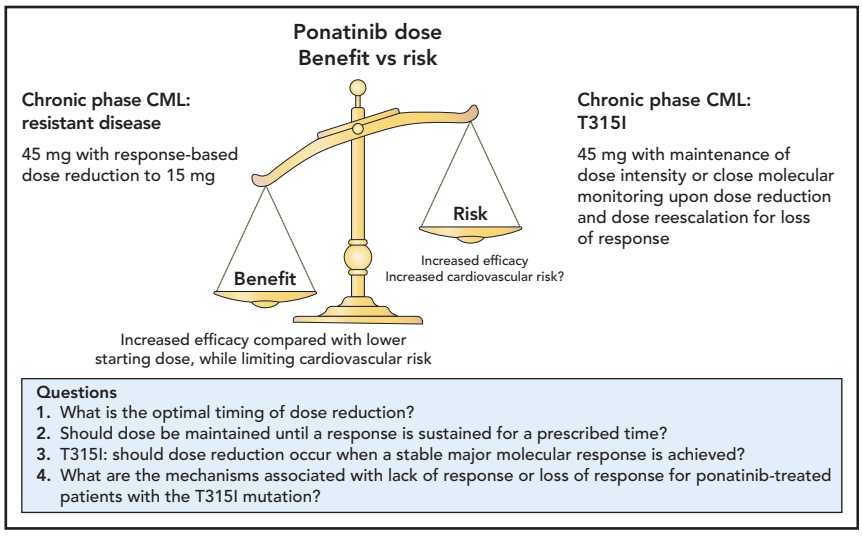
In this issue of *Blood*, Cortes et al demonstrate that the optimal benefit-to-risk outcome for ponatinib-treated patients with chronic myeloid leukemia (CML) who had failed prior therapy was a starting dose of 45 mg, which was reduced to 15 mg upon attainment of a response.[1]

In 2013, safety concerns related to arterial occlusive events led to the cessation of the EPIC trial of ponatinib for the treatment of newly diagnosed patients with CML.[2] Arterial occlusive events had occurred in 31% of patients with chronic phase CML enrolled in the PACE phase 2 trial, which used a dose of 45 mg ponatinib for patients with resistance or intolerance to prior tyrosine kinase inhibitor therapy.[3] Events appeared to be dose dependent.[4]

Ponatinib is a potent third-generation inhibitor of the tyrosine kinase activity of the BCR-ABL1 fusion, which is the CML initiating genomic lesion. Importantly, ponatinib can effectively inhibit a somatic mutation within the *BCR-ABL1* kinase domain that alters a threonine to an isoleucine at the gatekeeper 315 residue. Ponatinib is currently approved for the treatment of patients with CML for whom no other tyrosine kinase inhibitor is indicated or for adult patients with a T315I mutation. Various mutations within the kinase domain occur in ~50% of resistant patients. However, the T315I mutation eliminates a critical hydrogen bond interaction required for high-affinity binding of all first- and second-generation BCR-ABL1 inhibitors[5] and renders patients drug resistant. Prior to ponatinib, the overall survival for chronic phase patients with a T315I mutation was 22 months.[6] A high level of selection pressure in resistant patients treated with second-generation BCR-ABL1 inhibitors, where most *BCR-ABL1* mutations are sensitive, means that T315I is among the most frequently detected. Durable responses occurred for chronic phase patients enrolled in the PACE trial, irrespective of the *BCR-ABL1* mutation status.[7] Notably, the chronic phase patients with T315I mutations had superior responses overall, and 54% achieved an optimal response (major molecular response, *BCR-ABL1*^{IS} transcripts ≤0.1%). Nevertheless, among the patients with T315I, those with cooccurring *BCR-ABL1* mutations had substantially inferior responses.[8]



The efficacy of ponatinib for patients with CML with resistance to prior tyrosine kinase inhibitor therapy could be balanced against the risk of arterial occlusive disease by reduced dose intensity when a response is attained. Professional illustration by Patrick Lane, ScEYEnce Studios.

The OPTIC trial is the first prospective clinical trial to evaluate different dosing regimens for chronic phase patients resistant or intolerant to at least 2 prior BCR-ABL1 inhibitors or patients with a T315I mutation.[1] Of the patients enrolled, 99% were resistant to at least 1 prior inhibitor. Lower starting doses of ponatinib are recommended by the European LeukemiaNet for some patients, including those with increased cardiovascular risk profile.[9] However, dosing recommendations that are based on randomized clinical trial data of different dosing schedules have been lacking. Therefore, the OPTIC trial is important and addresses this gap.

The aim of the OPTIC trial was to establish the optimal dosing schedule for sustained responses while limiting the incidence of arterial occlusive events. Two hundred eighty-three patients were randomized to 45 mg, 30 mg, or 15 mg at 1:1:1 ratio. Dose was reduced to 15 mg upon attainment of a *BCR-ABL1*^{IS} level of ≤1% for patients randomized to 45 mg or 30 mg. The primary end point was *BCR-ABL1*^{IS} ≤1% at 12 months. This level of response is a robust predictor of overall survival. Safety evaluations included arterial occlusive events. The rate of *BCR-ABL1*^{IS} ≤1% at 12 months was superior for the 45-mg arm (44.1%) compared with the 30-mg (29.0%) and 15-mg (23.1%) arms. A similar pattern of superior response for *BCR-ABL1*^{IS} ≤1% by 12 months was observed for patients with a T315I mutation: 60%, 25%, and 10.5% for 45 mg, 30 mg, and 15 mg, respectively.

A closer examination of response for patients with a T315I mutation is warranted because these patients currently have limited approved treatment options. Nine patients with T315I prior to commencing ponatinib had additional *BCR-ABL1* mutations, and 7 of these (78%) did not achieve *BCR-ABL1*^{IS} ≤1% at any time. Furthermore, 5 other patients with T315I at study entry gained an additional *BCR-ABL1* mutation during therapy, and none of these patients achieved *BCR-ABL1*^{IS} ≤1% at any time. This is consistent with prior data and suggests that the occurrence of *BCR-ABL1* mutations in addition to T315I could be a powerful determinant of response to ponatinib.[8] Notably, the rate of loss of response upon dose reduction after achieving *BCR-ABL1*^{IS} ≤1% was highest for patients with T315I (54% in the 45-mg arm). Dose intensity may be required for maintenance of response. Therefore, the benefit and risk of dose reduction for patients with a T315I mutation must be carefully considered, and patients must be monitored closely after reduction. Whether maintenance of response for a prescribed length of time or achieving a deeper response before dose reduction would reduce the risk of loss of response is unknown.

The OPTIC response-based ponatinib dose reduction strategy demonstrated efficacy for patients who typically have poor response to second-generation BCR-ABL1 inhibitors. At study entry, 33% of all patients had at least 1 cardiovascular risk factor, and the 2 deaths related to adverse events in the 45-mg arm occurred for patients with cardiovascular risk factors. The overall rate of arterial occlusive disease was 6%, with a rate of 9.6% in those on 45 mg. A starting dose of 45 mg with response-related dose reduction was associated with an estimated 6.4 percentage-point increase in the rate of arterial occlusive events compared with 15 mg. However, this was offset by a 26.3 percentage-point improvement in the response rate by 12 months. When considering that optimal antileukemic effects should be maintained while minimizing the risk of adverse events, this benefit-to-risk data are informative (see figure).

Despite the efficacy of ponatinib for patients with a T315I mutation, a significant proportion fail to respond, which is likely related to the coexistence of other resistance mechanisms. The OPTIC trial provides a rich source of patient material ripe for further investigation beyond *BCR-ABL1* mutations to better understand these mechanisms and their possible connection with loss of response upon dose reduction. Lack of patient consent may preclude expanded studies. However, incorporation of exploratory analyses using new technologies, such as next-generation sequencing, in future trials involving patients with CML who have failed prior therapy is warranted.[10] Understanding genomic complexity could provide insight for treating refractory patients in the future.

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HEMATOPOIESIS AND STEM CELLS

Comment on Liu et al, page 2051

Dopamine motivates stem cells for reward

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In this issue of *Blood*, Liu et al describe how dopamine produced by sympathetic nerves in the bone marrow (BM) niche directly controls hematopoietic stem and progenitor cells (HSPCs) via D2 subfamily dopamine receptors.[1]

The BM niche is a highly complex microenvironment of many different coordinating cell types that support HSPCs throughout life.[2] Substantial evidence has demonstrated that the sympathetic nervous system innervates the BM microenvironment and regulates hematopoiesis.[3] Trafficking of HSPCs in and out of the BM even follows our circadian rhythms, with more HSPCs in circulation during sleep.[4] In this context, adrenergic peripheral nerves control HSPCs indirectly by contact with BM stromal cells. More recently, it was shown that HSPCs are directly regulated by the neurotransmitter γ-aminobutyric acid (GABA) via