Taming the gatekeeper: ponatinib dose holds the key

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In this issue of *Blood*, Cortes et al demonstrated 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 45mg that reduced to 15mg upon attainment of a response.[1]

In 2013 concerns related to arterial occlusive events led to the premature end of the EPIC trial of ponatinib for the treatment of newly diagnosed patients with CML.[2] Arterial occlusive events had occurred in 31% of chronic phase CML patients enrolled in the PACE Phase 2 trial of 45mg 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 indicated for the treatment of CML patients 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 co-occurring *BCR-ABL1* mutations had substantially inferior responses.[8]

The OPTIC trial is the first prospective clinical trial to evaluate different dosing regimens for chronic phase patients resistant or intolerant to at least two prior BCR-ABL1 inhibitors or patients with a T315I mutation.[1] Of the patients enrolled, 99% were resistant to at least one 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, recommendations that are informed by randomized clinical trial data of different dosing schedules have been lacking. Therefore, the OPTIC trial is important and necessary to address this lack of knowledge.

The aim of the OPTIC trial was to establish the optimal dosing schedule for sustained responses while limiting the incidence of arterial occlusive events. 283 patients were randomized to 45mg, 30mg or 15mg at 1:1:1 ratio. Dose was reduced to 15mg upon attainment of a *BCR-ABL1*^{IS} level of ≤1% for patients randomized to 45mg or 30mg. 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 45mg arm (44.1%) compared with the 30mg (29.0%) and 15mg (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 45mg, 30mg and 15mg, respectively.

A closer examination of response for patients with a T315I mutation is warranted since these patients currently have limited approved treatment options. Nine patients with T315I prior to commencing ponatinib had additional *BCR-ABL1* mutations and seven of these (78%) did not achieve *BCR-ABL1*^{IS} ≤1% at any time. Furthermore, five 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 45mg 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 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 one cardiovascular risk factor and the two deaths related to adverse events in the 45mg arm occurred for patients with cardiovascular risk factors. The overall rate of arterial occlusive disease was 6%, with 9.6% in the 45mg arm. A starting dose of 45mg with response-related dose reduction was associated with an estimated 6.4 percentage-point increase in the rate of arterial occlusive events compared with 15mg. However, this was offset by a 26.3 percentage-point improvement in the response rate by 12 months. When considering that optimal anti-leukemic effects should be maintained while minimising the risk of adverse events, this benefit-to-risk data is 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 co-existence of other resistance mechanisms. The OPTIC trial provides a rich source of patient material ripe for further investigation beyond *BCR-ABL1* mutations in order to 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 CML patients who have failed prior therapy is warranted.[10] Understanding genomic complexity could provide insight for treating refractory patients in the future.

Figure legend.

The efficacy of ponatinib for CML patients 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.

Disclosures

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