Clinical Impact of Dose Modification and Dose Intensity on Response to Ponatinib in Patients (pts) With Philadelphia Chromosome–Positive (Ph+) Leukemias

Background: Ponatinib is a potent oral pan–BCR-ABL tyrosine kinase inhibitor with clinical activity in pretreated pts with Ph+ leukemias. Dose modification of ponatinib was used to manage adverse events (AEs).

Aims: This post hoc analysis assessed the clinical impact of dose modification and dose intensity on outcomes of pts in the phase 2 PACE trial.

Methods: All pts provided informed consent. Ponatinib starting dose was 45 mg QD. Dose reduction was defined as any reduction below 45 mg/day; dose interruption was defined as treatment withheld for ≥3 consecutive days. Efficacy analyses were performed on chronic-phase chronic myeloid leukemia (CP-CML) pts (N=267). Analysis of arterial thrombotic events (ATEs) included all pts (CP-CML, blast-phase CML, accelerated-phase CML, Ph+ acute lymphoblastic leukemia; N=449). Data are as of 3 Sept 2013; median (range) follow-up was 24 (0.1-35) months for all pts. NCT01207440.

Results: 78% of CP-CML pts had dose modification within the first 12 months (82% at any time). Responses in pts with and pts without modification were comparable (Table). Of 149 responders, 87 (58%) achieved major cytogenetic response (MCyR) at 45 mg/day, 46 (31%) at 30 mg/day, and 16 (11%) at 15 mg/day. Most pts who had a dose reduction after achieving a response maintained that response: 97% maintained MCyR; 96% maintained complete cytogenetic response (CCyR); and 92% maintained major molecular response (MMR). Among pts with a dose reduction lasting ≥6 months after achieving a response at a higher dose, 100% (33/33) maintained MCyR (96% [26/27] CCyR and 93% [13/14] MMR). While dose intensity was the most significant predictor of MCyR by 12 months (multivariate analysis), substantial responses occurred at lower doses; estimated response rates were ~75% at 45 mg/day, ~60% at 30 mg/day, and ~30% at 15 mg/day. ATEs occurred in 17% of pts; each 15 mg/day reduction in average daily dose is predicted, by multivariate analysis, to lead to ~40% reduction in risk of ATE. 2-yr overall survival was similar for CP-CML pts who had dose modifications (86%) and those who did not (86%), and for pts who had ATEs (85%) and those who did not (87%). Of pts with ATEs, 46% had dose modifications.

Conclusion: Most of the CP-CML pts in the PACE trial had dose modifications. Pts who underwent dose modification still responded to treatment. Dose modification was an effective management tool for CP-CML patients. Careful consideration of the potential benefits and risks of ponatinib should guide treatment decisions.

<table>
<thead>
<tr>
<th>CP-CML</th>
<th>n</th>
<th>MCyR, %b</th>
<th>CCyR, %b</th>
<th>MMR, %a</th>
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<tr>
<td>Dose modification&lt;sup&gt;a&lt;/sup&gt;</td>
<td>218</td>
<td>58</td>
<td>47</td>
<td>38</td>
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<tr>
<td>No dose modification</td>
<td>49</td>
<td>47</td>
<td>45</td>
<td>35</td>
</tr>
</tbody>
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<sup>a</sup>At any time; <sup>b</sup>By 12 months
Abstract

INTRODUCTION

Aim: To determine the impact of dose modification on the efficacy and safety of ponatinib in chronic-phase chronic myeloid leukemia (CML) patients.

Study Design and Study Group

This was a multi-center, open-label, single arm Phase II study. Patients received ponatinib at a starting dose of 45 mg/day or modified to a lower dose per physician discretion. The primary efficacy endpoint was major cytogenetic response (MCyR) after 12 months and safety assessments were performed throughout the study.

METHODS

1. Study Population: Patients with CML or Ph+ ALL for whom no other TKI is indicated.
2. Efficacy Criteria: MCyR by 12 months in CP-CML, and occurrence of arterial thrombotic events.

RESULTS

1. Median time to dose modification: 29 (2-320) days.
2. Impact of dose intensity on arterial thrombotic events: Increasing intervals by 60% at 30 mg/day, and 30% at 15 mg/day.
3. Median time at any time: 15 30 45

OBJECTIVE

SUMMARY

The data presented herein are from an ongoing Phase III trial of ponatinib in patients with Philadelphia chromosome-positive leukemias.

Efficacy update from Oct 10, 2013 to Apr 7, 2014

1. Patients received ponatinib at a starting dose of 45 mg/day or modified to a lower dose per physician discretion.
2. The primary predictor variable was dose intensity up to the time of event/response for patients with an event/response, and time since diagnosis or exposure (in days) for events that did not reach an event.
3. Collectively, these data suggest that dose modification may be an effective management tool for some patients on ponatinib.

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