European Journal of Cancer 136 (2020) 107–112

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Ponatinib in childhood Philadelphia chromosome–positive leukaemias: an international registry of childhood chronic myeloid leukaemia study☆

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Received 29 February 2020; received in revised form 16 April 2020; accepted 19 May 2020

KEYWORDS
Children;
Ponatinib;
Chronic myeloid leukaemia;
Philadelphia chromosome–positive acute lymphoblastic leukaemia

Abstract ***Background:*** Ponatinib is effective in adults with Philadelphia chromosome–positive (Ph+) leukaemias, but scant data are available regarding the use of this tyrosine kinase inhibitor in children.
Aims: The aim of this study isto describe the tolerance and efficacy of compassionate use of ponatinib in a paediatric cohort of patients with Ph+ leukaemias.
Methods: Data from 11 children with chronic myeloid leukaemia (CML) registered to the international registry of childhood chronic myeloid leukaemia and from 3 children with Ph+ acute lymphoblastic leukaemia (Ph+ ALL) treated with ponatinib were collected retrospectively.
Results: In 11 girls and 3 boys (median age 14 years), ponatinib was used as a second- to eighth-line treatment. Ponatinib was administered as single therapy (9 patients) or in combination with chemotherapy (8 patients). The status of the disease when ponatinib was started was as follows: CML in advanced phases (n = 8), CML in chronic phase without achievement

☆ **Previous presentation**: Preliminary data was presented at the European Hematology Association Annual Meeting, Amsterdam, June 13–16, 2019.

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https://doi.org/10.1016/j.ejca.2020.05.020

of molecular response (n = 2) or presence of T315I mutation (n = 1) and Ph + ALL in molecular (n = 1) or marrow (n = 2) relapses. The median dose administered was 21.4 mg/m^2 and median duration of ponatinib was 2.5 months. Ponatinib alone or in combination with chemotherapy administered on 16 occasions led to achievement of major molecular response in 50% of cases. Ponatinib was used as a bridge to transplant in 4 cases. Among the 9 patients treated with ponatinib alone, toxicity grade III–IV (2 patients) was exclusively haematologic. No vascular events related to ponatinib were observed.

Conclusion: Ponatinib may be a reasonable additional treatment option for children with Ph+ leukaemias who have failed several lines of therapy.

1. Introduction

Tyrosine kinase inhibitors (TKIs) have revolutionised the treatment of patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukaemia (CML) and Ph+ acute lymphoblastic leukaemia (Ph+ ALL) by targeting the BCR-ABL oncoprotein underlying the malignant process. Imatinib was the first available TKI for the treatment of CML and Ph+ ALL, and second-generation TKIs, such as dasatinib and nilotinib, were successfully introduced in patients with failure or intolerance to imatinib. Recently, ponatinib, a third-generation TKI, was developed to overcome resistance to first- and second-generation TKIs in patients with CML and Ph+ ALL.

CML and Ph+ ALL are rare diseases in children and adolescents. Clinical studies have demonstrated the efficiency of first- and second-generation TKIs in children and adolescents with CML and Ph+ ALL [1–4]. However, scant data are available on the use of ponatinib in the paediatric population. The aim of this study was to describe the profile of tolerance and efficacy of compassionate use of ponatinib in children and adolescents with Ph+ leukaemias.

2. Methods

Children aged less than 18 years with CML diagnosed after 2000 enrolled in the international registry for childhood CML (international chronic myeloid leukemia pediatric study at www.clinicaltrials.gov, #NCT01281735) treated with ponatinib and children with Ph+ ALL treated with ponatinib in the International-BFM (I-BFM) study group were the subjects of the study.

Written informed consent was obtained from the children and/or their guardians. The phase of the disease was classified according to the criteria of the European LeukemiaNet recommendations [5]. The immunophenotype (myeloid or lymphoid) of blastic phases was determined by flow cytometry [6]. BCR-ABL1 transcript levels in the blood were performed using quantitative reverse transcriptase polymerase chain reaction (RT-PCR) and were expressed according to the International Scale [7]. Major molecular response (MMR), MR^4 and MR$^{4.5}$ were defined as a BCR-ABL1/ABL ratio of <0.1%, <0.01% and <0.0032%, respectively [7]. BCR-ABL1 kinase domain mutation analysis was performed as previously reported [8]. Overall survival was assessed from the diagnosis until the date of death or the last follow-up, and a survival curve was plotted using the Kaplan-Meier method [9].

3. Results

3.1. Patient characteristics

Data were retrospectively collected from 14 children treated with ponatinib between April 2013 and March 2019. Characteristics of the patients and details of treatments are reported in supplementary data. Eleven children were initially diagnosed with CML and 3 children with Ph+ ALL. The median age at diagnosis was 14 years (range 4.5–17). There were 11 boys and 3 girls. Six children (4 with CML and 2 with Ph+ ALL) were previously transplanted before the introduction of ponatinib. Among them, 1 patient was transplanted twice. Treatment with ponatinib was used as second (n = 2), third (n = 6), fourth (n = 1), fifth (n = 3), sixth (n = 1) or eighth (n = 1) lines of therapy. Ponatinib was administered as a single therapy in 9 children or in combination with chemotherapy in 7 children (patients 3 and 14 at 2 different times received ponatinib alone and in combination with chemotherapy, and patient 13 was treated twice with ponatinib in combination with chemotherapy). The type of chemotherapy administered in combination with ponatinib is reported in Supplementary data. This chemotherapy consisted of ALL-type or acute myeloblastic leukaemia–type induction regimens. The median dose of ponatinib administered was 21.4 mg/m2 (range: 10.7–43.6 mg/m^2). The median duration of ponatinib treatment was 2.5 months (range: 0.5–14 months). The status of the disease when ponatinib was started was advanced phase of

CML (n = 8; accelerated phase, n = 2; blast phase, n = 6), chronic phase CML without achievement of MMR (n = 2) or in $MR^{4.5}$ with T315I mutation (n = 1). Regarding the patients with Ph+ ALL, 1 patient was in molecular relapse and 2 patients were in marrow relapse when ponatinib was started. Three patients were treated a second time with ponatinib (alone or in combination with chemotherapy): at the onset of a second bone marrow relapse in a patient with Ph+ ALL (patient 13), in lymphoid blast phase in one patient (patient 3) with CML and as 'consolidation' post-allogeneic haematopoietic stem cell transplantation (HSCT) in 1 patient in MR^5 with Ph+ ALL (patient 14).

3.2. Overall response

Among the 8 patients with CML in advanced phases when ponatinib (alone in 4 patients or in combination with chemotherapy in the 4 remaining patients) was started, no response was seen in 3 patients receiving ponatinib alone, MMR in 4 patients (including one receiving ponatinib alone) and MR^4 in one patient receiving ponatinib in combination with chemotherapy. Among the 3 patients with CML in chronic phase at initiation of ponatinib alone, MMR was achieved in one patient, no response (non-achievement of MMR) in one patient and loss of $MR^{4.5}$ in the child harbouring a T315I mutation. No response occurred in the children (patient 3) with CML who received a second course of ponatinib.

Among the 3 children with Ph+ ALL, the 2 patients with bone marrow relapse achieved response levels of $MR^{4.5}$ and MR^5, although one of these children did not respond to ponatinib and chemotherapy in a subsequent relapse; the third patient receiving ponatinib alone for molecular relapse did not respond.

3.3. Ponatinib as a bridge to transplant

Satisfactory response (MMR to MR5) to ponatinib alone or in combination with chemotherapy made HSCT possible in 4 children (CML n = 3; Ph+ ALL n = 1). Duration of ponatinib administration before HSCT in these patients was 15 days to 5 months. No response was observed in one patient in accelerated phase receiving ponatinib as exclusive therapy before transplantation. One of these children received ponatinib as maintenance after HSCT and remained in deep molecular response.

3.4. Ponatinib in children with T315I mutation

The introduction of ponatinib was motivated by the identification of T315I mutation in 4 patients with CML in a context of lymphoid blast crisis and in one patient with Ph+ ALL in bone marrow relapse. The median time to emergence of T315I mutation was 29 months (range: 4–36 months) from the diagnosis of the disease. Treatment consisted of ponatinib (1.5–5 months) in combination with chemotherapy (4 patients) or ponatinib alone (47 days) as a consolidation of response ($MR^{4.5}$) to chemotherapy in the remaining children. A relapse of the lymphoid blast process occurred at this latter patient under ponatinib alone, one patient did not

Table 1
Side-effects in children and adolescents treated with ponatinib (patients with 1 or more toxicities).

Toxicities	Ponatinib alone n = 5/9	Ponatinib with chemotherapy n = 5/7
Haematologic toxicities	Platelet grade III (n = 2)	Platelet grade III–IV (n = 4)
	Platelet grade IV (n = 1)	Leucopenia grade III –IV (n = 4)
	Leucopenia grade I (n = 1)	neutropenia grade III (n = 1)
	Neutropenia grade III (n = 1)	Lymphopenia grade III (n = 2)
	Anaemia grade II (n = 1)	Anaemia grade II (n = 3) grade III (n = 1)
Non-haematologic toxicities	Nausea grade I (n = 1)	Liver enzymes increased grade III –IV (n = 2)
	Abdominal pain grade II (n = 1)	Lipase increased grade IV (n = 1)
	Abdominal pain grade I (n = 2)	Hypertriglyceridemia grade II (n = 1)
	Cutaneous grade I–II (n = 2)	Cutaneous grade III (n = 3)
	Headache grade I–II (n = 2)	Headache grade ND (n = 1)
	Fatigue grade I–II (n = 2)	Thromboembolic event[a] grade I (n = 1)
	Infection grade II (n = 1)	Infection grade ND (n = 2)
		Oral mucositis grade III (n = 1)
		Vomiting grade III (n = 1)
		Diarrhoea grade ND (n = 1)
		Erectile dysfunction grade I1 (n = 1)
		Angioedema grade III (n = 1)
		Thoracic pain grade I (n = 1)
		Osseous pain grade III (n = 1)
		Neuropathy grade ND (n = 1)
		Toxic encephalopathy grade ND (n = 1)

NC, not done.
[a] Venous thrombosis treated with anticoagulant and diagnosed few days before the start of ponatinib.

respond and 3 patients achieved MMR to $MR^{4.5}$ in 1, 2 and 4 months after introduction of ponatinib.

3.5. Toxicity

Side-effects were recorded in 5 of 9 patients receiving ponatinib alone. The median dose administered was 25 mg/m^2 in these 5 patients (range: 12.5–30 mg/m^2) with a median duration of treatment of 47 days (range: 15 days–14 months). Grade I–II toxicities represented the majority of the events. Grade III–IV toxicities were exclusively haematologic and were reported in 3 patients (Table 1). Side-effects were recorded in 5 of 8 patients treated with ponatinib in combination with chemotherapy, but it was difficult to identify events related exclusively to ponatinib. No vascular events related to ponatinib were observed in these subgroups of patients.

3.6. Survival

With a median follow-up of 41 months (range 10–152 months) from the diagnosis, 5 deaths were recorded including 3 patients who were transplanted. These 5 deaths were related to the disease. Nine patients were alive at the last follow-up including 2 patients diagnosed with Ph+ ALL. Seven patients were at least in MMR, and 2 patients did not achieve MMR. With a median follow-up of 41 months (range, 10–152 months), the probability of 5-year overall survival of the cohort of children was 59% (95%confidence interval: 33–85%) (Fig. 1).

4. Discussion

In the present study, ponatinib alone or in combination with chemotherapy administered on 16 occasions led to achievement of at least MMR in 50% of the cases indicating that ponatinib provided benefit for children with heavily pretreated CML or Ph+ ALL. Heiblig *et al.* [10] reported a cumulative incidence of 81.8% of MMR at 18 months in a cohort of adult patients with CML in chronic phase (CP) who had previously failed to at least 2 lines of TKIs.

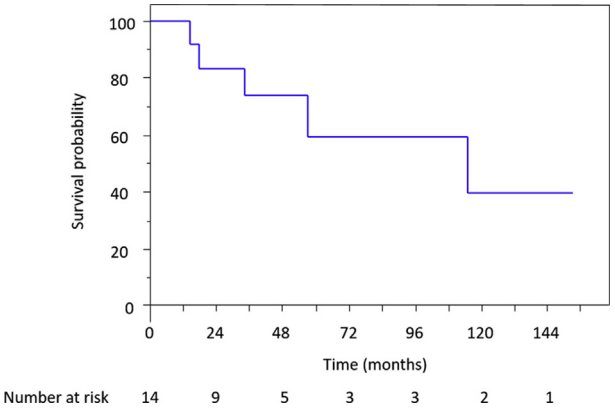

Fig. 1. Kaplan–Meier plot of the overall survival.

Ponatinib is active against most BCR-ABL1 kinase mutants including ABL1 kinase domain mutant T315I which are known to be resistant to first- and second-generation TKIs [11]. However, there are few data describing the responses in children. Nickel *et al.* [12] reported the control of the disease with ponatinib after occurrence of a T315I mutation and a cytogenetic relapse in a young boy treated with imatinib. A recent multicenter retrospective analysis reported on 21 paediatric patients mostly with Ph+ ALL (n = 12, CML n = 9) treated with varying doses of ponatinib after failure of first- and/or second-generation TKIs. Similar to our experience, 71% of the patients showed a decrease in disease burden after a median of three months with grade III toxicities being mostly haematologic and occurring in 29% of the cohort [13]. In the present study, ponatinib in combination with chemotherapy was effective in 3 of 5 children with the T315I mutation. However, the loss of molecular response under ponatinib in one of the 2 remaining children and the absence of response in the other one suggests that the mechanism other than T351I kinase domain mutation contributed to resistance.

In the present work, we report the utility of ponatinib as salvage treatment allowing reduction of tumour burden and thus bridging to HSCT in 5 children with CML or Ph+ ALL as previously reported in the adult population [14]. Ponatinib was administered as maintenance after transplantation in only one of these children and was well tolerated in this setting as previously reported in adults [15]. However, the role of ponatinib after HSCT remains to be confirmed.

The heterogeneity of the dose of ponatinib administered in the present study reflects the absence of recommended doses in the paediatric population. Teenagers represented most our patients, and the doses administered were based on the adult data including reports indicating that reduction of the dose was associated with a reduction of thrombotic events [16,17].

Ponatinib used without additional chemotherapy was well tolerated in 5 of 9 patients assessable for toxicity. Grade III toxicity was observed in only 3 patients and was exclusively related to haematologic adverse events (neutropenia, thrombocytopenia). Because of the small number of patients, it is not possible to correlate the occurrence of these side-effects with the doses administered. Mild toxicities were reported in the 7 children receiving a combination of ponatinib and polychemotherapy. Grade III pancreatitis was reported in one of our patients, but it is difficult to incriminate ponatinib because of the concomitant administration of polychemotherapy. Grade III and IV increase in lipase level was observed in 14% of adults in a phase III trial using ponatinib [18]. As reported with imatinib in children and adolescent, an impact of ponatinib as a TKI

class effect on growth in children is suggested by the growth deceleration in a young boy receiving ponatinib for 2.8 years [12,19]. However, the treatment duration of ponatinib in the cohort described here was too short to assess the impact on growth.

Frequently occurring cardiovascular toxicity was reported in adult patients with CML treated with ponatinib [10,18]. Interestingly, no vascular event related to ponatinib was observed in the present study. However, the duration of treatment with ponatinib (median time: 2.5 months) was shorter than the median times (11.5, 20.1 and 19.9 months) of onset of cardiovascular, cerebrovascular and peripheral arterial occlusive events, respectively, reported in the adult population treated with ponatinib [16]. In a case report, Nickel *et al.* reported administration of Ponatinib for 2.8 years without cardiovascular toxicity in a 12-year-old boy with CML [12].

The sparse data on ponatinib use in children with Ph+ leukaemia do not allow us to draw definite conclusions. Ponatinib could be proposed in children with CML after failure of first- and second-generation TKIs. Children harbouring T351I kinase domain mutation require treatment with this drug. Because the long-term outcome is poor in patients with CML who progressed to blast phase, children should proceed to HSCT within 3–6 months, and ponatinib can be used as a treatment for bridging this time window. A paediatric investigation plan comprising ongoing international prospective studies was set up to determine the appropriate dose and formulation, the tolerance and efficacy of ponatinib in children and adolescents with Ph+ leukaemias.

5. Conclusion

The present data provide insights into the efficiency and toxicity of ponatinib in heavily pretreated children. With the limitation of the retrospective nature of this study, ponatinib may be a reasonable additional treatment option for children with Ph+ leukaemias who failed to several lines of therapy. Prospective studies are definitely needed in a larger cohort of children, a goal that can only be achieved by international cooperation due to the rarity of CML in paediatric patients.

Conflict of interest statement

The authors declare no competing financial interest.

Acknowledgements

The authors gratefully acknowledge Irene Roberts (Department of Pediatrics, University of Oxford, UK) and François Guilhot (Inserm CIC 1402, Poitiers, France) for helpful comments on the manuscript, Violaine Goyeau for the data monitoring and Stéphanie Ragot for the analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.05.020.

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