A National Experience of Ponatinib in Patients failing Multiple TKI Confirms Efficacy in Heavily Pre-Treated Patients with Ph+ Leukaemias

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Background

Ponatinib is a potent third generation tyrosine kinase inhibitor (TKI) with efficacy against the kinase domain mutation, T315I. Data from the multi-centre international phase 2 study of ponatinib in Ph-positive leukaemias (PACE) showed that 46% of patients treated for chronic myeloid leukaemia (CML) in first chronic phase (CP1) achieved a complete cytogenetic remission (CCYR). Efficacy was higher in younger patients, those who were treated earlier in their disease course, had received fewer previous TKI and patients with a T315I mutation compared to those with no or other mutations. We wished to see if these results could be replicated in an independent cohort of patients, largely treated in a UK programme of availability by compassionate use .

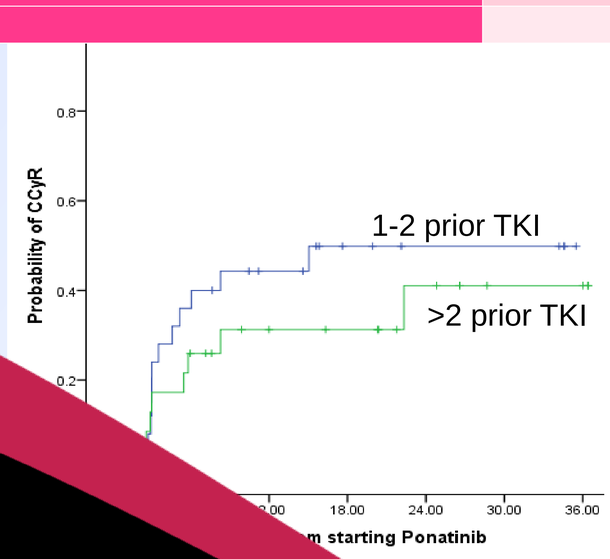
Methods

Patients were identified through the company records of requests for compassionate use followed by personal requests to individual clinicians, and through contacts in the UK National Cancer Research Institute (NCRI) CML Working Party. Questionnaires requesting additional data of response to prior TKI together with outcome of treatment with ponatinib including early dose intensity, toxicity and response, were completed by local clinicians.

All patients were considered evaluable for event free survival (EFS), defined as death from any cause, progression to advanced phase, loss of a previously established haematological, cytogenetic or molecular remission or stopping therapy. Only patients not in cytogenetic remission at the start of treatment were considered evaluable for efficacy assessment. EFS was calculated by Kaplan-Meier; the probability of CCyR by cumulative incidence.

Results

Age (years)	
Median	63
Range	20-70
Gender	
Male	35 (48%)
Female	38 (52%)
Time from diagnosis to ponatinib (months)	
Median	56
Range	71.-237.5
Stem cell transplant	
None	57
Pre-ponatinib	7
Post-ponatinib	9
Disease phase at start of ponatinib	
Chronic phase 1	61 (85%)
Acceleration	6 (8%)
Chronic phase > 1	3 (4%)
Blast crisis	2 (3%)
Disease status at start of ponatinib	
No haematological remission	2 (3%)
Complete haem remission	60 (84%)
Complete cytogenetic remission	4 (6%)
Major molecular remission	5 (7%)
Number of prior TKI	
1	6 (8%)
2	31 (43%)
3	29 (40%)
4	6 (8%)
Best response to prior TKI	
Complete haem remission	56 (81%)
Complete cytogenetic remission	8 (11%)
Major molecular remission	5 (8%)
Kinase domain mutations at start of ponatinib	
None	33 (45%)
T315I	16 (22%)
Other KD mutations	23 (33%)
Dose intensity first 3 months of ponatinib	
<15mg	7 (11%)
15mg - <30mg	23 (38%)
30mg	31 (51%)
Haematological toxicity first 3 months of ponatinib	
No	40 (56%)
Yes	32 (44%)
Non haematological toxicity first 3 months of ponatinib	
No	21 (41%)
Yes	51 (59%)



Results

	1yr EFS (%)	p-value	1yr CCyR (%)	p-value
Overall	35.9	-	38.5	-
Gender				
Male	35.5	0.77	32.9	0.28
Female	37.4		46.6	
Age (Yr)				
<60.7	48.0	0.12	52.2	0.035
>60.6	25.4		28.1	
Time diag-pon				
<5	33.0	0.77	51.4	0.091
>4.9	36.7		27.0	
Nos of prior TKI				
1-2	52.8	0.023	46.9	0.22
3-4	20.6		28.6	
CCyR on prior TKI				
Yes	34.8	0.61	28.2	<0.001
No	45.5		85.7	
Dose intensity				
<30	28.6	0.14	28.9	0.34
>29	48.7		49.2	
Haem toxicities				
Yes	37	0.99	52.1	0.029
No	34.6		20.0	
Non- Haem toxicities				
Yes	55.6	0.15	61.1	0.08
No	27.9		29.4	
Mutation				
T315I	50	0.62	62.5	0.14
None / Other	32.7		34.2	

Fig 1: 3 year probability of achieving CCyR

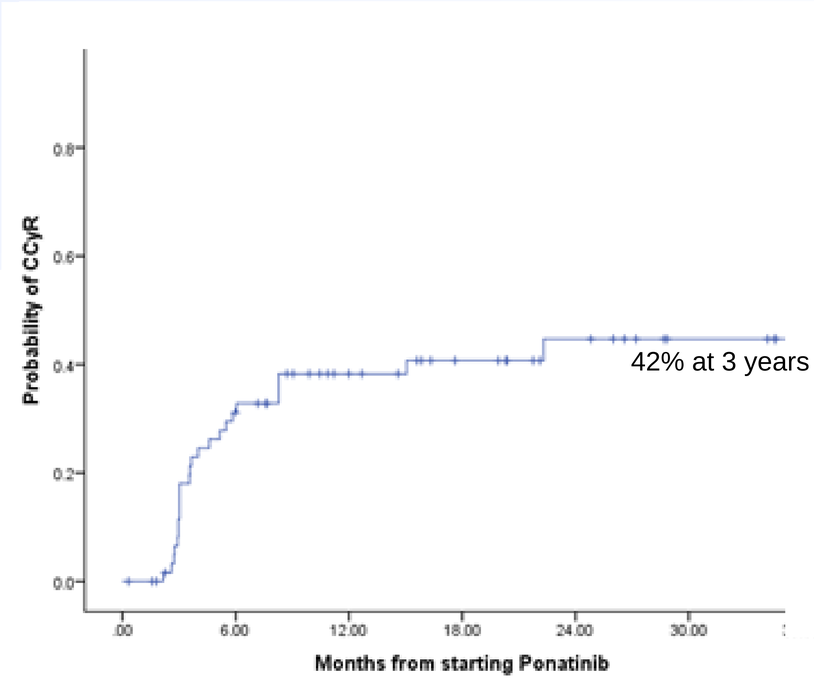


Fig 2: 2 year probability of CCyR by no. of prior TKI

Conclusion

- Ponatinib has confirmed efficacy in a group of heavily pre-treated patients with CML
- The probability of achieving CCyR on ponatinib is greater in younger patients, those with prior CCyR and those without early haematological toxicity, confirmed on multivariate analyses (data not shown)
- Event free survival is higher in patients who received fewer TKI prior to treatment with ponatinib