The outcome of post-transplant asciminib in patients with chronic myeloid leukaemia

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From the introduction of imatinib in the early 2000s, to the subsequent development of more potent 2nd and 3rd generation tyrosine kinase inhibitors (TKIs), the management of chronic myeloid leukaemia has evolved, and as a result, allogeneic haemopoietic stem cell transplant (HSCT) is now reserved for patients who have failed all available TKIs or who have presented with advanced phase disease. The most recently licensed TKI is asciminib, a novel selective allosteric inhibitor, targeting the myristoyl pocket of the BCR::ABL1 tyrosine kinase, with potency against both naïve and mutated BCR::ABL1, including the T315I mutation. Asciminib is currently approved in patients with CML in chronic phase (CP-CML), previously treated with two or more TKIs and also available for patients with the T315I mutation. Asciminib has shown increased tolerability and efficacy in comparison to the second generation TKI bosutinib (ref.1).

TKIs are used to treat molecular relapse post HSCT alone or in combination with donor lymphocyte infusions (DLI) (ref.2). They can also be administered as maintenance post HSCT in high risk patients. Whilst administration of TKIs in this setting has contributed to better overall survival (OS) and leukaemia free survival (ref.3), the timing and choice of TKI is not well established and poor tolerance remains an ongoing issue (ref.4) Furthermore, molecular relapse requiring treatment with DLI sooner than 6 months post-transplant negatively impacts on OS (ref.5). We report the use of asciminib therapy in the post-transplant setting.

We retrospectively reviewed data of 7 patients across 4 contributing centres, who received asciminib post HSCT for molecular relapse between 8th November 2018 and 8th August 2022. ABL1 kinase domain mutations (KDM) were analysed by Sanger sequencing. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0.

The median age of the cohort was 37 [22-61] years at diagnosis and 4 (57%) patients were male. All patients had a good performance status (PS) with an Eastern Cooperative Oncology Group (ECOG) 0/1. The majority of patients (85.7%) had an initial diagnosis of CML-CP, whilst one patient had CML-blast phase (CML-BP). EUTOS long-term survival (ELTS) scores at diagnosis were available for 5 patients (4 high risk and 1 low risk.)

The median number of TKIs prior to HSCT was 3 [2-5]. No patients had pre-transplant asciminib and 6 (85.7%) patients had received prior ponatinib, Two patients due to the identification of a T315I mutation. In the ponatinib pre-treated patients, ponatinib was stopped due to intolerance in 5 (83%) patients and 4 (66%) had concurrent resistance. Disease status pre-transplant for 5 patients was CP1 (71%), 1 in CP2 and 1 patient in blast crisis. Conditioning regimens were predominantly myeloablative (5 patients; 71.4%); 2 patients underwent reduced intensity conditioning.

The median time to commence asciminib post-transplant was 49 months [4-216] months. Post-transplant asciminib was administered in 3 (42.8%) patients who were in complete cytogenetic response (CCyR) or better at baseline (1 Complete molecular response (CMR), 2 CCyR), whilst the remaining patients were not in CCyR (57.1%). The median duration of time on therapy was 21.5 [0.76 -45.01] months. One patient, who was transplanted in CP2, relapsed in blast crisis, 26 months post-HSCT and received asciminib for only 23 days prior to death. In 6 patients who received more than 1-month of asciminib, 1 patient sustained CMR (and indeed *BCR::ABL1* transcript numbers continued to

decline) and of the 5 patients who improved their response; 1 patient achieved MMR, 2 MR4.5 and 2 MR5. All of the patients treated with ponatinib pre-transplant subsequently achieved or maintained a major molecular response (MMR), *BCR::ABL1* RT-qPCR $\leq$ 0.1% IS or better by 3 months of asciminib therapy post HSCT. Two (25%) patients had a T315I mutation prior to transplant and responded to post transplant asciminib, improving or maintaining their molecular response. No mutations were detected by Sanger sequencing at the time of commencing asciminib or whilst on post-transplant therapy.

Dose at initiation varied, 5 patients commenced asciminib at the standard dose of 40mg twice daily (BD), 2 of which underwent a dose reduction to 40mg once daily (OD), one due to non-haematological toxicity and the other patient due to grade 2 thrombocytopaenia, 2 patients continue on their initiation dose and 1 patient progressed to blast phase, leading to a dose increment to 200mg BD till their death. Two patients commenced treatment at 200mg BD, due to a previously identified T315I mutation, both underwent dose reductions, one patient to 120mg BD due to non-haematological toxicity and the other patient to 40mg on alternate days due to grade 4 thrombocytopaenia.

Patients frequently need to discontinue TKI therapy post-transplant due to toxicity (ref.3), however in this limited cohort, asciminib was well tolerated. Nonetheless, 50% (n=4) of the patients underwent dose reduction or temporary interruption due to a minimum of grade 2 thrombocytopenia (n=2) and any grade of non-haematological toxicity (n=2). No patients required permanent discontinuation due to intolerance. Most commonly reported non-haematological adverse events included grade 1-2 myalgia, fatigue and cramp, all commonly described post-transplant. Following asciminib dose reduction (Table 1), all patients are tolerating asciminib well and maintaining a deep molecular response.

Whilst there are some reports of TKI therapy, in particular ponatinib inducing GVHD (ref. 6, 7), this was not observed in this cohort. It is worth noting that as the median time to asciminib commencement post-transplant was 49 months, the adverse event profile, in particular haematological toxicity and incidence of GVHD may be different should therapy be commenced at an earlier time point. Also, limited drug interactions between ciclosporin and asciminib as opposed to other TKIs, may support better tolerability (ref. 8,9). *In vitro* studies using asciminib resistant BCR::ABL1+ cell lines demonstrated reversal of resistance with ciclosporin via the inhibition of ABCB1(ref 10), which may induce an improvement in molecular response in the post-transplant setting. Whilst this is interesting, no patients in our cohort were on concurrent immunosuppression and asciminib.

Post-transplant asciminib was well tolerated and induced improvement in molecular response in this heavily pre-treated cohort of patients, leading to acceptable control of disease. The majority of patients attained MMR or better, improving their molecular response from asciminib initiation, despite previous resistance to multiple TKIs. Within this patient group, those with pre-transplant ponatinib resistance (n=4) also achieved a deep molecular response, which is observed in only 30% of patients pre HSCT(ref. 11). Encouragingly, previous TKI resistance was not predictive of response to asciminib. Whilst the low rate of adverse events supports asciminib as an attractive therapeutic strategy post-transplant to induce molecular response and potentially defer the need for DLI post-transplant, its definitive role in this setting remains to be determined.

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Table 1 Patient Characteristics

Patient No	Age, Sex	Transcript Type	Disease phase at diagnosis	Previous TKI in sequence, best response on TKI, reason for TKI switch	ABL kinase domain mutation pre HSCT	Disease phase at HSCT	Donor source, conditioning	Start of asciminib post HSCT (months)	Asciminib Starting dose	BCR::ABL1 PCR (IS) at start of asciminib	Current asciminib dose	BCR::ABL1 PCR % (IS) at last FU	Molecular response on asciminib	Chimerism at last follow up	Presence of Haem Toxicity (Grade)	Mortality Status
1	41F	e14a2	Chronic Phase	1L Dasatinib-unknown-loss of response(T315I); 2L Ponatinib -unknown-toxicity	T315I	CP1	unrelated, Cy-TBI	77	200mg BD	0.00239	40mg alternate days	0.001, 36 months	Maintained	WB 100%, T cells 89% (pre asciminib)	Thrombocytopenia Grade 2	Alive
2	31F	e13a2/ e14a2	Chronic Phase	1L Imatinib-No response-Primary resistance; 2L Dasatinib-No response -Primary resistance; 3L Ponatinib -No response-Primary resistance; 4L Nilotinib-No response-Primary resistance	None	CP1	unrelated, Cy-TBI	13	40mg BD	5.1	40mg BD	0.000, 24 months	Improved	WB 100%, T cells 100%	None	Alive
3	27M	e14a2	Blast Phase (myeloid)	1L Dasatinib-unknown-toxicity; 2L Bosutinib-MR4-Blast phase relapse; 3L Ponatinib -MMR – toxicity	None	CP2	unrelated, Cy-TBI	26	40mg BD	2.6	Not applicable	Not applicable	Disease progressed	Not available	None	Deceased
4	22M	e13a2	Chronic Phase	1L Imatinib-No response-Primary resistance; 2L Nilotinib-No response -Primary resistance; 3L Dasatinib -No response-Primary resistance (T315I); 4L Ponatinib-No response-Progressed to Blast phase	T315I	BP (myeloid)	Unrelated, Bu-Cy	4	200mg BD	6.5	120mg BD	0.000, 18 months	Improved	WB 98%, T cells 99%	None	Alive
5	23F	e13a2	Chronic Phase	1L Imatinib-no response-primary resistance/toxicity; 2L Dasatinib-unknown-toxicity; 3L Nilotinib -no response - primary resistance;	None	CP1	Sibling, FMC	4	40mg BD	0.14	40mg BD	0.0032, 34 months	Improved	WB 98%, T cells 98%	None	Alive

				4L Bosutinib -no response-toxicity; 5L Ponatinib-no response- toxicity												
6	61M	e14a2	Chronic Phase	1L Nilotinib-no response-primary resistance/toxicity; 2L Dasatinib-no response-toxicity; 3L Ponatinib-no response-toxicity	None	CP1	Haplo, TBF-RIC	4	40mg BD	14.763	40mg OD	0.085, 4 months	Improved	WB 97%, T cells 44%	Thrombocyto-penia Grade 2	Alive
7	55M	e13a2/ e14a2	Chronic Phase	1L Imatinib -no response- primary resistance/intolerance; 2L Dasatinib- MMR – toxicity; 3L Nilotinib - MR4.5 – toxicity	None	CP1	Sibling, Cy-TBI	216	40mg BD	0.313	40mg OD	0.002, 4 months	Improved	WB 99%, T cells 100%	None	Alive

Abbreviations: F = female; M = male; int = intermediate; ELTS = EUTOS long-term survival score; MR4 = molecular response 4, MMR = major molecular response; CP1 = chronic phase 1; CP2 = 2nd Chronic phase; BP = blast phase; Cy-TBI = Cyclophosphamide-Total Body Irradiation; Bu-Cy = Busulfan-Cyclophosphamide; FMC = 5-fluorouracil, mitomycin C, cytosine arabinoside; TBF-RIC = Thiotepa, Busulfan, Fludarabine reduced intensity conditioning; D = Day; OD = once daily; BD: twice daily; L =line; Haplo = Haplo-identical; DLI = Donor Lymphocyte Infusion, WB = whole blood donor, NA = not available; Y = Yes; N = No