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Allogeneic stem cell transplantation for chronic myeloid leukaemia is safe and effective in high risk patients following second generation tyrosine kinase inhibitors: A single centre's experience

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ABSTRACT

Most patients now receiving a haematopoietic stem cell transplant (HSCT) for chronic myeloid leukaemia (CML) have been treated with first and second line TKIs pre-HSCT, raising concerns that these patients will have more resistant disease and accumulated greater toxicity from sequential lines of therapy, potentially compromising their outcome. We outline a series of 9 patients treated with imatinib then second generation TKIs for CML followed by HSCT and compare their outcomes with patients receiving imatinib-only pre-HSCT. Our case series demonstrates that second line and sequential tyrosine kinase inhibitors followed by HSCT is a safe and effective therapeutic approach for high risk CML.

1. Case series

Despite the indisputable success of tyrosine kinase inhibitors for chronic myeloid leukaemia (CML), there remains a subset of patients for whom haematopoietic stem cell transplantation (HSCT) remains necessary. A recent follow up of the International Randomised Study of Interferon and STI571 (IRIS) Study identified that almost 30% of patients discontinued imatinib because of suboptimal response or poor tolerance of therapy[1,2]. Furthermore, we know that patients presenting with advanced phase CML respond poorly to TKIs[3]. Data on imatinib use pre-transplant has not shown any deleterious effect[4] but data on second generation TKIs is sparse[5]. Although CML is exquisitely sensitive to the graft-versus leukaemia (GVL) effect of HSCT, toxicity of this procedure remains a concern. A further concern is the likelihood of HSCT success in patients who have failed successive targeted therapies and have potentially acquired more resistant disease. We report our single centre experience of the impact of second generation TKIs on the outcomes of allogeneic HSCT for CML, and compare these outcomes to our previously published historic controls[6].

Between March 2006 and December 2011, 9 patients with imatinib-resistant CML were treated with allogeneic HSCT following second generation TKI at the Beatson West of Scotland Cancer Centre. There were 7 males and median age at HSCT was 50 years (range 34–64 years). Four patients were in accelerated phase at diagnosis and 5 in chronic phase. Four patients had primary imatinib resistance and 5 had lost their response. Mutational analysis was positive in 1 patient (a binding site mutation not previously reported). At commencement of second generation TKI 7 patients were in chronic phase and 2 were in blast crisis. Nilotinib was used as a single agent in 1 patient, dasatinib in 4 patients; with sequential dasatanib and nilotinib use in 4 patients. The best response to second generation TKI was complete cytogenetic response (CCyR) in 5 patients, partial cytogenetic response (PCyR) in 1 and a complete haematological response (CHR) in 3 patients. These best responses were not all sustained at the time of HSCT (see Table 1). The median time on second generation TKI was 7 months (range 4–28 months) and in the majority of patients the TKI was stopped 2 weeks prior to HSCT. Conditioning was myeloablative in 5 patients and conditioning regimes varied according to patients' age and suitability for myeloablative or reduced intensity regimens. For patients receiving reduced intensity regimens with a history of lymphoid blast crisis busulphan was used instead of melphalan. Graft versus host disease prophylaxis was with cyclosporin (2.5 mg/kg day −2, 1.25 mg/kg day −1 and levels maintained at 200–300 mcg/l until dose reduction) and methotrexate 10 mg/m^2 on day +1, +3 and +6. In all peripheral blood stem cell grafts were used. Patient characteristics are summarised in Table 1.

All patients engrafted; 1 patient (Patient 6) developed secondary graft rejection following an A antigen mismatched graft from a male sibling and went on to receive a VUD HSCT with a female donor.

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Table 1
Patient and treatment characteristics.

Patient	Age at HSCT	Sex	Disease phase at diagnosis	Indication for HSCT	Months to HSCT	Time on imatinib: best response	2nd generation TKI use: best response and molecular response pre-HSCT	Disease phase pre-HSCT	Donor type and matching	Conditioning
1	61	M	AP	Previous AP including clonal evolution	23	18 months: CCyR	Nilotinib 4 months: CCyR	2nd CP	VUD 10/10 match	Flu/Bu/ Campath
2	64	M	CP	1° resistance 1st generation TKI, 2° resistance 2nd generation TKI	27	20 months: PCyR	1.Dasatinib 3 months: CCyR 2. Nilotinib 3 months: CHR	2nd CP	SIB 10/10 match	FLu/Mel/ Campath
3	35	M	AP	Previous AP, 2° resistance 1st and 2nd generation TKis	29	19 months: MCyR	Dasatinib 8 months: CCyR Lost CCyR and in CHR pre-HSCT	2nd CP	VUD 10/10 match	TBI/Cyclo/ Campath
4	52	M	CP	1°reistance 1st and 2nd generation TKIs	22	9 months: CHR only	1.Dasatinib 8 months: CHR only 2. Nilotinib 5 months: CHR only	1st CP	VUD 10/10 match	Flu/Mel/ Campath
5	50	M	AP	Previous myeloid blast crisis, 1° resistance to 1st and 2nd generation TKIs	10	5 months: CHR only	1.Nilotinib: 3 months: disease progression 2.Dasatinib 3 months: PCyR (pleural effusions)	2nd CP	VUD 10/10 match	Treo/Cyclo/ Campath
6	50	F	AP	Previous lymphoid blast crisis	21	16 months: CCyR	Dasatinib 4 months: CCyR	2nd CP	*1. SIB 9/10 match Ć('A' antigen mismatch) 2. VUD 10/10 match	1. Treo/ Cyclo/ Campath 2. Flu/Bu/ Campath
7	34	M	CP	Previous AP and poor tolerance TKIs	36	7 months: PHR	Dasatinib 28 months: CCyR	2nd CP	Volunteer unrelated donor 10/10 match	TBI/Cyclo/ Campath
8	41	M	CP	Previous myeloid blast crisis	25	18 months: CHR	Dasatinib 6 months: CHR only	3rd CP	VUD 10/10 match	Flu/Mel Campath
9	45	F	CP	1° resistance to 1st and 2nd generation TKIs	26	14 months: CHR	1. Nilotinib 9 months: CHR only 2. Dasatinib 2 months: disease progression	AP	VUD 9/10 match Ć ('A' antigen mismatch)	Treo/Cyclo/ Campath

Abbreviations: HSCT indicates haematopoietic stem cell transplant, CP indicates chronic phase; AP accelerated phase; VUD indicates volunteer unrelated donor; SIB is a sibling donor; CCyR is complete cytogenetic response, MCyR is a major cytogenetic response, PCyR is partial cytogenetic response, CHR is complete haematological response, PHR is partial haematological response (or incomplete haematological response)
Flu/Bu/Campath is Fludarabine (30 mg/m^2 day 7 to 3)/Cyclophosphamide (60 mg/kg day 3 and 2) and alemtuzumab (20 mg day 8, 10 mg bd day 7 to day 4); Flu/Mel/ Campath is Fludarabine (30 mg/m^2 day 7 to 3)/Melphalan (140 mg/m^2 day 2) and alemtuzumab, (20 mg day 8, 10 mg bd day 7 to 4) TBI/Cyclo/Campath is total body irradiation (1440 Gy in 8 fractions)/Cyclophosphamide (60 mg/kg day 3 and 2)and alemtuzumab(10 mg, day 5 to 1) Treo/Cyclo/Campath is Treosulphan (14 g/m^2), Cyclophosphamide (60 mg/kg day 3 and 2) and alemtuzumab (20 mg day 8, 10 mg bd day 7 to 4).

* This patient received 2 times HSCT owing to secondary graft failure of first HSCT which was an 'A' antigen mismatch.

There were no major conditioning related toxicities. Bacterial infections occurred in 6 patients prior to engraftment, and all responded to antibiotics. Seven out of 9 patients are alive at a median follow up of 46 months post HSCT (range 6–82 months). Patient 6 presented in chronic phase and progressed to lymphoid blast crisis with CNS disease on imatinib. She was subsequently treated with vincristine and prednisolone and 1 cycle of high dose methotrexate combined with dasatinib and obtained a complete morphological remission. She died of sepsis and chronic GVHD, in complete molecular remission (CMR), following her second allograft. Patient 8 was transplanted post second myeloid blast crisis (in 3rd responsive phase), and relapsed back into blast crisis 3 months post HSCT and died 5 months post-HSCT. The median times to engraftment, complications of HSCT, use of donor lymphocyte infusions (DLI) and outcomes are summarised in Table 2.

By definition, patients intolerant or resistant to TKIs will have higher EBMT scores than historical controls[7]. In 2008 our centre published a case series of 14 patients who had achieved a CCyR with imatinib and then went on to have a reduced intensity conditioned allograft followed by DLI to eradicate minimal residual disease in patients with a BCR-ABL:ABL $>0.02\%$[6]. Despite this group of patients having an inherently better risk profile (median EBMT score 2.5 versus 5 in this cohort)—engraftment times, toxicities from HSCT and outcomes from HSCT were similar. Engraftment in the imatinib only group was a median of 10 days to neutrophils $>0.5\times10^9$, versus 14 days in the second generation TKI group, and time to platelets $>20\times10^9$ was 10 days and 11 days respectively. GVHD was more frequent in the imatinib only group (57% of patients) compared with the second-generation TKI cohort (44%; not significant). In the imatinib only group all patients had at least a major molecular response (MMR) with 8 out of 14 patients achieving a complete molecular response (CMR). In the second generation TKI group 1 patient died of relapsed blast crisis and a second has incurred cytogenetic relapse at least in part due to poor compliance. The other surviving patients all achieved at least a MMR, with 4 patients obtaining a CMR. There was 1 treatment related death in each group.

The role of second generation TKIs post HSCT remains undefined. Relapse is the principal cause of treatment failure post HSCT. CML is exquisitely sensitive to DLI and this can be an effective means of treating molecular or cytogenetic relapse, but carries with it incumbent risks of GVHD[8]. Imatinib has previously been shown to be an effective therapy for post transplant relapse[9] and there is therefore a rationale for use of a TKI in high-risk patients post HSCT in a prophylactic setting[10]. It is intuitive that in these imatinib resistant/intolerant patients a second generation

Table 2
Summary of engraftment, HSCT complications and outcomes.

Patient	Days to ANC > 500/mm^3	Days to plts > 20,000/mm^3	Acute GVHD	Chronic GVHD	Other toxicity	DLI	Second generation TKI use post HSCT	Current status	F/U
1	12	9	No	Yes	No	No	Nilotinib commenced at day +38 for 2weeks. Stopped due to cytopenias. Recommenced at+4 months and stopped at +7 months owing to recurrent cytopenias despite GCSF	CMR	54 Months
2	9	9	No	No	Likely CMV pneumonitis	No	Dasatinib commenced day +50. Stopped after 2 weeks owing to GI side effects.	MMR	44 Months
3	17	8	No	No	PTLD[c]	Yes Total dose: 0.52×10^7/kg	1. Dasatinib started day+86, stopped after 6 weeks owing to cytopenias 2. Nilotinib then used for 4 months but stopped due to cytopenias despite GCSF	MMR	53 Months
4	11	11	No	Yes	Idiopathic thrombocytopenic purpura	Yes Total dose: 6.81×10^7/kg	Nilotinib started at day+88 but stopped after 4 weeks owing to cytopenias despite GCSF	CMR	51 Months
5	18	[a]	No	No	Seizures	Yes Total dose: $0.6 \times 1\ 0^7$/kg	Nilotinib started at day +74, stopped after 3 months owing to deranged LFTs	CMR	46 Months
6[b]	1.14 2.77	[a]	1. No 2. Yes[b]	1. No 2. Yes[b]	No	No	Dasatinib started day +56 for 5 months and stopped owing to secondary graft failure	Died	21 Months
7	14	12	No	No	No	No	Nil (poor compliance) with previous TKIs	CMR	82 Months
8	11	16	No	No	No	No	Nil (relapsed blast crises)	Died[d]	6 Months
9	19	11	Yes	Yes	PTLD[c]	No	Bosutinib started day+84, remains on at +8 months but poor compliance	Relapsed[e]	13 Months

Abbreviations: ANC is absolute neutrophil count, GVHD is graft versus host disease, DLI is donor lymphocyte infusion, TKI is tyrosine kinase inhibitor, HSCT is haematopoietic stem cell transplant, GI is gastrointestinal, CMV is cytomegalovirus, PTLD is post transplant lymphoproliferative disorder, LFTs is liver function tests, MMR is major molecular response and CMR is complete molecular response.

[a] Patients on LMWT heparin – thus platelet count maintained > 40 with transfusion throughout cytopenic phase.
[b] This patient received 2 times HSCT owing to secondary graft failure of initial HSCT.
[c] Both patients with PTLD responded to single agent rituximab.
[d] Relapsed blast crisis 3 months post HSCT (patient transplanted post second blast crisis in 3rd responsive phase).
[e] Cytogenetic relapsed likely secondary to poor compliance with post-HSCT TKIs, initial molecular relapse unable to be controlled with DLI owing to concurrent GVHD.

TKI would be more effective but we have found them to be åpoorly tolerated post HSCT with frequent haematologic and gastrointestinal toxicities. In addition, drug interactions can be a significant problem in the post HSCT period with the majority of patients on multiple medications including antibiotics and immunosuppressants.

In this cohort a second generation TKI post HSCT was attempted post HSCT in 7 patients (see Table 2). It was intended to commence TKIs approximately 4 weeks post engraftment routinely, regardless of BCR-ABL transcript number. TKI selection was based on previous response to TKI pre-HSCT and commenced post HSCT at a median of +65 days (range +38 to +88 days) for a median of 14 weeks (range 2–32 weeks) but all ultimately were stopped owing to toxicities, predominantly cytopenias. Patient 9 received bosutinib (having proven refractory to all other second generation TKIs pre-HSCT) for increasing BCR-ABL transcript numbers post HSCT and initially achieved a MMR (not a candidate for DLI owing to concurrent grade II GVHD) but has since suffered a cytogenetic relapse owing to poor compliance not caused by toxicities. In the context of our high rates of MMRs without successful use of prophylactic second generation TKIs post HSCT, we have now abandoned prophylactic second generation TKI usage. At our centre, post transplant TKIs are now considered for mixed chimerism and increasing BCR-ABL transcripts as a bridge to DLI or in patients with GVHD for whom DLI is inappropriate.

In conclusion, we demonstrate that HSCT for CML even in this case series of notably high-risk patients remains an effective and comparatively safe therapeutic tool for these patients in whom treatment options are limited. Furthermore, second generation TKIs should only be considered in selected patients post HSCT due to toxicities.

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A.L. designed the research, analysed the data and wrote the paper. M.C. designed the research and wrote the paper. G.MQ. and A.P. edited the paper and all authors approved the final manuscript.

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