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THE EFFECT OF IMATINIB ON CMV REACTIVATION IN HEMATOPOIETIC CELL TRANSPLANTATION

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Abstract

In-vitro studies have shown possible antiviral effects of tyrosine kinase (TK) inhibitors. In a retrospective study, we show that use of the TK inhibitor Imatinib does not appear to reduce cytomegalovirus reactivation during the first 100 days after transplant in a cohort of hematopoietic cell transplant recipients.

Keywords

Cytomegalovirus; Imatinib; Transplant

Background

Imatinib is a tyrosine kinase (TK) inhibitor licensed for the treatment of chronic myeloid leukemia (CML), Philadelphia chromosome positive acute lymphocytic leukemia (ALL), myeloproliferative disorders due to chromosome rearrangements in platelet derived growth factor receptor (PDGF-R), and gastrointestinal tumors with mutation in c-kit [1]. A recent in-vitro study demonstrated that Imatinib inhibited the TK PDGFR- α , a critical receptor required for CMV infection, suggesting that it could be a novel therapy for either treatment or prevention of primary infection [2]. Other studies have suggested that Imatinib may have antiviral activities [3], but increased rates of varicella-zoster virus (VZV) in patients treated with this medication have also been described [4,5]. Despite these observations, there are no clinical data evaluating the anti-CMV effects of Imatinib. We analyzed CMV outcomes in a cohort of hematopoietic cell transplant (HCT) recipients treated with or without Imatinib to assess the drug's potential effects on CMV.

Methods

We completed a retrospective cohort study of CMV seropositive subjects who underwent any HCT for ALL or CML at the Fred Hutchinson Cancer Research Center in Seattle, WA, between

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January 2004 and December 2008. Subject demographic and clinical information were abstracted from medical records, and all underwent standardized conditioning regimens and post-transplant care [6]. All subjects received standard graft-versus-host-disease (GVHD) prophylaxis with a combination of calcineurin inhibitors, methotrexate, and or mycophenolate mofetil; all received antiviral prophylaxis with low dose acyclovir for VZV and herpes simplex. Ganciclovir pre-emptive therapy was given as previously described [7]. Patients were excluded if they survived less ≤ 14 days.

Subjects had differing exposure to Imatinib after HCT because daily dosing was between 200 mg and 800 mg according to subjects' clinical conditions, and duration of therapy varied between individuals. The Imatinib treated group also included 4 patients that were part of an ongoing research study in which they received Imatinib for 1 year following post-transplant engraftment. Patients that were given other TK inhibitors (Dasatinib or Nilotinib) post-transplant were excluded from primary analyses.

CMV infection was defined as isolation of CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen. CMV reactivation was considered any positive antigenemia test and or a positive polymerase chain reaction (PCR) of CMV >50 copies per mL within the first 100 days post-transplantation. CMV disease was defined by standardized criteria [8]. For the purposes of analyses, specific CMV outcomes of interest were considered first CMV reactivation during the first 100 days after HCT and a composite endpoint for severe CMV infection which included CMV disease and/or a high viral load (PCR >1000 copies per mL and/or antigenemia >10 cells per 200,000 peripheral blood leukocytes).

We assessed the role of Imatinib using multivariate Cox proportional hazards models. All Cox models were adjusted for graft source, donor CMV serostatus, and severe GVHD (grade 3–4). Imatinib use and severe GVHD were considered time-dependent variables in all analyses since initiation and length of exposure varied between subjects. In January 2007 plasma PCR became the routine laboratory test for CMV detection, and prior to this in 2005 and 2006, plasma antigenemia testing was more frequently used for screening. As PCR has a higher sensitivity for CMV reactivation, we used January 2007 as proxy to separate the time points where different methods were used for CMV diagnosis.

All data were analyzed using SAS (version 9.1; SAS, Cary, NC). The study was approved by the Fred Hutchinson Cancer Center Institutional Review Board.

Results

We identified a total of 97 CMV seropositive subjects who met inclusion criteria; four subjects (4%) that received other TK-inhibitors post-transplant were excluded from primary analyses. Of the remaining 93 subjects, a total of 22 subjects (23%) received Imatinib (median treatment: 151 days [IQR 100–339] and median day onset for Imatinib: 28 days [IQR 17–43]) and 71 (77%) did not. Transplant and demographic characteristics were similar in the two groups except for graft source ($p=0.04$) (Table 1). Severe acute GVHD (grade 3–4) occurred in 3/22 (14%) in those treated with Imatinib and 10/71 (14%) in untreated subjects, and overall rates of acute GVHD were similar in the two groups.

CMV reactivation occurred in 18/22 (82%) subjects in the Imatinib group and in 47/71 (66%) in those without exposure. No subjects had a history or laboratory evidence of active CMV prior to transplantation. A total of 2/22 (9%) subjects in the Imatinib group developed CMV disease in the first 100 days, compared to 8/71 (11%) in subjects without exposure. CMV reactivation and disease also occurred during Imatinib therapy, as 10/18 (56%) of those with reactivation and 1/2 with disease occurred while on active Imatinib. We observed no impact of Imatinib exposure on hazards of CMV reactivation or severe CMV infection (Table 2).

Independent of the composite endpoint, neither a high CMV viral load nor CMV disease were associated with Imatinib treatment, and method of CMV testing (PCR vs. antigenemia) did not appear to alter these results (data not shown). Multivariate results were also repeated with subjects receiving post-transplant Dasatinib or Nilotinib added to the treatment group, but this did not alter our findings (data not shown).

Discussion

In this single center retrospective cohort study, subjects treated with or without Imatinib had similar rates of clinical CMV. In addition to demonstrating no overall effect on reactivation, Imatinib did not appear to alter more clinically significant CMV endpoints, such as high viral load and CMV disease.

Published studies have differed in their interpretation of the antiviral and immune effects of Imatinib [1]. Imatinib has been shown to inhibit the process of CMV internalization through TK inhibition [2], while clinical studies have demonstrated increased rates of VZV in those treated with Imatinib [4,5]. Other studies have shown adverse effects on the immune response including a reversible lymphopenia and hypogammaglobulinemia [9], and dose dependent inhibition of T cell-receptor-mediated T cell activation and proliferation [10]. Further complicating these data are reported effects on dendritic cells (DC). While some studies demonstrate negative effects such as lower responses of Imatinib exposed DCs against tumor and recall antigens [11], others have shown enhanced presentation of antigen by DCs exposed by Imatinib [1,12].

Our study is the first to assess the effect of Imatinib on CMV in a clinical setting, and these data fail to show alterations in CMV outcomes in those receiving Imatinib therapy. It is possible that Imatinib may need to be given earlier during the at-risk period to provide therapeutic benefits, or since Imatinib may prevent viral entry, it may be more important in primary infection. Finally, the antiviral effects of Imatinib may be overshadowed by the drug's adverse effects on the immune response.

The major limitation of this study was sample size, which hampered our ability to detect less prominent antiviral effects of Imatinib. We project that a 55% reduction in CMV reactivation was needed in order to detect a difference in treatment groups. To put this in context, ganciclovir prophylaxis reduces CMV reactivation measured by antigenemia by 70–80%. Thus, while our study was not able to detect a moderate antiviral effect of Imatinib, we had enough power to detect effects similar to those seen in presently used antiviral drugs. Because we completed time-to-event analyses based on weekly screening, it is possible that more frequent sampling could provide additional information on viral kinetics not available in these data. In order to clarify the role of immunosuppressive effects of Imatinib, additional information on lymphocyte recovery and incidence of lymphopenia will also be important to address in future studies. In contrast to these limitations, this study was strengthened by the high rate of CMV endpoints, the accuracy of data collection, and the use of standardized supportive care strategies in our population.

In summary, in this initial study, we were unable to demonstrate a major effect of Imatinib on CMV reactivation in this single center cohort of HCT recipients. While our data could not confirm a strong anti-CMV effect of the drug, larger studies would be needed to accurately define if there are smaller effects of Imatinib or other TK inhibitors on CMV, and to fully understand their potential role as primary or adjunctive antiviral therapy.

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Table 1

Demographics of CMV Seropositive Patients Treated With and Without Post-transplant Imatinib Therapy (n=93)

*

Characteristic	Imatinib (n=22) n (%)	No Imatinib (n=71) n (%)	p
Male	10 (45)	36 (51)	0.67
Age (median, IQR)	37 (17, 43)	30 (18, 47)	0.55
Underlying Disease			0.09 [‡]
ALL			
Ph positive	16 (72)	4 (6)	
Ph negative	0 (0)	59 (83)	
CML			
Ph positive	6 (28)	8 (11)	
Ph negative	0 (0)	0 (0)	
Ethnicity			0.73
Caucasian	13 (59)	39 (55)	
Other	9 (41)	32 (45)	
Donor Type[‡]			0.60
Matched-related	7 (32)	22 (31)	
Matched-unrelated	9 (27)	20 (28)	
Mismatched-unrelated	6 (41)	26 (37)	
Graft Source			0.04
Bone Marrow	11 (50)	16 (23)	
PBSC	8 (36)	45 (64)	
Cord Blood	3 (14)	10 (14)	
Conditioning Regimen			1.0
Myeloablative	20 (91)	62 (87)	
Non-myeloablative	2 (9)	9 (13)	
Conditioning Regimen			0.63
CY-TBI	14 (64)	49 (69)	
BU-CY	2 (9)	4 (6)	
Flu/CY	2 (9)	5 (7)	
CY/Flu/TBI	4 (18)	8 (11)	
Other	0 (0)	5 (7)	
GVHD Prophylaxis			1.0
CSA or FK506 + MTX	15 (68)	46 (65)	
Other regimen with MMF	6 (27)	19 (27)	
Other	1 (5)	6 (8)	
Acute GHVD			0.54
Grade 2–4	16 (73)	49 (69)	
Grade 3–4	3 (14)	10 (14)	1.0
Donor CMV Serostatus			0.20
Seronegative	14 (64)	36 (51)	
Seropositive	7 (32)	35 (49)	
Status[§]			1.0
High Risk	6 (27)	19 (27)	
Low Risk	16 (73)	52 (73)	

Abbreviations: CMV, Cytomegalovirus; IQR, Interquartile range; ALL, Acute Lymphoblastic Leukemia; CML, Chronic Myelogenous Leukemia; PBSC, Peripheral blood transplant; CSA, cyclosporine; MTX, methotrexate; MMF, Mycophenolate mofetil

Values may not equal 100% because of rounding

* Patients surviving ≤ 14 days were excluded

[‡] Comparison between ALL and CML distribution between groups.

[‡] 3 patients without Imatinib were haploidentical.

[§] High risk – accelerated phase, blast crisis, relapse; Low risk – remission, chronic phase

Table 2

Assessment of Risk Factors Associated with Post-Transplant CMV Outcomes in a Cohort of CMV Seropositive Hematopoietic Cell Transplant Recipients (n=93)*

Variable	HR (95% CI)	1 st CMV Reactivation [†] <i>p</i>	HR (95% CI)	Severe CMV [‡] <i>p</i>
Imatinib vs. No Imatinib	1.6 (0.7, 3.4)	0.26	2.2 (0.4, 11.8)	0.37
D+ vs. D-	1.3 (0.7, 2.2)	0.41	0.7 (0.2, 2.9)	0.63
Bone marrow vs. PBSC	0.7 (0.4, 1.3)	0.24	0.3 (0.04, 2.5)	0.26
GVHD grade 3-4 vs. 0-2	1.9 (0.8, 4.3)	0.10	7.0 (1.7, 28.1)	0.007

Abbreviations: D+ indicates CMV seropositive donor; D-, seronegative donor; PBSC, peripheral blood stem cell; GVHD, graft-versus-host disease; CMV, cytomegalovirus; CI, confidence interval; HR, hazard ratio.

* Cox multivariate models include all factors listed in table.

[†] In first 100 days after transplant.

[‡] Severe CMV includes CMV disease, PCR > 1000 copies per ml, or antigenemia > 10 cells/200,000 peripheral blood leukocytes.