Appropriate Antiviral Therapy can Prevent Hepatitis B Reactivation and Progression in Chronic Myeloid Leukemia on Therapy with Tyrosine Kinase Inhibitors

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Abstract

Background: Viral Hepatitis reactivation may occur in patients receiving Tyrosine kinase inhibitors, leading to potentially fatal complications. This study assessed the impact of antiviral therapy on reactivation of viral hepatitis in patients on TKIs.

Methods: We retrospectively reviewed the clinical and laboratory data including medical therapy in 98 CML patients.

Results: Imatinib was used as first line in 87 patients (92.5%), however, currently 35, 20 and 14 patients are on Imatinib, Nilotinib, and Dasatinib respectively. Further, two each are taking Ponatinib and interferon respectively. Nine patients had a successful treatment free remission (TFR), while five received BMT. Nine patients died and two were lost to follow-up. Six patients were HBsAg-positive with HBV PCR positivity. They received variable TKI therapy with Imatinib, Dasatinib and Nilotinib, while one patient each received Ponatinib and Interferon as appropriate. All six patients are now receiving Entecavir. Anti-HBc was positive in 16 patients (16.3%), including the six patients with HBsAg positivity. One patient, who was HCV RNA PCR positive, received Imatinib concomitantly with interferon-based antiviral therapy and remains in remission, with successful TFR.

Conclusion: We could not document viral reactivation in any patient on TKI therapy. HCV responded well to interferon-based antiviral therapy with successful TFR.

Keywords: Chronic myeloid leukemia; Tyrosine kinase inhibitors; viral Hepatitis prevalence; Hepatitis B virus reactivation, hepatitis C virus reactivation, CML survival.

Introduction

The prognosis of chronic myeloid leukemia (CML) has been revolutionized by the introduction of the tyrosine kinase inhibitors (TKIs), namely Imatinib (first-generation), Dasatinib, Nilotinib and Bosutinib (second-generation) and Ponatinib (third-generation).[1-5] The use of TKIs has allowed CML patients to enjoy a near-normal life, with life expectancy similar to the general population.[6]

Transforming growth factor-β1(TGF-β1) is a key regulator of immune homeostasis,[7] the upregulation or prolongation of it signaling by BCR-ABL, is considered as one of the mechanisms by which BCR-ABL promotes the transformation of haemopoietic progenitor cells.[8] Programmed death-ligand 1 (PD-L1) is responsible for T cell activation, proliferation, and cytotoxic secretion,[9] its decreased levels during TKI therapy suggesting at least partial reversal of immune cell exhaustion.[10] TKI discontinuation gives rise to musculoskeletal pain and/or flushing, known as TKI withdrawal syndrome (TWS), which is not a cytokine-release-like syndrome, but a distinct entity significantly associated with a decrease in IL10,[11] the latter is considered as an important immune-regulatory cytokine.

Chronic viral hepatitis (CVH) is a global health issue contributing significantly to the development of chronic liver disease, cirrhosis, and hepatocellular carcinoma.[12] Hepatitis B virus reactivation may occur in patients receiving TKIs and this may be a potentially fatal complication, prompting a recommendation for regular testing of CML patients for hepatitis prior to TKI therapy by the regulatory authorities.[13-18] Previous studies have shown that chemotherapy can induce HBV reactivation in Hepatitis B e antibody (anti-HBe)-positive and HBsAg-positive asymptomatic carriers, and much less in cases of resolved HBV infection.[19] TKIs were reported to lead to HBV reactivation (HBVr), probably due to the inhibition of T-cell proliferation and activation, leading to a defective immune response.[20,21] However, according to Yazici (2014), there has been no significant evidence of HCV reactivation in CML patients receiving TKIs.[22]

Although there are some prevalence studies on HBV and HCV infections from Oman, there is no data on viral hepatitis in Omani CML patients.[21,22] Thus, our study is assessing the prevalence of viral hepatitis in CML patients, and to study the impact of TKIs on hepatitis reactivation as well as assess the impact of viral hepatitis on CML molecular remission and survival.

Methods

This is a retrospective cohort study conducted at Sultan Qaboos University Hospital (SQUH). After obtaining ethical approval from medical research & ethics committee (MREC # 1667, 2nd May 2018), medical records of patients with CML who attended the hematology department at SQUH from 2006 to 2020 were examined. We obtained the clinical and laboratory data, medical therapy, as well as details of hepatitis screening from the hospital electronic medical records. The data collected includes demographic information like age, and sex; clinical data including date of diagnosis, spleen size, length of follow up, type of TKIs, and the outcome. Laboratory parameters including hemoglobin levels, WBC and platelet counts, blood chemistry at presentation, CML diagnostic markers, and viral hepatitis status. Monitoring of CML over the last 10 years was performed using GeneXpert machine (Cepheid, Sunnyvale, CA USA). We used the definition of HBVr as either a change in alanine transaminase (ALT) levels, or the presence of newly acquired HBV serological markers, or HBV DNA. Thus, HBVr was considered in any of the following namely; a 2- to 3-fold increase of ALT above baseline; hepatitis B surface antigen (HBsAg) seroconversion or detection of HBV DNA in the blood in the absence of HbsAg; newly detected HBV DNA or a 10-fold rise in HBV DNA level (compared with the baseline level before immunosuppression).

Statistical Analysis: Descriptive statistical analysis was performed using Statistical Package for Social Sciences, (IBM SPSS Statistics for Windows, Ver. 23.0., Armonk, NY). It was used to determine the prevalence of hepatitis infection among CML patients and to evaluate the percentage of viral hepatitis reactivation after receiving TKIs and its impact on CML molecular remission. The prevalence is reported as counts and percentages as appropriate. Survival analyses utilized the initial diagnosis date, date of remission and relapse, date of last visit, and the date of death of patients using the hospital records. Overall survival (OS) was calculated from the time of diagnosis of CML to the time of last follow-up or death. The progression-free survival (PFS) was measured from the time of diagnosis to the time of the last follow-up, progression, relapse or death based on the different treatment modalities. The Kaplan-Meier method was used for calculation of all survival endpoints. Survival comparisons were made using the log-rank test using $p<0.05$ as the statistical significance.

Results

Ninety-eight patients diagnosed with CML at our institution between 2006 and 2020 were included, with a mean age of 41 and a range between 4 to 77 years [Table 1]. The percentage of females (54%) exceeded the percentage of males (46%). Sixty-eight (69.4%) patients received Hydroxyurea before starting TKIs. Treatment with Imatinib as first line was given to 87 patients (92.5%), however currently 35, 20 and 14 patients are on Imatinib, Nilotinib, and Dasatinib therapy respectively. Nine patients had a successful treatment free remission (TFR) with persistent negative BCR-ABL with an RQ-PCR sensitivity of $MR^{4.5}$. Nine patients died, while five patients received a successful allogenic bone marrow transplant. Further, two each are taking Ponatinib and Interferon respectively, while two were lost to follow-up. Kaplan-Meir plots show the PFS and OS. [Figures 1 & 2] The overall 5–year and 10-year survival of patients in this CML cohort was excellent, reaching 93.4% and 89.6% respectively. Death rate was 9.2% (9 cases), but none occurred in the relapsed cases, as all the thirty-five relapsed cases were salvaged by additional therapeutic modalities including bone marrow transplantation (BMT). Fourteen cases had TFR, including five patients who underwent a successful BMT.

Table 1: Clinical, laboratory features, and viral hepatitis status in 98 CML patients on TKIs.

Parameters		**Results**
Mean age (range) yrs		41.1(4-77)
Sex M/F, n		45/53
Hematological parameters at presentation, mean, range	Hb g/dl	10.4 (4.1-14.9)
	WBC x 10^9/l	115 (2-600)
	Platelets x 10^9/l	456 (23-1710)
Spleen size (cms)		14.8 (6-26)
Median follow up time, months (range)		77 (2-237)
Alive, n (%)		89 (90.8%)
Exposure to TKIs	Imatinib	93 (94.9%)
	Dasatinib	23 (23.55)
	Nilotinib	25 (25.5%)
	Exposure to ≥ 2 TKIs	48 (48.9%)
Currently on CML therapy	Imatinib	35 (39.3%)
	Dasatinib	14 (15.7%)
	Nilotinib	20 (22.5%)
	Others	4 (4.5%)
	TFR	9 (10.1%)
Hepatitis B status	HBV immune, n (%)	45 (45.9%)
	HBV negative, n (%)	77 (78.6%)

	HBV positive (including core), n (%)	16 (16.3%)
	HBsAg positive, n (%)	6 (6.1%)
	HBsAg positive, positive HBV PCR, n (%)	6 (6.1%)
Hepatitis C status	HCV serology positive, n (%)	1 (1.1%)
	HCV PCR	0

HBV-hepatitis B virus, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, CML: chronic myeloid leukemia, TFR: treatment free remission, TKI: Tyrosine Kinase Inhibitors.

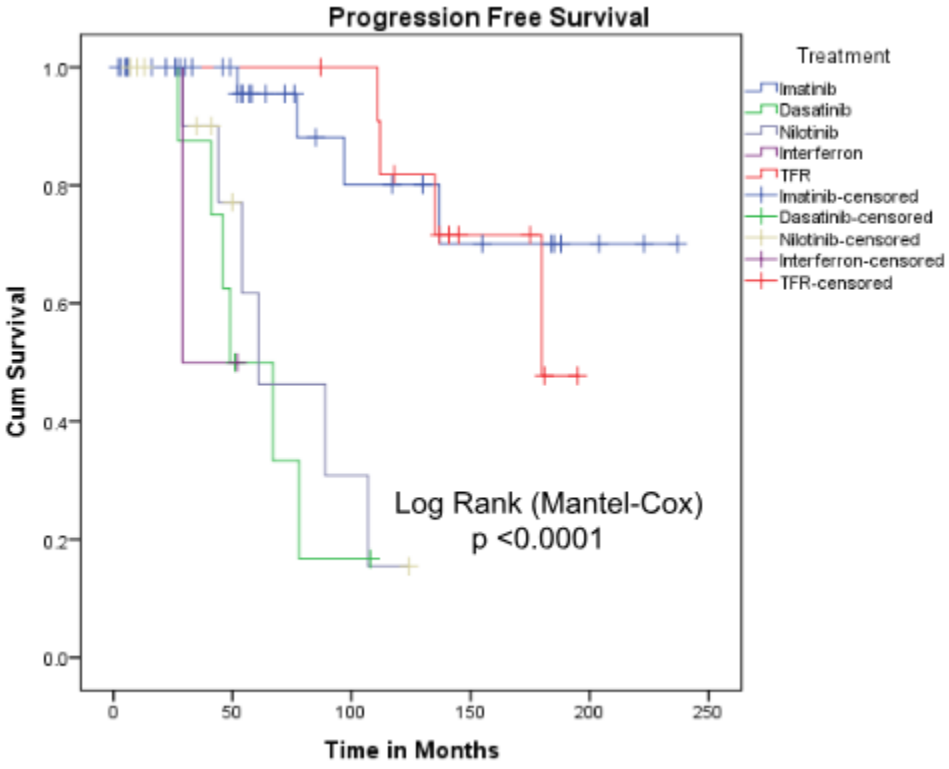

Figure 1: Kaplan Meier plot for progression free survival in the different categories of treatment modalities in this CML patient's cohort

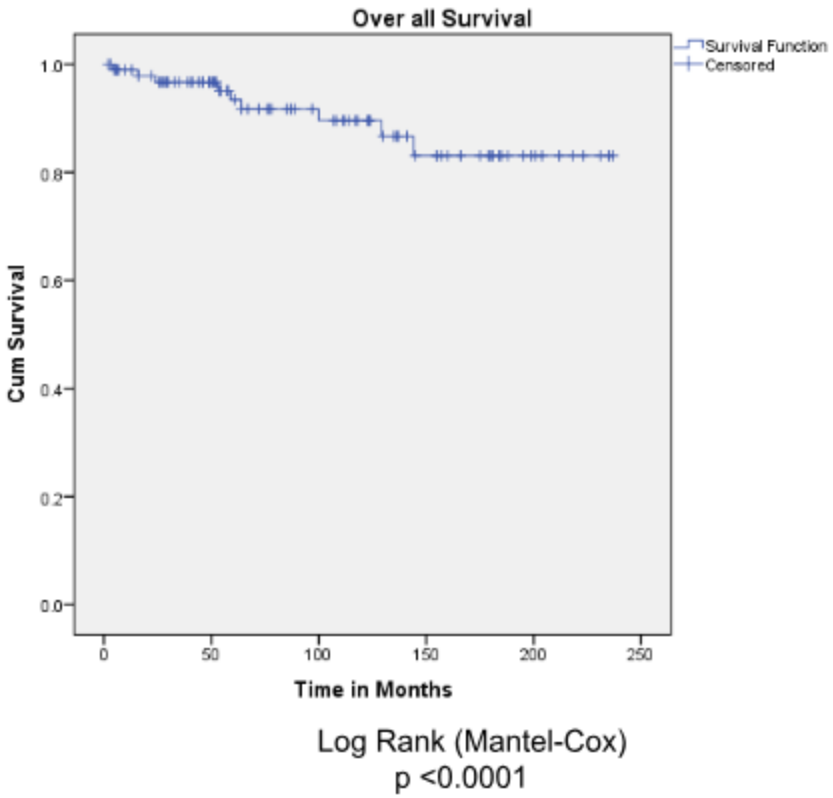

Figure 2: Kaplan Meier plot for overall survival in this CML patient's cohort

HBsAg-was positive in six patients (6.1%; 4 males, 2 female) at diagnosis, and all of them were HBV PCR positive [Table 2]. Anti-HBc was positive in 16 patients (16.3%), including all the six patients with hepatitis B surface antigen positivity. All the six HBV PCR positive patients were exposed to Imatinib, for a median of 58 months [4-132 months; Table 2]. Three patients were switched to Dasatinib, while three patients received Nilotinib and 2 received Ponatinib and interferon as a third line therapy. Although one patient was initially started on lamivudine, and Adefovir as anti-viral therapy, currently all of the six HBV PCR positive are on Entecavir [Table 2].

Table 2: Details of hepatitis B viruses & their therapy in 98 CML patients on TKI.

Patient No.		**1**	**2**	**3**	**4**	**5**	**6**
Year of diagnosis		2001	2006	2014	2016	2016	2017
Age at diagnosis		15	43	28	36	29	39
BCR ABL transcript	At diagnosis	NA	>1	19	18	84	39
	One year	NA	0.032	0.63	0.22	0.046	0.52
	Currently	0.072	0.0002	0.015	0.081	0.031	0.004
CML therapy	Imatinib	Yes	Yes	Yes	Yes	Yes	yes
	Dasatinib	Yes	Yes	Yes			
	Nilotinib			Yes*		Yes	Yes
	Ponatinib	Yes					
	Others						Interferon
Hepatitis diagnosis	At presentation	Yes	Yes	Yes	Yes	Yes	Yes

Hepatitis therapy	Lamivudine		Yes				
	Adefovir Dipivoxil		Yes				
	Entecavir	Yes	Yes	Yes	Yes	Yes	Yes
Antiviral duration (months)		100	188	110	92	83	70

**Started as the patient was intolerant to Dasatanib*
TKI: Tyrosine Kinase Inhibitor, NA: not available

HCV RNA (genotype 1) was positive in one patient, who received concomitantly Imatinib with interferon-based therapy, and she is in remission from CML and hepatitis C for over 10 years with currently on no therapy for either CML (successful TFR) or hepatitis C.

Detail of events in three specific patients with a complicated course, demonstrating successful combined anti-viral therapy and TKIs is shown separately [Table 3].

Table 3: Laboratory & Therapeutic Details in few selected patients.

Date	BCR-ABL transcript	ALT/AST	HBV PCR	Anti-viral therapy	TKI	Comments
Patient No 1.						
04/2009	12%	34/23	<50		Imatinib	
01/2011	65.5%	64/244	20		Imatinib	Obese, Fatty liver
11/2011	86.5%	74/44	23		Dasatinib	
02/2012	24%	66/28	892		Dasatinib	
09/2013	15%	38/28	2052		Dasatinib	
06/2014	8.5%	44/29	898		Dasatinib	
06/2015	25%	29/24	79		Dasatinib	
06/2018	16	46/27	285981		Dasatinib	
09/2018	13	24/24	1328		Ponatinib	
09/2019	0.27	19/17	13734		Ponatinib	
05/2020	0.019	26/21	undetectable	Entecavir	Ponatinib	
Patient No 2.						
12/2006	>1	55/37	Pos		Imatinib	
09/2007	0.1	44/25	Pos	Lamivudine	Imatinib	
04/2008	0.032	42/26	Pos	Lamivudine	Imatinib	
06/2010	Pos*	43/29	Neg	Adefovir	Imatinib	
07/2011	0.16	55/33	Neg	Adefovir	Imatinib	

07/2012	0.15	39/25	Neg	Adefovir	Imatinib	
12/2015	0.008	45/27	Pos	Entecavir	Imatinib	
03/2016	0.003	37/24	Neg	Entecavir	Imatinib	
05/2017	0.001	137/81	Neg	Entecavir	Dasatinib	
06/2018	0.001	20/22	Neg	Entecavir	Dasatinib	
06/2019	0.0001	21/22	Neg	Entecavir	Dasatinib	
03/2020	0.0002	19/19	Neg	Entecavir	Dasatinib	
Patient No 3.						
12/2014	19	11/17	28805	Entecavir	Imatinib	
12/2015	0.41	14/21	<20	Entecavir	Imatinib	
10/2016	0.19	14/18	Neg	Entecavir	Imatinib	
02/2017	0100	14/21	Neg	Entecavir	Dasatinib	Severe diarrhea
12/2018	0.06	26/18	Neg	Entecavir	Nilotinib	
03/2019	0.032	26/19	Neg	Entecavir	Nilotinib	
03/2020	0.015	25/22	Neg	Entecavir	Nilotinib	

Pos positive, but not quantifiable, Pos: positive, Neg: negative, ALT: Alanine transaminase, AST: Aspartate Transaminase, HBV: Hepatitis B virus, TKI: Tyrosine Kinase Inhibitor*

Cases of Significance

Case 1 was started on Imatinib shortly after diagnosis, and then switched to Dasatinib (for 8 years) due to CML resistance, and is currently receiving Ponatinib with reduced transcript level. Unfortunately, he also showed evidence of viral DNA progression, and was started an anti-viral therapy with Entecavir with good response. He has now undetectable HBV PCR, with normal liver enzymes on Entecavir.

Case 2 was commenced on both Imatinib and Lamivudine. He quickly went into deep molecular remission with undetectable BCR-ABL1 transcripts at sensitivity of >MR^4. However, he remained HBV PCR positive, with a low level of viral transcripts, and mild elevation of transaminases. He was shifted to Adefovir, and subsequently to Entecavir for persistent positive HBV PCR and mild transaminitis. Unfortunately, after 10 years, he had CML relapse, and after treatment with Dasatinib he is currently BCR-ABL negative, with an RQ-PCR sensitivity of $MR^{4.5}$. He remains stable with negative transcript for hepatitis B on Entecavir.

Case 3 was treated with Imatinib and Entecavir. He cleared the virus and went into remission, but unfortunately, he did not respond to Imatinib and was thus switched to Dasatinib, achieving a deep molecular remission. However, he developed a severe bloody diarrhea and was thus switched to Nilotinib, which he tolerated well, while maintaining a good molecular response. He remains negative for HBV PCR, with normal liver enzymes.

Discussion

Patients receiving various forms of chemotherapy and targeted treatments including TKIs are at an increased risk of viral hepatitis reactivation.[6,12-16] In this retrospective study cohort of patients with CML who attended our institution, the mean age was 41.1 years, which is similar to other studies reported in the region, although much lower than that reported in western countries.[2,23,24] However, this group of patients show a female preponderance, unlike reports in other studies from western countries, which had a male predominance.[2,24]

At presentation, the hemoglobin (Hb), white cells (WBC) and platelets were similar to other studies reported from our region.[24,26] Our study shows that Imatinib was more frequently used as first-line treatment. About 50% were treated with Imatinib on long-term basis, including 10.1% who discontinued this drug after a successful TFR attempt.[27] Nilotinib and Dasatinib were used in lesser numbers of cases, and with almost equal frequency. The overall 5–year and 10-year survival of patients in this CML cohort is excellent, reaching 93.4% and 89.6% respectively, similar to data seen internationally.[2] Death rate was 9.2% (9 cases), but no CML related deaths occurred in the relapsed cases, as all the thirty-five relapsed cases were salvaged by switching to other TKIs (n=30) or received bone marrow transplantation (n=5).

Oman is a country with an intermediate prevalence of HBV carriers according WHO criteria and the prevalence of HBV infection in Oman is 5.8%,[28] whereas the prevalence of HCV is 0.41%.[29] Interestingly, in this study, we found that the prevalence of HBV and HCV in CML patients was higher than that reported in general Omani population. Although hepatitis is associated with an increased risk of cancer, our numbers are small and the cross-sectional follow-up was not long enough, thus, further conclusions regarding hepatitis B infection contributing to CML progression or complications cannot be drawn.

HBVr in patients who are receiving highly immunosuppressive agents is defined as a rise in transaminases about 3 times the upper limit of normal, with an abrupt increase in the HBV DNA.[16-19] This event can be a potentially fatal complication.[15] Depending on the immunosuppressive agent used, the risk for reactivation is divided into low, intermediate and high.[30] Although TKIs are not believed to be immunosuppressant, they are identified as a moderate risk for hepatitis B reactivation, and there have been few reported cases of hepatitis reactivation in relation to Imatinib and Nilotinib treatments.[14-18] Imatinib was shown in vitro to inhibit T cell activation and Nilotinib is known to inhibit Src-family kinase LCK and interfere with T cell proliferation and function.[31,32] Its suggested that TGFB as well as PD-L1 is responsible for T cell activation, proliferation, and cytotoxic secretion,[8] its decreased levels during TKI therapy suggesting at least partial reversal of immune cell exhaustion.[10] However, HBVr has not been previously reported in patients receiving Dasatinib, except in one case report from Japan, in a patient receiving low-dose Dasatinib, with previous resolution of HBV infection.[12] All of the reported cases of HBVr occurred in HBsAg-positive carriers.[14]

Our data on hepatitis is interesting as we have seen 6 patients with surface antigen positive (HBS-Ag) with positive HB-DNA, with varying level of viral transcripts, before the start of TKIs, and all of them received nucleoside analogues (NA) therapy as outlined in Tables 2&3. In addition, more than 16% of our patients were total anti-HBc positive, however, no evidence of HBV reactivation has been detected so far. The guidelines for treating patients with hepatitis surface antigen /DNA positive recommends indefinite therapy with either interferon based, or NA inhibitors.[33-35] Three of our patients were started on Entecavir, and showed consistent response with absence of viral DNA including the patient who received both Imatinib and Nilotinib, with no evidence of viral progression. Entecavir is a potent NA inhibitor and associated with reduced risk of resistance.[36]

Chen CY et al,[17] showed that HBVr not only appeared in HBsAg-positive patients, but also in HBsAg-negative patients, with anti-hepatitis B core antibody positivity and/or anti-hepatitis B surface antibody positivity. Although we had 16% of our patients with anti-HBc positivity, but with negative HBV DNA PCR, none of them showed evidence of HBVr, despite exposure to both first and second generation TKIs. Alternatively, HBV infection (HBVi) who have detectable HBV DNA, but HBsAg is negative can also have HBVr. In this situation, HBVr defined as either seroconversion of HBsAg or an increase of at least 10-fold above the lower limit of detectable HBsAg and HBV DNA, if they were previously undetectable. Thus, for patients with HBVi who had detectable HBV DNA, a 1 log increase above the baseline could also be regarded as HBVr.

In keeping with the current recommendations for patients who are at risk of HBVr,[24] all our patients who were hepatitis B positive received Entecavir or Adefovir for prophylaxis, and therapy, except one patient who was started initially on lamivudine, and shifted to Entecavir following progression. All these patients are now HBV PCR negative, with normal liver enzymes. We thus recommend that patients with hepatitis and on TKIs should have regular PCR (every 3 months) for HBV-DNA positivity, and/or HBsAg sero-conversion to detect any recurrence and treat it immediately. It is important to note that four of our patients with hepatitis B, failed first generation and needed second generation therapy, and one of them, is in fact, on a third generation TKI. This gives us a hint of possible potential negative impact of hepatitis B infection on response to TKI therapy, however as the number of these patients is small, no definitive conclusion can be derived regarding this issue. Further, since the median time of HBVr is 9-10 months (range 1 month to 69 months) after TKI commencement, based on currently available evidence, the cost-effective recommendation is that HBV prophylaxis for patients with positive HBsAg receiving TKIs should begin from the start of TKI treatment itself, and continued for at least 2 years after the commencement of TKIs.[24]

There was only one patient among our cohort, who had HCV RNA positivity and received Imatinib. Although, there has been no reported case of hepatitis C reactivation, while on Imatinib therapy,[16] our patient had a rising viral load, while receiving Imatinib and had therefore received concomitant interferon-alpha based therapy. This resulted in the patient achieving deep molecular remission, with a negative BCR-ABL transcript, and also showed absent viral replication with a negative HCV RNA for more than ten years now. In fact, we were able to successfully stop Imatinib treatment in this patient. Although this patient needed intermittent GCSF, to deliver both therapies on time, however it is possible to successfully combine both anti-HCV and TKI therapy. It may also highlight the role of interferon combination with TKIs in CML patients.[36]

Conclusion

Our study showed that CML patients in this cohort were younger with a female preponderance with higher HBV and HCV than the general population. Among six patients positive for hepatitis B, we have not been able to demonstrate any evidence of reactivation of virus even with the use of all three available generation of TKIs. Appropriate antiviral therapy has prevented reactivation of viral hepatitis in patients on TKIs with all patients being HBV PCR, with normal liver enzymes. We saw only one hepatitis C infection, which responded well to interferon therapy and with a DMR leading to TFR.

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