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A phase 2 study of alpha interferon for molecularly measurable residual disease in chronic myeloid leukemia after allogeneic hematopoietic cell transplantation

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Abstract

CML therapy has improved dramatically with the development of tyrosine kinase inhibitors (TKIs). Prior to the TKI era, we conducted two trials of alpha-interferon (IFN) for post-transplant hematologic and cytogenetic relapse. The complete cytogenetic response rate was 33% and 57% respectively. This report describes a third trial in which 40 patients with molecular relapse between 6–12 months post-transplant were treated with IFN. The projected cytogenetic relapse at 4.5 years was 12.6% compared with 42% in the historical control group. Although this data may not apply to most patients with CML today due to the availability of multiple TKIs, the effectiveness of short term IFN in post-transplant molecular relapse is supported by long-term treatment-free-survival in 75% of patients after a median follow-up of 15.6 years. This report suggests that alpha-interferon is potentially useful in the rare patient who has post-transplant molecular relapse who does not tolerate, or is resistant to TKIs.

Keywords

CML; molecular relapse; MRD; interferon; HCT

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Contributors

E.D.B. collected the data, performed statistical analyses and wrote the paper. M.E.F. enrolled and followed subjects, reviewed the data and wrote the paper. D.C. followed subjects and collected the data. L.E.O. performed statistical analyses and wrote the paper. J.R. supervised BCR-ABL PCR tests of all subjects, reviewed the data and wrote the paper. C.S.H. designed the study, enrolled and followed the subjects, reviewed and analyzed the data and wrote the paper.

Data sharing statement

All individual participant data collected during this trial will be available after de-identification. The study protocol and the consent forms will also be available. The data will be made available from publication through the following 36 months. The data will be provided to researchers who require it to achieve a methodological proposal. Proposal should be addressed to the corresponding author.

Introduction

Patients with chronic myeloid leukemia (CML) who have evidence of minimal residual disease (MRD) by polymerase chain reaction (PCR) between 6 and 12 months after allogeneic hematopoietic cell transplantation (HCT) are at high risk of subsequent disease progression. The Kaplan Meier estimate of cytogenetic or clinical relapse at 4.5 years from HCT is 42%, while only 3% of those who remain on molecular remission during the same period will relapse.¹ Today CML relapse after HCT is often treated by donor lymphocyte infusion (DLI) or tyrosine kinase inhibitors (TKI).²⁻⁵ However, these options may not be always available or feasible. Currently most patients who receive HCT for CML have already failed or have not tolerated TKIs prior to HCT⁶⁻⁷ and, in patients with chronic graft-versus-host disease (GvHD), DLI is contraindicated.⁸ In some patients, DLI is not available such as in the case of umbilical cord blood HCT or when the donors are not able to provide a second cell collection for health or other reasons.⁸

In the pre-TKIs era, alpha-interferon (IFN) was shown to induce up to 20% complete cytogenetic responses (CCR) in patients with CML.⁹⁻¹⁰ Because CML was also one of the diseases with best evidence of the graft-versus-leukemia (GvL) effect.¹¹⁻¹², use of IFN to treat relapse of CML after HCT was explored as an alternative to a more toxic second HCT prior to the availability of TKIs. In hematologic relapse of CML after allogeneic HCT, IFN resulted in a 33% CCR¹³ while in cytogenetic relapse, the CCR rate was 57%¹⁴, suggesting that IFN is more effective in the post HCT setting when the disease burden is lower.¹³⁻¹⁶ Other data has shown that IFN had better results in recipients of grafts without T-cell depletion, underscoring the importance of donor T-cells to the GvL response.¹⁵ This historical study explored the effect of IFN on the next lower level of MRD, patients with PCR relapse 6–12 months after allogeneic HCT.

Patients and Methods

Study design and participants:

This was a phase II clinical trial conducted at Fred Hutchinson Cancer Research Center (FHCRC). We enrolled patients with CML who had molecular MRD between approximately 6 and 12 months after allogeneic HCT. We defined molecular MRD as a positive qualitative reverse transcriptase polymerase chain reaction (RT-PCR) assay for BCR-ABL mRNA, sensitivity $10^{(-5)}$, in the absence of Philadelphia (Ph) chromosome in the bone marrow (BM) by conventional cytogenetics. Patients with severe cytopenias or comorbidities, poor performance status or second transplant were excluded. Of note, patients with uncontrolled GvHD were excluded but GvHD per se was not an exclusion criteria and it was not required that immunosuppression be tapered off before study entry.

Procedures:

The starting dose of IFN (alpha 2a interferon, Roche) was $1 \times 10^{(6)}$ units (U)/day given subcutaneously to be administered over 12 months. Patients were regularly monitored for toxicity by their primary oncologist and telephone calls from the research nurse (DC). Dose adjustments were made by the principal investigator (PI, CSH) based on hematologic or

non-hematologic toxicity. IFN was held or discontinued for GvHD flare. Patients who progressed from molecular to cytogenetic relapse were taken off protocol. Cytogenetic relapse was defined by the presence of 2 or more Ph chromosomes within 20 counted metaphases. Toxicities were retrospectively graded based on the “Common Terminology Criteria for Adverse Events version 4.0”. GvHD flare was defined as the need to start immunosuppression or to increase the existing immunosuppressive regimen for uncontrolled GvHD activity.

Objectives:

The primary objective of this study was to explore the potential efficacy of IFN decreasing cytogenetic or clinical relapse in comparison to historical control data for untreated patients with molecular MRD between 6 and 12 months after HCT. The treatment was considered efficacious if the KM estimate of relapse of PCR-positive patients was decreased from 40% to 20% at 4.5 years from HCT. The other study objectives included evaluation of IFN toxicities and rate of molecular response. In addition, treatment-free-survival (TFS), overall survival (OS), treatment related mortality (TRM), non-relapse mortality (NRM) and GvHD activity were analyzed. Molecular response was defined as no evidence of BCR-ABL by qualitative RT-PCR after initiation of IFN.¹ TFS was defined as time from IFN to further CML therapies or death. TRM was defined as non-relapse death during IFN or within 4 months of its discontinuation. GvHD flare was defined as the need to start immunosuppression or to increase the existing immunosuppressive regimen for uncontrolled GvHD activity.

Statistical analysis:

The data for this study were abstracted from each subject’s research records and the FHCRC clinical database. The estimate of cytogenetic or clinical relapse at 4.5 years was defined based on KM method.¹⁷ Using a two-sided significance level of 0.10, 32 patients would allow detection of the difference of 40 to 20% in the relapse at 4.5 years, with 80% power (normal approximation to the binomial distribution). The survival curves (TFS and OS) were calculated using the KM method. Molecular disease free survival (DFS) could not be accurately calculated due to the lack of longitudinal PCR data, however, TFS is assumed to be an indicator of DFS. Comparisons of rate of molecular response and cytogenetic relapse among binary subgroups were based on Fisher’s Exact Test. The statistical analysis and graphics were performed using SAS software version 9.4. An informed consent was obtained from all enrolled patients and this study was approved by the FHCRC Institutional Review Board (IRB).

Results

Forty subjects enrolled and were treated with INF between 1995 and 1999, median age 42 years, (interquartile range [IQR] 34–47 years). Table 1 depicts the characteristics of the study population. None had previously received TKI therapy and 19 (47.5%) had received IFN prior to the HCT for CML. At HCT, 27 (67.5%) subjects were in chronic phase (CP), 10 (25%) in accelerated phase (AP), and 3 (7.5%) were in complete hematologic remission (CHR) after blast crisis (BC), chronic phase 2 (CP2). All subjects received a myeloablative conditioning HCT and methotrexate with calcineurin inhibitors (CIN) for GvHD

prophylaxis. Four patients (10%) also received *in vivo* T-cell depletion with anti-thymocyte globulin (ATG) for GvHD prophylaxis. There were 18 (45%) HLA-matched related, 13 (32.5%) HLA-matched unrelated, and 9 (22.5%) HLA-mismatched donors. The graft source was BM in 95% and mobilized peripheral blood stem cells in 5% of the subjects. The median time from HCT to molecular MRD was 6 months (IQR 6–9).

The median time from transplant to start of IFN was 9 months (IQR 8–11) and the median length of IFN treatment was 6 months (IQR 3–12). The median maximum tolerated IFN daily dose was 1×10^6 units. Of the 40 subjects, 16 (40%) completed the planned one year of treatment with IFN. Reasons for early discontinuation of IFN in 24 are grade 1/2 adverse effect in 11 (27.5%), GvHD in 5 (12.5%), grade 3/4 adverse events in 4 (10%), disease progression in 3 (7.5%) and unknown in 1 case (2.5%).

There was no treatment related mortality associated with IFN. Table 2 shows all grades of hematological and non-hematological adverse events observed in the study. Most common grade 3/4 hematologic adverse events was uncomplicated neutropenia in 7 of the 11 cases, with none developing grade 4 neutropenia or neutropenic fever. Of the 3 subjects who required transfusion support, 1 had immune thrombocytopenic purpura and 1 had autoimmune hemolytic anemia. The most common non-hematologic adverse events were grade 1/2 fatigue (62.5%), gastrointestinal symptoms (60%) and febrile symptoms including fevers, chills or night sweats (37.5%). There were 3 cases of grade 3/4 non-hematologic adverse events including one case of idiopathic pneumonitis, and 2 cases of community acquired pneumonia that required hospital admission. One of these patients also had grade 3 elevation of liver enzymes. One patient developed nephrotic syndrome that was attributed to GvHD.

Characteristics of GvHD and immunosuppression treatment (IS), before and during treatment with INF, are summarized in Table 3. At enrollment, 35 patients (87.5%), were receiving immunosuppression for prophylaxis or treatment of prior GvHD. During the study, 24 of the 35 patients (68.6%) were able to be tapered off IS. Nine patients (22.5%) developed GvHD during IFN treatment that required additional or increased dose of IS for either new diagnosis of GvHD (n=5) or exacerbation of prior GvHD (n=4).

A swimmer plot shown in Figure 1 depicts major disease outcomes for each of the 40 study participants. The KM estimate cytogenetic or clinical relapse at 4.5 years after HCT was 12.6%, a relative decrease of 70% when compared to the historical data, $p < 0.01$. The cumulative incidence of cytogenetic and clinical relapse is shown in Figure 2. With a median follow-up of 15.6 years, 4 patients (10%) developed cytogenetic-only relapse and 6 (15%) hematologic relapse. Only 10 patients (25%) required further CML therapy. Among these, 2 (5%) received a second course of IFN, 5 (12.5%) TKIs, 1 (2.5%) DLI and 1 (2.5%) a second HCT. During follow-up, relapse related mortality was 12.5% and non-relapse related mortality was 15%. Median TFS and OS were not reached as shown in Figure 3. Molecular remission was achieved by 30 patients (75%) after IFN. Without any further CML therapy after IFN, 27 of the subjects (67.5%) did not have measurable residual disease by PCR at the end of follow-up. Regarding recipients of *in vivo* T-cell depleted grafts by ATG, 2/4 patients

(50%), experienced further cytogenetic relapse. Among patients at AP or CP2 at transplant, 6/13 (46.2%) had further cytogenetic relapse, while only 4/27 (14.8%) on CP, $p = 0.052$.

Discussion

Since this study was designed and executed, the development of TKIs targeting bcr-abl have made a major impact on the treatment of patients with CML. Prior to that time, HCT was the only possible curative therapy. However, today most patients are treated with TKI therapy and never need HCT. Nonetheless, the data clearly demonstrate the principle that the GvL effect of IFN is best when there is molecular MRD compared to either cytogenetic or hematologic relapse after HCT. The activity and long-term follow-up of patients treated with IFN in this setting has never been reported.

For this high risk CML population with MRD detected between 6 and 12 months after HCT who received IFN treatment in this study, the 4.5 year estimate of subsequent relapse was 12.6%. This finding contrasts with our historical previously reported estimate of relapse of 42% at 4.5 years in a similar high risk population who received no intervention despite MRD during the same window of time as the current study.¹ Another remarkable outcome of this clinical trial was that only 25% of the patients required further CML therapies like TKI (12.5%) or DLI (2.5%) over a very long median follow-up of 15.6 years, suggesting that IFN prevented disease progression and de facto cured 75% of the patients.

Although this clinical trial was conducted 20 years ago, treatment with interferon to prevent or treat malignancy after HCT via optimizing the graft-versus-leukemia (GVL) effect remains a great interest, especially as we gain better understanding of the power of the immune system and new immune modulation therapies are emerging to eradicate malignancies.^{18–19} Of note, Mo et al reported that patients with AML who had MRD after HCT who were treated with IFN decreased relapse rate from 57 to 30% at 2 years, similar to treatment with DLI, but with less GvHD exacerbation.^{20–21}

Treatment with IFN less than one year after HCT was associated with significant side effects in our study resulting in early discontinuation of treatment before 1 year in 50% of the patients. Nonetheless, there were no deaths related to IFN treatment and most of the early treatment discontinuation was due to grade 1/2 toxicities. Of note, major toxicities seen in this study such as ITP, AIHA, pneumonia and pneumonitis are common complications in the post-transplant setting even without IFN therapy.

Development of or flare of previous GvHD during treatment with INF was observed in 22.5% of patients and no patient died as a consequence of this complication. The GvHD rates in our study are similar to those previously reported with post-transplant interferon for hematological relapse.^{13–16} The cumulative incidence of GvHD reported after DLI is 40%, higher than that observed after INF, albeit lower rates of GvHD after DLI are possible using lower initial cell dose.^{8, 22}

IFN at the dose of 3×10^6 U/M²/day is often associated with significant toxicity.^{13–16} In this study, a substantially lower dose of IFN 1MU/day was not only effective but also safe, even in such close proximity to HCT. In spite of using a lower dose of IFN and a shorter duration

of therapy than originally planned, IFN resulted in a higher rate of complete molecular response, 75%, than that previously reported for patient treated for hematologic and cytogenetic relapse after HCT.^{13–16} In Mo's study of IFN treatment of post-HCT MRD in AML, IFN was administered at 3×10^6 units 2–3 times per week rather than daily, and the median duration of treatment was only 35 days.^{20–21}

Both TKI and DLI represent alternative strategies for prevention or treatment of post-transplant relapse of CML.^{2–5, 23} The largest report of TKI in this clinical scenario of molecular MRD was published by Hess *et al*, where 15 of 18 patients (83.3%) achieved complete molecular remission^{22–24}, compared to 75% seen with IFN in this study. Nonetheless, the rates of post-transplant TKI intolerance are not insignificant, 31–38%.^{25–26} Other potential restrictions to TKIs are pregnancy, significant cardiac dysfunction, and lack of worldwide availability of ponatinib for patients harboring T135I mutation.^{27–29} Radujkovic *et al* showed that DLI resulted in failure free survival of 68% at 5 years in 80 patients with molecular relapse and Chalandon *et al* saw a 59% of molecular remission at 5 years in 85 subjects.^{30–31} Neither of these studies restricted the timing of molecular relapse and therefore their outcomes may be inflated due to the inclusion of those who became PCR positive after 12 months who have a very low relapse rate.^{1, 32} The 67.5% of molecular remission observed in this study includes only those at high risk. The rate of new onset GvHD at Radujkovic *et al* was at least 28%, while our data with IFN was only 12.5%.³⁰ Chalandon *et al* reported 81% of OS and non-relapse mortality of 11% at 5 years, compared to 85% and 5% in our study respectively.³¹ Both Chalandon *et al* and Radujkovic *et al* also showed that there are no differences in outcome when DLI is given for molecular versus cytogenetic relapse while we have consistently shown that the magnitude of response to IFN is related to disease burden.^{13–16}

The current study has several limitations. First, the study was conducted 20 years ago prior to the advent of TKI's and with limited DLI reports. Likewise, the technology for identifying PCR positivity and cytogenetic relapse has improved over time. However, these limitations might be overcome by the fact that the historical control data and our trial used the same older technologies. Another limitation is the formulation of interferon used in our study is no longer available, thus extrapolation of dosing of other interferons may be difficult. However, modern formulations of IFN (eg pegylated) may be better tolerated.

Our results are aligned with Talpaz *et al* who suggest that IFN may still be a treatment option for CML in selected cases.^{33–34} For instance, most CML patients who currently undergo allogeneic HCT have either failed or not tolerated treatment with TKIs. In addition, after HCT, patients often relapse with the same TKI resistance profile as they had before transplant.³⁵ For such patients, treatment of post-transplant relapse of CML with TKIs may be problematic. Given that DLI has higher rates of complications than does IFN and that DLI has the same outcomes when given either in molecular or cytogenetic relapse, the few patients who progress to cytogenetic relapse on IFN could theoretically still be salvaged by DLI without worse outcomes. While this study of IFN does not examine its performance after prior TKI therapy and HCT, IFN should still be effective if the mechanism of action is related to GvL rather than direct cytotoxic effect.

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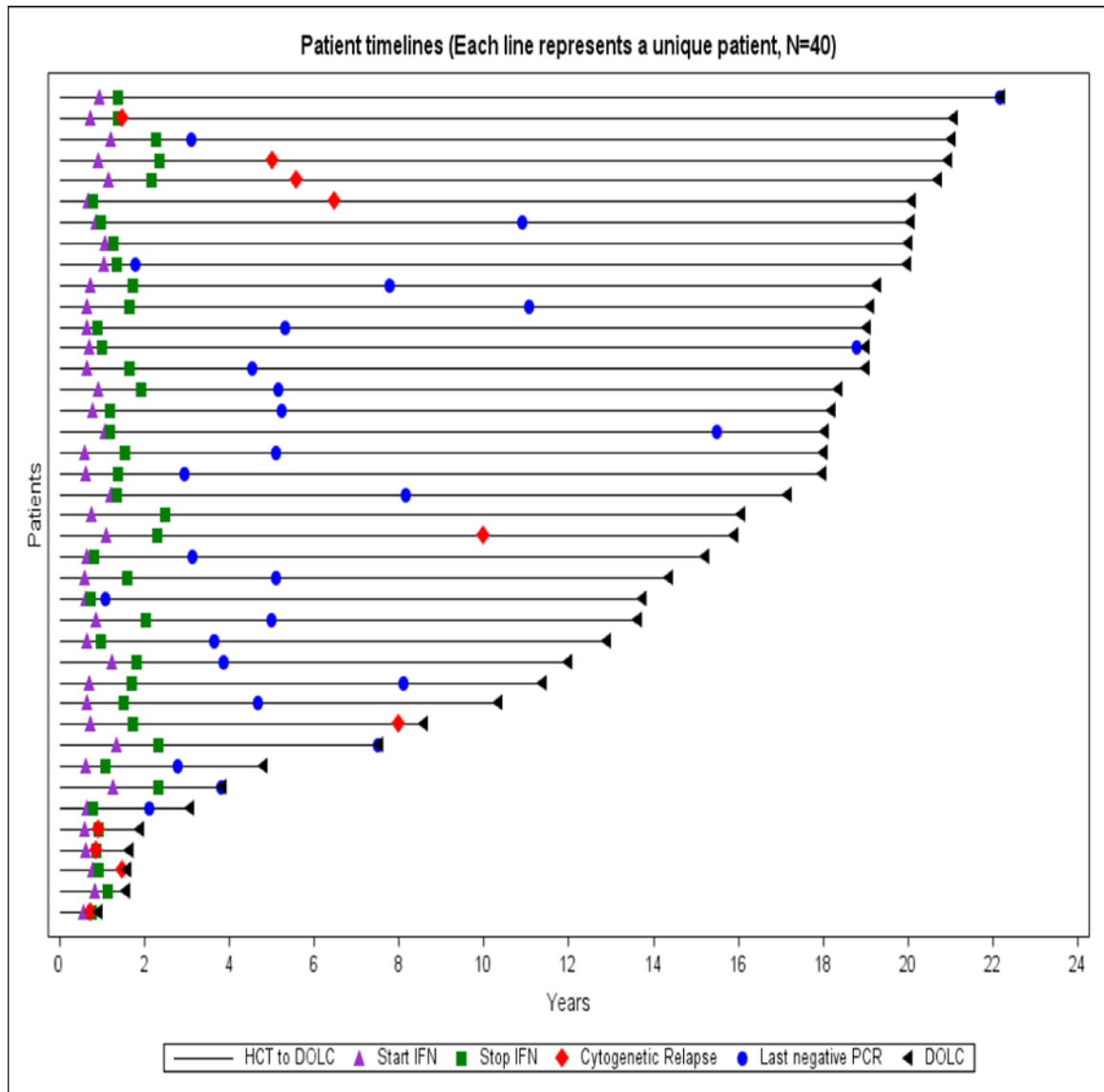


Figure 1:
Individual disease status after study enrollment:



Figure 2:
Cumulative incidence of cytogenetic relapse by Kaplan-Meier:

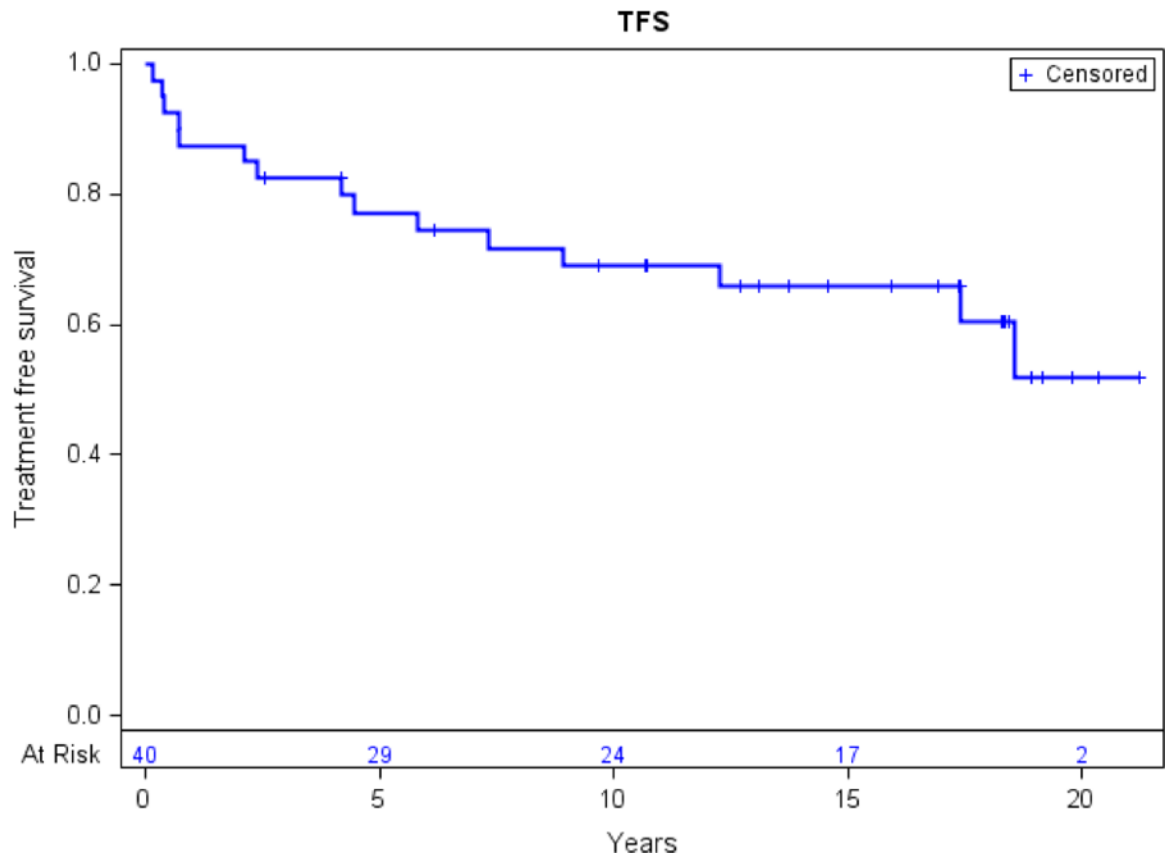


Figure 3:
Treatment free survival:

Table 1:

Patient characteristics

Patients, n (%)	40 (100)
Age at study entry, median (range)	42 (16–67)
Gender, female, n (%)	20 (50)
Phase of chronic myeloid leukemia at HCT, n (%)	
Chronic	27 (67.5)
Accelerated	10 (25)
Blast crisis in complete hematologic remission	3 (7.5)
Donor type, n (%)	
Matched related	18 (45)
Matched unrelated	13 (32.5)
Mismatched related	4 (10)
Mismatched unrelated	5 (12.5)
Graft source, n (%)	
Bone Marrow	38 (95)
Peripheral blood stem cells	2 (5)
Conditioning regimen, n (%)	
Total body irradiation + cyclophosphamide	22 (55)
Busulfan + cyclophosphamide	18 (45)
GvHD prophylactic regimen, n (%)	
Methotrexate + calcineurin inhibitor	40 (100)
Anti-thymocyte globulin	4 (10)
Months from HCT to molecular relapse, median (range)	6.3 (5.6–13.6)
Complete cytogenetic remission at enrollment, n (%)	40 (100)
Use of TKIs prior to enrollment, n (%)	0
Use of IFN prior to transplant, n (%)	19 (47.5)

Table 2:

Adverse events

Adverse event	CTCAEv4 Grade		Total
	1-2	3-4	
n (%)			
Non-Hematologic			
Fatigue	25 (62.5)	0	25 (62.5)
Gastrointestinal	24 (60)	0	24 (60)
Fevers/Chills	15 (37.5)	0	15 (37.5)
MSK pain	11 (27.5)	0	11 (27.5)
Depression	6 (15)	0	6 (15)
Weight loss	6 (15)	0	6 (15)
Pneumonia	2 (5)	2 (5)	4 (10)
Liver	2 (5)	1 (2.5)	3 (7.5)
Pneumonitis	0	1 (2.5)	1 (2.5)
Hematologic			
Anemia	7 (17.5)	3 (7.5)	10 (25)
Neutropenia	13 (32.5)	7 (17.5)	20 (50)
Thrombocytopenia	22 (55)	2 (5)	24 (60)

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Table 3:

GvHD and Immunosuppression (IS) characteristics before and during interferon

Characteristics	
Prior history of grade II-IV acute GvHD, n (%)	29 (73)
Prior history of chronic GvHD requiring IS, n (%)	14 (35)
Receiving IS at time of molecular relapse, n (%)	35 (87)
With corticosteroids > 0.5 mg/kg/day	3 (7)
With corticosteroids 0.5 mg/kg/day	14 (35)
Without corticosteroids	18 (45)
Patients tapered off IS during IFN, n (%)	24/35 (69)
New GvHD requiring IS during IFN, n (%)	5/26 (19)
Exacerbation of prior GvHD requiring IS, n (%)	4/14 (29)
Receiving IS during IFN, n (%)	26 (65)
Highest level of IS at any point on INF, n (%)	
With corticosteroids > 0.5 mg/kg	5 (12)
With corticosteroids 0.5 mg/kg	13 (32)
Without corticosteroids	8 (20)

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