Published in final edited form as:

Leuk Res. 2014 August ; 38(8): 886–890. doi:10.1016/j.leukres.2014.05.012.

Granulocyte-macrophage colony stimulating factor (GM-CSF) enhances the clinical responses to Interferon- α (IFN) in newly diagnosed chronic myeloid leukemia (CML)

Joshua F Zeidner^a, Douglas E Gladstone^a, Marianna Zahurak^b, William H Matsui^a, Christopher Gocke^c, Richard J Jones^a, and B Douglas Smith^a

^aDivision of Hematologic Malignancies, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD

^bDivision of Oncology Biostatistics and Bioinformatics, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD

^cDepartment of Pathology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD

Abstract

The majority of chronic myeloid leukemia (CML) patients treated with tyrosine kinase inhibitors (TKIs) remain with residual disease. In contrast to TKIs, interferon (IFN) is directly toxic to CML progenitor cells, and myeloid growth factors such as GM-CSF may enhance IFN's cytotoxicity. We performed a phase 2 study of IFN+GM-CSF in 58 newly diagnosed CML patients before imatinib approval. Short-term clinical responses included: 60% major cytogenetic response, 28% complete cytogenetic response and 19% complete molecular response. Six patients remain off all therapy for CML (range: 15 months–12 years) after IFN+GM-CSF treatment. IFN+GM-CSF shows promise as an adjunctive therapy for CML.

Keywords

chronic myeloid leukemia; tyrosine kinase inhibitor; cure; discontinuation of therapy; interferon; growth factors

Corresponding author: B. Douglas Smith, MD, 1650 Orleans St, CRB1, room 246, Baltimore, MD 21287, Phone: 443-287-2935, Fax: 410-614-7437, bdsmith@jhmi.edu.

Conflict of Interest: All authors report no conflicts of interest.

None of the authors report any conflicts of interest.

Contribution: JFZ performed research, analyzed the data, and wrote the manuscript; DEG performed research, enrolled patients and edited the manuscript; MZ principal statistician, analyzed the data and edited the manuscript; WHM performed research and enrolled patients; CDG performed research; RJJ performed research and enrolled patients; BDS principal investigator, performed research, analyzed the data, and wrote the manuscript. All authors approved the final manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Interferon- α (IFN) was the standard front-line agent for chronic myeloid leukemia (CML) before the introduction of tyrosine kinase inhibitors (TKIs). IFN resulted in hematologic responses of 60–80% and cytogenetic responses of 30–40% in newly diagnosed chronic phase (CP) CML patients [1–3]. Reports of complete cytogenetic response (CCyR) on IFN therapy ranged from 13–27%, with a median time to CCyR of 19 months [4–5]. Importantly, Kantarjian et al. [5] found that approximately 10% of CML patients treated with up-front IFN therapy could achieve durable CCyRs even with the discontinuation of IFN. Thus, it appears that there is a subset of patients that may in fact be cured of their disease with IFN therapy alone. Imatinibmesylate, a TKI targeting the *BCR-ABL1* fusion protein, revolutionized the treatment for CML, and quickly replaced IFN as the standard front-line therapy for CML [6–7]. Although the majority of patients initially respond to imatinib, approximately 20–30% of patients eventually become resistant to imatinib over time due to mutational selection, and a small proportion of patients will progress to accelerated phase (AP) and blast crisis (BC) each year [7–12]. Potent second- and third-generation TKIs (e.g., dasatinib, nilotinib, bosutinib, and ponatinib) are able to salvage some patients with imatinib-resistance. However, prognosis still remains poor among this subset of patients, with only about 30% of patients remaining on second-generation TKIs long-term in the second-line setting (due to lack of response, resistance or progression) [13–15].

IFN has a unique mechanism of action in CML, distinct from imatinib and other TKIs. Laboratory findings suggest that IFN is directly toxic to CML progenitor cells and this cytotoxicity is enhanced with the addition of myeloid growth factors, such as granulocyte-macrophage colony stimulating factor (GM-CSF) [16]. TKIs, in contrast, do not appear to impact *BCR-ABL1*⁺ CML stem cells [17]. Given the resistance of CML progenitor cells to TKIs, it is not surprising that the French Intergroup found that discontinuing imatinib in CML patients with at least a 2-year durable complete molecular response (CMR) resulted in a relapse rate >60% [18]. Therefore, short of an allogeneic stem cell transplant (alloSCT), the only known curative therapy for CML, it is necessary to explore novel agents to be used either concurrently or sequentially after TKI treatment in order to increase the chances of achieving long-term remissions and ultimately a cure for CML. The combination of IFN and GM-CSF may substantially add to the therapeutic armamentarium of CML by depleting CML progenitor cells, in which TKIs are lacking, and ultimately improving the chances of cure. We present the clinical results and long-term follow-up of a cohort of newly diagnosed patients with CP-CML treated with a combination of IFN and GM-CSF.

2. Methods

2.1 Patient Population

We conducted a clinical trial of IFN in combination with GM-CSF for patients with newly diagnosed CP-CML between 1998–2002 at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC) and Drexel University College of Medicine. Eligibility for this trial included: 1) all adults ≥ 18 years old with newly diagnosed CML, defined by the presence of the Philadelphia chromosome (Ph) by peripheral blood (PB) or bone marrow (BM) cytogenetics, or FISH and/or *BCR-ABL1* detection by RT-PCR, 2) achieving a

complete hematologic response (CHR) on IFN (defined as white blood cell (WBC) $<10 \times 10^3/\text{mL}$, platelets $<450 \times 10^3/\text{mL}$, $<5\%$ circulating blasts, and absence of all signs and symptoms of disease including progressive splenomegaly), 3) duration of IFN treatment 6 months prior to study enrollment, and 4) patients were expected to perform self-injection. Patients were excluded if: 1) diagnosed with AP or BC CML prior to enrollment, or developed disease progression on IFN (ie. 5% blasts in PB or BM, hematologic unresponsiveness to conventional therapy, extramedullary disease including progressive splenomegaly/lymphadenopathy, $>10\%$ basophilia in PB or BM, or additional cytogenetic abnormalities other than Philadelphia chromosome), 2) previous history of intolerance to GM-CSF, 3) receiving myelosuppressive therapy other than IFN with or without hydroxyurea, and 4) pregnant women or those planning pregnancy. A BM biopsy for confirmation of disease and stage was required prior to enrollment. All patients signed a Johns Hopkins SKCCC IRB-approved informed consent prior to enrollment.

2.2 Treatment Plan

All patients received recombinant IFN therapy as standard of care, with a goal of 5×10^6 units/ m^2/day , or the maximally tolerated dose necessary to achieve a CHR. Patients with leukocytosis (WBC $>10 \times 10^3/\text{mL}$) were permitted to receive concurrent hydroxyurea until a CHR was achieved and maintained on single-agent IFN. Patients with CHR on stable IFN dosing for at least 14 days were initiated on rhu-GM-CSF (Berlex) at a dose of $125 \text{ ug}/\text{m}^2$ subcutaneously per day (Figure 1). Patients were then followed with weekly WBCs for the first 4 weeks and then monthly (or as clinically indicated) thereafter. Dose modification of GM-CSF initially occurred if WBC $>10 \times 10^3/\text{mL}$; however, this parameter was changed to $>20 \times 10^3/\text{mL}$ after 2 of the first 3 patients had persistent WBC $>10 \times 10^3/\text{mL}$ necessitating dose reductions. GM-CSF was held for 1 week if WBC $>20 \times 10^3/\text{mL}$ and then restarted at a 25% dose reduction once WBC $<10 \times 10^3/\text{mL}$. Patients were removed from the study if the addition of GM-CSF resulted in the WBC $>20 \times 10^3/\text{mL}$ more than three separate occurrences. GM-CSF dose was reduced (25% dose reduction) or held if there was unmanageable bone pain, fever $>38.5^\circ\text{C}$ for >3 days in a row, elevated liver function enzymes >2.5 times upper limit normal, or any grade 3 adverse events not related to the above conditions as graded by the National Cancer Institute Common Toxicity Criteria (version 2.0). Patients continued GM-CSF therapy for a total of 6 months while continuing IFN. Injection sites were rotated to avoid excessive local reactions. After 6 months of GM-CSF, patients were continued on single-agent IFN.

2.3 Disease Assessment

BCR-ABL1 FISH analysis was performed on all patients prior to initiation of GM-CSF and then every 3 months for the first year, and at 6 month intervals after the first year. BM analysis for karyotype and *BCR-ABL1* PCR was performed at 6 months after initiation of GM-CSF and every 6 months thereafter until a CCyR was achieved. Patients achieving a CCyR were then followed with *BCR-ABL1* RT-PCR test for molecular analysis at least every 6 months. The following definitions were used to assess response: 1)CHR: WBC $<10 \times 10^3/\text{mL}$, platelets $<450 \times 10^3/\text{mL}$, $<5\%$ circulating blasts, and absence of all signs and symptoms of disease including progressive splenomegaly, 2) Major Cytogenetic Response (MCR): 1–34% *BCR-ABL1* FISH detected on PB or BM analysis, and 3) CCyR: $<1\%$ *BCR-*

ABL1 FISH detected on PB or BM analysis or absence of Ph+ metaphases on karyotype analysis with a minimum of 20 marrow cells.

2.4 PCR Assay

The t(9;22)(q34;q11) chromosomal translocation (reciprocal translocation of the *ABL1* proto-oncogene and the *BCR* gene) is detected by a one-step real-time RT-PCR protocol using the IpsogenFusionQuant FQPP-10 kit according to the manufacturer's directions, detected on the Taqman 7900 thermocycler (ABI). The relative standard curve method was used for quantitation with *ABL1* as the internal control. Each sample is assayed in duplicate, with a minimum of 20,000 copies of *ABL1* mRNA in each. Complete molecular response (CMR) was defined as absence of *BCR-ABL1* mRNA in the duplicates, for a 4.3 log decrement from the 100% International Standard, performed on PB or BM.

2.5 Statistical Analysis

The primary endpoint of this study was to estimate the proportion of patients achieving an MCR at 6, 9, and 12 months following the combination of IFN and GM-CSF therapy. Secondary endpoints included CCyR, CMR and overall survival (OS). The event-time distribution for OS was estimated with the method of Kaplan and Maier [19]. The duration of IFN therapy prior to initiation of GM-CSF was included in the OS analysis. The database was locked on December 15, 2012.

3. Results

3.1 Patient Characteristics

Between July 29, 1998 through January 15, 2002, 58 patients with newly diagnosed Ph+ chronic phase CML were enrolled on study (n = 52 at SKCCC and n = 6 at Drexel University College of Medicine, Table 1). The median age was 48 years (range: 24–74 years). The median time on IFN before enrolling on study was 118.5 days (range: 43–185 days), and the median total duration of IFN therapy was 19.5 months (range: 2–96 months). The median IFN dose while on study was 8×10^6 units/day.

3.2 Toxicities

Overall, the combination of IFN and GM-CSF was reasonably well tolerated with 45 patients (78%) completing the 6 months of planned combination therapy. Of the 45 patients who completed 6 months of combination therapy with IFN and GM-CSF, 30 patients (67%) did not require any dose reductions (95% confidence interval (CI): 51%, 80%). The majority of patients (n=12/13) who stopped combination therapy early due to side effects did so within 3 months for the following reasons: persistently elevated WBC (n = 5), persistent grade 3 bone pain (n=3), persistent grade 3 fatigue (n=2), severe skin reactions (n=1), and patient preference (n=1). One patient discontinued GM-CSF at 4 months due to lack of a cytogenetic response on combination therapy.

3.3 Clinical Responses on Study

Using an intent-to-treat analysis, the treatment responses for all 58 patients are shown in Table 2: 35 patients (60%) achieved a MCR (median time to response of 3 months), 16

patients (28%) achieved a CCyR (median time to response of 9 months) and 11 patients (19%) achieved a CMR (median time to response of 17 months). Despite these excellent IFN responses, 69% (31/45) of those receiving 6 months of combination therapy discontinued IFN within 3 years due to suboptimal response (n=14), progressive disease (n=6), patient and/or physician preference (n=6), and intolerability (n=5).

3.4 Long-term Outcomes After Study

A total of 46 patients (80%) switched to imatinib therapy, 5 (9%) were lost to follow up, 3 (5%) achieved sustained remissions off of all therapy (CMR n=2; MMR n=1), 2 (3%) transitioned directly to alloSCT, 1 patient (2%) died secondary to BC-CML progression, and 1 patient (2%) continues with fluctuating minimal residual disease on IFN therapy. The patients who switched to imatinib continued to show excellent responses with 14 patients (30%) achieving a CMR while on imatinib and another 8 patients (17%) continue on imatinib with a favorable response (but less than a CMR). A total of 6 patients (13%) went on to receive a second-generation TKI for either progression or lack of response to imatinib. Six patients (13%) had an alloSCT for progression on TKI therapy and 9 patients (20%) were lost to follow-up after being started on imatinib.

The outcomes for the 11 patients who achieved CMR on study are shown in Figure 2. One patient continues on IFN for > 11 years with fluctuating *BCR-ABL1* PCR levels between a major molecular response (MMR) and CMR, 1 patient progressed on IFN and switched to imatinib and achieved a second CMR, 2 patients switched to imatinib due to patient preference while continuing to maintain a CMR, 5 patients discontinued IFN after a minimum of 3 years in continued CMR, and 2 patients were lost to follow-up. Three of the 5 patients discontinuing IFN relapsed, whereas 2 of the 5 patients continue to remain in CMR for seven plus years with no additional therapy. Interestingly, one patient who relapsed after discontinuing IFN was salvaged with imatinib and has maintained a CMR for > 18 months after subsequently discontinuing imatinib.

3.5 Patients Off All Therapy

Six out of 58 (10%) patients remain off all therapy for CML during last follow up. Three of these 6 patients remain off therapy with IFN and GM-CSF being their only treatment. The CMR (n=2) and MMR (n=1) off therapy have been very stable with each patient having at least 3 years of follow-up post-therapy (range: 3–12 years). The remaining 3 patients who are currently off all CML treatment stopped treatment following successful transition to imatinib with 2 of these patients in CMR for >15 months and 1 having been lost to follow-up while in CMR.

3.6 Follow-Up and Survival

The median follow-up of this study was 11.5 years (minimum: 8.5 months, maximum: 14 years). During the 13-year follow-up period, 6 patients (10%) died due to the following reasons: infections (n=3, with 2 of these patients undergoing an alloSCT), BC-CML (n=2), and unknown cause (n=1). Figure 3 displays the Kaplan-meier OS estimate for this study. OS is 89% at 10 years (95% CI: 81%, 99%).

4. Discussion

Treatment of newly diagnosed CML patients with IFN was the standard approach prior to the success and widespread use of TKIs. IFN therapy is associated with disease stabilization and prolongation of survival when compared to hydroxyurea [20–22], and can result in long-term durable responses in a proportion of patients, even after discontinuing therapy [5]. However, IFN therapy leads to a variety of undesirable side effects, and takes a significantly longer time to achieve CML milestones (i.e. CCyR and CMR) when compared with TKI therapy.

The goal of this study was to determine whether GM-CSF could improve the short-term response rate (i.e. MCR and CCyR) in CML patients. Although this study was not randomized, the overall response rate of the combination of IFN and GM-CSF (60% MCR; 28% CCyR) compares favorably with responses to IFN alone (11% MCR; 8% CCyR) in a large randomized study by the Italian Cooperative Group [20], with similar findings from a randomized clinical study of IFN versus hydroxyurea or busulfan conducted by the German CML Study Group [21]. Moreover, 17% of patients achieved a CMR on study, which may underrepresent the impact of IFN + GM-CSF, given the number of patients over time that switched to imatinib, even while achieving a response. However, the small numbers of patients enrolled on this study preclude any generalizations or conclusions regarding the efficacy of this combination of agents.

Cortes et al [23] added GM-CSF therapy to patients with CML on IFN who had not achieved an optimal cytogenetic response. Although only 15 patients were included on this study, responses were seen, including 2 CCyRs on trial. Furthermore, Cortes et al. [24] also conducted a randomized clinical trial of front-line high-dose imatinib therapy with or without IFN and GM-CSF. Unfortunately, due to a high drop-out rate in the IFN and GM-CSF group, the response rates were no different in the combination group versus high-dose imatinib alone. IFN-based strategies are rational therapeutic approaches for the treatment of CML as IFN +/- GM-CSF may more effectively target CML progenitor and stem cells compared to TKIs alone where CML stem cells appear to persist despite years of therapy [16–18]. Although the precise mechanism of IFN's anti-leukemic effect is unknown, it is postulated that IFN modulates gene expression and cytokine secretion, promotes cell differentiation, activates anti-tumor immunity, and inhibits the proliferation and stability of CML progenitors [25]. The addition of GM-CSF supports terminal differentiation of CML progenitor cells, and enhances IFN's anti-leukemic effect in CML [16, 26].

Despite the early and long-lasting responses to the combination of IFN and GM-CSF, completing this study was difficult due to the availability and clinical activity of TKI therapy, which quickly replaced IFN as the standard up-front treatment for all newly diagnosed CML patients. The main limitation of TKI therapy is the concern that therapy is lifelong and likely not curative for most patients. In addition, many patients stop responding to TKIs and develop resistance over time. Moreover, TKIs can contribute to a significant number of adverse events, including cardiovascular-related disease, pulmonary arterial hypertension, pleural effusions, hyperglycemia, thyroid diseases, and hepatic toxicities [27]. These toxicities appear to be increasing as longer-term data are analyzed. Additionally,

compliance remains a challenge for many patients having to take TKI therapy for years and this has led to suboptimal responses, disease progression, and resistance [28–30]. Developing therapies that may allow patients to more effectively and safely discontinue treatment for their CML remains an important goal.

Although we have made major strides in the management of CML, the next frontier of CML treatment will undoubtedly involve treatment strategies to improve treatment-free remissions after discontinuation of TKIs with an eye towards curing the disease. The combination of IFN and GM-CSF relies on a distinctive biologic anti-leukemic effect that may enhance the possibility of curing CML due to its activity at the early progenitor and stem cell levels. The results of 3 randomized clinical trials combining IFN with imatinib as front-line therapy have suggested that IFN may enhance the molecular responses and duration when combined with imatinib compared with imatinib alone [31–33]. Importantly, pegylated IFN- α was used in 2 of these studies [31–32], and appears to be a promising adjunct for CML largely due to its weekly subcutaneous dosing (as opposed to daily dosing with recombinant IFN- α). It is unclear, however, whether the combination of pegylated-IFN + GM-CSF would have the same efficacy and toxicity profile as seen with recombinant IFN + GM-CSF on this study. Additionally, Burchert et al. [34] showed that IFN treatment was effective in leading to the discontinuation of imatinib combined with IFN as front-line therapy, followed by IFN maintenance in newly diagnosed CML patients. Our results also supports this as 4 patients treated on study never transitioned to a TKI, and 3 of these patients have safely discontinued IFN therapy for > 3 years. Moreover, although the outcomes of patients who switched to imatinib appear to be similar to prior studies of imatinib as front-line therapy [11–12], an additional 3 patients remain off imatinib for > 15 months (2 with continued CMR), after being treated with the combination. While toxicities remain a concern of using the combination of IFN and GM-CSF as primary therapy compared to first-line TKIs, IFN-based strategies +/- GM-CSF should be further explored and incorporated into treatment strategies for patients with CML and may increase the possibility of long-term cure.

5. Conclusion

This study demonstrates the safety and efficacy of the combination of IFN and GM-CSF in the front-line setting for patients with newly diagnosed CML, leading to better and faster responses than historical data of IFN alone. However, this non-randomized comparison will need to be confirmed in larger clinical studies. The combination therapy also allowed 10% of patients to successfully discontinue their therapy for CML, with half of these patients never receiving TKI therapy. IFN and GM-CSF should be further explored in CML at various stages of disease, with or without TKI therapy, in order to increase the possibility of a cure for CML.

Acknowledgments

We would like to thank the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center nursing and research staff for their superb medical care, and the patients and their families, from whom we have learned valuable information to help us improve the treatment for these diseases.

This study was supported by NIH Core Grants T32CA009071 and P30CA006973. JFZ is supported by the 2013 Conquer Cancer Foundation Young Investigator Award, in memory of Dr. John R. Durant.

References

1. Talpaz M, Kantarjian H, McCredie K, Trujillo JM, Keating MJ, Gutterman JU. Hematologic remission and cytogenetic improvement induced by recombinant human interferon alpha in chronic myelogenous leukemia. *N Engl J Med*. 1986; 314(17):1065–9. [PubMed: 3457264]
2. Talpaz M, Kantarjian H, Kurzrock R, Trujillo JM, Gutterman JU. Interferon-alpha produces sustained cytogenetic responses in chronic myelogenous leukemia. *Ann Intern Med*. 1991; 114(7): 532–8. [PubMed: 2001086]
3. Kantarjian HM, O'Brien S, Anderlini P, Talpaz M. Treatment of chronic myelogenous leukemia: current status and investigational options. *Blood*. 1996; 87(8):3069–81. [PubMed: 8605319]
4. Bonifazi F, de Vivo A, Rosti G, Guilhot F, Guilhot J, Trabacchi E, et al. Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders. *Blood*. 2001; 98(10):3074–81. [PubMed: 11698293]
5. Kantarjian HM, O'Brien S, Cortes JE, Shan J, Giles FJ, Rios MB, et al. Complete cytogenetic and molecular responses to Interferon-alpha based therapy for chronic myelogenous leukemia are associated with excellent long-term prognosis. *Cancer*. 2003; 97(4):1033–41. [PubMed: 12569603]
6. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med*. 2001; 344(14):1031–7. [PubMed: 11287972]
7. O'Brien SG, Guilhot F, Larsen RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003; 348(11):994–1004. [PubMed: 12637609]
8. O'Dwyer ME, Mauro MJ, Blasdel C, Farnsworth M, Kurilik G, Hsieh YC, et al. Clonal evolution and lack of cytogenetic response are adverse prognostic factors for hematologic relapse of chronic phase CML patients treated with imatinibmesylate. *Blood*. 2004; 103(2):451–5. [PubMed: 14512312]
9. Kantarjian H, Talpaz M, O'Brien S, Giles F, Rios MB, White K, et al. Prediction of initial cytogenetic response for subsequent major and complete cytogenetic response to imatinibmesylate therapy in patients with Philadelphia chromosome-positive chronic myelogenous leukemia. *Cancer*. 2003; 97(9):2225–8. [PubMed: 12712475]
10. Soverini S, Martinelli G, Rosti G, Bassi S, Amabile M, Poerio A, et al. ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA Working Party on Chronic Myeloid Leukemia. *J Clin Oncol*. 2005; 23(18): 4100–9. [PubMed: 15867198]
11. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006; 355(23):2408–17. [PubMed: 17151364]
12. Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia*. 2009; 23(6):1054–61. [PubMed: 19282833]
13. Kantarjian H, O'Brien S, Talpaz M, Borthakur G, Ravandi F, Faderl S, et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinibmesylate failure. *Cancer*. 2007; 109(8):1556–60. [PubMed: 17342766]
14. Hochhaus A, Baccarani M, Deninger M, Apperley JF, Lipton JH, Goldberg SL, et al. Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. *Leukemia*. 2008; 22(6):1200–6. [PubMed: 18401416]
15. Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, Gattermann N, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24 month follow-up results. *Blood*. 2011; 117(4):1141–5. [PubMed: 21098399]
16. Angstreich GR, Matsui W, Huff CA, Vala MS, Barber J, Hawkins AL, et al. Effects of imatinib and interferon on primitive chronic myeloid leukaemia progenitors. *Br J Haematol*. 2005; 130(3): 373–81. [PubMed: 16042686]

17. Graham S, Jorgensen HG, Allan E, Pearson C, Alcorn MJ, Richmond L, et al. Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. *Blood*. 2002; 99(1):319–25. [PubMed: 11756187]
18. Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukemia who have maintained complete molecular remission for at least 2 years: the prospective, multicenter Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010; 11(11):1029–35. [PubMed: 20965785]
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958; 53:457–80.
20. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon alpha-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. *N Engl J Med*. 1994; 330(12):820–5. [PubMed: 8114834]
21. Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, et al. The German CML Study Group . Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. *Blood*. 1994; 84(12):4064–77. [PubMed: 7994025]
22. Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials: Chronic Myeloid Leukemia Trialists' Collaborative Group. *J Natl Cancer Inst*. 1997; 89(21):1616–20. [PubMed: 9362160]
23. Cortes J, Kantarjian H, O'Brien S, Kurzrock R, Keating M, Talpaz M, et al. GM-CSF can improve the cytogenetic response obtained with interferon-alpha therapy in patients with chronic myelogenous leukemia. *Leukemia*. 1998; 12(6):860–4. [PubMed: 9639411]
24. Cortes J, Quintas-Cardama A, Jones D, Ravandi F, Garcia-Manero G, Verstovsek S, et al. Immune modulation of minimal residual disease in early chronic phase chronic myelogenous leukemia. *Cancer*. 2011; 117(3):572–80. [PubMed: 20886606]
25. Talpaz M, Hehlmann R, Quintas-Cardama A, Mercier J, Cortes J. Re-emergence of interferon- α in the treatment of chronic myeloid leukemia. *Leukemia*. 2013; 27(4):803–12. [PubMed: 23238589]
26. Bedi A, Griffin CA, Barber JP, Vala MS, Hawkins AL, Sharkis SJ, et al. Growth factor-mediated terminal differentiation of chronic myeloid leukemia. *Cancer Res*. 1994; 54(21):5535–8. [PubMed: 7923192]
27. Breccia M, Alimena G. Occurrence and current management of side effects in chronic myeloid leukemia patients treated frontline with tyrosine kinase inhibitors. *Leuk Res*. 2013; 37(6):713–20. [PubMed: 23473918]
28. Jabbour EJ, Kantarjian H, Eliasson L, Cornelison AM, Marin D. Patient adherence to tyrosine kinase inhibitor therapy in chronic myeloid leukemia. *Am J Hematol*. 2012; 87(7):687–91. [PubMed: 22473898]
29. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachée P, Berneman Z, et al. The ADAGIO Study . Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia. *Blood*. 2009; 113(22):5401–11. [PubMed: 19349618]
30. Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol*. 2010; 28(14):2381–8. [PubMed: 20385986]
31. Preudhomme C, Guilhot J, Nicolini FE, Guerci-Bresler A, Rigal-Huguet F, Maloisel F, et al. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. *N Engl J Med*. 2010; 363(26):2511–21. [PubMed: 21175313]
32. Simonsson B, Gedde-Dahl T, Markevörn B, Remes K, Stentoft J, Almqvist A, et al. Combination of pegylated IFN- α 2b with imatinib increases molecular response rates in patients with low- or intermediate-risk chronic myeloid leukemia. *Blood*. 2011; 118(12):3228–35. [PubMed: 21685374]
33. Hehlmann R, Laussek M, Jung-Munkwitz S, Leitner A, Müller MC, Pletsch N, et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon- α in newly diagnosed chronic myeloid leukemia. *J Clin Oncol*. 2011; 29(12):1634–42. [PubMed: 21422420]
34. Burchert A, Muller MC, Kostrewa, Erben P, Bostel T, Liebler S, et al. Sustained molecular response with interferon alpha maintenance after induction therapy with imatinib plus interferon

alpha in patients with chronic myeloid leukemia. J Clin Oncol. 2010; 28(8):1429–35. [PubMed: 20142590]

Highlights

- IFN + GM-CSF may enhance the possibility of cure in CML by targeting the immune system and *BCR-ABL1* progenitor cells
- IFN combined with GM-CSF appears to be safe and effective in patients with CML
- A proportion of patients treated with IFN and GM-CSF appear to be cured with no evidence of residual disease
- IFN + GM-CSF should be further studied in CML in order to eradicate *BCR-ABL1* progenitor cells and increase the chances of long-term cure

Figure 1.
Treatment Schema

Figure 2.
Long-Term Follow-Up Schema of CMR Patients (n=11)
IM = imatinib

Figure 3.

Kaplan-Meier Estimate of OS

Black solid line = Kaplan-Maier estimate of OS, dotted lines = 95% confidence interval OS

at 10 years = 89% (95% CI: 81%, 99%)

Table 1

Patient Characteristics (n= 58):

Patient information	N
Median Patient Age	48 (range: 24–74)
Males	33 (57%)
Females	25 (43%)
Median time on IFN before GM-CSF	118.5 days
Median total time on IFN	19.5 months
Median patient dose of IFN	8×10 ⁶ units/m ² /day
Duration of therapy with GM-CSF	Total (%)
Complete therapy without dose reduction	30 (52%)
Complete therapy with dose reduction	15 (26%)
3–5 months of therapy with dose reductions	5 (9%)
Less than 3 months of therapy	8 (14%)
Median follow-up	11.5 years (range: 8.5 months– 14 years)

Table 2

Response Estimates

Disease Status	N	Proportion	Exact CI
MCR	35	0.6	[0.47, 0.73]
MCR by 6 months	30	0.52	[0.38, 0.65]
MCR by 9 months	32	0.55	[0.42, 0.68]
MCR by 12 months	34	0.59	[0.45, 0.71]
CCyR	16	0.28	[0.17, 0.41]
CMR ¹	11	0.19	[0.10, 0.31]

¹CMR definition: Undetectable BCR-ABL1 mRNA in PB or BM. Sensitivity of BCR-ABL1 PCR = 4.3 log decrement from the 100% International Standard.