Survival More Than 19 Years After the Diagnosis of Accelerated Phase of Chronic Myelocytic Leukemia

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Introduction

Long-term survival in chronic phase chronic myeloid leukemia (CML) in the pre-imatinib (Gleevec, Novartis) era was occasionally reported (Table 1). Long-term survival in the accelerated phase (AP) was extremely unusual, and survival for more than a decade was not reported. We report a patient diagnosed in the AP of CML and currently on imatinib who has survived for more than 19 years.

Case

In October 1991, a 52-year-old white woman with no significant family or exposure history presented with mid-epigastric abdominal and back pain. Her internist found splenomegaly, and a complete blood count showed a white blood cell count (WBC) of 200,000/µL, a hematocrit of 34%, and a platelet count of 73,000/µL. A computed tomography scan demonstrated hepatosplenomegaly. She was later seen by a hematologist who, after examining a bone marrow aspirate and biopsy, made a diagnosis of CML. Marrow cytogenetics are not available from that time. The patient was started on hydroxyurea 1 g/day, which she received for 2 weeks prior to coming to our center in the end of November 1991 for a second opinion. In the spring of 1990, she had normal routine blood studies, except for a WBC count of 11.5/µL with a normal differential WBC.

On initial examination by Dr. Wiernik in December 1991, the patient appeared to be well and was afebrile. She was found to have splenomegaly and a WBC count of 36,500/µL, with 51% segmented polymorphonuclear granulocytes, 2% bands, 14% lymphocytes, 10% monocytes, 2% eosinophils and 4% basophils, 4% metamyelocytes, and 13% myelocytes. Her hematocrit was 36.1%, and her platelet count was 340,000/µL. A bone marrow biopsy and aspiration demonstrated a hypercellular marrow with no other significant morphologic abnormalities. Cytogenetic studies on the marrow aspirate revealed 46, XX, inv(3)(p13;q11), t(9;22)(q34;q11) in 10 metaphases and 46, XX, t(9;22)(q34;q11) in another 10. Results of immunophenotyping of marrow mononuclear cells (MNC) showed slight monocytosis (13% of MNC) but normal myeloid maturation consistent with CML. A diagnosis of AP CML was made, as defined by standard criteria,[1] which requires a clinical diagnosis of chronic phase CML in the presence of a Philadelphia chromosome and an additional cytogenetic abnormality, along with increasing splenomegaly while receiving treatment with hydroxyurea or busulfan. The patient opted to enroll in a trial of plicamycin (mithramycin) 25 µg/kg as an intravenous infusion over 2–4 hours, 3 times a week for 2 weeks, and interferon 5×10^6 U/m^2 as a subcutaneous injection, 3 times a week.[2] This trial was suggested by previously reported major activity for plicamycin in myeloid blast crisis of CML.[3] Maintenance therapy following 2 weeks of induction therapy consisted of interferon 5×10^6 U/m^2 subcutaneously thrice weekly, and plicamycin 25 pg/kg monthly. After 2 months of treatment, marrow cytogenetic studies revealed that all 20 metaphases contained the Philadelphia chromosome, but inv(3) was not detected. The patient achieved complete hematologic response within 3 months. Plicamycin and interferon were continued for 51 months, until imatinib became available. During this period, she achieved a complete hematologic response and cytogenetic response (Table 2).

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Table 1. Reported Cases of Long-Term Survival in Chronic Phase Chronic Myeloid Leukemia Treated Prior to the Imatinib Era

Author	Age (yrs)/ Sex	Survival from Dx (yrs)	Ph Chromosome at Dx	Comments
Amikam et al[14]	42/F	29+	ND	Alive.* Ph+ 19 years after dx. BU only Rx.
Nowell et al[15]	9/F	27+	Ph1+	Alive.* Ph1+ 26 yrs. Polymerase chain reaction: b3a2. BU only.
Selleri et al[16]	32/F	17	Ph1+ 22/22 cells	Died in myeloid blast crisis with karyotype evolution. BU only.
	49/M	19+	Ph1+ 22/22 cells	Alive.* Splenic RT + BU. Only Ph1+ 18 yrs after dx.
	30/M	21	Ph1+	Splenic RT + BU. Died in myeloid blast crisis. Ph1+ with clonal evolution at death.
Benjamin et al,[17] Djaldetti et al[18]	42/F	23+	ND	Alive.* 2 BU-induced CRs. Mosaic at 1st relapse 8 yrs after dx, Ph1- later.
Dreazen et al[19]	30/M	26+	Ph1+	Alive* in accelerated phase. BU + hydroxyurea as initial Rx
	56/M	11+	Ph1+	Alive.* BU alone.
Weinberger et al[20]	27/F	16+	ND	AML 13 yrs after dx of CML. CR of AML for 18+ mos. Alive.* Ph1- 13 yrs after dx. Single course of BU.
Singer et al,[21] Sproul et al[32]	54/F	31+	ND	Normal karyotype after BU-induced aplasia. Alive.* 5% Ph1 at 4 yrs, none + at 24 yrs. BCR/ABL neg 31 yrs post dx.
Stein et al[22]	25/F	22+	ND	Alive.* Splenic RT, then BU. Hypoplasia. Ph1- at 22 yrs post dx.
Golde et al[23]	41/M	14+	ND	Alive.* Mosaic 13 yrs post dx. BU alone.
Brandt et al[24]	62/M	17+	ND	Alive.* Mosaic at yr 16.
Bennett et al[25]	55/F	8+	ND	Prolonged aplasia with BU. Ph+ 100% at 8 yrs post dx.
Najean et al[26]	32/F	28	ND	BU-induced aplasia. AML after 27 yrs, died 3 months later. BCR/ABL neg at death.
Maurice[27]	35/F	18+	ND	Nl karyotype at 11 yrs. Dx with Ph- ALL at 18 yrs. Hypoplasia after BU. Alive.*
Prischl et al[28]	26/F	27	ND	Ph+ and trisomy 8 at 21 yrs post dx. Died with myeloid extra-medullary blast crisis.
Wolf et al[29]	65/M	14	ND	Ph1 mosaic at 13 yrs. Died with myeloid blast crisis.
	48/M	19+	ND	100% Ph+ later. Died, myeloid blast crisis.
	56/M	14	ND	Ph1+ at 13 yrs. Died, myeloid blast crisis.
	44/F	11+	ND	100% Ph+ at 8 yrs.
Appelbaum et al[30]	23/M	14	ND	Ph1 mosaic 7 mo. after dx. Died with mosaic lymphoid blast crisis.
Tharapel et al[31]	22/F	12	+	BU only. Died in blast crisis with clonal evolution.
Inbal et al[33]	43/M	22	+	BU initially. Six yrs later, BU + thioguanine for ↑ WBC. Died in blast crisis 21 yrs 10 mos after dx. Ph1+ and clonal evolution.
Müller et al[34]	55/F	24	+	BU initially, hydroxyurea later. Died, blast crisis. 100% Ph1+.
Rak et al[35]	9/F	15	ND	Splenic RT only.
Steinberg et al[36]	35/M	13.5	ND	Initial Rx: 6-mercaptopurine, BU later. Mosaic 12 yrs post dx. Died with myeloid blast crisis and extramedullary leukemic infiltrates.
Kiley et al[37]	1.5/M	12	+	6-mercaptopurine + BU.

(Table continued on following page)

Table 1. *(Continued)* Reported Cases of Long-Term Survival in Chronic Phase Chronic Myeloid Leukemia Treated Prior to the Imatinib Era

Author	Age (yrs)/ Sex	Survival from Dx (yrs)	Ph Chromosome at Dx	Comments
Hansen[38]	53/F	13	+	Splenic RT only.
Berman et al[39]	NA/M NA/M NA/M	18 20 23	+ + +	
Tanzer et al[40]	NA NA NA NA NA 30/M 61/F	18 18 19 21 24 22 22	+ mosaic + ND + mosaic +	BU alone. BU alone. BU alone. BU alone. BU alone. BU alone. BU alone.
Birnie et al[41]	55/F	17+	100% Ph1+	Pancytopenic after 7 mos. BU Rx 4/12 metaphases. Ph1+ 12 yrs 10 mos after dx. Alive.*

*At time of case publication.

AML=acute myelogenous leukemia; BU=busulfan; CML=chronic myeloid leukemia; dx=diagnosis; ND=not done; Ph=Philadelphia chromosome; RT=radiation therapy; Rx=treatment; WBC=white blood cell.

She was started on imatinib 400 mg daily in July 2001. At this time, she had a normal karyotype, but molecular analysis of bone marrow RNA by polymerase chain reaction (PCR) disclosed the presence of the b3a2 BCR/ABL transcript. Within 3 months of imatinib therapy, PCR demonstrated a complete molecular response. As of December 2010, the patient continues to be well more than 19 years after the diagnosis of AP CML. Her spleen is not palpable, and her hemogram is normal. She has been in a cytogenetic complete remission since October 2000, although nested PCR studies in 2005 and 2007 transiently detected b3a2 BCR/ABL transcripts in her peripheral WBC. PCR studies have otherwise been negative since September 2001.

Discussion

Cytogenetic clonal evolution (CE), a phenomenon observed in 20–40% of AP patients, is a marker of disease progression and refractoriness to treatment, but its prognostic significance is not uniform. The characteristics associated with a longer survival include a lower percentage of abnormal metaphases, time to cytogenetic CE of 24 months or more, and absence of other features of accelerated disease.[4] Newer CML classification schemes, such as the World Health Organization classification,[5] include CE as a manifestation of accelerated phase only if it was not present at the time CML was originally diagnosed. Our patient did not have cytogenetics performed at diagnosis, but her diagnosis was made only 1 month before CE was demonstrated. Patients who had CE as the only evidence of AP have been reported to have a better prognosis than those with multiple features of AP when treated with imatinib.[6] However, our patient was not treated with imatinib initially and did not receive it until 51 months after her diagnosis, at which time she already had a cytogenetic complete response. Approximately 50% of patients with CE experienced clinical improvement with interferon treatment, and that response was associated with longer survival.[7] Despite the occurrence of splenomegaly in addition to CE, our patient had a remarkable recovery, with complete suppression of CE within 2 months of plicamycin plus interferon therapy and a complete hematologic response after 3 months of that treatment.

Imatinib, a specific inhibitor of the BCR-ABL tyrosine kinase improved the overall survival rate for previously untreated patients with chronic phase CML to 88% at 6 years, a result that surpasses those of all prior treatments.[8] Our patient—who has been in complete cytogenetic remission for more than 10 years and complete hematologic remission for more than 19 years—is the longest reported survivor of CML accelerated phase. However, it is possible that current studies listed in Table 3 may eventually yield long-term survivors of accelerated phase

Table 2. Course of the Patient

Date	WBC Counts $\times 10^3/\mu L$	Cytogenetics (Marrow)	PCR	Treatment
12/12/1991	36.5	46,XX,t(9;22)(q34;q11) [10] 46 XX, inv (3) (p13;q11) [10]	NA	INF + plicamycin
1/21/1992	NA	46,XX,t(9;22)(q34;q11) [20]	NA	INF + plicamycin
10/28/1994	NA	46,XX,t(9;22)(q34;q11) [4] 46,XX [16]	NA	INF + plicamycin
2/21/1997	NA	46,XX,t(9;22)(q34;q11) [20]	NA	INF + plicamycin
10/30/2000	4.7	46,XX [20]	b3a2-positive	INF + plicamycin
9/6/2001	2.9	46,XX [20]	b3a2-negative	Imatinib 400 mg/day
7/23/2002	5.9	46,XX [20]	b3a2-negative	Imatinib 400 mg/day
11/03/2005	5.8	NA	b3a2-positive	Imatinib 400 mg/day
10/09/2007	7.4	NA	b3a2-positive	Imatinib 400 mg/day
11/06/2008	7.4	NA	b3a2-negative	Imatinib 400 mg/day
10/10/2009	6.4	NA	b3a2-negative	Imatinib 400 mg/day

INF=interferon; NA=not available; PCR=polymerase chain reaction; WBC=white blood cell.

Table 3. Thymidine Kinase Inhibitor Treatment of Accelerated Phase Chronic Myeloid Leukemia

Reference	Regimen	No. Patients	CHR (%)	CCyR (%)	1 yr PFS (%)	1 yr OS (%)
Kantarjian et al[44]	Imatinib 400–600 mg	176	82	43	44	53
Palandri et al[45]	Imatinib 600 mg	111	71	21	36.5% at 7 yrs	Median survival, 37 months
Apperley et al[46]	Dasatinib 70 mg bid (prior imatinib)	174	45	32	66	82
Le Coutre et al[47]	Nilotinib 400 mg bid (prior imatinib)	119	47 (total responses)	29 (major)	NA+	79

bid=twice a day; CCyR=complete cytogenetic response; CHR=complete hematologic response; NA=not available; OS=overall survival; PFS=progression-free survival.

CML. Fluctuating molecular response while on imatinib reflects the persistence of a low level of disease activity. Thymidine kinase inhibitor therapy suppresses disease activity but is not curative. It does not eliminate leukemia stem cells, which may mutate and become refractory to it.[9,10]

Interferon differentiates primitive CML progenitors,[11] presumably reducing the number of aberrant leukemic stem cells harboring BCR/ABL. Additionally, our patient received plicamycin, which sensitizes cancer cells to tumor necrosis factor–related apoptosis-inducing ligand–mediated apoptosis.[12] Combined chemoimmunotherapy can completely eradicate BCR/ABL transcripts from the bone marrow of rats.[13] In our clinical trial of plicamycin and interferon, the median survival of patients after development of AP of CML was 24 months, with

4 of 13 patients surviving more than 5 years, which was substantially longer than expected from previous clinical reports of patients in this advanced stage of CML at that time. Whether the prolonged survival of the present patient is the result of that treatment regimen is not clear. However, this remarkable case raises the question of whether combinations of TKIs with other agents active against CML should be investigated further.[13]

Virtually all reported cases of long-term survival of CML patients in chronic phase prior to the imatinib era are listed in Table 1. Survival as long as 31 years or longer has been reported with busulfan-based treatment.[14-41] There are no constant features among the long-term survivors reported that distinguish them from other less fortunate CML patients, including presenting hematologic counts, gender, age, initial treatment, presence or absence of mosaicism, induction of severe marrow aplasia, or BCR/ABL breakpoint,[42,43] except possibly longer response to initial therapy in the long-term survivors,[28] which, in a sense, is obvious. Therefore, the question why rare patients with CML have unusually long survival remains unanswered. However, the fact that long-term survival can occur after treatment with busulfan alone raises the question of whether some success of allogeneic stem cell transplantation results from the preparative regimen rather than the graft versus leukemia effect of the transplant.

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Review

CML: A Model Disease With a Defined Oncogenic Driver

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Wiernik and colleagues[1] describe a patient with BCR-ABL-positive chronic myelocytic leukemia (CML) who is still alive 19 years after diagnosis of accelerated phase (AP), before the availability of imatinib (Gleevec, Novartis). This report is placed in context with other long-term survivors of CML, where there are apparently no consistent clinical or cytogenetic features that distinguish them from poor outcome cases. Clearly, understanding the basis for long-term survival in CML could be of importance for understanding disease progression and relapse.

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Accelerated Phase of CML Is Poorly Defined

Clinically, CML starts in a chronic phase (CP) in 85–90% of the cases and can be asymptomatic (15–20%). After passing through a brief AP, it eventually culminates in blast phase (BP). Historically, the median survival for CP is 3–5 years. Although survival for AP patients varies according to the diagnostic criteria, it usually ranges from 1–2 years. Average survival for BP patients is typically only 3–12 months.[2] Diagnostic features for AP were more recently defined by the World Health Organization as having 10–19% of blasts and more than 20% basophils, among others.[3] In this classification, clonal evolution (CE) is only a feature of AP when it is not present at diagnosis. The prognostic significance of CE is not uniform, and is related to specific abnormalities such as isochromosome 17, trisomy 8, or a second Ph chromosome.[4] In the imatinib era, CE is often found in patients who have developed imatinib resistance. In a series of 177 patients from the MD Anderson Cancer Center, who were treated with a second tyrosine kinase inhibitor (TKI) after imatinib resistance, Verma and colleagues[5] identified 30 patients who only had CE, whereas 24 patients had AP with CE. Two-year overall survival and event-free survival were the same in patients in CP with or without CE. CE also had no major impact on major cytogenetic remission. In contrast, patients in AP fared significantly worse if concurrent CE was present. Patients in AP do not present uniformly, but rather show a continuum with one or more of the many features that are characteristic of advanced disease. Recently, gene expression analysis seemed to argue against

the notion that CML is a triphasic process. When the expression profile of approximately 24,000 genes from patients in CP, AP, and BP were compared, the molecular signatures were far more similar between the AP and BP than between CP and AP.[6] This observation echoes the fact that current criteria used to diagnose AP of CML is not sufficiently sensitive to identify early critical changes occurring at the molecular level in CML patients. Molecular profiling in the future may help define those early, but critical, changes that signal the transition from CP to BP.

Curing CML Requires Stem Cell Targeting

Since the landmark IRIS (International Randomized Study of Interferon and STI571) study, and before the second generation TKIs became available, imatinib had been the standard of care for patients in all phases of CML due to its unprecedented efficacy. Currently, 85% of patients in CP that are treated with imatinib survive more than 5 years.[7] Despite this degree of success, imatinib is not considered curative. In the latest study by Mahon and associates,[8] 100 patients treated with imatinib were followed for relapse using polymerase chain reaction analysis of the BCR-ABL fusion for a median follow-up period of 17 months after the fusion gene was no longer detected for 2 years (5 log reduction in BCR-ABL and in complete molecular remission). Of the 69 patients analyzed, 42 (61%) relapsed. Due to short follow-up, it is not known whether the other 40% are cured. The question of why imatinib is not curative for CML may be explained by its inability to eradicate the CML stem cell. It has been shown in CML that the leukemia-initiating cells express high levels of BCR-ABL, making it difficult to suppress the ABL kinase activity.[9] In addition, these cells express high levels of the drug transporter in the membrane, which results in decreased accumulation of imatinib inside these stem cells.[10] Until there is a way to eliminate the CML stem cell, curing CML may not be possible. It is interesting to note from the case report by Wiernik and coauthors, however, that long-term survival for CML existed before the imatinib era, and most of these long-term survivors were treated with a busulfan-based regimen. Busulfan is commonly used as a conditioning regimen together with cyclophosphamide before stem cell transplantation due to its relative stem cell toxicity.[11] It is especially effective in patients with myeloid leukemia compared to lymphoid leukemia. The efficacy, however, is mainly due to its ability to eradicate stem cells in the marrow. In this respect, it may not be difficult to understand why busulfan treatment could result in long-term survival. Whether busulfan could be used to preferentially eliminate leukemic stem cells is worth serious consideration.

Conclusion

CML is a triphasic disease, although current diagnostic criteria cannot readily identify those patients whose disease is evolving due to unknown molecular changes. The prognostic significance of CE in the absence of other AP criteria is uncertain. That imatinib does not cure CML is probably due to its inability to eliminate leukemic stem cells, emphasizing the need to define novel regimens to selectively target these cells. Busulfan and possibly other known stem cell toxins deserve further testing. The identification of long-term survivors also provides an opportunity to determine whether there is an underlying molecular genetic basis for this phenotype.

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