CASE REPORT

Case of relentless chronic phase of chronic myeloid leukaemia

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SUMMARY

Initial treatment of chronic phase chronic myeloid leukaemia is straightforward in today's era of tyrosine kinase inhibitors. However, managing refractory cases remain a major challenge due to the multiple factors that can influence decision-making, including medication tolerance, disease burden, mutation status, comorbidities, availability of donor, and fitness for an ablative conditioning. We report a male patient presenting with chronic phase chronic myeloid leukaemia who was treated with 5 different tyrosine kinase inhibitors either due to intolerance and/or failed response. He subsequently received 2 haploidentical haematopoietic stem cells transplants before achieving complete remission. This case highlights various treatment options, need for vigilant disease monitoring, and the possibility of complete positive response even after many lines of therapy failure.

BACKGROUND

Chronic myeloid leukaemia (CML) is a rare malignancy with incidence rate of 1.7 per 100 000 and mortality rate of 0.3 per 100 000 each year based on the data from 2008 to 2012.¹ A previously fatal disease, with a typical expected survival of only 2–3 years, has seen dramatic improvement since the introduction of tyrosine kinase inhibitor (TKI), imatinib, near the turn of the century.² Overall survival for 5 years is now over 60%.¹ CML is associated with the oncogene BCR/ABL1, and typically results from reciprocal translocation between chromosomes 9 and 22, t(9;22) (q34;q11) that subsequently gives rise to the Philadelphia (Ph) chromosome.³ Protein product, such as p210 derived from this gene, exhibits deregulated tyrosine kinase activity that largely explains the success of imatinib.⁴ Several other TKIs have since been developed, including second generation (nilotinib, dasatinib and bosutinib) and third generation (ponatinib),⁵ allowing for multiple therapeutic options even after failure of a prior line of therapy. However, haematopoietic stem cells transplant (HSCT) remains an important treatment modality for patients who failed multiple TKIs or with advanced CML. We present a case of chronic phase CML (CP-CML) in which our patient achieved complete remission only after trying all five TKIs and receiving two haploidentical HSCTs. This is followed by a review of the treatment options and some of the difficulties in choosing treatment for CP-CML.

CASE PRESENTATION

A previously healthy 53-year-old Hispanic man was diagnosed with CML in 2010. At that time, he presented with 6 months history of fatigue, general malaise and a 35 lb (16 kg) weight loss. Pertinent physical findings included mild tachycardia and palpation of an enlarged spleen extending ~10 cm below the costophrenic angle.

INVESTIGATIONS

Laboratory workup (table 1) revealed significant leukocytosis with white cell count of 307 000/μL, haemoglobin of 10.1 g/dL and platelet count of 429 000/μL. The differential was notable for bandemia 32%, blasts 5% and basophils 5%. CT abdomen/pelvis showed mild hepatomegaly and massive splenomegaly (figure 1). He underwent a bone marrow biopsy (BMB) for further evaluation of his leukocytosis, with pathology revealing findings consistent with CML in chronic phase. Increased basophils, eosinophils, and bands along with myelocyte and metamyelocyte are evident on the marrow (figure 2A), with almost 100% marrow cellularity (figure 2B). Flow cytometric analysis showed a CD33+ and CD117+ myeloblast population, which is 2.3% of the gated events. Fluorescence in situ hybridisation analysis with BCR/ABL+9q34 showed evidence of 9;22 translocation resulting in the fusion of ABL1 with BCR in 169/200 cells scored (84.5%). Cytogenetic profiling revealed presence of the Ph chromosome: 46, XY,t(9;22) (q34;q11.2) [20].

TREATMENT

Patient was started on hydroxyurea during his hospital stay and later transitioned to imatinib dosage of 400 mg daily. Two months after diagnosis, patient achieved complete haematological response with BMB at 6 months showing no morphological evidence of CML. However, Giemsa-banded study on the marrow continues to show all cells with Ph chromosome, which indicates persistence of the disease. Given the lack of complete cytogenetic response (CCyR) of 0% Ph+ CCyR and major molecular response (MMR) BCR/ABL/control gene ≤0.10 MMR by 9 months, imatinib was changed to dasatinib. Owing to a number of side effects, such as severe headaches, nausea, diarrhoea, fatigue, and persistence of Ph chromosome with 17/21 metaphases (80%) that remained positive for t9;22 on BMB 1-month later, the patient was started on nilotinib. Analysis for BCR/ABL kinase domain mutation was negative. About 1 year after being on

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Table 1 Initial laboratory work up

CBC	Value	Reference	Unit
White cell count	300.7	(3.4–10.4)	1000 μ L
Red blood cell count	3.50	(4.4–5.6)	10e6 μ L
Haemoglobin	10.1	(13.5–17.5)	g/dL
Haematocrit	30.3	(40.0–48.0)	%
MCV	86	(80–100)	fL
MCH	28.8	(27.0–34.0)	pg
MCHC	33.4	(32.0–35.0)	%
RBC distribution width	18.4	(<14.6)	
Mean platelet volume	9.2	(5.5–9.0)	fL
Platelet count	429	(150–425)	1000 μ L
Segmented neutrophils	41	(44–76)	%
Band neutrophils	32		%
Eosinophils	5	(0–5)	%
Basophils	5	90–2)	%
Myelocytes	9	90)	%
Blasts	5	(0)	%
Segmented neutrophils (absolute)	123.28		1000 μ L
Band neutrophils (absolute)	96.22		1000 μ L
Eosinophils (absolute)	15.04	(0.0–0.3)	1000 μ L
Basophils (absolute)	15.04	(0.0–0.1)	1000 μ L
Myelocytes (absolute)	27.06	(0)	1000 μ L
Blasts	15.04	(0)	1000 μ L

CBC, complete blood count; MCH, mean corpuscular haemoglobin; MCHC, mean cell haemoglobin concentration MCV, mean corpuscular volume; RBC, red blood cells.

nilotinib, patient's BCR/ABL p210 messenger RNA PCR showed a significant increase from 17% to 26%. He was switched to bosutinib for 1.5 years and subsequently changed to ponatinib due to intolerable diarrhoea. CCyR and MMR were never achieved on any of the TKIs. Mutational analysis failed to reveal any particular mutation as cause of TKI failure.

Figure 1 CT scan of the chest/abdomen/pelvis showed mild hepatomegaly and massive splenomegaly (arrow).

Figure 2 (A) Increased basophils (red arrow), eosinophils (green arrow) and bands are evident on the bone marrow biopsy. (B) The marrow showed almost 100% cellularity.

Five years after his initial diagnosis, patient decided to undergo haploidentical HSCT since a fully human leucocyte antigen matched donor was not available. He had a reduced intensity conditioning (RIC) regimen based on BMT CTN 1101 protocol (fludarabine 30 mg/m²×5, cytoxan 14.5 mg/kg×2, total body irradiation (TBI) 200 Gy) and received marrow source 3.02×10⁸ CD34+ cells (donor brother). Unfortunately, after initial engraftment at day +18, patient had disease relapse by day +30, confirmed by BMB. Second haploidentical HSCT with a different donor (sister) was performed 5 months later. During this second treatment therapy, he received a myeloablative regimen (fludarabine 30 mg/m²×4, a total of TBI 9.9 Gy)⁶ and 3.31×10⁶ CD34+ cells). Day +30 BMB showed complete remission with 100% donor chimerism and p210<0.01% positive.

OUTCOME AND FOLLOW-UP

Figure 3 depicts the patient's disease and treatment course. He has been doing very well clinically, and is in remission for more than day +180 at the time of this report writing.

DISCUSSION

CML can be categorised into three phases, including chronic, accelerated, and blastic, which roughly represent the natural progression of the disease.⁷ Classification is slightly different depending on the criteria used, but the main parameters are the percentage of blasts, counts in different cell lines, and presence of extramedullary manifestation.³

There are five different TKIs approved by Food And Drug Administration with imatinib being the oldest medication, and

Figure 3 Patient achieved complete cytogenetic and molecular response after being on multiple tyrosine kinase inhibitors, and ultimately underwent two haploidentical stem cells transplantations. Each one of the green or yellow boxes represents a bone marrow biopsy. The p210 indicates normalised ratio of BCR/ABL1 (p210) to endogenous ABL1 messenger RNA with conversion to a percentage with reference to the international scale. Pink asterisk indicates patient received stem cells transplant consultation (12/2012); however, no fully human leucocyte antigen-matched donor was available. BMB, bone marrow biopsy; CML, chronic myeloid leukaemia; Haplo-SCT, haploidentical stem cells transplant; NME, no morphological evidence; m, month(s); Ph+, Philadelphia chromosome positive; RIC, reduced intensity condition.

has extensive long-term data regarding efficacy and toxicities. Dasatinib and nilotinib are also approved for first-line use based on the results from the DASISION trial (dasatinib vs imatinib) and the ENESTnd trial (nilotinib vs imatinib) showing earlier and deeper treatment responses in terms of MMR.⁷ However, in both cases, there were no significant differences in survival compared to imatinib at 5 years follow-up.⁸ Bosutinib is currently being evaluated under the BELA trial (bosutinib vs imatinib) with promising results at 2 years.⁹ EPIC trial (ponatinib vs imatinib) was stopped prematurely due to unacceptable rates of arterial thrombotic events.⁹

The widely followed European LeukemiaNet (ELN) recommendations outline their definition of the response to first-line TKI into three grades (optimal, warning and failure)¹⁰ which help as a guide for when to change treatment (table 2). For example, BCR/ABL1 <10% at 3 months, <1% at 6 months and <0.01% at 12 months would be considered as optimal responses.¹⁰ Certain TKIs appear to be more effective in patients with certain BCR/ABL1 mutations. For instance,

dasatinib is preferred in patients with Y253H, E255 or F359, while nilotinib is for F317 and V229.¹¹ Besides development of resistance to TKI, such as BCR/ABL1 kinase domain mutations that would prompt switching to a different TKI, side effects (which are rarely severe) are also an important consideration given the chronicity of consumption.¹² Therefore, selection of initial and salvage therapy should take into account the patient's BCR/ABL1 mutation status and comorbidities.

With the discovery of TKI, allogeneic HSCT in CP-CML became the therapy of last resort; however, it provides a lifesaving option for patients who had failed multiple TKIs.¹³ Current recommendations suggest consideration of allogeneic stem cell transplant (AlloSCT) consultation with donor search at first TKI failure for patients who are at high risk and fit to receive transplant.¹⁴ Indications for allogeneic HSCT in chronic phase include high risk with first failure of imatinib, first failure of second generation TKI, failure of 2+ TKIs and T315L mutation.¹⁴ Since CML occurs mostly in older patients, with median age at diagnosis being 64 years,¹ RIC regimen is frequently used for AlloSCT. However, it has a higher rate of relapse compared to myeloablative recipients.¹⁴ The trade-off between taking the risk of progressing into blastic phase with dismal chances for recovery or early HSCT with the risk of immediate mortality can be a difficult reality for both the patient and the guiding physician.¹³

In the case of our patient, imatinib was chosen as the first line treatment for his CP-CML given its time-tested therapeutic activity and safety profile. After inadequate response evident by his BMB, second generation TKI-dasatinib then nilotinib due to intolerable side effects was started as per guidelines. Meanwhile, BCR/ABL1 p210 was being closely monitored every 3–4 months as suggested by ELN.¹⁰ A significant increase from 17.2% to 26.4% was noted after about 1.5 years on the therapy. Given this increase and the fact that patient was on his third TKI, he agreed to take a consultation with our transplant team. Unfortunately, no fully matched donor was available. Bosutinib

Table 2 ELN definition of the response to TKIs, first line^{10 16}

Time	Optimal	Warning	Failure
Baseline	NA	High risk or CCA/Ph+, major route	NA
3 months	BCR/ABL1 ≤10% or Ph+ ≤35%	BCR/ABL1 >10% or Ph+ 36–95%	Non-CHR or Ph+ >95%
6 months	BCR/ABL1 ≤1% or Ph+ 0 (CCyR)	BCR/ABL1 1–10% or Ph+ 1–35% (PCyR)	BCR/ABL1 >10% or Ph+ >35%
12 months	BCR/ABL1 ≤0.1% (MMR)	BCR/ABL1 0.1–1%	BCR/ABL1 >1% or Ph+ ≥1%

CCA/Ph+, clonal chromosome abnormality in Ph+ cells; CCyR, complete cytogenetic response; CHR, complete haematological response; ELN, European LeukemiaNet; MMR, major molecular response; NA, not applicable; PCyR, partial cytogenetic response; TKIs, tyrosine kinase inhibitors.

and ponatinib were subsequently tried. While p210 had been decreasing, it never reached <0.1%. Patient ultimately decided to receive haploidentical HSCT knowing the risk and benefits involved. He was given RIC regimen since it is well known that CML consistently demonstrates graft-versus-leukaemia effect.¹³ After the disease relapse, he received myeloablative haploidentical HSCT;¹⁵ patient finally achieved complete remission since the disease was first diagnosed 5 years ago.

Learning points

- ▶ There are five different Food And Drug Administration-approved tyrosine kinase inhibitors (TKIs) available, and its selection depends on patient's stage of disease, mutation status, tolerance and comorbidities.
- ▶ Haematopoietic stem cells transplant continues to serve an important role for refractory chronic myeloid leukaemia.
- ▶ Haploidentical alternate donor options are routinely being used after multiple line of TKI failure.
- ▶ Close monitoring is required in order to change treatment when indicated in a timely manner.
- ▶ There is the possibility of complete response and subsequent cure even after many lines of therapy failure.

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