Therapeutics, Pharmacology and Clinical Toxicology
Vol XVIII, Number 2, June 2014
Pages: 83-86

CASE REPORT

THERAPEUTIC SUCCESS IN CHRONIC MYELOID LEUKAEMIA-ACCELERATED PHASE AT ONSET

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Abstract. Tyrosine kinase inhibitors based therapy has completely changed the prognosis for patients with chronic myeloid leukaemia in the sense that most of them have a life expectancy almost similar with the healthy population. The best responses occur in patients diagnosed while in chronic phase of the disease, with a 60-65% probability to maintain a complete cytogenetic response up to five years. For the cases whose illness begins already in an advanced phase (accelerated or blastic) and who present new unfavourable cytogenetic or molecular prognosis factors, complete cytogenetic response under therapy with tyrosine kinase inhibitors (TKIs) is obtained rather late or it is not obtained at all, making allotransplant a curative therapy. The current paper describes the case of a female patient, diagnosed with accelerated phase chronic myeloid leukaemia, high risk group, who lost the complete cytogenetic response with first generation TKIs therapy and presented trisomy 8, clonal cytogenetic abnormality and unfavourable prognosis marker in Ph + cells. Despite this evolution our patient has been under oral therapy with Dasatinib for six years (IInd generation TKIs) and for the past four years in complete molecular remission, in other words the disease is currently undetectable.
Keywords: chronic myeloid leukemia- advanced phase; tyrosine kinase inhibitors; complete molecular response; complete cytogenetic response; clonal chromosome abnormality, trisomy 8

Introduction

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder of the pluripotent hematopoietic stem cell that generates proliferation of the myeloid elements in all growth stages. The symptoms follow unspecific patterns while the most frequent clinical sign is splenomegaly. The disease presents 3 stages: chronic, accelerated and blastic, but in most cases patients are diagnosed in the chronic stage [1].

This condition represents the very first for which the term leukaemia was used and also the first malignant illness associated with a chromosomal anomaly (Philadelphia chromosome) which is the result of the ABL gene translocation, between chromosomes 9 and 22, t[(9;22)(q34;q11)]. At molecular level this translates into the emergence of a new hybrid fusion gene (BCR-ABL) that encodes for an oncoprotein (p210, and more rarely p190 or p230) with tyrosine-kinase activity. [2,9]

If during the 1990s Interferon alfa treatment was considered a top choice, in the early 2000s a tyrosine-kinase inhibitor molecule was discovered, based on the essential role of BCR-ABL molecule in CML. This is a 2-phenylamidopyrimidine named STI571, Imatinib mesylate or Imatinib that occupies the BCR-ALB kynase site, thus blocking ATP access and preventing phsophorylation in any substratum. Consequently, in a relatively short amount of time tyrosine-kinase inhibitors therapy (TKIs) became the gold standard for patients diagnosed with CML, given the promising results released by clinical studies on first generation TKIs (Imatinib) and second generation TKIs (Dasatinib, Nilotinib) [3,4,5,6].

Given the evolution in CML's treatment, this condition is no longer considered incurable or fatal, the rate of prevalence being quite high due to a substantial expansion of the survival rate.

Oral therapy with Imatinib (the first TKI used for first line regimens during the chronic, accelerated or blastic phase) continues to be the basic option throughout the world, while obtaining a complete cytogenetic response and complete molecular response is the main target of CML therapy. Assessment of the hematologic, cytogenetic and molecular responses is performed every three months and obtaining them represents the most important prognostic factor for the patient's follow up, as ESMO and ELN Guidelines recommend. [7,8,9,10]

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	Optimal	Warning	Failure
Baseline	NA	High risk Or CCA/Ph+, major route	NA
3 mo	BCR-ABL1 ≤10% and/or Ph+ ≤35%	BCR-ABL1 >10% and/or Ph + 36-95%	Non-CHR and/or Ph+ >95%
6 mo	BCR-ABL1 <1% and/or Ph+ 0 (CCyR)	BCR-ABL1 1-10% and/or Ph+ 1-35%	BCR-ABL1 >10% and/or Ph+>35%
12 mo	BCR-ABL1 ≤0.1% (MMR)	BCR-ABL1 >0.1-1%	BCR-ABL1 >1% and/or Ph+ >0
Then, and at any time	BCR-ABL1 ≤0.1%	CCA/Ph– (–7, or 7q–)	Loss of CHR Loss of CCyR Confirmed loss of MMR Mutations CCA/Ph+

Table I. Definition of the response to TKIs (any TKI) as first-line treatment (ELN criteria, 2013)

Other considerable prognostic factors are: Sokal scores [11], Euro [12] or more recently EUTOS [13] (during the debut phase), certain chromosome abnormalities as trisomy 8, trisomy Ph (der(22)t(9;22)(q34;q11)), isochromosome 17 (i(17)(q10)), trisomy 19 and ider(22)(q10)t(9;22)(q34;q11) as well as BCR-ABL 1 kinase domain mutations, whose discovery at the time of diagnosis or during the clinical course of the disease raise big concerns [3].

An optimal answer usually associates with a life expectancy similar to the one measured in the general population; therapeutic failure entails switching to second generation TKIs therapy in order to limit the risk of disease progression to accelerated or blastic phases.

Case presentation

Given the general presentation above, we aim to discuss the case of a female patient who in 2006, at the age of 34 was diagnosed with chronic myeloid leukaemia: Ph (+), accelerated phase, high risk group, Ph (+) in 100% of assessed metaphases, Sokal score= 3.33 (increased score >1.2). The bone marrow biopsy was showing granulocyte hyperplasia with left shift and 10% myeloblasts, 16% eosonophiles and 10% basophiles. (Figure 1)

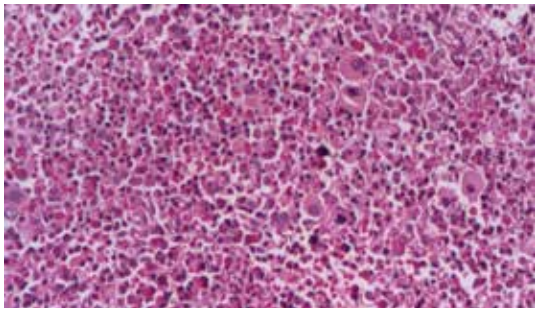

Figure 1. Diagnostic bone marrow biopsy

Blasts in blood or marrow 10-19%
Basophils in blood >20%
Persistent thrombocytopenia (<100x109/L) unrelated to therapy
CCA/Ph+ on treatment
Thrombocytosis (>1000x109/L) unresponsive to therapy
Increasing spleen size and increasing white blood cell count unresponsive to therapy

Table II. Definition of the accelerated phase of CML according to WHO criteria

We initiated cytoreductive therapy with Hydroxyurea, Purinethol (initially WBC count was $367x10^3/\mu L$ and CBC count $770x10^3/\mu L$) associated with chemotherapy (2 courses of Cytarabine), under which WBC and haemoglobin level decreased significantly. In March 2007, three months after the first diagnostic and following haematology rebalancing, we introduced single dose 400mg/day Imatinib therapy that enabled our patient to obtain hematologic remission (CHR), based on ELN guidelines, while bone marrow biopsy displayed chronic CML with 4% myeloblasts. (figure 2)

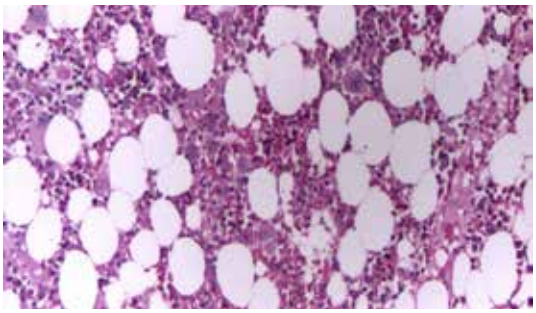

Figure 2. Bone marrow biopsy at 4 months after starting therapy with Imatinib

The patient continued therapy with Imatinib but adjusted the doses (300-400 mg/day) and, temporarily, she even discontinued therapy due to treatment induced anaemia and leukopenia, with hepatic cytolytic syndrome. Considering that after six months of therapy our patient presented minor cytogenetic response (44,44% Ph+ marrow cell metaphases) that was no longer present at the nine months assessment (100% Ph+ metaphases), we decided to introduce second generation TKIs : primarily Dasatinib 140 mg/day, at a later phase 100 mg/day. The loss of cytogenetic response to first generation TKIs in a young patient made us look for a match donor, in view of a possible allotransplant.

Dasatinib is known to have a 325 higher inhibitor activity on tyrosine kinase than Imatinib and is also very active in all Imatinib resistance mutations, except for BCR-ABL T 315I kinase domain [5,7].

In December 2008, at six months after the new therapy initiation, our patient presented complete cytogenetic response (0 Ph+ metaphases) and obtained major molecular response (0.019% BCR-ABL1 transcripts level) after one year of second generation TKI therapy. The cytogenetic assessment performed in 2010 revealed the occurrence of a major route clonal abnormality with significant prognostic value: trisomy 8 present in 23% of assessed metaphases and no Ph+ metaphases. (figure 3)

Figure 3. Cytogenetic assessment by chromosome banding technique (CBA) of bone marrow cell : no Ph+ metaphases, trisomy 8 present

The absence of Ph+ metaphases was confirmed through cytogenetic assessment by fluorescence in situ hybridization of interphase nuclei (I-FISH) : no identification of BCR-ALB+ nuclei. (figura 4)

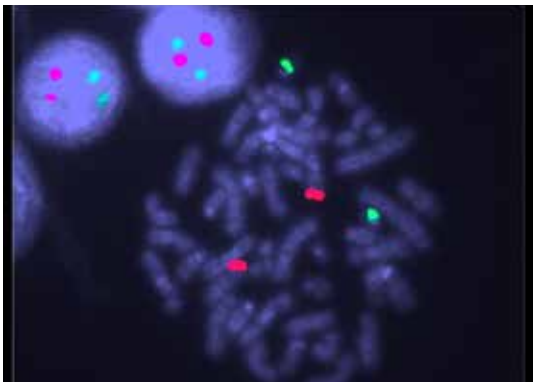

Figure 4. Interphase FISH patterns of BCR/ABL - nuclei

Subsequent molecular assessments confirmed major molecular remission (MMR) until April 2012 when our patient was declared in complete molecular remission (undetectable BCR-ABL translocation).

Discussions

We opted to present this case due to its particularities in terms of disease onset and evolution under TKIs therapy.

First, our patient was very young at the time of diagnosis, a rare situation considering that chronic myeloid leukaemia often occurs in persons over 60 years of age. Another atypical aspect is the disease onset directly in an accelerated phase, with no sign of splenomegaly but with a high WBC count.

Poor evolution under Imatinib therapy was due either to adverse effects that generated a decrease and even discontinuation of therapeutic doses or due to suboptimal dosage for the accelerated debut phase. [14,15,16].

Second generation tyrosine-kinase inhibitor therapy obtained rapidly a CCR (complete cytogenetic response) and maintained it, despite the occurrence of a major route clonal cytogenic abnormality (CCA) with unfavourable prognosis. Clonal cytogenetic abnormalities in Ph– cells (CCA/Ph–) occur in a small number of patients (5% to 10%) and almost all of them, in the absence of dysplasia, do not seem to adversely affect outcome. The identification of trisomy 8 under therapy determined us to examine more frequently the peripheral blood morphology for cytopenia or dysplastic elements but the patient maintained haematological and cytogenetic responses and, even more, obtained molecular remission [16,17,21]

Data in literature suggest that shifting to a different TKI as well as using chemotherapy or investigational therapies offer limited possibilities during an accelerated or blastic phase of disease.

Allotransplant remains the best option for these patients, provided it is performed prior to progression to the blastic phase. Should our patient loose the complete cytogenetic response and the disease advances again to the accelerated phase we will also opt for it [18].

From another standpoint, TKI therapy can be administered for an indefinite period, but currently there are data that suggest Imatinib can be safely discontinued in patients with undetectable illness by molecular assessment for minimum two years. This contributes to the increase in the patients' quality of life and will probably represent the endpoint for future studies [19,20]

Taking into account her disease history, it is hard to predict whether our patient will continue being in remission so that she qualifies for a future study on Dasatinib discontinuation.

Conclusions

TKI therapy demonstrated its efficacy in a case with multiple unfavourable factors, identified both at onset and throughout the therapeutic course, despite the fact

that treatment for advanced or blastic stages is rather an unconquered territory.

Aknowledgements: *This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romania Government under the contract number POSDRU/159/1.5/S/137390/".The present article has been elaborated and written by Oana Patrinoiu, MD and third year PhD student since 2011, at UMF Carol Davila Bucharest, under the coordination of Prof. Dr. Anca Lupu, MD PhD- Hematology Department.*

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