THERAPEUTICAL APPROACH AND PROGNOSTIC FACTORS IN CHRONIC MYELOID LEUKEMIA

Patrinoiu Oana1

Abstract. Chronic myeloid leukemia is one of the most studied malignancy and also a very successful model of targeted oral therapy in cancer. Over the last decade, the majority of chronic phase CML patients treated with tyrosine kinase inhibitors (TKIs) enjoy excellent overall survival and disease-free survival. In the TKI era, complete cytogenetic response (CCyR) stands firmly as a response milestone affording critical protection against transforming disease. The odds of CCyR (0 Ph+ metaphases) at 12 or 18 month of treatment are lower for patients with higher Sokal risk score but once achieved it improves outcome. Also, a small increase of BCR-ABL transcript level at patients that achieved and maintain CCyR does not necessarily mean a change of therapy but a more careful follow-up. Allo-HSCT remains a vital therapeutic approach for patients with CP-CML that fail TKIs treatment and also for those diagnosed in a more advanced phase of disease.

Keywords: chronic myeloid leukemia, blastic phase, tyrosine kinase inhibitors, Allo-HSCT, complete cytogenetic response, BCR-ABL transcript level

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that accounts for around 15% of newly diagnosed cases of leukemia in adults. Central to the pathogenesis of CML is the fusion of the Abelson murine leukemia (ABL) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22, which results in expression of an oncprotein, termed BCR-ABL[1]. BCR-ABL is a constitutively active tyrosine kinase that promotes growth and replication through downstream pathways such as RAS, RAF, JUN kinase, MYC and STAT[2].

About 30 to 50% of patients with CML are asymptomatic, so the disease is found by routine physical examination or blood tests. Diagnosis is most commonly made during the CP but the patient can be found in a more advanced phase: accelerated phase (AP) or, rarely, blast phase (BP).

Leukostatic symptoms (dyspnea, drowsiness, loss of coordination, confusion) are uncommon in CP despite WBC counts exceeding 100x10³/µL. Splenomegaly is the most consistent physical sign in CML and is detected in 50 to 60% of cases[3,6].

The diagnosis of typical CML consists of documenting, in the setting of persistent unexplained leukocytosis, the presence of the Ph chromosome abnormality: the t(9;22)(q34;q11) by routine cytogenetics, or the Ph-related molecular BCR-ABL abnormalities by fluorescent in situ hybridization (FISH) or by molecular studies[4].

The Ph chromosome is usually present in 100% of metaphases, often as the only abnormality. A small percent of patients have the so called "major route abnormalities": additional chromosomal changes (CCA/Ph+) involving trisomy 8, trisomy Ph or 19, isochromosome 17, additional loss of material from 22q that have an adverse prognostic value[5].

Around eighty-five percent of patients have a typical t(9;22) and 5% have variant translocations which can be simple or complex (one or more chromosomes in addition to those already involved); patients with Ph variants have response to therapy and prognosis similar to Ph-positive CML.

Until a little more than a decade ago treatment for CML was limited to nonspecific agents such as busulfan, hydroxyurea, and interferon-alfa (INF-a) [10]. INF-a led to regression of the disease and improved survival but had a lot of toxicities.

Allogeneic stem cell transplantation (AlloSCT) was the curative intervention for patients with a very good performance status and an appropriate stem cell donor but carries with it a high risk of morbidity and mortality[5,6].

Tyrosine kinase inhibitors (TKIs) represent a "targeted" approach developed to exploit the presence of the aberrantly expressed BCR-ABL protein in CML cells. They revolutionized dramatically the treatment of CML and changed the natural history of the disease, improving 10-year overall survival (OS) from almost
20 to 80–90%[1,6]. Tyrosine kinase inhibitors have proven ability to reduce clonal disease burden rapidly, significantly and durably, especially in the chronic phase of the disease. CML therapy with TKIs represents a paradigm for cancer treatment based on some facts: they are the initial oral therapy administered indefinitely (maintenance of intial induction therapy) in the presence of response, with the potential of a very deep remission in almost half of patients[7].

The response to TKI treatment, monitored every 3 months at first, is now considered the most important prognostic factor for patients with CP-CML[5]. This is the reason that the definition of the response is very well established by European LeukemiaNet (ELN) even since 2006. The newest one, from 2013, include optimal response and failure, irrespective of the TKI used in frontline. Any response in between is designed as warning[5].

**Treatment Options**

Three TKIs are available for the frontline treatment of CML and these include imatinib, dasatinib, and nilotinib. Current guidelines endorse all three as viable options for the initial management of CML in the chronic phase (CML-CP).

![Table I. Efficacy Data for Studies of BCR-ABL Inhibitors in the First-Line Treatment of CML-CP [6]](image)

<table>
<thead>
<tr>
<th>Study</th>
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**Imatinib mesylate** was the first TKI for the treatment of patients with CML-CP. It acts via competitive inhibition at the ATP-binding site of the BCR-ABL protein, so results in the inhibition of phosphorylation of proteins involved in cell signal transduction. It efficiently inhibits the BCR-ABL kinase, but also blocks the platelet-derived growth factor receptor (PDGFR), as well as the C-KIT tyrosine kinase[15].

The results using Imatinib are quite impressive but only 55% of patients enrolled in the IRIS study remained on therapy at the 8-year follow up point. This led to the development of 2nd generation TKIs[8].

**Dasatinib** is an oral, 2nd generation TKI that is 350 times more potent than Imatinib in vitro. Dasatinib induced more major molecular responses (MMR) compared to the Imatinib group in the DASISION trial and, with 18 months of follow up, the benefits of dasatinib persisted[9,10].

**Nilotinib** is a structural analog of Imatinib with affinity for the ATP binding site on BCR-ABL up to 50 times more potent in vitro[23]. At first, like Dasatinib, it induced hematologic and cytogenetic responses in patients who had failed Imatinib. After that followed studies regarding nilotinib’s potential role in the frontline setting.

At 36 months of follow up, the benefits conferred by Nilotinib persisted[11,12].

Current guidelines recommend any of the three TKIs as options for the initial treatment of CML-CP[5,6]. Second generation TKIs have shown inducing higher rates of early optimal responses; their impact on long-term over survival remains to be determined.

What is certain is that STIM study on Imatinib showed that for nearly half patients that were in CCyR and CMR for more than 2 years it was possible to stop treatment and maintain the response[19].

**Bosutinib** and **Ponatinib** were approved more recently for second- or subsequent line treatment of CML patients intolerant of or in whom Imatinib treatment failed, based on two phase 2, single-arm studies reporting MCyR rates of more than 56% and CCyR rates of more than 46% in imatinib-resistant patients.

Ponatinib had higher rates of response in patients with a shorter history of disease and/or with the T315I mutation (PACE study)[13].

Allo-HSCT remains the therapeutic option for 20 to 80–90%[1,6]. Tyrosine kinase inhibitors have proven ability to reduce clonal disease burden rapidly, significantly and durably, especially in the chronic phase of the disease. CML therapy with TKIs represents a paradigm for cancer treatment based on some facts: they are the initial oral therapy administered indefinitely (maintenance of initial induction therapy) in the presence of response, with the potential of a very deep remission in almost half of patients[7].

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**Table II. Treatment strategy recommendations for CML in AP or BP (ELN 2013)**

| AP and BP in newly diagnosed, TKI-naıve patients | Imatinib 400 mg twice daily or Dasatinib 70 mg twice daily or 140 mg once daily. Stem cell donor search. Then, alloSCT is recommended for all BP patients and for the AP patients who do not achieve an optimal response. Chemotherapy may be required before alloSCT to control the disease.
| AP and BP as a progression from CP in TKI-pretreated patients | Anyone of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients. Chemotherapy is frequently required to make patients eligible for alloSCT. |
CML-CP in the following situations: presence of T315I mutation and failure of 2nd generation TKIs.[14]

In addition to that. Allo HSCT is indicated as an important treatment option for all newly diagnosed BP patients and AP patients that do not achieve an optimal response[5,15].

This are very rare situations but the approach and prognostic is different.

**Case presentation**

As an example I will present the case of a 41 years old women without significant medical history, that was admitted in our Hematology Department in April 2012 with normochromic normocytic anemia (Hb = 7,42 g/dl) and normal white blood count. Peripheral blood morphology reveals the presence of myeloblasts (15%) and no metamyelocytes or myelocytes. We performed a bone marrow aspirate that showed rich marrow cellularity with left deviation of the leukocyte formula and 22% marrow blasts, some with Auer rods. Spleen size is normal but Sokal score is 2.3 (high score). This added to the advanced phase of disease at baseline indicate two poor prognostic factors.

By flow cytometry the majority of the marrow blasts express myeloid-associated antigens as in acute myeloid leukemia with maturation (AML FAB 2); the cytogenetic and molecular biology analysis showed 48% Ph+ metaphases of the analyzed nuclei and 16.755% BCR-ABL1 transcript level.

The diagnosis in this case is chronic myeloid leukemia -blastic phase at onset and we initiated induction treatment (intensive chemotherapy) with Cytarabine and Mitoxantrone. After 5 days of treatment the patient developed agranulocytosis and persistent fever. The radiography showed left lower lobe pneumonia. We decided to discontinue cytostatic therapy and escalated antibiotics treatment; the patient progresses favourably with the remission of symptoms and reduction of marrow blasts as in chronic phase. Simultaneously the patient started treatment with Imatinib 400mg twice daily. At that moment, in our country, Imatinib was the only TKI approved in first line. The patient was informed that an Allo-HSCT is indicated in her case but she had no compatible donor in her family so it was her wish to continue oral treatment. Stem cell donor search continued in the international data base.

After one month of treatment with Imatinib the patient developed intense muscle pain, predominantly in her thighs, so we reduced the dose to 400mg daily; the molecular and cytogenetic exams performed at 3 months from diagnosis revealed complete cytogenetic response (0 Ph+ metaphases) and MMR (0.05% BCR-ABL1 transcripts level), according to the monitoring guidelines by ELN[5]. An early molecular response (<10% BCR-ABL1 transcript level) in addition to a major cytogenetic response (MCR) by 3 months of therapy define the optimal response for patients under TKI treatment, especially those in CP-CML. This new concept of response, EMR, is mentioned in multiple recent reports that confirm the 10% threshold and emphasized its prognostic value so soon after diagnosis[5,7].

Our patient continued evolving favourably until February last year when the last three determinations of BCR-ABL transcript level have increased slowly. She was asked first about compliance, since it is well known that lower adherence rate means worse outcome[16]. Also drug-drug interaction was ruled out. The patient was told again about the necessity to perform an Allo-HSCT, but her wish was to postpone it. Since February the Imatinib dose was increased to 600mg daily.

The cytogenetic exam performed in July and October last year indicated no Ph+ metaphases (CCR) and no additional clonal chromosomal abnormalities (CCAs). In the absence of cytopenias or dysplastic peripheral blood morphology, the CCA/Ph− do not seem to adversely influence the outcome if chromosome 7 is not involved[17]. On the other side, point mutations in the kinase domain of BCR-ABL is one of the most common mechanisms of resistance to treatment in CML and they are detectable in almost 50% of patients with treatment failure and progression. In association with resistance to imatinib more than 80 amino acid substitutions have been reported.

In vitro studies have shown that some mutations confer resistance specifically to one 2nd generation TKI. For example, T315A, V299L, and F359V confer resistance to Dasatinib only, whereas Y253H, E255K/V, L273M, and F359V specifically to Nilotinib [18].

The mutation T315I it is known as the “gatekeeper” mutation as it causes resistance to all three TKIs[5,6,13]. The exam of T315I mutation done in February was also negative.

**Discussions**

Some patients appear to have rising levels of BCR-ABL transcripts while maintaining a CCyR. This may indicate an increased risk for TKI resistance by development of mutations. However, this value should be considered with caution because a small increase in BCR-ABL transcript levels does not necessarily indicate treatment failure or loss of response. If a patient who has previously achieved a MMR is noted to have a 1 log or fivefold increase in BCR-ABL transcripts, the molecular analysis should be repeated in 1–3 months. If confirmed, a bone marrow aspirate should be done to evaluate for loss of CyR,
since this is still one of the most important goals of treatment. The loss of a CHR or CCyR or clonal evolution during treatment at any time is considered treatment failure, while patients who achieve and maintain CCyR seem to have a low probability of eventually progressing[6].

For our patient the cytogenetic exam will be performed again in January 2015 and in case of Imatinib-resistance and loss of CCR the decisions will be made accordingly.

Hopefully the patient will finally accept allo-HSCT as the only curative option, given the adverse prognostic factors from diagnosis.

Otherwise the switch to a 2nd generation TKI has to take into account the safety and tolerability of the chosen drug. Also very important for the patient are the side effects of the previous treatment and the comorbidities that can be of concern with different TKIs.

Both Dasatinib and Nilotinib are available at this point, in our country, for both front or second line of treatment.

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References
19. Mahon FX, Rea D, Guilhot J et al. Discontinuation of Imatinib in patients with chronic myeloid leukemia who have maintained complete molecular response remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial; Lancet Oncol 2010;118:1208-1215.