Analysis of the pharmacotherapeutic effectiveness of the tyrosine kinase inhibitors therapy in patients with Chronic Myeloid Leukemia in a single hematology center in Plovdiv, Bulgaria

Veselina Goranova-Marinova¹, Daniela Grekova¹, Vania Georgieva², Kalina Andreevska³, Yana Gvozdeva¹,⁴, Margarita Kassarova¹, Zhanet Grudeva-Popova¹

¹ Medical University Plovdiv, Plovdiv, Bulgaria
² Prof. Assen Zlatarov University, Burgas, Bulgaria
³ Sofia University "St. Kliment Ohridski", Sofia, Bulgaria
⁴ Research Institute at Medical University of Plovdiv, Plovdiv, Bulgaria

Corresponding author: Veselina Goranova-Marinova (veselina.goranova@mu-plovdiv.bg)

Received 30 August 2023 ♦ Accepted 3 October 2023 ♦ Published 21 November 2023

Citation: Goranova-Marinova V, Grekova D, Georgieva V, Andreevska K, Gvozdeva Y, Kassarova M, Grudeva-Popova Z (2023) Analysis of the pharmacotherapeutic effectiveness of the tyrosine kinase inhibitors therapy in patients with Chronic Myeloid Leukemia in a single hematology center in Plovdiv, Bulgaria. Pharmacia 70(4): 1355–1362. https://doi.org/10.3897/pharmacia.70.e111923

Abstract

Aim. The aim of this study is to evaluate treatment retrospectively, response to the therapy and outcomes in patients with chronic myeloid leukemia (CML) and to what extent the European recommendations of LeukemiaNET (ELN) are followed at the Hematology Clinic, University Hospital "St. Georgi", MU Plovdiv.

Methods. All patients with Ph+, BCR-ABL1+ CML who were treated and observed between 01.01.2018 and 12.31.2022 at the clinic were included in the study and were analyzed retrospectively.

Results. One hundred and eighty-eight patients with a mean age of 61.26 (21–91) years were analyzed. 151 (80.3%) were in chronic phase (CP), 27 (14.4%) in accelerating one and 10 (5.3%) in blast crisis. The actual overall survival rate was 79.26%, while for CP it is very high – 86.75%, and the mortality rate is 20.74%. All patients received some form of tyrosine kinase inhibitors therapy (TKIs-therapy). The first line TKI was imatinib in 120 patients (64%), and 68 (36%) received a second-generation TKI. Treatment response was monitored with TKIs by RT-qPCR.

Conclusion. CML patients treated in the hematology clinic receive standard care in accordance with ELN and BMSH recommendations. Overall survival (OS) in routine care is comparable to published data from international studies. Molecular monitoring provides a good basis for disease control in CP. There are unmet needs in the treatment of patients in advanced stages.

Keywords

Chronic myeloid leukemia, Tyrosine kinase inhibitors, molecular response to therapy, pharmacoeffectiveness
Introduction

Chronic myeloid leukemia (CML) was first described in 1840s initially in France and short afterwards in Edinburgh and Berlin (Geary 2000; Deininger 2008). Historically the therapeutic options included radiotherapy, chemotherapy, interferon-alpha and in the 1980s allogeneic stem cell transplantation (Pavlovsky et al. 2009). Critical achievements in the understanding of the biological basis of the disease were the discovery of the Philadelphia (Ph) chromosome in 1960, the characterization of the breakpoint cluster region on chromosome 22 in 1984, and the demonstration of BCR-ABL (now renamed BCR-ABL1) fusion gene in 1986. These crucial steps led to the successful development of a 2-phenyl-aminopyrimidine compound, now known as imatinib mesylate or simply imatinib, which inhibited the kinase activity of the BCR-ABL1 oncprotein and was first used in the clinic for a treatment of patients with CML resistant to interferon alfa in 1998 (Druker et al. 2001). The team that developed and brought into clinical practice the first tyrosine kinase inhibitor (TKI) imatinib to treat CML included Alex Matter and Brian Druker (physicians), Jurg Zimmermann (chemist), Elizabeth Buchdunger (biologist) and Nick Lydon (researcher).

Dramatic improvement in CML therapy has been the introduction of imatinib, which was approved by FDA in the US and EMA for the treatment of patients with CML in November 2001 (Reilly 2002; Druker et al. 2006; Deininger et al. 2009; Hasford et al. 2011; Baccarani et al. 2006, 2013). In Bulgaria, CML is mostly diagnosed in the chronic phase due to frequent routine blood count analyses by general practitioners. The referral to a hematologist for additional diagnostic work – up is fast and takes from several days to one or two weeks. With this study, we look for answers of the following questions:

1. Are the recommendations of Leukemianet and the Bulgarian Medical Association of Hematology followed?
2. What is the outcome of patients with CML in terms of OS and progression-free survival (PFS) in conditions of routine medical care in our country?
3. What is the death rate from CML?
4. How clinically effective is the patient’s therapy by determining the molecular response to TKI therapy?

Aim

TKIs are highly effective in the treatment of newly diagnosed chronic myeloid leukemia (CML) patients in CP. Most of the available data, which are frequently cited in the specialized literature, come from multicenter studies in which some of the patients were censored for various reasons. Here, we report the Bulgarian experience in the treatment of CML patients at a single institution in a setting where almost all events are documented.

Materials and methods

All patients with Philadelphia chromosome-positive and/or BCR-ABL1-positive CML who were diagnosed and treated between 1.01.2018 and 31.12.2022 in the the Hematology Clinic, University Hospital “Sv.Georgi” at MU-Plovdiv were included in the study. Statistical analysis was performed using SPSS 20 and Excel 19. Written informed consent was obtained from all patients for data documentation, processing, analysis and publication during the diagnosis and treatment of CML. At diagnosis, the following data were collected: date of birth, sex, date of diagnosis, method of diagnosis, source of material (bone marrow versus peripheral blood), phase of the disease (chronic and accelerated phase, blast crisis) (Baccarani et al. 2006, 2013). Data during therapy are: type of TKI therapy (imatinib, nilotinib, dasatinib, bosutinib, ponatinib), duration of each therapy, lines of therapy defined as any change in therapeutic regimen, mutational analysis, molecular response assessment during of therapy (QPCR for BCR ABL1) according to European Leukemianet recommendations (Baccarani et al. 2006, 2013), classified as major (MMR), deep (DMR) and very deep (VDMR) molecular response. Date of death was also recorded and survival analysis was performed.

Results

The demographic characteristics of the patients at the time of diagnosis are illustrated in Table 1. Currently, 520 patients with chronic myeloid leukemia are being treated in Bulgaria, distributed in nine hematological centers, situated in Sofia, Plovdiv, Varna and Pleven. The 188 patients with CML included in the study are a representative sample of all CML patients in Bulgaria. A total of 188 patients with a mean age of 61.26 years (21–91) were documented. The distribution of patients by age group is as follows: in the group of young people aged 18–40 there are 19 patients (10.1%), in the group of 41–65 (working age) there are 89 patients (47.3%) and in the third group over 65 years old is 80 patients (42.6%). From a total of 188 patients, 96 (51.1%) were women with an average age of 62.03 years (30–91) and 92 (48.9%) were men with an average age of 60.52 years (30–91). At initial diagnosis: 151 patients (80.3%) were in the chronic phase, of which 79 patients (52.3%) were women and 72 patients (47.7%) were men; 27 patients (14.4%) were in an accelerating phase, of which 10 patients (37%) were women and 17 patients (63%) were men; and 10 patients (5.3%) were in blast crisis, of which 7 patients (70%) were women and 3 patients (30%) were men. Median follow-up was 80 months (range 3–226 months). At the end of the follow-up period of all
188 patients, 149 are alive, of which 78 are women and 71 are men. The number of deceased is 39, of which 18 are women and 21 are men. The actuarial overall survival rate was 79.26% and the mortality rate was 20.74%. The lower average survival of patients in accelerating phase -59.26% and especially in blast phase 20% negatively affects overall survival, while for chronic phase it is very high-86.75%.

Analysis for overall survival (OS) and progression-free survival (PFS) were performed. OS was defined as survival from diagnosis to death or last contact and PFS was defined as survival without progression to accelerated phase (AP) or blast phase (BP) or death or last contact. All the patients with CML documented in the period 2018 -2022 and treated with any TKI, regardless of disease phase were included in the analysis. Statistical methods were descriptive, specific hypotheses were not tested. OS and PFS were calculated using the Kaplan–Meier method. They are presented in Figs 1, 2 by gender and by age group and cumulative overall survival, and in Fig. 3 – survival without disease progression in the first line of treatment compared with overall cumulative survival including disease progression with subsequent therapy.

We can conclude that a large part of first line patients live without disease progression, and in case of progression, the subsequent treatment with second, third, etc. lines again gives reliable high survival.
Bonifaci F et al to achieve durable CCyR that persisted with interferon-alpha in the 1990s have been reported by as treatment options. A small number of patients treated stem cell transplantation, and clinical trial enrollment mends for the T315I mutation omacetaxine, allogeneic
Ponatinib: T315I. The NCCN guidelines also recom-
F359V/C/I Nilotinib: F317L/V/I/C, T315A, or V299L; Dasatinib: Y253H, E255K/V; or
C/I, T315A, or Y253H; Dasatinib: Y253H, E255K/V; or
Bosutinib: E255K/V; F317L/V/I/C, F359V/
NCCN (US National Comprehensive Cancer Network
TKI may be most likely to be effective in resistance. The
1358
Garanova-Marinova V et al.: Pharmacotherapeutic effectiveness of the TTKIs in CML
piec (33.33%), nilotinib 400mg in 2 therapies (11.11%),
and 18 TKI therapies consisted of nilotinib in 6 thera-
tinib 400mg in 12 therapies (18.2%), imatinib in 31 thera-
sions (13.6%), nilotinib in 13 therapies (19.7%), nilo-
400mg day, and 44 patients (40%) received a second generation TKI [38 patients (34.5%) –
6 patients (5.5%) – dasatinib]. The question arises whether one of the new TKIs should be used instead of imatinib as initial therapy in patients with early chronic
phases (38 patients (38.6%) – dasatinib]. The question arises whether one of the new TKIs should be used instead of imatinib as initial therapy in patients with early chronic
175 patients with CML received TKI as first line ther-
apy of patients with CML
Main characteristics of the drug thera-
py of patients with CML
All 188 patients (100%) received some form of TKI thera-
py. 175 patients with CML received TKI as first line ther-
apy, and only 13 patients, most diagnosed in the period 2001–2007, received another form of therapy before the prescription of TKI. In the event of toxicity, the treatment of the patients was changed. The study did not specifically analyze the adverse drug reactions (ADRs) observed in the patients, as they are described in the summary of each TKI medicine and were overcome following the guidelines of the Bulgarian Society of Hematology (Micheva 2022).
Presence of additional mutations in the kinase domain of the BCR-ABL1 gene may lead to therapeutic resistance with subsequent change of therapy and initiation of therapy with another TKI. The most important from a therapeutic point of view are the T315I and P-loop mutations. The T315I mutation is unique because of its resistance to most approved TKIs – IMA, NIL, DAS, BOS. Every 6 of 9 cases of advanced CML that was IMA-resistant was found to be due to the T315I mutation (Pavlovsky et al. 2009). The only TKI that was approved in 2013, for use as a second-line treatment for CML with the T315I mutation is PON. In our study, there was a confirmed T315I mutation in 10 patients, of which 4 men in AP and 4 women and 2 men in CP. There are thousands of possible mutation points, but the most common have been tested in vitro, and the tables show to which TKI an individual mutation is sensitive. This may help clinicians decide which TKI may be most likely to be effective in resistance. The NCCN (US National Comprehensive Cancer Network – www.NCCN.org) treatment recommendations for BCR-ABL1 mutation profiles in patients with CML are as follows: Bosutinib: E255K/V; F317L/V/I/C, F359V/C/I, T315A, or Y253H; Dasatinib: Y253H, E255K/V; or F359V/C/I Nilotinib: F317L/V/I/C, T315A, or V299L; Ponatinib: T315I. The NCCN guidelines also recommends for the T315I mutation omacetaxine, allogeneic stem cell transplantation, and clinical trial enrollment as treatment options. A small number of patients treated with interferon-alpha in the 1990s have been reported by Bonifaci F et al to achieve durable CCyR that persisted for many years after interferon discontinuation (Bonifazi et al. 2001). In 2007, Rousselot and colleagues first reported details of 12 CML patients in France who received imatinib as first line treatment or after prior interferon treatment and achieved a complete molecular response (CMR) (Rousselot et al. 2007). For various reasons, these patients stopped imatinib and after 2 or more years were still in CMR, 6 had relapsed at the molecular level, and 6 were still in CMR at the time of report (Rousselot et al. 2007). Fortunately, patients who relapse at the molecular level respond to re-introduction of imatinib just as well as when initially started (Goh et al. 2009). A French study of 12 patients in 2007 (Rousselot et al. 2007) has extended and equivalent data in 70 patients who stopped imatinib and after 2 or more years have been in complete molecular response (CMR). Data are accumulating data, proving that a certain number of patients who take TKIs for an extended period of time and achieve and maintain deep molecular responses are able to stop the drug without evidence of relapse over the next several years (Mahon et al. 2013; Saussele et al. 2018). The main goal today is to find therapeutic strategies that allow increasing the proportion of patients who can safely stop treatment. There are such patients in the hematology clinic at University Hospital “St. George” in Plovdiv.
Main characteristics of the drug therapy of patients with CML-CP
Over 2/3 of all CML patients are in the chronic phase – a total of 151 patients (80.3%), and this is the reason for our decision to analyze them separately. 110 patients with CML-CF received first line TKI treatments, as 66 of them (60%) received imatinib 400 mg/day, and 44 patients (40%) received a second generation TKI [38 patients (34.5%) – nilotinib and 6 patients (5.5%) – dasatinib]. The question arises whether one of the new TKIs should be used instead of imatinib as initial therapy in patients with early chronic phase (ECP). Approved for first line therapy are imatinib – first generation and second generation TKIs: nilotinib, bosutinib and dasatinib. The goal is all affected patients to survive with a normal quality of life (Deininger et al. 2003). The second generation TKIs have been shown as first line to result in faster and deeper molecular remissions (MR 4–5 log) and show improved efficacy as compared with imatinib. Therefore, second generation TKIs are also recommended as first line therapy in the updated guidelines and are actually used in the clinic as first line therapy in 40% of CP patients (Baccarani et al. 2006, 2013). Imatinib and dasatinib are the TKIs of choice for patients with CML-CP at very high cardiovascular risk.
Second-line TKI treatment in 33 CML-CP patients (21.9%) with 66 TKI therapies consisted of dasatinib in 9 therapies (13.6%), nilotinib in 13 therapies (19.7%), nilotinib 400mg in 12 therapies (18.2%), imatinib in 31 therapies (47%) and bosutinib in 1 therapy (1.5%).
Third line TKI treatment in 6 CML-CP patients (3.97%) and 18 TKI therapies consisted of nilotinib in 6 therapies (33.33%), nilotinib 400mg in 2 therapies (11.11%),
Dasatinib in 3 therapies (16.67%), imatinib 400 mg in 4 (22.22%), and bosutinib in 3 therapies (16.67%).

The fourth line of TKI treatment in 2 patients (1.33%) consisted of 8 TKI therapies: nilotinib in 2 therapies (25%), imatinib, bosutinib and ponatinib in 1 therapy each (12.5%), and dasatinib in 3 therapies (37.5%). In total, the 151 patients with CML-CP received 202 TKI-therapies (110 TKI-therapies in the first line, 66 TKI therapies in the second line, and 26 therapies in the following lines). The mean number of lines of TKI therapies per patient was 1.34 (1–4). Reasons for switching TKI therapy were ADRs, resistance, or intolerance. In the total number of patients with CML, 37 patients (19.7%) who were diagnosed with advanced phases of CML were included in this study, of which 27 (73%) were in AP (10 women and 17 men) and 10 patients (27%) were in BP (7 women and 3 men). For patients in advanced phases (accelerated and blast phase) the initial dose of imatinib is 600–800 mg daily or higher, preferably second generation TKIs are recommended. The long term outcome of such patients is much worse compared with those in the chronic phase. Patients who meet the criteria for an accelerating phase are actually heterogeneous; at one end of the spectrum, the term encompasses patients whose leukemia is only slightly more advanced than late chronic phase, while at the other end of the spectrum, leukemia may border on blast phase. Patients with an “early” accelerating phase may have long term responses to imatinib as monotherapy, while others may have much shorter responses.

Patients presenting in the blast phase (BP), however, require a much more aggressive initial strategy (Ottmann and Wassmann 2005; Thomas 2007). They can start treatment with imatinib, but dasatinib with its broader spectrum of activity against SRC and SRC family kinases is the preferred option. For patients in lymphoid BPh, extrapolation from results obtained in the treatment of Ph-positive acute lymphoblastic leukemia (ALL) (Ottmann and Wassmann 2005; Thomas 2007) suggests that combining TKI with cytotoxic drugs together with TKI is recommended. For patients with myeloid BP, the combined use of TKIs with chemo-therapeutical protocols for acute myeloid leukemia (AML) may be the best approach (Ottmann and Wassmann 2005; Thomas 2007). In BPh, the relapse rate is high and these patients are candidates for allogeneic stem cell transplantation (allo-SCT) while in best response. It is logical to continue the use of TKI after allo-SCT. A typical feature of patients in BP of CML, in contrast to patients in CP, can very quickly go from very deep MR to overt relapse, which is why molecular monitoring should be performed at much more frequent intervals than in patients treated in the early chronic phase (Jain et al. 2017). The main characteristics of the drug therapy of all 188 CML patients in CP, AP and BP included in the analysis are presented in Fig. 4. The share of Imatinib in the treatment of 188 patients is the highest (48.7%), which is the result of its most frequent prescription as a first line of therapy (63.8%). In second place in use is Nilotinib, respectively with 33.9% in the therapy of all CML patients and 27.7% as first line therapy. Ponatinib was the least used in three therapies as fourth line and in one therapy as second line, which is logical for the small number of confirmed cases of the T135I mutation.

The share of Imatinib in the treatment of 188 patients is the highest (48.7%), which is the result of its most frequent prescription as a first line of therapy (63.8%). In second place in use is Nilotinib, respectively with 33.9% in the therapy of all CML patients and 27.7% as first line therapy. Ponatinib was the least used in three therapies as fourth line and in one therapy as second line, which is logical for the small number of confirmed cases of the T135I mutation.

**Evaluation of therapeutic effectiveness by the achieved molecular response to therapy**

The most sensitive test available for low grade leukemia is to measure the number of BCR-ABL1 transcripts in blood or bone marrow using real time quantitative transcriptase PCR (RT-qPCR). Molecular response to TKI therapy was defined as: major molecular response (MMR 3log); deep molecular response (DMR 4 or 4.5log); and very deep molecular response (VDMR 5log) (Cross et al. 2008). Also according to the definitions of failure and suboptimal response to TKIs proposed by the European Leukemia Network (ELN), these responses were calculated at 12 months (Van Dongen et al. 1999). In the hematology clinic, RT-qPCR and MR were observed during the first year of TKI therapy every 3 months, in the second year – every 6 months and in the third year – once a year.

**Table 2.** Molecular response to TKI therapy – Logarithmic reduction of the BCR-ABL/ABL ratio.

<table>
<thead>
<tr>
<th>Logarithmic reduction of the BCR-ABL/ABL ratio</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>no molecular response</td>
<td>58</td>
<td>29.7</td>
</tr>
<tr>
<td>3 Log reduction (MMR)</td>
<td>24</td>
<td>12.3</td>
</tr>
<tr>
<td>4 or 4.5 Log reduction(DMR)</td>
<td>70</td>
<td>35.9</td>
</tr>
<tr>
<td>5 Log reduction(VDMR)</td>
<td>43</td>
<td>22.1</td>
</tr>
<tr>
<td>Total</td>
<td>195</td>
<td>100</td>
</tr>
</tbody>
</table>
Main characteristics of first-line therapy

For 151 patients in CP of CML, 202 TKI-therapies were administered and 162 (83%) RT-qPCR and MR were performed. For 3 of them, there is no data on the phase of the disease in the medical documentation of the clinic, but since they are on the first line of therapy and have an excellent response to it, we included them in the CP of CML.

For 37 patients in advanced phases of CML (AAP and BP), 59 TKI-therapies were used and 33 RT-qPCR and MR analyses were performed, i.e. more than ½ of the treatments were observed with RT-qPCR and MR (56%). In our study, from a total of 188 patients treated with 261 TKI therapies and followed up in the Hematology Clinic, 3 patients had molecular variants of the disease in which the achieved response to the therapy could not be quantitatively monitored due to the lack of a standardized molecular genetic method. For the remaining 185 patients, 258 TKI therapies were administered and these were monitored and evaluated with 195 RT-qPCR and MR analyses (75.6%). The percentage of analyses is less than 100 because the results are reflected in the electronic system with the patients’ data correctly only from the beginning of 2017, until now. The molecular response to first line therapy included 109 analyses for CML – CP patients, 16 for AP patients, and 4 for BP patients, or a total of 129 MR, in second line therapy respectively 45 for CP patients, 9 in AP and 3 in BP or a total of 57 MR and for third line therapy 8 for patients in CP and 1 in AP, or a total of 9 MR. Results are presented graphically in Figs 5, 6.

Molecular studies are an integral part of monitoring the therapy of chronic myeloid leukemia. It begins with them to confirm the diagnosis and to determine the target treatment and continues throughout the treatment period. The research is important because it can detect very small amounts of leukemic cells, and this is precisely what allows a personalized approach to the treatment of cancer patients. In this way, as early as the third month, an answer can be given to the question of which patient responds well to the therapy and who does not, in whom another medicinal product should be included to guarantee a better result (Baccarani et al. 2012b; Mahon et al. 2013). The fall of leukemic cells below 0.1% indicates that no progression of the disease can be expected, and their complete clearing already speaks of a permanent remission. The tests help to keep the situation under control, and they continue even after the stage of cessation of the disease. In this study, an MMR (3 log reduction) of 12.8% was achieved. A deep and very deep molecular response was observed in 60.1%, and these patients are candidates for discontinuation of therapy and monitoring at more frequent intervals during treatment-free remission. High levels of BCR-ABL transcripts predict absence or loss of molecular response. The relative non-response rate was 27.1%. The highest therapeutic efficacy was achieved with imatinib with longer treatment, followed by nilotinib and dasatinib. In case of failure (no MR or low levels of log reduction), its replacement with nilotinib or another second generation TKI leads to faster and better MRs in CML patients in CP. In the advanced phases of the disease, especially in BP and the presence of mutations regardless of one or two changes of therapy, the risk of loss of efficacy and fatal outcome remains high. Due to the limited evidence and still many unmet needs, it would be desirable for a dedicated expert panel to provide updated recommendations for the management of CML in advanced stages.

The molecular response is very good to TKI treatment with an increase in MR log 4–5. Patients achieving DMR and VDMR are possible candidates for treatment-free remission. It is considered that to be discontinued, treatment must have lasted at least 3 years and 1 year of deep molecular response. In the presented analysis, follow-up of MR of CML patients is mainly carried out with the gold standard RT-PCR in a laboratory centralized for the country. In the last 2 years, there has been a transition to monitoring the treatment effect with digital PCR (dPCR) at MU-Plovdiv. MR data are presented on the international scale. An advantage of dPCR is the possibility of absolute quantification of BCR-ABL1 at different levels of disease with remarkable precision and clinical sensitivity, as well as the fact that dPCR is a validated method for establishing minimal residual disease in intention to discontinue TKI treatment.

Novartis’ newly approved asciminib differs from currently approved ABL1 kinase inhibitors in that it does not bind to the ATP binding site of the kinase, but acts as an allosteric inhibitor binding to an empty pocket at a site in the kinase domain. The pocket is normally occupied by the myristoylated N-terminus of ABL1. By binding to the myristoyl site, the drug can mimic the effect of myristate and restore the inhibition of kinase activity. Due to the

Figure 5. The achieved molecular responses to the therapy with the 5 TKI products.

Figure 6. Molecular response /proportion of deep and very deep molecular response/ during TKI treatment.
unique conformation of the myristoyl pocket, ascinimib not only has high selectivity for ABL1 (and possibly ABL2 kinase), but targets both native and mutant BCR-ABL1, including the T315I mutant. With its introduction into practice, the probability of success in the treatment of CML patients increases.

Conclusions

Although the use of TKIs has led to better patient outcomes, CML is still not easy to cure. Quantification of residual disease by RT-qPCR is a reliable method for monitoring molecular response that provides critical analytical data for monitoring CML patients. The conclusion of our study is that regular molecular monitoring (every 3, 6, or 12 months) of BCR-ABL1 by RT-qPCR provides essential information to assess responses as well as to predict progression-free or relapse by time of TKI therapy in patients with CML. The high therapeutic efficiency is the result not only of the appropriate choice of TKI therapy, but to a much greater extent of the improved monitoring of the molecular response to it.

References


