Deep molecular response (MR4.5) as a target of therapy with tyrosine kinase inhibitors. MR4.5 – goal of CML treatment

Tomasz Sacha, MD PhD
Chair of Hematology, Collegium Medicum Jagiellonian University

ABSTRACT

Chronic myeloid leukemia (CML) accounts for 15% of diagnosed leukemias. The annual incidence in two Polish regions has been calculated for 0.7/100,000 of general population. Introduction of tyrosine kinase inhibitors (TKIs) have substantially improved not only the prognosis of CML, but also changed the treatment goals, and the expectations of patients and physicians. The goals of CML therapy include: to prevent the progression towards accelerated phase and blastic phase, to eliminate the risk of death from leukemia, to prolong the length of survival to comparable of healthy population and to attain a quality of life comparable to healthy people. Patients treated up-front with second generation TKIs (2GTKI) have a better chance to achieve faster and deeper response to therapy. Most of patients receiving 2GTKI in first line or e.g. nilotinib after initial phase of imatinib therapy can achieve very deep molecular response (MR4.5), which is a key criterion for discontinuation studies. The results of stop-trials suggest that substantial proportion of patient could achieve sustained treatment-free survival, and that the disease could be controlled despite of persistence of minimal residual disease, which does not require a clinical intervention. Patients group that could benefit most from discontinuation study include younger people, those who have achieved MR4.5 and patients reporting TKI – associated side effects. Achievement of MR4.5 could be considered as a target of CML therapy for considerable proportion of patients. The question of safe TKI dose reduction or therapy cessation should be addressed in the future planned clinical trials.

KEY WORDS: chronic myeloid leukemia, tyrosine kinase inhibitors, therapy targets, possibility cure

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder resulting from a recurrent chromosomal abnormality known as a *Philadelphia* chromosome occurring in pluripotential stem cells, detectable in more than 90% of patients. CML accounts for approximately 15% of diagnosed leukemias. The annual incidence assessed in the population of United States was reported of 1–2/100,000 [1]. One of the aims of the registry initiated within *The European Treatment Outcome Study* (EUTOS) in 2007 was to evaluate the most recent annual incidence of CML in European countries. Poland was divided into two regions with general population of about 5 million each. The data for the registry were collected by hematologists supervising the therapy with tyrosine kinase inhibitors (TKIs) in CML-centers, and additionally supplied by reference molecular laboratories, standardized in accord with *European Leukemia Net* regulations responsible for molecular diagnostics of CML in each region. The annual incidence of CML in both (North-Poland, and South-Poland) regions calculated after three years of data collection is approximately 0.7/100,000 of general population (data not published). Introduction of TKIs have substantially improved the prognosis of patients suffering from CML, and also have changed the treatment goals, and the expectations of patients and physicians. Patients randomized to imatinib arm of an *International Randomized Study of Interferon and STI571* (IRIS) comparing imatinib at a single daily dose 400 mg to IFNα plus cytarabine in newly diagnosed patients with CML in CP at 8-year data cut off continue to have a durable hematologic and cytogenetic responses, low progression rates to acceleration phase (AP) or blast crisis (BC), and remarkable survival outcomes. An overall survival (OS) rate is 85% for patients receiving imatinib and 93% if only CML--related deaths and those prior to stem cell transplantation are considered. The annual rates of progression to AP or BC are very low: 0.9%, 0.5%, 0%, 0%, and 0.4% (in year 4 to 8 after imatinib therapy onset, respectively). Of note, the progression to AP or BC was observed only in 3% of patients who achieved CCyR, and in none of patients who achieved major molecular response (MMR, < 0.1% *BCR-ABL1*/control gene ratio on international scale) at 12 months of therapy [2]. The absence of detectable *Philadelphia* chromosome (Ph) in majority of patients treated with TKI created the need for development of new monitoring tools for assessment of continuous decreasing burden of *BCR/ABL1* positive leukemic cells. The quantity of residual leukemia reflected by the *BCR-ABL1* transcript level is assessed in those patients by Real-Time Quantitative Polymerase Chain Reaction (RQ-PCR) which results are expressed as the log reduction from a baseline, standardized value for untreated patients, and recently by using the international scale (IS) which makes the results obtained by different laboratories more comparable [3, 4]. Table 1 lists the definitions for molecular response.

GOALS OF TARGETED THERAPY FOR CML

In the "pre-TKI era" the goals of CML therapy was to maintain the quality of live and to prolong the survival. The chance for cure was considered only for patients eligible to allogeneic stem cell transplantation (alloSCT). Nowadays, the goals are more complex; first of all it is the prevention of the progression to more advanced stages of the disease (AP/BC), to eliminate the risk of death from leukemia, secondly to prolong survival to comparable with survival length of healthy population, and finally to attain a quality of life comparable to healthy people. In order to predict more accurately the outcome of patients during the course of treatment with TKIs the surrogates of response to TKI therapy has been used since several years now. One of the most validated is complete cytogenetic response (CCyR), which is achieved at 12

TABLE 1.

Definitions of molecular responses.

***BCR/ABL1* (%) (International Scale)**	**MR**	**Comments**
0.1	MR3	Major Molecular Response = 3 log reduction from a standardized value for untreated patients, where 100% is the arbitrary value estimated at diagnosis
0.01	MR4	Either detectable disease ≤ 0.01% ***BCR/ABL1***^{IS} or undetectable disease in cDNA with ≥ 10,000 ***ABL*** or ≥ 24,000 ***GUSB*** transcripts
0.0032	MR4.5	Either detectable disease ≤ 0.0032% ***BCR/ABL1***^{IS} or undetectable disease in cDNA with ≥ 32,000 ***ABL*** or ≥ 77,000 ***GUSB*** transcripts
0.001	MR5	Either detectable disease ≤ 0.001% ***BCR/ABL1***^{IS} or undetectable disease in cDNA with ≥ 100,000 ***ABL*** or ≥ 240,000 ***GUSB*** transcripts

months by most of newly diagnosed patients treated with TKIs. The life expectancy in those good responders is supposed to be equal to healthy population. However in the analysis of data collected from 204 consecutive newly diagnosed at Hammersmith Hospital patients showed that 44% of them failed to achieve a CCyR at 12 months of imatinib therapy. Progression-free survival (PFS) and overall survival (OS) of those patients were lower than in those achieving CCyR at one year [9]. The other valuable surrogate marker is a major molecular response. The risk of progression for patients who achieved MMR at 18 months of TKI therapy is minimal during the next year of treatment [4]. Achievement of MMR is associated with improved outcome by 5 years of follow-up. The survival free from progression toward AC or BC was 100%, 98% and 87% in patients who achieved CCyR and MMR, CCyR without MMR, and did not achieved CCyR respectively [5]. The best observed rate of MMR achieved after 8-years of follow--up in the IRIS trial is 86%. Many other reports underlined the importance of achievement of MMR for improvement of event--free survival (EFS) and PFS [6–8]. In order to reduce the rate of resistance and suboptimal responses or treatment failures the second generation of tyrosine kinase inhibitors (2GTKI) in the first line therapy for CML has been introduced. The use of 2GTKI in first line setting increases the chance for faster and deeper response to therapy and improves the rates of CCyR, MMR and deep molecular response (DMR) which includes complete molecular response (CMR) and MR4.5 (molecular response with 4.5 log transcript reduction). Second generation of TKIs does not require to be transported actively into the cells by human cationic organic pump (hOCT-1). Low activity of this molecular pump could be the cause of low imatinib concentration inside leukemic cells and therefore is together with the high Sokal score considered as an independent adverse prognostic factor for achievement of MMR [10, 11]. At 36 months of therapy the second generation TKIs induced higher rates of therapeutic responses than imatinib did. The rates of CCyR achieved on imatinib, dasatinib and nilotinib therapy were 58%, 78% and 76% and rates of MMR were 44%, 76% and 73% respectively. Complete molecular response has been achieved by 32% of patients treated with imatinib, 52% of patients treated with dasatinib and 59% of patients receiving nilotinib [12]. By 5 years of ENESTnd trial the cumulative rates of MMR and MR4.5 were significantly higher in patients treated with nilotinib than with imatinib (77% vs. 60%, and 53–54% vs. 31% respectively). Better responses with nilotinib were achieved across all Sokal risk categories [13]. Moreover in the ENESTcmr trial higher rates of MR4.5 were achieved in patients who switched the therapy from imatinib to nilotinib than in patients who continued imatinib treatment. The response to nilotinib was better irrespectively from the level of molecular response achieved on imatinib before the switch [14]. Similar results were obtained during the DASISION trial. By 4 years dasatinib improved the rates of response if compared to imatinib, the cumulative rates of MMR, MR4 and MR4.5 were 76%, 53% and 37% respectively for patients treated with dasatinib, and 63%, 42% and 30% respectively for those who received imatinib [15]. In both trials the rates of PFS, EFS and OS were higher, and incidence of progression to AC or BC were lower in patients treated with 2GTKI [13, 15]. Similar results were achieved in other trials where EFS and transformation-free survival (TFS) were better in patients treated with dasatinib or nilotinib than in those receiving imatinib (91–95% vs. 85% and 97–100% vs. 89% respectively) [12]. There is a body of publications demonstrating the importance of early molecular response (EMR). The reduction of *BCR/ABL1* transcript to ≤ 10% at 3 months of TKI treatment was associated with better chance for achievement of MMR [13, 15–18], lower cumulative rate of treatment failure [18], and higher rates of PFS, OS [19], TFS, and time to second line therapy onset (TFSA) [20]. In the ENESTnd trial the rates of EMR achieved with nilotinib were higher than achieved with imatinib. The reduction of *BCR/ABL1* transcript to ≤ 10% (IS) and to ≤ 1% (IS) at 3 months was achieved in 91% and 56% patients treated with nilotinib and in 67% and 16% patients receiving imatinib [13]. In DASISION trial early reduction of *BCR/ABL1* transcript to ≤ 10% (IS) and to ≤ 1% (IS) was achieved in 84% and 64% of patients treated with dasatinib and in 50% and 15% of patients receiving imatinib respectively. Progression-free survival and overall survival calculated by 5 years for patients who failed to achieve the reduction of *BCR/ABL1* transcript to ≤ 10% (IS) at 3 months of TKI therapy within ENEStnd trial were significantly lower than for those with deeper reduction of *BCR/ABL1* transcript. Similar results were obtained within DASISION trial after 4 years of follow-up [15]. The of reduction of *BCR/ABL1* transcript to ≤ 1% (IS) at 3 months of TKI therapy can identify the group of patients with the best outcome. Those patients have the highest chance to achieve deep molecular response, which is the key entry criterion for TKI discontinuation studies. By 5 years of ENESTnd trial the rate of DMR was 70% in patients treated with nilotinib and 67% in patients receiving imatinib [13]. Etienne et al. demonstrated that patients who have achieved complete molecular response have better PFS and OS (120 months of follow-up) than those who achieved MMR only, without CMR (98% vs. 80%) [21], however the number of patients analyzed after 80 months of study duration was very low. Nine--year overall survival rate was improved (92% vs. 83%) in 26.4% of patients who achieved MR4.5, as compared to those who achieved the molecular response equivalent to CCyR only (the

level of *BCR/ABL1* transcript between 0.1% and 1% [IS]). By 4 years of this study MMR, and MR4 without MR4.5 was achieved by 34.8% and 25.5% of patients respectively [22].

COULD THE ACHIEVEMENT OF MR4.5 BE A REASONABLE TARGET OF CML THERAPY WITH TKIs?

The number of publications demonstrating the possibility to achieve an "operational cure" by patients suffering from CML treated with TKIs and the clinical experience with this group of patients is still growing. Publications describe the experience of more than 100 patients who had discontinued imatinib after achieving sustained (for at least 2 years) CMR defined as undetectable *BCR/ABL1* transcript with a detection threshold corresponding to 4.5 log with ≥ 50,000 copies of ABL gene co-amplified as an internal control [23–25]. Molecular relapse is defined as a positivity of *BCR/ABL1* transcript in quantitative RT-PCR confirmed by a second analysis point indicating the increase of one log in relation to the first analysis point, at two successive assessments, or loss of MMR at one point. After 8 years from the first inclusion into the STIM1 study the median follow-up is now 50 months (range 9–72) with a mean of 51 months. The cumulative rate of molecular relapses (60%) is maintained in the last analysis performed in July 2013. Of note, all but three molecular relapses (at month 19, 20 and 22) occurred within first 7 months from imatinib discontinuation. It has been demonstrated that high Sokal score, female sex and the duration of imatinib therapy < 50 months were independent adverse risk factors for molecular relapse [23, 27]. The most recent analysis of STIM2 study which included patients who prior to the trial entry have received only imatinib showed, that after 12 months of the median follow-up (range 1–25) a molecular relapse occurred in 39% of patients [24]. Takahashi et al. showed in his report that the duration of CMR > 24 months is associated with significantly lower rate of molecular relapse [28]. Using similar definitions of response as in STIM1 and STIM2 study the rates of treatment-free survival for patients who achieved CMR while receiving dasatinib or nilotinib was assessed. The rate of molecular relapse and the need for therapy re-introduction was 55.8% and 32.7% respectively [28]. The sustained MR4.5 for 2 years was the criterion for TWISTER – Australian discontinuation study. It was demonstrated that for patients in CMR who discontinued imatinib, the chance of sustained MMR at 2 years was 47% [29]. Very important observation of *BCR/ABL1* transcript level fluctuation without clear molecular relapse in approximately 30% of patients who discontinued therapy was made within STIM2 study. This finding confirms the notion that *BCR/ABL1* reappearance does not mean automatically clinical relapse and needs therapeutic intervention [24]. Although the impact of achievement of DMR on overall survival remains unsupported directly by clinical data yet, there is a growing experience and indirect evidence emphasizing the importance of DMR achievement for improvement of long-term patients outcome. Those, who could benefit the most from treatment discontinuation are younger patients, who have achieved at least MR4.5, and suffer from TKI-associated side effects. The proportion of patients suffering from grade 3 or 4 (according to CTCAE scale) side effects is very low, however majority of patients receiving TKIs reports a low-intensity adverse effects, which if persistent, could impair significantly the quality of life. The most frequently reported adverse effect attributed to TKI in the publication evaluating the quality of life in 448 patients with CML was fatigue, followed by muscle cramps, muscle and bone pains and edema [30]. The impairment of quality of life varied among the studied population and was related to the age and sex. The patients who suffered the most from TKI-associated side effects and reported the biggest impairment of quality of life were aged between 18 and 39. The quality of live of patients aged 60 or above were equal to that of comparable healthy population. Females reported much bigger deterioration of quality of life under TKI therapy than males [30]. A growing number of patients with CML treated with TKIs, improvement of first line treatment efficacy, possible therapy modification according to the molecular milestones achieved, and last but not least the economic issues are the facts that should be taken into consideration as far as the current modern CML treatment strategy is regarded. The concept of very fast induction of deep molecular response using upfront the most potent inhibitor or drug combinations, followed by a consolidation phase with elimination of minimal residual disease continued up to the clinically optimal moment for discontinuation trial, seems to be an attractive treatment option for considerable number of patients. The achievement of MR4.5 sustained for at least 2 years, which is the key entry criterion for current discontinuation studies could be therefore considered as a reasonable goal of CML therapy. Currently available data demonstrate that it is possible to obtain a long-term treatment-free survival in patients who have achieved deep molecular response even without complete elimination of *BCR/ABL1* positive cells. It suggests further that in those patients existing minimal but still detectable residual disease does not require clinical intervention. It is needed however that the question if it would be possible to reduce the dose or discontinue safely the TKI therapy in patients with detectable but stable low-level residual disease will be addressed in the planned future clinical trials.

References

1. Altekruse SF, Kosary CL, Krapcho M et al. SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD [online: http://seer.cancer.gov/csr/1975_2007/], based on November 2009 SEER data submission, posted to the SEER web site, 2010.
2. Deininger M, O'Brien SG, Guilhot F et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. Blood 2009; ASH Abstract: 1126.
3. Cross NC, White HE, Müller MC et al. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia 2012; 26: 2172--2175.
4. Hughes T, Deininger M, Hochhaus A et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: Review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006; 108: 28-37.
5. Druker BJ, Guilhot F, O'Brien SG et al. Five-year follow-up of imatinib therapy for newly diagnosed chronic myelogenous leukemia in chronic phase shows sustained responses and high overall survival. N Engl J Med 2006; 355: 2408-2417.
6. Branford S, Lawrence R, Grigg A et al. Long Term Follow up of Patients with CML in Chronic Phase Treated with First-Line Imatinib Suggests That Earlier Achievement of a Major Molecular Response Leads to Greater Stability of Response. Blood 2008: abst. 2113.
7. Mueller MC, Hanfstein B, Erben P et al. Molecular Response to First Line Imatinib Therapy Is Predictive for Long Term Event Free Survival in Patients with Chronic Phase Chronic Myelogenous Leukemia – An Interim Analysis of the Randomized German CML Study IV. Blood 2012: abst. 333.
8. Press RD, Galderis C, Young R. A Half-Log Increase in BCR-ABL RNA Predicts a Higher Risk of Relapse in Patients with Chronic Myeloid Leukemia with an Imatinib-Induced Complete Cytogenetic Response. Clin Cancer Res 2007; 13: 6136-43.
9. De Lavallade H, Apperley JF, Khorashad J et al. Imatinib for Newly Diagnosed Patients With Chronic Myeloid Leukemia: Incidence of Sustained Responses in an Intention-to-Treat Analysis. J Clin Oncol 2008; 26: 3358-3363.
10. Thomas J, Wang L, Clark RE et al. Active transport of imatinib into and out of cells: Implications for drug resistance. Blood 2004; 104: 3739--3745.
11. White DL, Dang P, Engler J et al. Functional activity of the OCT-1 protein is predictive of long-term outcome in patients with chronic-phase chronic myeloid leukemia treated with imatinib. J Clin Oncol 2010; 26: 2761-2767.
12. Alattar M, Kantarjian H, Jabbour E et al. Clinical Significance of Complete Cytogenetic Response (CCyR) and Major Molecular Response (MMR) Achieved with Different Treatment Modalities Used As Frontline Therapy In Chronic Myeloid Leukemia (CML) Chronic Phase (CP). Blood 2011; 118: abst. 745.
13. Saglio B, Hochhaus A, Hughes TP et al. ENESTnd Update: Nilotinib vs Imatinib in Patients With Newly Diagnosed CML-CP and the Impact of Early Molecular Response and Sokal Risk at Diagnosis on Long-Term Outcomes. Blood 2013; abst. 92.
14. Leber B, Cervantes F, Spector N et al. Achievement and Maintenance Of Deeper Molecular Response By Switching To Nilotinib In Patients With Chronic Myeloid Leukemia In Chronic Phase (CML-CP) With Residual Disease On Long-Term Imatinib: ENESTcmr 36-Month Follow-Up. Blood 2013; abst. 94.
15. Cortes J, Hochhaus A, Kim D-W et al. Four-Year (Yr) Follow-Up of Patients (Pts) With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Receiving Dasatinib or Imatinib: Efficacy Based on Early Response. Blood 2013; abst. 653.
16. Hughes TP, Deininger M, Hochhasus A et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendation for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006; 108: 28-37.
16. Hanfstein B, Mueller MC, Hehlmann R et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). Leukemia 2012; 26: 2096-2112.
17. Hanfstein B, Mueller M, Erben P et al. Molecular Response After 3 Months of 1st Line Imatinib Therapy Is Predictive for Treatment Failure and Disease Progression In Patients with Chronic Phase Chronic Myeloid Leukemia - a Follow-up Analysis of the German CML Study IV. Blood 2010; abst. 360.
18. Hochhaus A, Hughes TP, Saglio G et al. Outcome of Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Based On Early Molecular Response and Factors Associated with Early Response: 4-Year Follow-up Data From Enestnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients). Blood 2012; 120: abst. 167.
19. Sacha T, Czekalska S, Gniot M et al. Bcr-abl transcript levels at 3 and at 6 months are predictive for survival, time to transformation and time to second line treatment onset in chronic myeloid leukemia patients on imatinib therapy. Haematologica 2013; 98(supl. 1): 551-552 (abst. B 1360)
20. Etienne G, Nicolini F, Dulucq S et al. Achieving a Complete Molecular Remission Under Imatinib Therapy Is Associated with a Better Outcome in Chronic Phase Chronic Myeloid Leukaemia Patients On Imatinib Frontline Therapy. Blood 2012; 120: abst. 3754.
21. Hehlmann R, Müller MC, Lauseker M et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: Results from the randomized CML-Study IV. J Clin Oncol 2013 [online: doi:10.1200/JCO.2013.49.9020].
22. Mahon FX, Réa D, Guilhot J et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: The prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010; 11: 1029-1035.
23. Mahon FX, Nicolini FE, Noël MP et al. Preliminary Report Of The STIM2 Study: A Multicenter Stop Imatinib Trial For Chronic Phase Chronic Myeloid Leukemia De Novo Patients On Imatinib. Blood 2013; 122: 654.
24. Rousselot P, Huguet F, Rea D et al. Imatinib mesylate discontinuation in patients with chronić myelogenous leukemia in complete molecular remission for more than 2 years. Blood 2007; 109: 58-60.

25. Mahon FX, Rea D, Guilhot J. et al. Long Term Follow-Up After Imatinib Cessation For Patients Indeep Molecular Response: The Update Results Of The STIM1 Study. Blood 2013; 122: abst. 255.
26. Legros L, Rousselot P, Giraudier S et al. Second attempt to discontinue imatinib in CP-CML patients with a second sustained complete molecular response. Blood 2012; 120: 1959-1960.
27. Takahashi N, Kyo T, Maeda Y et al. Discontinuation of imatinib in Japanese patients with chronic myeloid leukemia. Haematologica 2012; 97: 903-906.
28. Rea D, Rousselot P, Guilhot F et al. Discontinuation of Second Generation (2G) Tyrosine Kinase Inhibitors (TKI) in Chronic Phase (CP)-Chronic Myeloid Leukemia (CML) Patients with Stable Undetectable BCR-ABL Transcripts. Blood 2012; abst. 916.
29. Ross DM, Branford S, Seymour JF et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: Results from the TWISTER study. Blood 2013; 122: 515-522.
30. Efficace F, Baccarani M, Breccia M et al. Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. Blood 2011; 118: 4554-4560.

Correspondence:
Tomasz Sacha, MD PhD
Chair of Hematology, Collegium Medicum Jagiellonian University
31-501 Kraków, ul. Kopernika 17, Poland
tel.: (+48 12) 424-76-00
fax: (+48 12) 424-74-26
e-mail: sachatom@gmail.com