

ORIGINAL ARTICLE

Hammersmith Prognostic Score as a predictor of cytogenetic and molecular response to second-line therapy in chronic myeloid leukemia

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Summary

Introduction: Following failure or loss of response to imatinib in patients with chronic myeloid leukemia, selecting optimal second-line therapy and predicting treatment response are clinically important. This study aimed to evaluate the Hammersmith prognostic score as a predictor of cytogenetic and molecular response during second-line nilotinib treatment.

Methods: This retrospective study included 89 patients with chronic-phase chronic myeloid leukemia who experienced treatment failure or loss of response during standard-dose imatinib therapy. In the second-line setting, 34 patients received escalated-dose imatinib at 800 mg daily, while 55 received nilotinib at 800 mg daily. Clinical and laboratory parameters, cytogenetic and molecular responses, prognostic scores, adverse events, and survival outcomes were analyzed.

Results: Primary imatinib failure occurred in 35/89 patients (39%), while secondary failure was recorded in 54/89 patients (61%). Complete cytogenetic response during second-line therapy was achieved in 76.5% of patients receiving escalated-dose imatinib and 76.4% of those receiving nilotinib. In the nilotinib group, complete cytogenetic response was associated with higher hemoglobin levels, lower leukocyte counts and lactate dehydrogenase levels, and less pronounced hepatosplenomegaly. The Hammersmith score was the most significant independent predictor of cytogenetic and molecular response to nilotinib (HR 2.977; 95% CI 1.061–8.353; p=0.038).

Conclusion: The Hammersmith prognostic score is a simple, clinically useful tool for identifying patients more likely to achieve complete cytogenetic and molecular responses to second-line nilotinib after imatinib failure.

Keywords: chronic myeloid leukemia, nilotinib, Hammersmith score, cytogenetic response, imatinib

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome and the *BCR::ABL1* fusion oncoprotein tyrosine kinase. The introduction of tyrosine kinase inhibitors (TKIs) represents one of the most important milestones in modern hematology, transforming CML from a disease with limited therapeutic options into a chronic condition for many patients. Imatinib, the first selective *BCR::ABL1* tyrosine kinase inhibitor, established the basis of targeted therapy and significantly improved hematologic, cytogenetic, and molecular responses, as well as overall survival in patients with chronic-phase disease (1,2).

Despite the long-term efficacy of imatinib, some patients develop primary treatment failure, loss of a previously achieved response, or drug intolerance. According to current recommendations, treatment response in CML is assessed by monitoring defined therapeutic milestones at specified time points, particularly the molecular response expressed as the *BCR::ABL1* transcript level on the International Scale. Failure to meet treatment milestones, a confirmed increase in *BCR::ABL1* transcripts, loss of cytogenetic or molecular response, and the emergence of *BCR::ABL1* kinase-domain mutations indicate the need for reassessment of the therapeutic approach (2,3).

In patients with imatinib failure, the choice of second-line therapy is a particularly important clinical challenge. Second-generation TKIs, including nilotinib and dasatinib, have demonstrated substantial efficacy in patients with chronic-phase CML who were previously resistant or intolerant to imatinib. Nilotinib is a more potent *BCR::ABL1* tyrosine kinase inhibitor than imatinib and is a standard therapeutic option after prior treatment failure. However, the response to second-line nilotinib is not uniform, and some patients do not achieve optimal cytogenetic and/or molecular responses. Therefore, identifying clinical, laboratory, and prognostic factors that may help estimate the probability of response before or shortly after starting second-line therapy is of particular importance (4,5).

In clinical practice, the choice of the next TKI depends not only on drug efficacy but also on patient characteristics, comorbidities, prior toxicity, adverse event profile, adherence, mutation status, and the depth of the previously achieved response. The modern approach to CML treatment increasingly entails individualized therapy, aiming not only for hematologic and cytogenetic responses but also for a deep molecular response, prolonged progression-free survival, and, in selected patients, potential treatment discontinuation after a sustained stable deep molecular remission (3). Nevertheless, in patients who have already experienced imatinib failure, an early and reliable estimate of the probability of response to second-line therapy remains highly important, as it enables

timely identification of patients who require closer monitoring and consideration of other treatment modalities.

Cytogenetic response played a central role in assessing treatment efficacy before the imatinib era. The introduction of TKIs established a new treatment goal: achievement of a molecular response. Achievement of complete cytogenetic and molecular responses in the second-line setting is associated with more favorable outcomes and a lower risk of disease progression; therefore, predictors of both responses have considerable clinical value (4,6).

The Hammersmith prognostic score was developed to estimate the probability of response to second-generation TKIs in patients with CML who have failed imatinib. This score integrates clinical and treatment-related parameters associated with an unfavorable outcome, including previous response to imatinib, disease phase, and other characteristics that may indicate a more aggressive biological course or a lower probability of response to subsequent therapy. Previous studies have suggested that the Hammersmith score may predict response to second-generation TKIs. Still, its applicability in real-world clinical practice and during long-term follow-up requires further validation (6,7).

Real-world clinical studies are particularly valuable because they include more heterogeneous patient populations than clinical trials, including patients of different ages, disease durations, comorbidities, and prior treatment responses. Such data may provide insight into the actual effectiveness and clinical utility of individual prognostic models. In this context, analysis of the long-term experience at a single center may contribute to a better understanding of factors influencing the response to nilotinib after imatinib failure.

This study aimed to assess clinical outcomes in patients with chronic-phase CML after failure or loss of response to imatinib, with particular emphasis on the Hammersmith prognostic score as a predictor of complete cytogenetic and molecular responses to nilotinib administered as second-line therapy.

MATERIALS AND METHODS

Study Design and Patients

A retrospective single-center study was conducted in patients with chronic-phase CML who experienced treatment failure or loss of a previously achieved response during therapy with standard-dose imatinib (400 mg daily). Patients were diagnosed, treated, and followed at the Clinic of Hematology, University Clinical Center of Serbia, between January 2003 and June 2019.

The analysis included patients with available data on baseline clinical and laboratory characteristics, treatment course, cytogenetic and molecular responses, and treatment outcomes. Patients lacking data required to

assess treatment response, as well as those in whom the type of imatinib failure could not be reliably determined, were excluded.

Clinical Assessment and Treatment Protocol

All patients underwent an initial assessment that included medical history, physical examination, performance status assessment, complete blood count with differential, standard biochemical tests, clinical and ultrasonographic assessment of liver and spleen size, morphological analysis of the bone marrow aspirate, conventional cytogenetic analysis, and quantitative PCR measurement of *BCR::ABL1* transcripts.

Patients presenting with a leukocyte count $\geq 50 \times 10^9/L$ initially received short-term cytoreductive therapy with hydroxyurea, at a dose adjusted to the leukocyte count, together with appropriate hydration and allopurinol.

In the first-line setting, all patients were treated with standard-dose imatinib (400 mg daily). Following failure of standard-dose imatinib, second-line treatment was selected in accordance with the therapeutic options available at the time and prevailing clinical practice. Some patients received escalated-dose imatinib (800 mg daily) administered as two 400-mg doses, while the remaining patients received nilotinib at a total daily dose of 800 mg, also administered as two 400-mg doses.

In cases of resistance to both TKIs available in our country, further treatment was determined based on the patient's age and comorbidities. It included allogeneic hematopoietic stem cell transplantation or cytoreductive therapy with hydroxyurea. Patients whose disease transformed to blast crisis received chemotherapy adapted to age and comorbidities, after which allogeneic hematopoietic stem cell transplantation was considered depending on the response achieved.

Primary imatinib failure was defined as failure to achieve the expected hematologic, cytogenetic, or molecular response according to European LeukemiaNet (ELN) recommendations. Secondary failure was defined as loss of a previously achieved complete hematologic response, complete cytogenetic response, or major molecular response, as well as the emergence of additional cytogenetic abnormalities in the Philadelphia chromosome-positive clone.

Biochemical Analyses

Biochemical analyses were performed as part of routine clinical assessment and follow-up. Parameters of liver and kidney function, lactate dehydrogenase, uric acid, electrolytes, and other available biochemical parameters relevant to disease activity, general condition, and treatment safety were analyzed. Particular attention was paid to lactate dehydrogenase levels because of their potential prognostic significance for treatment response.

Assessment of Treatment Response

Treatment response was assessed based on hematologic, cytogenetic, and molecular responses in accordance with the European LeukemiaNet (ELN) recommendations applicable to the respective follow-up period.

Complete hematologic response was defined as normalization of the blood count with no clinical signs of active disease, including no palpable splenomegaly.

Cytogenetic response was assessed by conventional cytogenetic analysis of bone marrow metaphases and classified as complete, partial, minor, or minimal, or as no cytogenetic response. Complete cytogenetic response was defined as the absence of Philadelphia chromosome-positive metaphases, that is, 0% Ph-positive metaphases in the analyzed sample.

Molecular response was assessed by quantitative PCR measurement of *BCR::ABL1* transcript levels. Molecular responses were classified as major molecular response (MR3/MMR) and deeper molecular responses (MR4 and MR4.5).

Prognostic Scores

Initial prognostic assessment was performed using the available prognostic systems, including the Sokal, Hasford/Euro, EUTOS, and ELTS scores. The Hammersmith prognostic score was additionally calculated for patients receiving second-line therapy.

The Hammersmith score was determined from the corrected Sokal risk, the best cytogenetic response achieved during prior imatinib treatment, and the presence of recurrent grade III or IV neutropenia during imatinib therapy.

The primary objective of the analysis was to assess the association between the Hammersmith prognostic score and achievement of cytogenetic and molecular responses in patients receiving second-line therapy.

Statistical Analysis

Descriptive statistics were used to present baseline clinical, laboratory, and treatment characteristics. Continuous variables were expressed as the mean with standard deviation or the median with range or interquartile range, depending on the data distribution. Categorical variables were presented as absolute numbers and percentages. Normality of distribution was assessed using the Kolmogorov–Smirnov test.

Between-group comparisons were performed using appropriate parametric or nonparametric tests for continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test, depending on sample size and expected frequencies. Survival was estimated using the Kaplan–Meier method, and between-group differences were analyzed using the log-rank test.

Regression analysis was used to identify factors associated with treatment outcome and achievement of complete cytogenetic response. Cox regression analysis was used to assess variables associated with time to event, including treatment failure and survival. A *p* value <0.05 was considered statistically significant.

Statistical analysis was performed using SPSS software (SPSS for Windows, release 21.0; SPSS, Chicago, IL, USA).

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. It was reviewed and approved by the Ethics Committee of the University Clinical Center of Serbia (approval no. 499/5, dated November 30, 2021). Given the retrospective study design and the use of anonymized medical-record data, the requirement for individual informed consent was waived by the competent Ethics Committee.

RESULTS

Baseline Characteristics of the Study Cohort

The study included 89 patients with CML who experienced treatment failure or loss of a previously achieved response during therapy with standard-dose imatinib (400 mg daily). The cohort comprised 55 men (61.8%) and 34 women (38.2%), with a median age of 47 years. Splenomegaly was present in 70 patients (78.7%). According to the ELTS prognostic model, 41 patients (46.1%) were classified as low risk, 33 (37.1%) as intermediate

risk, and 15 (16.9%) as high risk. Additional cytogenetic abnormalities were present in eight patients (9.0%), while a variant translocation at diagnosis was recorded in five (5.6%). Baseline clinical and laboratory characteristics are presented in **Table 1**.

Response to Standard-Dose Imatinib and Type of Treatment Failure

During treatment with standard-dose imatinib (400 mg daily), complete cytogenetic response was the best response achieved in 34 patients (38.2%), major cytogenetic response in 20 (22.5%), and minor cytogenetic response in 10 (11.2%). In contrast, 25 patients (28.1%) achieved no cytogenetic response. Loss of the best previously achieved cytogenetic response during continued treatment was recorded in 44 patients (49.4%): 33 (75.0%) lost a complete response, 8 (18.2%) a major response, and 3 (6.8%) a minor response.

According to the ELN criteria in effect during the study period, primary imatinib failure was recorded in 35 patients (39.3%), whereas secondary failure was recorded in 54 (60.7%). Secondary failure included loss of a previously achieved hematologic, cytogenetic, or molecular response, as well as the emergence of additional cytogenetic abnormalities in the Ph-positive clone. Compared with patients with secondary failure, those with primary failure had a significantly higher leukocyte count, more frequent leukocytosis $\geq 200 \times 10^9/L$, a higher percentage of peripheral-blood blasts, and a larger spleen diameter. Primary failure was significantly more frequent among patients classified as high risk by the Sokal and ELTS models. In contrast, in multivariable Cox regression analysis, the Sokal model emerged as the

Table 1. Clinical and laboratory characteristics at diagnosis of patients with CML who experienced failure or loss of response during standard-dose imatinib therapy

Characteristics	$\bar{x} \pm SD / n$ (%)	Median (range)
Age (years)	47 $\pm$ 2	46 (18–69)
Sex, M/F, n	55/34	—
Liver diameter (mm)	148 $\pm$ 3	140 (110–240)
Spleen diameter (mm)	181 $\pm$ 6	188 (92–320)
Hemoglobin (g/L)	120 $\pm$ 2	119 (61–170)
Leukocyte count ($\times 10^9/L$)	181 $\pm$ 14	143 (15.7–598)
Platelet count ($\times 10^9/L$)	519 $\pm$ 36	418 (105–1763)
Peripheral-blood eosinophils (%)	2 $\pm$ 0.2	1 (0–11)
Peripheral-blood basophils (%)	4 $\pm$ 0.4	3 (0–16)
Peripheral-blood blasts (%)	3 $\pm$ 0.6	2 (0–14)
LDH (U/L) *	1502 $\pm$ 77	1444 (353–4295)
Presence of CCA*/Ph+, n (%)	3 (3.4)	—
Presence of CCA*/Ph–, n (%)	3 (3.4)	—
Presence of CCA*/Ph–/Ph+, n (%)	2 (2.2)	—
Variant translocation, n (%)	5 (5.6)	—

*CCA, clonal cytogenetic abnormalities; Ph+, Philadelphia-positive clone; Ph–, Philadelphia-negative clone

Table 2. Differences in characteristics between Group A patients with primary failure and Group B patients with secondary failure (imatinib 400 mg), according to ELN criteria

	Group A - Primary failure	Group B - Secondary failure	P value
Imatinib 400 mg daily, N (%)	35 (39)	54 (61)	
Age (years), median (IQR)	46 (17)	48 (19)	0.849
Sex (M/F)	23/12	33/21	0.661
Hemoglobin level (g/L)	114 ± 3	126 ± 3	0.073
Leukocyte count (×10 ⁹ /L)	242 ± 24	139 ± 16	0.019
Leukocyte count ≥200×10 ⁹ /L	19/35 (54.3%)	14/54 (25.9%)	0.012
Platelet count (×10 ⁹ /L)	548 ± 58	441 ± 56	0.290
Peripheral-blood blasts (%)	4.4 ± 0.7	1.6 ± 0.4	0.002
Serum lactate dehydrogenase (U/L)	1598 ± 128	1436 ± 101	0.361
Spleen size (cm)	20.5 ± 1	15.9 ± 0.8	0.004
Additional cytogenetic abnormalities			
Initially	6/35 (17.1)	5/54 (9.3)	0.270
During monitoring	10/35 (28.6)	12/54 (22.2)	0.498
Sokal score			
Low	4/35 (11.4)	19/54 (35.1)	0.001
Intermediate	12/35 (34.3)	25/54 (46.3)	
High	19/35 (54.3)	10/54 (18.5)	
Hasford score			
Low	11/35 (31.4)	25/54 (46.3)	0.072
Intermediate	16/35 (45.7)	25/54 (46.3)	
High	8/35 (22.8)	4/54 (9.4)	
EUTOS score			
Low	27/35 (77.1)	44/54 (81.5)	0.105
High	8/35 (22.8)	10/54 (18.5)	
ELTS score			
Low	10/35 (28.6)	31/54 (57.4)	0.007
Intermediate	17/35 (48.6)	18/54 (33.3)	
High	8/35 (22.8)	5/54 (9.2)	
Survival duration, median (range), months	68 (12–131)	93 (27–177)	0.005
Death, N (%)	8/35	15/54	0.604

most significant independent predictor of primary imatinib failure (Table 2).

Distribution of Patients According to Second-Line Therapy

In the second-line setting, 34 patients (38.2%) received escalated-dose imatinib (800 mg daily), while 55 (61.8%) received nilotinib at a total daily dose of 800 mg. Both options were available for patients with primary or secondary failure of standard-dose imatinib, and treatment selection was based on the recommendations in force at the time, drug availability, and individual clinical assessment. There were no statistically significant differences between the treatment groups in age, sex distribution, time to initiation of second-line therapy, or the percentage of Ph-positive metaphases at second-line initiation. This supports comparability of the groups for these baseline characteristics and reduces the possibility that observed outcome differences resulted from selection bias.

Cytogenetic and Molecular Responses to Second-Line Therapy

A complete cytogenetic response in the second-line setting was achieved by 26/34 patients (76.5%) treated with escalated-dose imatinib and 42/55 patients (76.4%) treated with nilotinib. The median time to complete cytogenetic response was 6 months. The cumulative type of cytogenetic response did not differ significantly between patients treated with imatinib 800 mg and those treated with nilotinib. Time to a secondary complete cytogenetic response also did not differ significantly between the groups.

The duration of the secondary complete cytogenetic response was significantly longer in patients treated with escalated-dose imatinib than in those treated with nilotinib, as was the duration of follow-up.

Cytogenetic response to second-line therapy, stratified by the type of failure during prior imatinib treatment, is shown in Table 3. Patients with primary imatinib failure had a less favorable cytogenetic response to

Table 3. Cytogenetic response according to the second-line treatment used and the type of failure during standard-dose imatinib therapy

Parameter	Primary failure with IM 400 mg N (%)		Secondary failure with IM 400 mg N (%)	
Response to second-line therapy*	IM dose escalation	Nilotinib	IM dose escalation	Nilotinib
CCgR	8 (66.6)	12 (52.2)	18 (81.8)	30 (93.7)
PCgR	0	3 (13)	0	0
NR	4 (33.4)	8 (34.8)	4 (18.2)	2 (6.3)
Total, N	12	23	22	32

second-line therapy than those with secondary failure. Complete cytogenetic response was achieved by 20/35 patients (57.1%) with primary failure compared with 48/54 (88.9%) with secondary failure. No response was recorded in 12/35 patients (34.3%) with primary failure and 6/54 (11.1%) with secondary failure.

Second-line nilotinib was better tolerated than escalated-dose imatinib to 800 mg, primarily due to lower hematologic and nonhematologic toxicity. Subjective adverse reactions were recorded in 8/55 patients (14.5%) receiving nilotinib and 12/34 (35.3%) receiving imatinib ($p=0.023$), objective reactions in 10/55 (18.2%) and 14/34 (41.2%), respectively ($p=0.018$), and laboratory abnormalities in 24/55 (43.6%) and 27/34 (79.4%), respectively ($p=0.001$). Imatinib was more often associated with nausea, edema, and hematologic toxicity, whereas skin changes, increased lipase levels, and cardiometabolic complications were more frequently recorded with nilotinib. Cardiovascular complications were numerically more frequent with nilotinib (21/55; 38.2%) than with imatinib (9/34; 26.5%), but the difference was not statistically significant ($p=0.256$).

Kaplan–Meier analysis showed no statistically significant difference in survival between patients treated with nilotinib and those receiving escalated-dose imatinib 800 mg ($p=0.697$). Descriptively, the survival curve for patients treated with escalated-dose imatinib remained above that for patients treated with nilotinib during most of follow-up. Still, this difference was not statistically significant (**Figure 3**).

Predictors of Complete Cytogenetic Response to Nilotinib

Among patients receiving second-line nilotinib, factors associated with achievement of complete cytogenetic response were analyzed. Differences in patient characteristics according to cytogenetic response achieved during nilotinib treatment are presented in **Table 4**.

Age did not differ significantly between patients who achieved a complete cytogenetic response and those with treatment failure. Time to initiation of second-line nilotinib also did not differ significantly between the two groups.

The median age of patients who achieved CCgR with second-line nilotinib was 45 years, compared with 54

years among those with treatment failure; this difference was not statistically significant. Patients who achieved CCgR had significantly higher hemoglobin levels (125 ± 3 vs. 111 ± 5 g/L), lower leukocyte counts (157 ± 21 vs. $269 \pm 40 \times 10^9/L$), and lower serum LDH levels (1290 ± 100 vs. 2093 ± 273 U/L). Patients with treatment failure had larger liver (16.2 ± 0.8 vs. 14.0 ± 0.4 cm) and spleen dimensions (22.5 ± 1.5 vs. 16.7 ± 0.8 cm), while all prognostic scores were significant predictors of response to nilotinib. Patients who achieved CCgR had a mean proportion of Ph-positive metaphases of $53 \pm 6\%$, compared with $80 \pm 8\%$ in those with failure; $\geq 70\%$ Ph-positive metaphases were recorded in 35.7% of patients with CCgR and 84.6% of those with failure.

All analyzed prognostic scores were significant predictors of response to nilotinib. In the treatment-failure group, 92.3% of patients were in the intermediate- or high-risk Sokal categories, compared with 50.0% of those who achieved CCgR ($p=0.010$). High risk according to the Hasford score was present in 46.1% of patients with failure and 7.1% of those with CCgR ($p=0.003$); the corresponding proportions were 38.6% and 11.9% for EU-TOS ($p=0.009$), and 38.4% and 9.5% for ELTS ($p=0.005$) (**Table 4**).

Hammersmith Score and Response to Nilotinib

According to the Hammersmith prognostic score, 23 patients (41.8%) were classified as low risk, 19 (34.5%) as intermediate risk, and 13 (23.6%) as high risk. A clear association was observed between the Hammersmith score and the probability of achieving a complete cytogenetic response during nilotinib therapy. The cumulative incidence of complete cytogenetic response during nilotinib treatment differed significantly across Hammersmith risk groups (**Figure 2**).

Deep molecular response, defined as MR4–MR4.5, showed a decreasing trend as Hammersmith risk increased. MR4–MR4.5 was achieved by 54.5% of low-risk patients, 36.8% of intermediate-risk patients, and 15.4% of high-risk patients according to the Hammersmith score.

All three variables underlying the Hammersmith prognostic model were significant predictors of complete cytogenetic response during nilotinib therapy. The corrected Sokal score was significantly associated with the cumulative incidence of complete cytogenetic response.

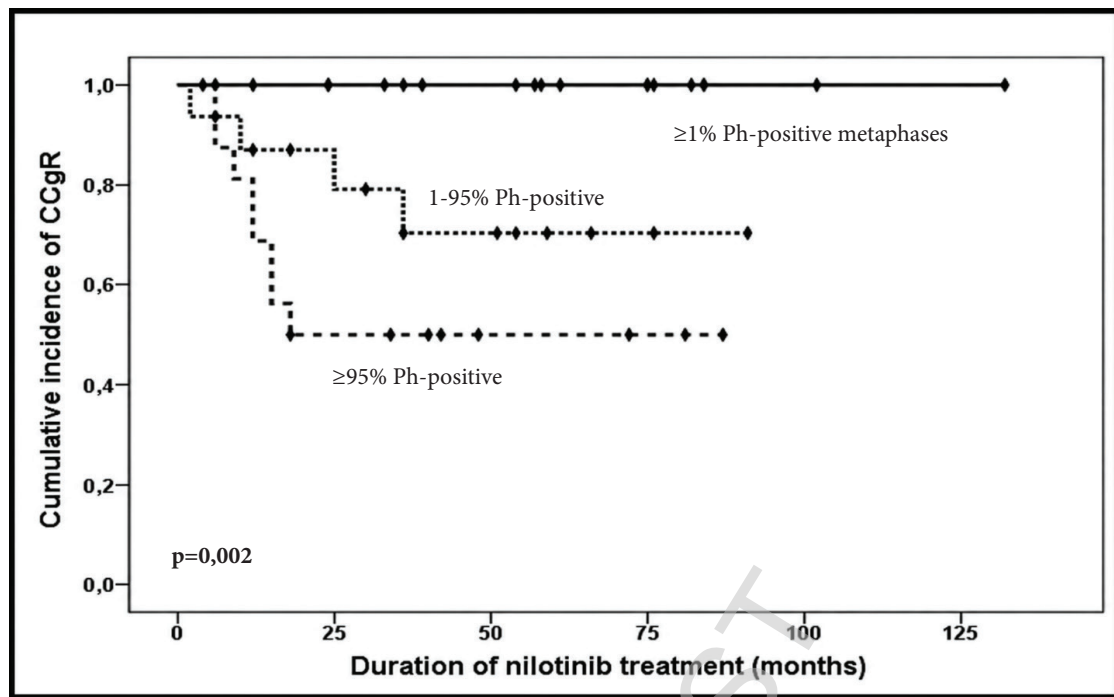


Figure 1. Cumulative incidence of CCgR during second-line nilotinib therapy according to the best cytogenetic response achieved with standard-dose imatinib in the first-line setting

Table 4. Differences in patient characteristics according to the cytogenetic response achieved during second-line nilotinib 800 mg therapy

Characteristics	Group A CCgR 42 patients	Group B Failure 13 patients	P
Age (years), median (IQR)	45 (20)	54 (27)	0.682
Sex (M/F)	22/20	9/4	0.284
Hemoglobin level (g/L)	125 ± 3	111 ± 5	0.024
Leukocyte count ($\times 10^9/L$)	157 ± 21	269 ± 40	0.011
Leukocyte count $\geq 200 \times 10^9/L$	11/42 (26.2%)	9/13 (69.2%)	0.006
Platelet count ($\times 10^9/L$)	511 ± 52	507 ± 87	0.870
Peripheral-blood blasts (%)	2.5 ± 0.4	4.5 ± 1.2	0.083
Serum lactate dehydrogenase (U/L)	1290 ± 100	2093 ± 273	0.001
Liver size (cm)	14 ± 0.4	16.2 ± 0.8	0.022
Spleen size (cm)	16.7 ± 0.8	22.5 ± 1.5	0.001
Additional CA* in the Ph+ clone, N (%)	4/42 (9.5)	2/13 (15.4)	0.554
Sokal score			0.010
Low	21/42 (50)	1/13 (7.7)	
Intermediate-high	21/42 (50)	12/13 (92.3)	
Hasford score			0.003
Low	22/42 (52.4)	2/13 (15.4)	
Intermediate	17/42 (40.5)	5/13 (38.5)	
High	3/42 (7.1)	6/13 (46.1)	
EUTOS score			0.009
Low	37/42 (88.1)	8/13 (61.5)	
High	5/42 (11.9)	5/13 (38.6)	
ELTS score			0.005
Low	24/42 (57.2)	2/13 (15.4)	
Intermediate	14/42 (33.3)	6/13 (46.2)	
High	4/42 (9.5)	5/13 (38.4)	
Survival duration, median (range), months	93 (27-177)	68 (12-131)	<0.001
Death, N (%)	4/42	7/13	<0.001

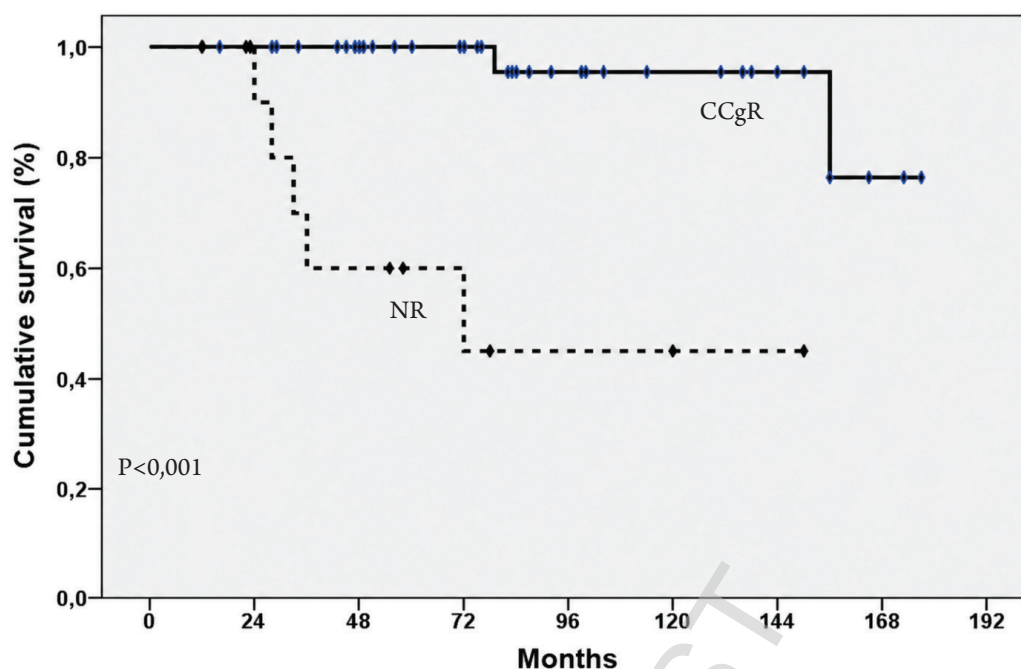


Figure 2. Kaplan–Meier survival curve according to response during second-line nilotinib 800 mg therapy in patients with CML

The best cytogenetic response to prior imatinib treatment was also associated with a response to nilotinib, and recurrent grade III/IV neutropenia during prior imatinib therapy was a statistically significant predictor of response to nilotinib.

In Cox regression analysis, the Hammersmith prognostic model emerged as the most significant predictor of response to second-line nilotinib. In univariable analysis, the Sokal, Hasford, EUTOS, ELTS, and Hammersmith scores were significant, while in multivariable analysis the Hammersmith score remained an independently significant predictor of response to nilotinib (**Table 5**).

Long-Term Outcomes and Survival

At the study cut-off, of the 89 patients, 17 (19.1%) were receiving escalated-dose imatinib, 45 (50.6%) were receiving nilotinib, 4 (4.5%) were in remission after allogeneic hematopoietic stem cell transplantation, and 1 female patient (1.1%) was receiving hydroxyurea. At the same time, a donor registry search was ongoing. Death was recorded in 22 patients (24.7%).

Median overall survival in the entire cohort was 173 months (95% CI, 150–195). Five-year overall survival was 76.9%, while seven-year overall survival was 61.0%. Patients with primary imatinib failure had shorter mean survival than those with secondary failure, although the difference was not statistically significant.

Achievement of complete cytogenetic response during second-line nilotinib therapy was associated with significantly longer survival. Patients who achieved complete cytogenetic response had significantly longer survival than those without a response, as shown by the Kaplan–Meier survival curve (**Figure 2**). Mean survival was 230 months among patients treated with escalated-dose imatinib in the second-line setting and 154 months among those treated with nilotinib, with no statistically significant difference between the treatment modalities.

DISCUSSION

This retrospective single-center cohort study analyzed long-term outcomes in patients with chronic-phase CML

Table 5. Univariable and multivariable Cox regression analysis of prognostic scores significant for response to second-line nilotinib therapy

Prognostic model	Univariable			Multivariable		
	Exp (B)	95%CI	p	Exp (B)	95%CI	p
Sokal	4.242	1.156-9.348	0.042			
Hasford	4.416	1.816-10.734	0.001			
EUTOS	2.227	1.281-4.050	0.005			
ELTS	5.072	1.780-14.445	0.002			
Hammersmith	5.111	2.170-11.880	<0.001	2.977	1.061-8.353	0.038

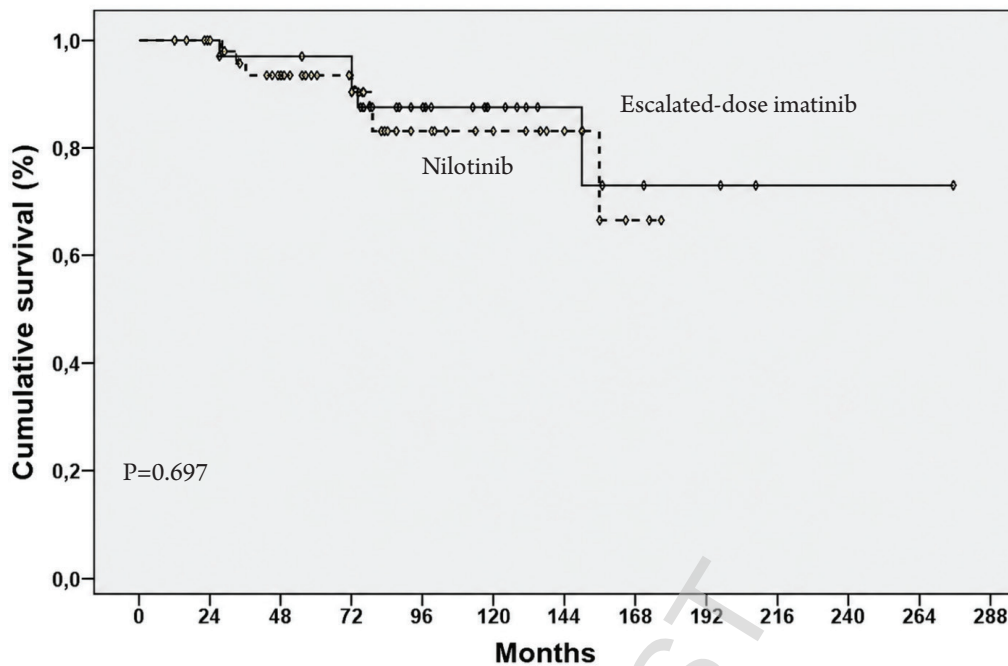


Figure 3. Kaplan–Meier survival curve according to the treatment modality used in the second-line setting in patients with CML

who experienced failure or loss of response during standard-dose imatinib therapy. The main working hypothesis was that clinically available prognostic parameters could help predict response to second-line treatment. The principal finding was that the Hammersmith prognostic score emerged as an independent predictor of complete cytogenetic and molecular responses. This finding is clinically relevant because the score is based on parameters available in routine practice and may help identify patients with a higher probability of a favorable response after imatinib failure.

The analyzed group represents a selected population with a less favorable disease course, because the study included only patients with failure or loss of response to first-line imatinib. Within this group, patients with primary imatinib failure had more pronounced clinical and laboratory indicators of disease burden and were more frequently classified in high-risk prognostic categories. In our study, the prognostic scores clearly distinguished between low- and high-risk patients based on the probability of achieving a complete molecular response. This is consistent with the concept that primary imatinib resistance often reflects more aggressive disease biology, a greater initial leukemic-clone burden, and a lower probability of achieving an optimal response to subsequent therapy. Current recommendations therefore emphasize dynamic monitoring of treatment response rather than exclusive reliance on baseline prognostic scores (2,3).

The overall efficacy of second-line therapy in our study was similar in patients treated with escalated-dose imatinib and those treated with nilotinib. This finding should be interpreted cautiously given the retrospective design, lack of randomization, and the long follow-up

period during which drug availability, criteria for switching therapy, and molecular monitoring capabilities changed. During the earlier TKI era, imatinib dose escalation was a viable therapeutic option for some patients. In contrast, current practice in cases of confirmed resistance more often involves switching to an alternative TKI, with mandatory consideration of *BCR::ABL1* mutation status, prior toxicity, and comorbidities (2,3).

Among patients treated with nilotinib, complete cytogenetic response was more frequent in those with a lower disease burden at second-line initiation. Higher hemoglobin, lower leukocyte counts, lower LDH levels, less pronounced hepatosplenomegaly, and a lower percentage of Ph-positive metaphases indicate lower disease activity and better-preserved hematopoiesis, which may explain the higher probability of response to nilotinib. These results are consistent with previous studies showing that response to second-generation TKIs after imatinib failure can be predicted by a combination of disease characteristics before second-line initiation and the early kinetics of cytogenetic response (4,6).

A particularly important finding was that achieving a complete cytogenetic response during nilotinib therapy was associated with improved long-term survival. Although molecular monitoring is now the gold standard for CML follow-up, cytogenetic response played a central role in assessing treatment efficacy during the period covered by this study. Therefore, the cytogenetic and molecular responses in this study represent relevant, clinically interpretable indicators of disease control. Current ELN recommendations indicate that treatment response should be interpreted according to definitions of optimal response; an increase in *BCR::ABL1* and loss

of cytogenetic and/or molecular response require further assessment, including cytogenetic analysis and mutation testing when indicated (3).

In our analysis, the Hammersmith score showed greater predictive value than the other prognostic scores. This may be explained by the fact that it assesses not only baseline disease risk but also the previous treatment course, including the best cytogenetic response achieved with imatinib and the occurrence of recurrent severe neutropenia during prior treatment. Thus, the Hammersmith score simultaneously reflects the biological aggressiveness of the disease, the sensitivity of the leukemic clone to TKIs, and the tolerance to previous therapy. Our results are consistent with those of Milojkovic et al., who showed that response to second-generation TKIs after imatinib failure can be predicted before and early during treatment, and with the findings of Breccia et al., who indicated that the Hammersmith score can identify patients with an unfavorable prognosis before initiation of a second-generation TKI (6,7).

The clinical value of the Hammersmith score in our study lies in its clear discrimination of patients based on the probability of achieving a complete cytogenetic response to nilotinib. Low-risk patients had a clearly favorable response, whereas response was substantially less frequent among high-risk patients. This finding suggests that the score may be a useful additional tool in assessing patients after imatinib failure (3).

CONCLUSION

In patients with chronic-phase CML after failure or loss of response to standard-dose imatinib, no difference was observed in the frequency of cytogenetic and molecular responses between those treated with escalated-dose imatinib and those treated with nilotinib in the second-line setting. Patients with primary failure had a significantly

lower frequency of complete cytogenetic response and a higher frequency of no response during second-line treatment. Escalated-dose imatinib more frequently resulted in complete cytogenetic response among patients with primary failure, whereas nilotinib was more successful among those with secondary failure. The percentage of Ph-positive metaphases at treatment initiation was a significant predictor of response to second-line nilotinib.

The Hammersmith prognostic score proved to be the most significant independent predictor of molecular and cytogenetic responses to second-line nilotinib. Its value lies in the ability to identify, using clinically available parameters, patients with a higher probability of a favorable response after imatinib failure. It also clearly identifies high-risk patients who may fail a second-generation TKI; in such cases, a third-generation TKI or, for eligible patients, allogeneic hematopoietic stem cell transplantation should be considered. In current clinical practice, this score may be a useful additional tool when planning second-line therapy.

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Ethical Approval: The study was reviewed and approved by the Ethics Committee of the University Clinical Center of Serbia (Approval No. 499/5, November 30, 2021).

Informed Consent: Given the retrospective study design and the use of anonymized medical record data, the competent Ethics Committee waived the requirement for individual informed consent.

REFERENCES

- O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348(11):994-1004. doi:10.1056/NEJMoa022457.
- Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):966-984. doi:10.1038/s41375-020-0776-2.
- Apperley JF, Milojkovic D, Cross NCP, Hjorth-Hansen H, Hochhaus A, Kantarjian H, et al. 2025 European LeukemiaNet recommendations for the management of chronic myeloid leukemia. *Leukemia*. 2025;39:1797-1813. doi:10.1038/s41375-025-02664-w.
- Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, Palandri F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood*. 2007;110(10):3540-3546. doi:10.1182/blood-2007-03-080689.
- Tiribelli M, Bonifacio M, Binotto G, Iurlo A, Cibien F, Maino E, et al. Excellent outcomes of 2G-TKI therapy after imatinib failure in chronic phase CML patients. *Oncotarget*. 2018;9(18):14219-14227. doi:10.18632/oncotarget.24478.
- Milojkovic D, Nicholson E, Apperley JF, Holyoake TL, Shepherd P, Drummond MW, et al. Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. *Haematologica*. 2010;95(2):224-231. doi:10.3324/haematol.2009.012781.
- Breccia M, Stagno F, Gozzini A, Abruzzese E, Latagliata R, Rossi AR, et al. Hammersmith score application identifies chronic myeloid leukemia patients with poor prognosis before treatment with second-generation tyrosine kinase inhibitors. *Am J Hematol*. 2011;86(6):523-525. doi:10.1002/ajh.22020.
- Aghel N, Lipton JH. Cardiovascular disease in patients with chronic myeloid leukemia: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2025;7(6):668-682. doi:10.1016/j.jacc-cao.2025.06.007.

9. Hochhaus A, Réa D, Boquimpani C, Minami Y, Cortes JE, Hughes TP, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibi-

tors: longer-term follow-up of ASCEMBL. *Leukemia*. 2023;37(3):617-626. doi:10.1038/s41375-023-01829-9.

HAMMERSMITH PROGNOСТИČKI SKOR KAO PREDIKTOR CITOGENETSKOG I MOLEKULARNOG ODGOVORA DRUGE TERAPIJSKE LINIJE U HRONIČNOJ MIJELOIDNOJ LEUKEMIJU

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Sažetak

Uvod: Nakon neuspjeha ili gubitka odgovora na imatinib kod bolesnika sa hroničnom mijeloidnom leukemijom, izbor optimalne druge linije terapije i predviđanje terapijskog odgovora imaju važan klinički značaj. Cilj rada bio je da se proceni značaj Hammersmith prognostičkog skora kao prediktora citogenetskog i molekularnog odgovora tokom lečenja nilotinibom u drugoj liniji.

Metode: Retrospektivno je analizirano 89 bolesnika sa hroničnom fazom hronične mijeloidne leukemije kod kojih je tokom lečenja imatinibom u standardnoj dozi uočen neuspeh ili gubitak odgovora. U drugoj terapijskoj liniji 34 bolesnika lečena su eskaliranom dozom imatiniba od 800 mg dnevno, dok je 55 bolesnika lečeno nilotinibom u dozi od 800 mg dnevno. Analizirani su kliničko-laboratorijski parametri, citogenetski i molekularni odgovor, prognostički skorovi, neželjeni događaji i preživljavanje.

Rezultati: Primarni neuspeh imatiniba zabeležen je kod 35/89 bolesnika (39%), dok je sekundarni neuspeh imalo 54/89 bolesnika (61%). Kompletan citogenetski odgovor u drugoj liniji postiglo je 76,5% bolesnika lečenih imatinibom u eskaliranoj dozi i 76,4% bolesnika lečenih nilotinibom. U grupi lečenoj nilotinibom, postizanje kompletnog citogenetskog odgovora bilo je povezano sa višim vrednostima hemoglobina, nižim brojem leukocita, nižim vrednostima laktat-dehidrogenaze i manje izraženom hepatosplenomegalijom. Hammersmith skor izdvojio se kao najznačajniji nezavisni prediktor citogenetskog i molekularnog odgovora na nilotinib (HR 2,977; 95% CI 1,061–8,353; p=0,038).

Zaključak: Hammersmith prognostički skor predstavlja jednostavan koristan klinički skor za identifikaciju bolesnika sa većom verovatnoćom postizanja kompletnog citogenetskog i molekularnog odgovora na nilotinib u drugoj liniji terapije nakon neuspjeha imatiniba.

Ključne reči: hronična mijeloidna leukemija, nilotinib, Hammersmith skor, citogenetski i molekularni odgovor

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