Impact of hospital experience on the quality of tyrosine kinase inhibitor response monitoring and consequence for chronic myeloid leukemia patient survival

The importance of adequate response monitoring during the treatment of chronic myeloid leukemia (CML) with tyrosine kinase inhibitors (TKIs) and testing for BCR-ABL1 kinase domain (KD) mutations in case of TKI failure is generally acknowledged and clearly outlined in guidelines and recommendations on CML management.[1-6] Recent studies from the USA have indicated that TKI response monitoring may be suboptimal in clinical practice.[7-9] This was found to be of major clinical importance, as those patients undergoing the recommended molecular assessments 3-4 times annually experienced a reduced risk of progression and mortality,[7] had improved TKI adherence[8] and generated lower health care costs[9] compared to patients who were monitored less frequently. Since no population-based European data have been published on the quality of response monitoring in CML thus far, we conducted an evaluation of response monitoring in an unselected population-based CML patient cohort in the Netherlands in the first year after diagnosis. In our study, we observed suboptimal monitoring of response to TKI treatment in a quarter of the patients. Inadequate monitoring was associated with a reduced overall survival, and hospital CML treatment experience was the strongest predictor for proper monitoring. We also found that KD domain mutation testing was performed in only 34% of patients switching TKI therapy due to TKI failure.

Data were obtained from two complementary population-based registries for newly diagnosed CML patients in the Netherlands,[10,11] together covering 75 out of 90

Table 1. Baseline characteristics.

	Total (n=382)	Less experienced hospitals (n=66)	Medium experienced hospitals (n=97)	Most experienced hospitals (n=219)	*P*§
Male, n (%)	219 (57)	38 (58)	56 (58)	125 (57)	0.993†
Age, years					**<0.001‡**
Median (IQR)	58 (43-69)	65 (55-75)	57 (46-69)	54 (39-68)	
Year of diagnosis, n (%)					0.329†
2008	90 (24)	10 (15)	31 (32)	49 (22)	
2009	77 (20)	16 (24)	15 (15)	46 (21)	
2010	80 (21)	14 (21)	17 (18)	49 (22)	
2011	72 (19)	16 (24)	16 (16)	40 (18)	
2012 – April 2013	63 (17)	10 (15)	18 (19)	35 (16)	
Charlson Comorbidity index*, Age-adjusted, n (%)					**0.001†**
0	125 (33)	7 (11)	27 (28)	91 (42)	
1-2	120 (31)	27 (41)	34 (35)	59 (27)	
3-4	83 (22)	18 (27)	22 (23)	43 (20)	
≥5	54 (14)	14 (21)	14 (14)	26 (12)	
Sokal risk group, n (%)					0.443†
Low	80 (24)	10 (17)	24 (30)	46 (24)	
Intermediate	148 (45)	31 (53)	32 (40)	85 (44)	
High	103 (31)	17 (29)	25 (31)	61 (32)	
Unknown	51	8	16	27	
First-line treatment					0.848†
Imatinib	295 (77)	51 (77)	78 (81)	166 (76)	
Nilotinib	65 (17)	11 (17)	13 (13)	41 (19)	
Dasatinib	22 (6)	4 (6)	6 (6)	12 (5)	
Treating hospital, n (%)					**<0.001†**
Non-academic	280 (73)	66 (100)	92 (95)	122 (56)	
Academic	102 (27)	0 (0)	5 (5)	97 (44)	
Inclusion in 1st-line clinical trial, n (%)					**<0.001†**
No	309 (83)	59 (92)	89 (93)	161 (75)	
Yes	65 (17)	5 (8)	7 (7)	53 (25)	
Unknown	8	2	1	5	

*2 points for CML not included. †Chi-square test. ‡Kruskal Wallis test. §Unknown groups were excluded from analysis. IQR: interquartile range.

Dutch hospitals, including seven of the eight academic hospitals. In the Netherlands, a total of 15 specialized laboratories perform cytogenetic, molecular and mutational analyses. The frequency of cytogenetic and molecular response assessments in the first year was calculated as the total number of tests performed between 15 and 407 days from the start of TKI treatment (allowing for a six-week margin from the one-year landmark). Assessments performed within a 30-day period were counted as one. Based on National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) guidelines,[1-6] we defined the minimum standard of care for response monitoring as at least three molecular and/or cytogenetic assessments performed in the first year following treatment initiation. The performance of mutational analysis was assessed during the entire follow-up period during first-line treatment. Based on the number of CML treatment initiations over the five-year inclusion period between 2008 and 2013, hospitals were categorized into three groups as a proxy for hospital CML treatment experience: less experienced (≤5 patients), medium experienced (6-10 patients), and most experienced (>10 patients). Data on survival and causes of death were obtained from the Netherlands Cancer Registry with a follow up until the 1st of February 2016. The Medical Ethics Committee of the Erasmus Medical Center in Rotterdam approved this study and the exemption from informed consent. The study was conducted in accordance with the Declaration of Helsinki. Details on statistical analysis are included in the *Online Supplementary Material.*

The current analysis included a total of 382 patients aged 18 years or older, who were in chronic phase at diagnosis and were treated with a TKI as first-line treatment with at least one year of follow-up data available. Most patients were treated with first-line imatinib (77%), in non-academic centers (73%) and were not included in a clinical trial (83%) (Table 1). Slightly more than half (57%) of the patients were treated in one of the 18 most experienced hospitals; the remainder (26% and 17%, respectively) in medium or less experienced hospitals. In the most experienced hospitals, the median age at diagnosis was significantly lower and patients experienced less comorbidities at baseline. Patients treated in the most experienced hospitals were more likely to have participated in clinical trials. Although the academic centers were mainly categorized as being the most experienced hospitals for CML treatment, the majority of CML patients across all hospital experience subgroups were treated in non-academic centers

Monitoring relied predominantly on molecular testing. In 74% of patients three or more molecular assessments were performed (Figure 1A). A minority of the patients (18%) underwent three or more cytogenetic tests, whereas almost one third of the patients did not receive any cytogenetic follow up in the first year of treatment. Together, 84% of patients met the minimum standard of care and had at least three molecular and/or cytogenetic assessments performed in the first year. Therefore, monitoring was suboptimal in 26% of cases, with 4% of patients not receiving any cytogenetic or molecular response assessment at all in the initial year after diagnosis.

The median survival time of living patients was 5.6 years (2.8 to 8.0 years). During follow up 72 patients died (19%); 18 (5%) due to CML. Univariable analysis demonstrated that the performance of a minimum of one cytogenetic response assessment, three molecular response tests or three response tests of any type in the first year of treatment were all associated with a better overall survival (*Online Supplementary Figures S1-S3*). In a multivariable Cox proportional hazards model, a minimum of three molecular response tests in the first year was the only response monitoring method, with a marginally sig-

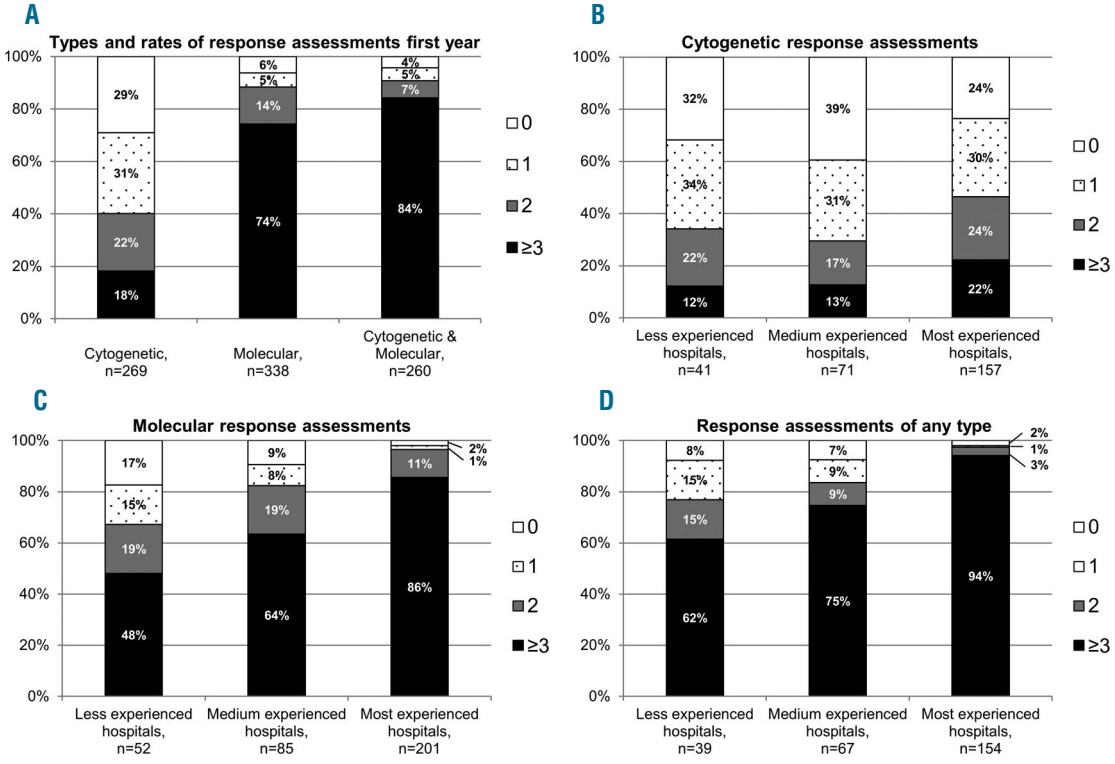

Figure 1. Monitoring frequencies during the first year of TKI treatment. (A) per assessment type and (B-D) per hospital experience category.

nificant positive association on overall survival (HR 0.52, 95%CI [0.27-1.00]) (*Online Supplementary Tables S1-S3*). The age-adjusted comorbidity index was negatively associated with overall survival in all three models.

A binary logistic regression model (based on n=333) demonstrated that treatment in a hospital which was categorized as most experienced was the strongest independent predictor for the performance of a minimum of three molecular response assessments in the first year of treatment (OR 4.87, 95%CI [2.29-10.58]; Figure 2). A higher age-adjusted Charlson comorbidity index was negatively associated with the performance of three or more molecular tests in the first year (OR 0.86, 95%CI [0.75-1.00]). The odds of adequate molecular testing for a patient in our cohort increased per year of diagnosis and thus moment of entry of the patient in the cohort (OR 1.42, 95%CI [1.12-1.83]), indicating that the practice of molecular monitoring during the first year of TKI treatment improved over time. Response monitoring rates per hospital experience category are presented in Figure 1B-D.

After initiation of first-line TKI treatment, 97 patients met the criteria for TKI failure.[1,2] Mutational analysis was performed in only 24 of these patients (25%). Some patients (n=36) continued their TKI despite meeting treatment failure criteria. Of the 61 patients who switched to second-line TKI due to failure, 21 patients underwent mutational assessments (34%) to potentially direct the choice of second-line TKI. No association between hospital experience and KD domain mutation assessment was found.

This is the first European population-based evaluation of the quality of TKI response monitoring in CML. In comparison with response monitoring evaluations performed in the USA, we found relatively high rates of adequate molecular response monitoring in the first year of TKI treatment (74%). A physician-administered chart-review of 402 CML-chronic phase (CP) patients on first-line imatinib therapy in the USA showed the rate of three or four molecular tests per year to be 46%.[7] A claim-based analysis performed in the USA showed a much lower rate of three or four molecular tests performed in the first year of TKI treatment (27%).[8,9] Goldberg *et al.* determined that patient resource barriers were an important factor which negatively influenced physician adherence to CML monitoring guidelines in the USA.[12] This factor might also explain the superior results found in the Dutch patient cohort studied herein, since healthcare insurance is mandatory in the Netherlands and it covers all laboratory assessment expenses without additional costs for the patient. We are confident that the large observational SIMPLICITY study will provide us with more information regarding factors that influence monitoring frequencies in the USA and Europe.[13]

Although the life expectancy of patients with CML is approaching the life expectancy of the general population,[14] the study herein suggests that a potential survival benefit of 9% over a period of four years can be gained by the optimization of molecular response monitoring in the first year of TKI treatment. Promoting adequate TKI response monitoring has been a priority of the HOVON (Dutch-Belgian Cooperative Trial Group for Hematology-Oncology) leukemia working group. The improvement in monitoring practice observed during our study observation period may indeed reflect a growing awareness. It has to be taken into account that potential (unmeasurable) confounders might have attributed to the observed association between molecular monitoring in the first year and overall survival. Whether the centralization of CML care indeed improves patient outcome remains speculative according to our observational study, it should be prospectively monitored if applied. Of note,

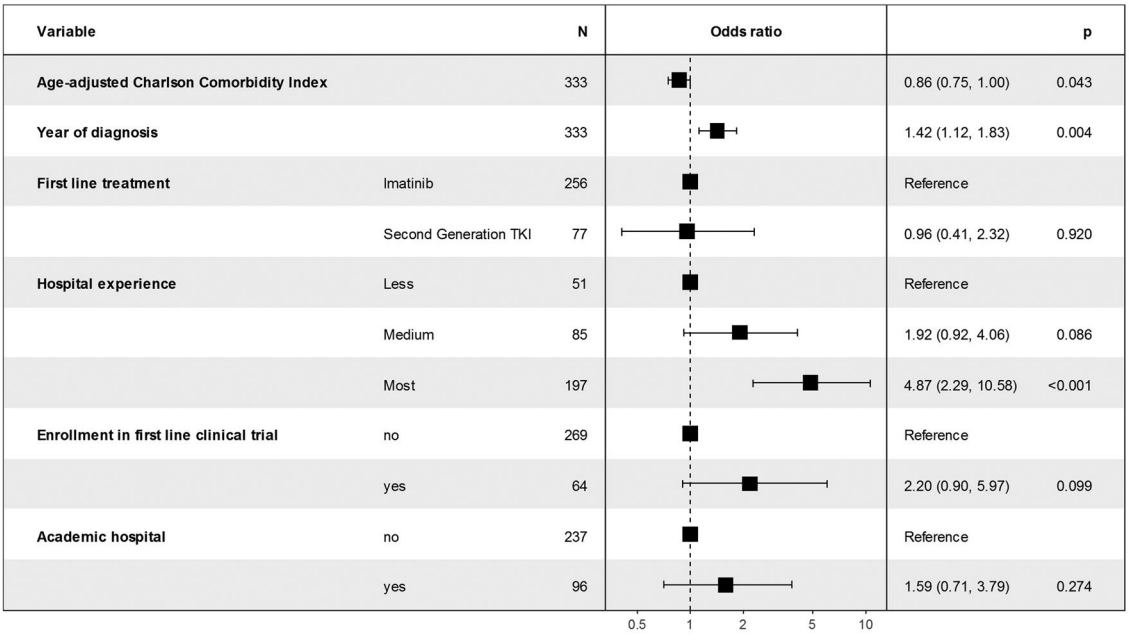

Figure 2. The performance of three or more molecular assessments in the first year. Forest plot with odds ratios for the performance of three or more molecular assessments in the first year of TKI treatment, based on a one-year landmark binary logistic regression model of 333 patients. Hosmer and Lemeshow goodness of fit test: $\chi^2 = 5.18$, df = 8, *P*-value=0.74. TKI: tyrosine kinase inhibitor.

we did not find an association between hospital experience and overall survival, although this may relate to the fact that more than half of those patients present in less and medium experienced hospitals were monitored adequately. Nor did Lauseker *et al*. observe an effect of hospital experience on overall survival, but an association between hospital type and overall survival was demonstrated.[15]

In conclusion, the study herein has further underlined the importance of close monitoring for response to TKI treatment in CML patients with a survival advantage for optimally monitored patients. Although we show relatively high rates of optimal monitoring in Dutch clinical practice, there is substantial room for improvement, particularly in hospitals with low CML patient numbers receiving treatment. In contrast, the use of KD mutation testing was poor across the patient cohort, independent of the hospital experience. Physicians and patients should continue to work to improve the quality of CML care to optimize the benefits of available TKIs.

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