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CORRESPONDENCE

Age and gender effects on molecular responses in chronic myeloid leukemia patients by first-line treatment: an Italian CML network cohort study

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Abstract

Among prognostic factors influencing the achievement of molecular responses in chronic myeloid leukemia (CML) patients treated with tyrosine kinase inhibitors (TKIs), age has been suggested with contrasting results, while the role of gender is still uncertain. A large cohort of 1,394 newly diagnosed CML patients was analyzed by data collected in the Italian CML Network, evaluating the effect of age and gender on the probability of deep molecular responses (DMR). With

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a median follow-up of 5 years, female patients showed a higher rate of DMR as compared to males. The effect, constant over time, was more evident with imatinib and dasatinib. Indeed, age did not influence the probability of DMR, when considered overall or stratified according to the type of TKI. In a real-world analysis, it seems that age has no effect on DMR regardless of the TKI class, while female gender can be confirmed as significant prognostic factor.

To the Editor

Tyrosine kinase inhibitors (TKIs) have revolutionized the outcomes of patients with chronic myeloid leukemia (CML), allowing the majority to achieve a normal life expectancy [1]. Previous studies have reported conflicting results regarding the role of age as a prognostic factor for achieving molecular milestones [2, 3], while the impact of gender remains largely unexplored. We analysed the probability of reaching a deep molecular response (DMR) according to gender and age, overall and by type of first-line treatment, in a large real-world cohort from the Italian CML network.

The Italian CML network (including 68 Hematology Centers across 19 Italian regions) prospectively collected clinical and biological data of consecutive newly diagnosed adult (≥18 years) Ph + CML patients in the chronic phase, diagnosed from January 2013 onwards, in a dedicated web-based database (https://www.epiclin.it/lmc). Quantitative reverse transcription polymerase chain reaction (RQ-PCR) analyses were performed in certified laboratories nationwide, and results were expressed according to the International Scale. Patients with at least 3 years of follow-up and a minimum of two molecular response assessments within the first two years after diagnosis were included.

In this analysis, the proportion of patients achieving at least an MR4 (BCR::ABL1 ratio ≤ 0.01% International Scale or IS) within the first two years was compared between age groups and genders, overall and stratified by first-line therapy, using a logistic regression model accounting for repeated measures within subjects and adjusting for Eutos Long Term Survival (ELTS) score, Charlson Comorbidity Index, and either age or sex.

Among 1,394 patients (mean age = 58 years; 58% males), 703 (50.4%) received imatinib, 413 (29.6%) nilotinib, and 278 (20.0%) dasatinib as first-line therapy. ELTS risk stratification identified 61.3% of patients as low risk, 27.9% as intermediate, and 10.5% as high risk. Median follow-up was 5.0 years.

Overall, when analyzing the relationship between molecular response and sex (Fig. 1A), females showed a higher and faster response compared with males (55.6% vs. 45.1% at 24 months), with an adjusted OR = 1.67 (95% CI 1.36–2.05; $p < 0.001$) (Table 1). Indeed, with a median follow-up of 5 years, the median duration of DMR was 36 months for both gender ($p = 0.48$). When stratified by therapy (Table 1), the stronger treatment effect among females was more evident for imatinib (OR = 1.91; 95% CI 1.41–2.60; $p < 0.001$) and dasatinib (OR = 2.12; 95% CI 1.38–3.26; $p = 0.001$), and less pronounced for nilotinib (OR = 1.25; 95% CI 0.86–1.81; $p = 0.25$). These differences remained relatively constant over time.

The effect of age on the probability of achieving MR4 was not significant (Fig. 1B). No trend was observed, either overall (OR per 10-year increase = 1.04; 95% CI 0.96–1.13; $p = 0.319$) or after stratification by first-line TKI (Table 1).

Contrasting results have been reported regarding age and response to TKIs: a previous analysis by the GIMEMA group showed no differences between patients aged less than 65 years and older than 65 years when treated with imatinib [2]. Indeed, specifically in young adult patients was reported an inferior rate of response and overall survival by one group [3] but similar cytogenetic, molecular and progression rates by another [4]. Our analysis showed that age does not influence the achievement of a DMR regardless of the type of TKI, even considering different definitions of age groups and not the conventional WHO stratification.

Female sex, along with early molecular response, has previously been associated with long-term sustained DMR and potential treatment discontinuation [5]. This advantage for female patients was also confirmed by an independent analysis [6]. Our findings further support a higher rate of DMR at 12 and 24 months among female patients, while no significant effect of age was observed. Higher response rate in women is reported likely due to potential hormonal influences (estrogen), pharmacokinetic differences, and lower rates of mutation development [7, 8]. In conclusion,

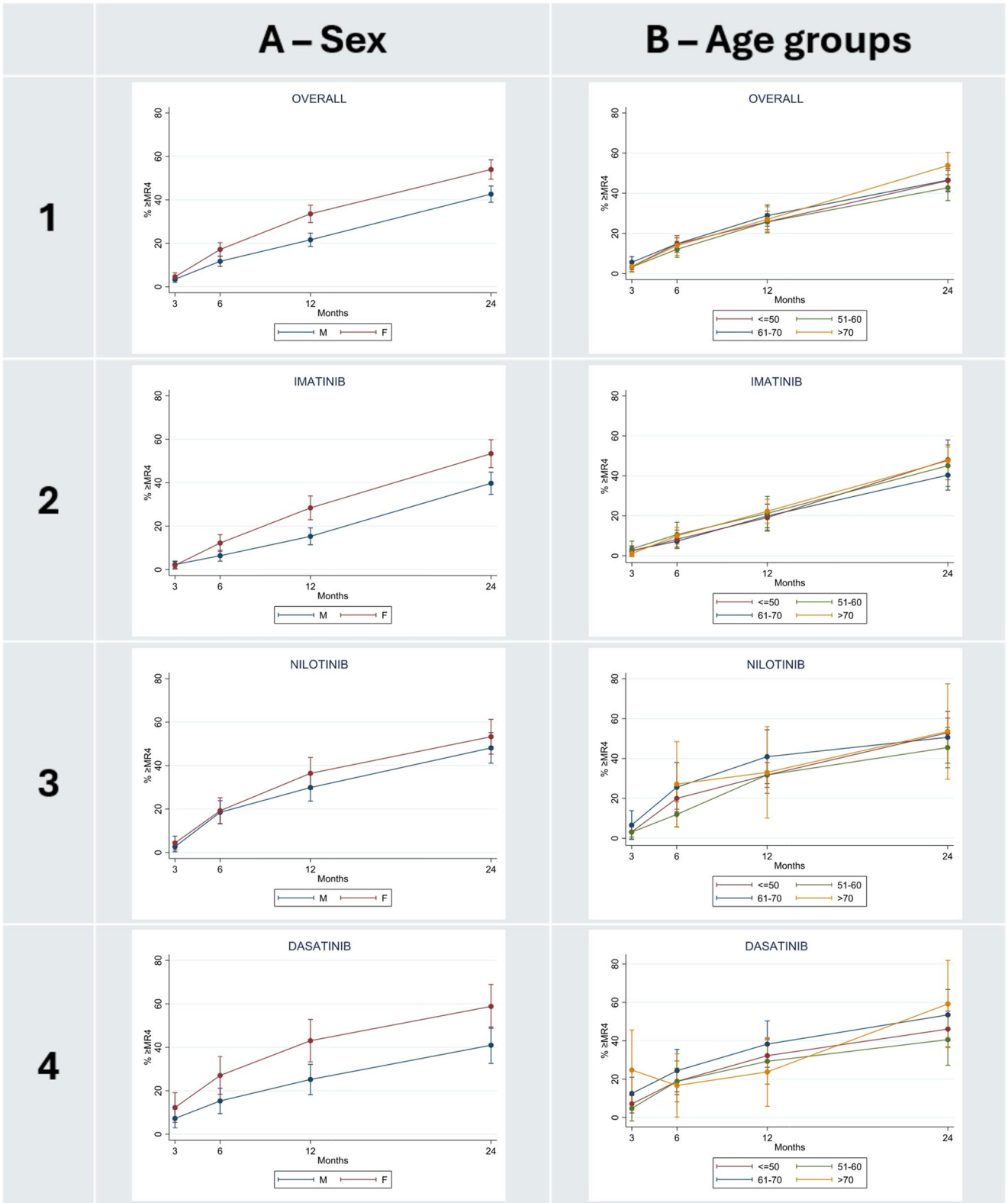

Fig. 1 Probability of reaching at least an MR4 during the first 24 months, by sex (**A**) and age group (**B**), in the whole cohort of patients (1A, 1B), and by first-line TKI: imatinib (2A, 2B), nilotinib (3A, 3B) and dasatinib (4A, 4B). Age groups were stratified as: ≤50 years, 51–60, 61–70, > 70

Table 1 Effect of sex and age on the probability of reaching at least an MR4 within the first 24-months from diagnosis in a cohort of 1394 CML patients. Adjusted odds ratios estimated for the whole cohort (overall) and by first-line treatment

	Sex (females vs. males)			Age (per 10-yrs increase)		
	OR*	95%CI	*p*	OR§	95%CI	*p*
Overall	1.67	1.36–2.05	<0.001	1.04	0.96–1.13	0.319
Imatinib	1.91	1.41–2.60	<0.001	0.99	0.88–1.12	0.944
Nilotinib	1.25	0.86–1.81	0.250	1.05	0.91–1.22	0.473
Dasatinib	2.12	1.38–3.26	0.001	1.08	0.92–1.28	0.345

*ORs estimated with a logistic regression model adjusted for age, Charlson Comorbidity Index and ELTS score

§ORs estimated with a logistic regression model adjusted for sex, Charlson Comorbidity Index and ELTS score

our results from a large CML cohort indicate that age is not a prognostic factor for achieving DMR, regardless of first-line TKI, confirming a consistent advantage for female patients. These results suggest that no age group should be excluded from a potential TFR, considering the female sex as a potential candidate at an earlier time.

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Author contributions MB analyzed the data and wrote the manuscript; TR, GC analysed the data; GS, GS revised the manuscript; all the other authors collected data and revised the final manuscript.

Data availability Data are included in the Epiclin system available after request.

Declarations

Ethics approval This study was approved by the Local Ethics Committee at AOU Città della Salute e della Scienza, Torino, Italy.

Competing interests Massimo Breccia is the Editor in Chief of the journal.

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