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Choice of Frontline Tyrosine-Kinase Inhibitor and Early Events in Very Elderly Patients With Chronic Myeloid Leukemia in Chronic Phase: A "Campus CML" Study

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ABSTRACT

Objectives: The study aimed to evaluate the utilization of frontline TKI therapy in a large cohort of elderly CP-CML patients.

Methods: A retrospective analysis was conducted on 332 CP-CML patients aged 75 years or older among 1929 diagnosed from January 2012 to December 2019 followed at 36 participating Hematology Centers involved in the "Campus CML" project.

Results: Among the patients analyzed, 85.8% received imatinib (IM) while 14.2% received second-generation TKIs (2G-TKI), 59.5% dasatinib, and 40.5% nilotinib. Most patients initiated IM at standard dose (67.3%) while 32.7% at reduced dose. A similar trend was observed with 2G-TKIs. The cumulative incidence of permanent TKI discontinuation at 12 months was 28.4%, primarily due to primary resistance (10.1%) and extra-hematologic toxicity (9.5%), with no significant difference between IM and 2G-TKI groups. Following the introduction of generic IM in Italy in 2018, IM usage increased significantly compared with 2G-TKIs.

Conclusions: IM was in our Centers the preferred frontline therapy for older CP-CML patients, with increasing utilization after the introduction of generic formulations. However, 2G-TKIs are still used in a substantial proportion of patients, suggesting individualized physician assessments regarding patient suitability and expectations. Further investigation is needed to assess efficacy and safety of reduced TKI doses in this patient population.

1 | Introduction

Chronic myeloid leukemia (CML) is a relatively rare disease, with an incidence of one or two cases per 100 000 people every year; its prevalence is rapidly increasing: it is expected to double in the next 15 years and to reach a plateau in 30–40 years [1]. The median age at diagnosis is 65 years in Western Countries [2–4] and its incidence increases with age [1, 5]. This means that nowadays up to 50% of CML patients are older than 60 years and that many more will be over 60 in the future [2].

The prognosis of CML was substantially improved in the last 20 years by the introduction in the frontline treatment of first-generation tyrosine-kinase inhibitor (TKI) imatinib and the second-generation TKIs (2G-TKI). At present, complete cytogenetic response (CCyR) is achieved by >80% of newly diagnosed CML patients, with a high rate of molecular responses and an overall survival comparable to that of the normal population [6]. This impressive improvement is actually common also in elderly CML patients, and older age is no longer considered as a worse prognostic factor.

Despite this, management of older patients with CML may be challenging due to the presence of comorbidities, the higher number of concomitant medications, the worst tolerance to TKI treatment, the impaired physical function, and fewer opportunities for be included in clinical trials.

Concerning this last point, older patients have not been adequately represented in clinical trials, since the median age in population-based registries is significantly higher than the one reported in clinical trials (65 vs. 50 years old) [7–10]. Most of the available "clinical study" data on imatinib efficacy and safety were generally drawn from the IRIS study [11], but since patients older than 70 years were not included in this study, these data cannot be considered really informative for what concerns the effects of imatinib in elderly patients [12]. Outside clinical trials, in the context of real life clinical management, the use of TKIs is supported as generally safe and efficacious also in the subset of older patients, in whom the goal sometimes should be to obtain a complete cytogenetic remission and thereby extended survival, being deep molecular response and TFR not the main goal. About management of CML elderly patients without comorbidities, it should be superimposable of younger patients, with the aim of obtaining deep molecular response and sometimes also permanent TKI discontinuation. In the current clinical practice, imatinib and other TKIs are widely used also in older patients with CML [13–15]; however, what is the best dosage and what are the possible dose adjustments based on tolerance and side effects are still unclear issues in this specific setting. In the "real world" clinical practice, often physicians choose to treat older CML patients with TKIs at reduced dose in order to avoid the onset of side effects.

Aim of the present study was to analyze the use of frontline TKI therapy in a large and unselected cohort of older (≥75 years old) chronic phase (CP) CML patients.

2 | Materials and Methods

2.1 | Inclusion Criteria

Thirty-six centers belonging to CAMPUS-CML project, an active research network of physicians involved in CML management throughout Italy, were asked to collect data on all consecutive newly diagnosed CML patients from January 2012 to December 2019 in order to have at least 4 years follow-up. At the start of the frontline TKI, patients had to fulfill the following inclusion criteria, regardless of their enrollment or not in controlled clinical trials:

- Age ≥75 years
- CP of disease

The following key disease characteristics were recorded for each patient aged over 75 years: socio-demographic and clinical variables, risk scores (Sokal and ELTS), type of TKI, and starting dose. Any clinical illness requiring specific, prolonged treatment, as well as previous cancers, was considered as concomitant disease. The number of drugs required by each patient to manage concomitant diseases was also recorded.

2.2 | Statistical Analysis

Data were expressed as mean ± standard deviation (normally distributed data), median, and interquartile range (IQR; non-normally distributed data), or as percentage frequencies, and within-patient comparisons were made by paired t-test and χ^2 test, as appropriate, at significance levels of $p < 0.05$.

3 | Results

Overall, out of 1929 CP-CML patients, 332 aged ≥75 years at CML diagnosis were retrospectively evaluated. Median age of patients at TKI start was 79.3 years (IQR 77.1–82.5).

As to frontline TKI treatment, 285 patients (85.8%) received imatinib and 47 (14.2%) a second generation TKI. Among patients treated with a second generation TKI, 28 (59.5%), started with dasatinib and 19 (40.5%) with nilotinib. No patients received bosutinib since the drug was reimbursed in Italy in first line from 2019.

Among patients treated with imatinib, 192 (67.3%) started with a standard dose (400 mg/day) and 93 (32.7%) with a reduced dose (300 mg/day $n = 64$, 22.5%; <300 mg/day $n = 29$, 10.2%). Among patients treated with imatinib <300 mg/day, 25 (86%) started with 200 mg/day while the remaining 4 (14%) with a minimum dose of 100 mg/day.

In the group of patients starting a 2G-TKIs, 35 (74.4%) received initial standard doses and 12 (25.6%) a reduced dose: in particular, 3 patients started with nilotinib <600 mg/day, 4 with dasatinib 80 mg/day, and 5 with dasatinib 50 mg/day.

At univariate analysis, there were no differences between patients treated with imatinib or 2G-TKI (Table 1); age at TKI start ($p = 0.208$), Sokal score ($p = 0.570$), ELTS score ($p = 0.214$), and number of concomitant drugs ($p = 0.584$) were all not significant for the choice of first line TKI. As concern comorbidities, only a previous cerebrovascular event was reported as significant for the choice of frontline TKI ($p = 0.043$), as no patients with this type of vascular event was treated with second generation TKI.

Even if no statistical difference exists due to the low number of patients treated with second generation TKI, the distinct toxicity profiles of nilotinib and dasatinib had an impact on the choice and no patient with diabetes or ischemic heart disease was treated with nilotinib.

The choice of first line TKI in this subset of very elderly patients was also analyzed according to the introduction of generic imatinib in Italy in early 2018. With this purpose, the entire cohort was divided in two groups: the first one with 238 subjects diagnosed from 2012 to 2017 and the second one with 94 subjects diagnosed in 2018–2019 after the advent of generic imatinib. In the first group, 198 patients (83.1%) received imatinib and 40 (16.9%) a 2G-TKI, while in the second group 87 patients (92.5%) were treated with imatinib and 7 (7.5%) with a 2G-TKI ($p = 0.028$) (Figure 1).

TABLE 1 | Main clinical features of entire cohort and according to frontline TKI choice.

	All patients (332)	Frontline imatinib (285)	Frontline 2G-TKI (47)	*p*
Gender, M/F (%)	188/144 (56.6–43.4)	165/120 (57.9–42.1)	23/24 (48.9–51.1)	0.251
Median age (years) (IQR)	79.3 (77.1–82.5)	79.5 (77.2–82.7)	78.9 (76.9–81.1)	0.208
Hb, g/dL (IQR)	12.4 (10.9–13.7)	12.2 (10.7–13.6)	13.0 (11.4–14.6)	0.424
WBC, $\times 10^3/mm^3$ (IQR)	43.0 (26.5–86.2)	45.0 (26.3–91.2)	41.1 (28.6–69.4)	0.521
PLTS, $\times 10^3/mm^3$ (IQR)	364 (227–585)	351 (227–565)	452 (212–702)	0.314
Spleen, n° evaluable (%):	320	276	44	0.349
Not palpable	198 (61.9)	175 (63.4)	23 (52.2)	
<5 cm below costal margin	96 (30.0)	80 (29.0)	16 (36.4)	
≥5 cm below costal margin	26 (8.1)	21 (7.6)	5 (11.4)	
Sokal score, n° evaluable (%):	316	271	45	0.570
Low	13 (4.1)	12 (4.4)	1 (2.3)	
Intermediate	215 (68.1)	186 (68.6)	29 (64.4)	
High	88 (27.8)	73 (27.0)	15 (33.3)	
ELTS score, n° evaluable (%):	305	263	42	0.214
Low	41 (13.4)	32 (12.2)	9 (21.4)	
Intermediate	162 (53.1)	140 (53.2)	22 (52.4)	
High	102 (33.5)	91 (34.6)	11 (26.2)	
Arterial hypertension, n° (%)	218 (65.7)	188 (66.2)	30 (63.8)	0.751
Diabetes, n° (%)	66 (19.9)	57 (20.1)	9 (19.1)	0.884
Previous neoplasm, n° (%)	76 (22.9)	65 (22.9)	11 (23.4)	0.938
COPD, n° (%)	59 (17.8)	49 (17.3)	10 (21.3)	0.512
Ischemic heart disease, n° (%)	44 (13.3)	41 (14.4)	3 (6.4)	0.132
Cerebrovascular events, n° (%)	23 (6.9)	23 (8.1)	0	0.043
Concomitant drugs, n° evaluable (%):	315	269	46	0.584
0–2	99 (31.4)	81 (30.1)	18 (39.1)	
3–5	124 (39.4)	109 (40.5)	15 (32.6)	
>5	92 (29.2)	79 (29.4)	13 (28.3)	

Data on the first 12 months of treatment were available in 306/332 patients (92.2%). Concerning outcome, major molecular response or deeper at the 3rd, 6th, and 12th month was achieved by 8.8%, 23.2%, and 38.2% of patients, respectively. (Table 2). On the whole, 219 patients (71.6%) were still in treatment with frontline TKI at the 12th month, while 87 (28.4%) permanently discontinued frontline TKI due to early adverse events: the different types of early adverse events leading to frontline TKI discontinuation are listed in Table 3.

Cumulative incidence of permanent frontline TKI discontinuation for the entire cohort at the 3rd, 6th, and 12th month was 9.5% (95%CI 6.2–12.8), 17.4% (95%CI 13.1–21.7), and 27.6% (95%CI 22.5–32.7), respectively.

Cumulative incidence of discontinuation was similar between patients treated with standard or reduced doses of imatinib (Figure 2). Major molecular response or deeper at 12th month was superimposable between patients treated with TKI standard dose or reduced dose, being superior in patients treated with 2nd generation TKI. (Table 4).

The only features at baseline related to a higher cumulative rate of permanent frontline TKI discontinuation were WBC $>100\times10^3/mm^3$ ($p=0.006$) and Hb levels <10 g/dL ($p=0.046$); gender ($p=0.627$), arterial hypertension ($p=0.246$), diabetes ($p=0.696$), COPD ($p=0.300$), previous neoplasia ($p=0.291$), number of concomitant drugs ($p=0.918$), PLT number ($p=0.522$), spleen enlargement ($p=0.229$), Sokal score

($p = 0.157$), ELTS score ($p = 0.594$), and type of TKI ($p = 0.147$) did not affect the rate of frontline TKI discontinuation.

4 | Discussion

After the introduction of TKIs, most of the literature regarding the efficacy and safety of imatinib showed that this drug overcomes the negative impact of age on response rate and survival [13]: in imatinib-treated elderly patients, the rates of complete cytogenetic and major molecular responses were comparable to those of adult patients (30–59 years old) and even higher than those in young adults (18–29 years old), with significantly lower probability of transformation to advanced phases. However, the overall survival of elderly patients was inferior due to deaths unrelated to CML [16]. Therefore, all the patients with CML, irrespective of their age, should be treated with TKIs as first-line therapy [15, 17–19].

The subsequent approval of 2G-TKIs for first-line treatment of CML allowed the possibility to treat even the elderly with these drugs, with a significant proportion of patients achieving optimal response at the 3-month milestone and an equally efficacy when comparing response data of older patients with younger CML, in both first and second lines [20–24]. It is also important to underline that age per se lost its prognostic relevance in the TKI era, as reported in many studies: however, it remains one factor in calculating risk of disease for new patients in both Sokal and ELTS scores. As a consequence, as reported in our cohort, quite all patients aged >75 years fall in the intermediate/high risk categories mainly for older age, leading to an overestimation of the real risk of disease: in our opinion, a new score system independent by the age is thus warranted in this subset of patients.

In a recent real-world report on the safety and efficacy of nilotinib as first-line treatment in elderly patients (>65 years) with CP CML, 85% of subjects started treatment at the standard dose (300 mg BID), with 10% of patients reporting cardiovascular events after a median time of 20.9 months from the start, demonstrating that nilotinib could be effective and relatively safe even in elderly [25]. On the other hand, dasatinib was effective with an acceptable toxicity in very elderly patients (>75 years), as reported by Stagno et al. [26]: in this real-life retrospective

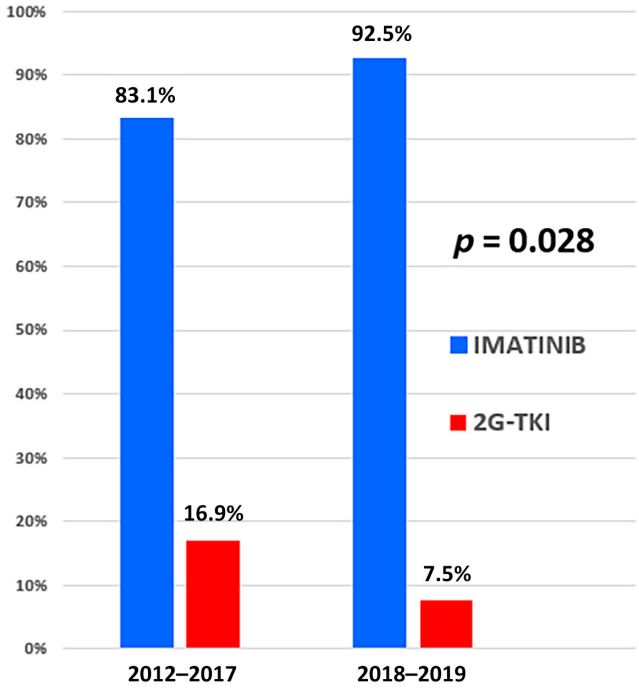

FIGURE 1 | Frontline TKI choice before and after generic imatinib introduction.

TABLE 3 | Different adverse events leading to permanent frontline TKI discontinuation.

Type of adverse event	Number of patients	%
Hematologic toxicity	10	3.3
Extra-hematologic toxicity	29	9.5
Primary resistance	31	10.1
Secondary resistance	1	0.3
Blast phase evolution	4	1.2
Unrelated death	10	3.3
Other	2	0.7

TABLE 2 | Molecular response at different time-points in the whole cohort.

	3rd month	6th month	12th month
Evaluable	306	306	306
Not done	46 (15.0%)	33 (10.8%)	23 (7.5%)
Already discontinued	17 (5.6%)	36 (11.8%)	87 (28.5%)
No MR	148 (48.3%)	82 (26.8%)	33 (10.8%)
MR 2.0	68 (22.2%)	84 (27.4%)	46 (15.0%)
MR	27 (8.8%)	71 (23.2%)	117 (38.2%)
MR 3.0	18 (5.8%)	44 (14.4%)	62 (20.3%)
MR 4.0	3 (1.0%)	14 (4.6%)	23 (7.5%)
MR 4.5	6 (2.0%)	13 (4.2%)	32 (10.4%)

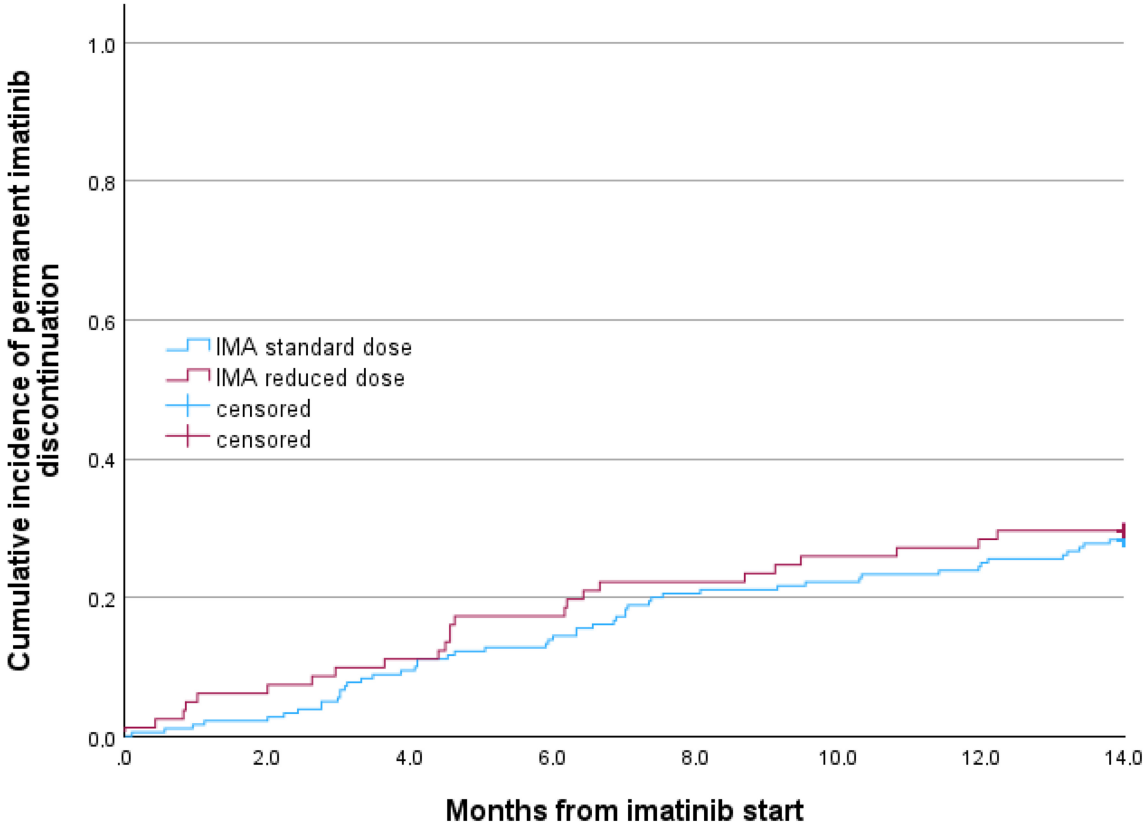

FIGURE 2 | Cumulative incidence of permanent discontinuation according to initial imatinib dose ($p = 0.736$).

analysis, dasatinib was started at the standard dose of 100 mg/day in 77.7% of patients, with acceptable Grade 3 and 4 both hematologic and non-hematologic side-effects [27].

The challenge to treat older patients is related to the higher proportion of concomitant comorbidities, so that a more flexible dosing scheme may be warranted to increase tolerability while maintaining efficacy: personalized selection of the most appropriate TKI and dosage are of paramount importance to guarantee long-term safety and compliance. Different sponsored trials and real-life series demonstrated that dose reduction did not affect the efficacy of treatment, even with a possible impairment in achieving TFR [28]. However, regarding this specific topic, a recent real-life study by Iurlo et al. [29] demonstrated that the use of low-dose TKIs did not appear to affect the likelihood of achieving a DMR and consequently the possibility of TFR. When choosing 2G-TKI treatment in first line, however, surveillance and optimal management of side effects are important to enable long-term continuous therapy, overcoming the impact of comorbidities. In our cohort of very elderly patients, imatinib was the predominant choice as expected, but a sizeable rate of patients (14.2%) were treated with 2G-TKIs. A reduced starting dose was used in 32.7% and 25.6% of patients treated with imatinib or second generation TKI, respectively. The lower rate of patients treated with second generation TKIs at reduced doses is probably due to the selection of the most fitting cases for this approach, thus not requiring dose reduction.

Interestingly, no correlation was found between first line TKI and number of concomitant drugs, probably more related to the TKI dosage than TKI type. It is to be underlined the lack of statistical power due to the low number of same events like ischemic heart diseases.

Combining these considerations and outside clinical trials, our data highlight that CML very elderly patients without comorbidities should be managed in the same way as younger patients and it could be a reasonable policy to offer them a 2G-TKIs, with sometimes also the aim of treatment discontinuation. Conversely, imatinib probably remains the best option to manage very elderly patients with severe comorbidities, when treatment discontinuation is not the main objective. In very elderly patients with mild–moderate comorbidities, imatinib should be preferred but second generation TKIs might be used, selecting dasatinib or nilotinib according to the kind of comorbidity.

However, elderly patients, especially those older than 75 years, are a heterogeneous group in which also polypharmacy and socio-economic considerations may be of concern. The advent of generic imatinib, since 2018 in Italy, had an impact on the choice of first line TKI, since a larger rate of patients (92.5%) than before was treated with generic imatinib. It is also a matter of debate if the advent of COVID19 pandemic had an impact on the treatment choice, since the use of imatinib may be related to less monitoring and consequent less hospital admissions for side effects surveillance. Anyway, a retro-prospective analysis of patients with CML treated with generic imatinib in 12 Italian institutions demonstrated that generic imatinib does not have deleterious effects on CML control and present an acceptable safety profile, similar to the brand imatinib [30], with unquestionably reduction of economic burden for CML treatment. As a consequence, gathering all these aspects, it is reasonable that

TABLE 4 | Molecular response at the 12th month according to initial TKI dose.

	IMA		2G-TKI	
	400 mg	**<400 mg**	**Standard dose**	**Reduced dose**
Evaluable	182	82	30	12
Not done	11 (6.0%)	10 (12.1%)	1 (3.3%)	/
Already discontinued	54 (29.7%)	25 (30.4%)	6 (20.0%)	2 (16.7%)
No MR	17 (9.4%)	16 (19.5%)	/	/
MR 2.0	31 (17.0%)	14 (17.1%)	2 (6.7%)	/
MR				
MR 3.0	36 (19.8%)	11 (13.4%)	9 (30.0%)	6 (50.0%)
MR 4.0	13 (7.1%)	4 (4.9%)	3 (10.0%)	2 (16.7%)
MR 4.5	20 (11.0%)	2 (2.4%)	9 (30.0%)	2 (16.7%)

generic imatinib will represent the first line choice for very elderly patients in Italy.

Concerning early events, in our cohort, cumulative incidence of permanent frontline TKI discontinuation at 12th month was 28.4%, with primary resistance as the main reason for switching therapy (10.1%) followed by extra-hematologic toxicity (9.5%).

Interestingly, type of TKI did not affect the rate of frontline TKI discontinuation.

These data seem superimposable to that reported in a recent retrospective real world study in which the rate of CML elderly patients requiring switch to second-line therapy was 25.2%, being also in this cohort resistance to treatment the primary reason for first line discontinuation [31].

Progression to blast phase was reported in 1.2% of patients while four patients (3.3%) died for CML unrelated death.

5 | Conclusions

Imatinib remains the frontline drug of choice in older CML patients followed in Italian institutions, and this trend seems to increase after the introduction of the generic formulation. However, 2G-TKIs are used in a small but sizeable group of patients, without a clear correlation with baseline CML features, thus probably reflecting a physician's evaluation of patient's fitness and/or expectation. Dose reduction strategies represent reasonable approaches in this setting of older patients, aiming to achieve molecular response, improve treatment adherence, and avoid toxicity. As a direct comparison between elderly aged over 65 and less than 75 years is missing, also efficacy of initial reduced TKIs doses in this setting warrant further analyses.

Author Contributions

C. Bucelli: study design, data interpretation, and writing – original draft. **R. Latagliata:** study design, analysis, data interpretation, and writing – original draft. **I. Capodanno, M. C. Miggiano, F. Cavazzini, S. Leonetti Crescenzi, S. Russo, I. Carmosino, M. Annunziata, F. Sorà, M. Bonifacio, L. Luciano, G. Caocci, G. Loglisci, C. Elena, F. Lunghi, R. Mullai, I. Attolico, G. Binotto, E. Crisà, P. Sportoletti, A. Di Veroli, A. R. Scortechini, A. P. Leporace, A. Maggi, M. Crugnola, F. Stagno, R. Sancetta, P. Murgano, D. Rapezzi, D. Luzi, D. I. Vincelli, S. Galimberti, M. Bocchia, C. Fava, A. Malato, E. Abruzzese:** data collection. **G. Saglio, G. Specchia, M. Breccia, A. Iurlo, M. Tiribelli:** writing – review and editing.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Statement

Ethics declaration approval and consent to participate data on patients were retrospectively collected by the 1975 guidelines of the of Helsinki.

Data Availability Statement

The data reported in this manuscript are available from the corresponding author upon reasonable request.

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