Real-world evidence of imatinib treatment in younger and older patients with chronic myeloid leukaemia: A retrospective single centre analysis

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Abstract. Chronic myeloid leukaemia (CML) is characterized by the genetic alteration BCR-ABL. The introduction of the tyrosine kinase inhibitor (TKI), imatinib, in 2002, inhibiting BCR-ABL signalling, has revolutionized CML therapy and is still one of the preferred first-line treatment options. The present study aimed to assess possible differences in older and younger patients with BCR-ABL-positive CML treated with imatinib, with regards to remission rates, remission depth, remission duration or discontinuation of imatinib due to adverse events. Data was collected retrospectively from the records of patients with BCR-ABL-positive CML treated with imatinib at the University Hospital Krems from January 2011 to December 2021. Exclusion criteria included the administration of other first line therapies besides imatinib, an age of <18 years or other cancer types. Overall, 22 patients were included in the present study and separated into two age groups: <60 and ≥60 years old. The results revealed no significant difference in remission rates, remission depth, progression-free survival or overall survival between these age groups. In conclusion, the findings indicate that the TKI, imatinib, is highly effective and well tolerated in both younger and older patients with CML. However, further studies with larger patient groups and the inclusion of newer TKIs are required.

Introduction

Chronic myeloid leukaemia (CML) is a neoplastic disease of hematopoietic stem cells (1). Reports from European CML registries show incidence rates ranging from 0,7-1/100.000 persons per year. The incidence rises with age, and men are more likely to develop CML than women. Both sexes have an incidence peak of between 57-60 years of age (2). However, notably, the disease burden of CML has decreased globally in the past 3 decades in countries with high social-demographic indices. Programmes to control modifiable risk factors such as smoking and high body mass index may be helpful in further diminishing the mortality of this disease (3).

The majority of patients with CML harbour the pathognomonic BCR-ABL gene. This specific cytogenic aberration is distinguished by a reciprocal translocation of chromosomes 9 and 22. The BCR-ABL gene is formed on chromosome 22, when a subunit of chromosome 9 attaches, and this newly formed chromosome 22 is called the 'Philadelphia Chromosome' (4).

CML is a triphasic disease comprising a chronic phase, an accelerated phase and, finally, the terminal blast crisis. Most patients are diagnosed and start their treatment in the chronic phase (5).

Imatinib is a tyrosine kinase inhibitor (TKI), which was approved by the United States Food and Drug Administration in 2001 for the first-line treatment of BCR-ABL-positive CML, and it is still one of the preferred choices of treatment agents. However, if a patient does not respond to imatinib, second- and third-generation TKIs can be applied. A curative treatment approach is allogeneic stem cell transplantation (6). Moreover, the goal of treatment in CML is to achieve a complete remission under TKI application. The endpoints for treatment efficacy are either the normalization of blood cell count, loss of the Philadelphia Chromosome, or a specific decrease in BCR-ABL gene expression, which are classified as complete hematologic response, complete cytogenetic response and complete molecular response (CMR), respectively (7).

Imatinib is the first approved TKI in this indication and still represents one of the standard first-line therapies, regardless of age (6). Older patients are often underrepresented in clinical studies due to stringent inclusion and exclusion criteria of co-morbidities; however, they comprise a high percentage of haemato-oncological patients in real-world settings. Therefore, the present study aimed to determine to what extent older patients with CML differ from younger patients in terms of response and tolerability of imatinib.

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Patients and methods

Study design and population. The present study had a single-centre retrospective design. Patients diagnosed with BCR-ABL positive CML and treated with imatinib between January 2011 and December 2021 at the University Hospital Krems (Krems, Austria) were included in the analysis. Patients with a first-line therapy other than imatinib, were aged <18 years of age or were diagnosed other cancer types were excluded.

Included patients were divided into 2 groups: Patients aged ≥60 years and patients aged <60 years at the onset of treatment with imatinib. The United Nations define 'older' people as those aged ≥60 years (emergency.unhcr.org/protection/persons-risk/older-persons; accessed April 24, 2025); therefore, this age limit was chosen.

The present study was approved by the Institutional Review Board and the Ethics Committee of the Lower Austria federal state (approval no. GS4-EK-4/825-2022), which is the legal entity of the 'Niederösterreichische Landesgesundheitsagentur' that operates all hospitals in Lower Austria, including the University Hospital Krems. Furthermore, the present was performed according to the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was waived by the Commission for Scientific Integrity and Ethics at the Karl Landsteiner University of Health Sciences.

Data collection. Patients were identified via the International Classification of Diseases-10 Code C92.1. Data were taken from the electronic records of the routine medical visits of patients. Information was stored either at the data management system 'Medical Process Administrator' implemented at the University Hospital Krems or the 'Oncology Information System' of Lower Austria. The information on remission rates was obtained from case records. The CMR was used to obtain information about remission rate, duration and depth.

Data on remission depth was acquired by reviewing reverse transcription-quantitative polymerase chain reaction (RT-qPCR) tests detecting the BCR-ABL1 gene. These tests were performed by the commercial provider Labdia Labordiagnostik GmbH. The specific forward and reverse primer sequences, including that of the normalization control, used for RT-qPCR were not disclosed by the company. CMR was defined as CMR 3, CMR 4 or CMR 4,5: CMR 3, also known as major molecular response, was defined as ≤0.1% BCR-ABL1 international scale (IS) or ≥3.0 log reduction; CMR 4 was defined as ≤0.01% BCR-ABL1 IS or ≥4.0 log reduction; and CMR 4,5 was defined as ≤0.0032% BCR-ABL1 IS or ≥4.5 log reduction. The limit for a detectable BCR-ABL1 gene level was set to 0.000319.

Variables under consideration were stage at diagnosis, remission rate, remission duration, remission depth, relapse, duration of medication, side effects and survival.

Statistical analysis. The following patient characteristics were analysed descriptively: Age; sex; stage at initial diagnosis; lactate dehydrogenase (LDH) level at diagnosis; LDH at the start of imatinib therapy; spleen size at the start of imatinib therapy; number of leukocytes at diagnosis; and number of leukocytes at the start of imatinib therapy. The parameter spleen size was divided into 2 groups: Normal spleen, <12 cm in length; and enlarged spleen, ≥12 cm in length.

The normality of the two persistent variables were assessed using the Shapiro-Wilk test, and for group comparisons, the Mann-Whitney test was used. Categorical variables were assessed using the χ^2 test or Fisher's exact test. Overall survival (OS) and progression-free survival (PFS) were assessed using Kaplan-Meier curves and evaluated using the log-rank test. An OS event was defined by death, whereas PFS was defined as progression of disease or death from any cause.

The data were analysed according to an intent to treat approach: Each patient that received first-line therapy with an imatinib regimen was eligible.

All statistical analyses were performed using SPSS v26 (IBM Corp.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients' characteristics. The present retrospective single-centre analysis included patients with BCR-ABL-positive CML who were treated with imatinib between January 2011 and December 2021 at the University Hospital Krems. A total of 22 patients were included, of whom 9 were aged ≥60 years ('older' group) and 13 were aged <60 years ('younger' group). Moreover, 5/22 patients were female. All patients were diagnosed in a chronic state of CML. The median age was 44 years in the younger group and 73 years in the older group. The median LDH level at diagnosis was 457 U/l in the younger group and 413 U/l in the older group (normal range, 20-250 U/l). The median LDH level at the start of imatinib therapy was lower, with a median value of 428 U/l in the younger group and 385 U/l in the older group. The LDH levels ranged from 204-1,027 U/l at diagnosis and 168-934 U/l at the start of imatinib therapy. The median white blood cell (WBC) level at diagnosis was 61.45 G/l in the younger group and 38.51 G/l in the older group (normal laboratory reference value, 3.90-10.20 G/l). By contrast, the median WBC level at the start of imatinib therapy was 51.69 G/l in the younger group and 30.25 G/l in the older group. Overall, the WBC level at diagnosis ranged from 12.73-421.94 G/l and 11.08-156.55 G/l at the start of imatinib therapy (Table I).

Spleen size was categorized into 2 groups: Normal and enlarged. In the younger group, 10 patients had enlarged spleens, two had normal-sized spleens and one patient had no record of spleen size. No splenectomies were reported in this group. A total of 5 patients had normal-sized spleens in the older group, two had enlarged spleens and one patient had no record of spleen size. In this group, one patient underwent a splenectomy prior to CML diagnosis (Table I).

Treatment discontinuation due to progression or side effects. Overall, 5/22 patients (22.7%) had to end imatinib therapy due to disease progression. Moreover, 4/22 patients (18,2%) ended imatinib therapy due to side effects during treatment, comprising severe nausea, joint pain, bloating, lack of concentration, fatigue, exanthema, oedema, pruritus, muscle cramping and wound healing disorder.

Table I. Patient characteristics (n=22).

Parameter	Age group	
	<60 years	≥60 years
Sex		
Male	9 (69)	8 (89)
Female	4 (31)	1 (11)
Age, years	44 (23, 57)	73 (60, 86)
Diagnosis in chronic stage	13 (100)	9 (100)
LDH, U/l		
At diagnosis	457 (237, 1,027)	413 (204, 878)
At start of imatinib therapy	428 (243, 934)	385 (168, 642)
WBC, G/l		
At diagnosis	61.45 (14.77, 421.94)	38.51 (12.73, 195.47)
At start of imatinib therapy	51.69 (14.77, 156.55)	30.25 (11.08, 56.89)
Spleen size		
Normal	2 (15.4)	7 (55.6)
Enlarged	10 (76.9)	2 (22.2)
Missing data	1 (7.7)	1 (11.1)
Splenectomy performed prior to CML diagnosis	0 (0)	1 (11.1)

Data are presented as n (%) or median (min, max). LDH, lactate dehydrogenase; WBC, white blood cell; CML, chronic myeloid leukaemia.

Table II. Remission rate.

Group	Remission (%)		Total
	No	Yes	
<60 years	5 (38.5)	8 (61.5)	13
≥60 years	4 (44.4)	5 (55.6)	9
Total	9 (41.0)	13 (59.0)	22

In the younger group, 3/13 patients (23.1%) had to end imatinib therapy due to progression and 1/13 (7.7%) ended the therapy due to side effects. In the older group, 2/9 patients (22.2%) had to end imatinib therapy due to progression and 3/9 (33.3%) due to side effects. Furthermore, 1/9 (11.1%) patients in the older group died; however, this was not associated with CML.

Remission rates. Overall, 13/22 patients (59.1%) went into remission, of which eight were aged <60 years (61.5%) and five were aged ≥60 years old (55.6%) (Table II). No significant difference in the remission rates between the different age groups was demonstrated.

Remission depth. A total of 61.5% of patients went into remission in the younger group, compared with 55.6% in the older group. A total of 6 patients in the younger group (46.2%) and 3 in the older group (33.3%) achieved CMR 4,5 (Fig. 1). In both groups, one patient achieved CMR 4 (younger group, 7.7%; older group, 11.1%). Moreover, one patient achieved CMR 3

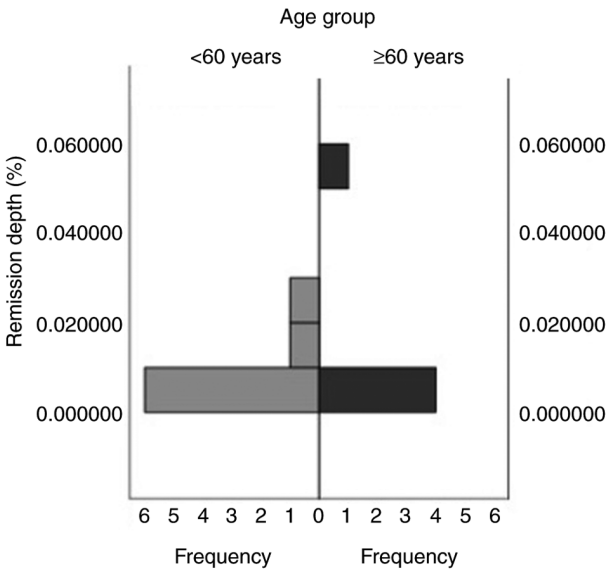

Figure 1. Remission depth (complete molecular remission).

in both groups. No significant difference was demonstrated between the two age groups with regard to remission depth.

OS. Only 1 patient included in the present study died (4.5%), who belonged to the older group (11.1%). Thus, a 10-year survival rate of 100% in the younger group and 90% in the older group was observed. Kaplan-Meier curves were plotted, and a log-rank test was performed to assess any significant differences between the 2 groups. The results revealed a nonsignificant P-value of 0.229 (Fig. 2).

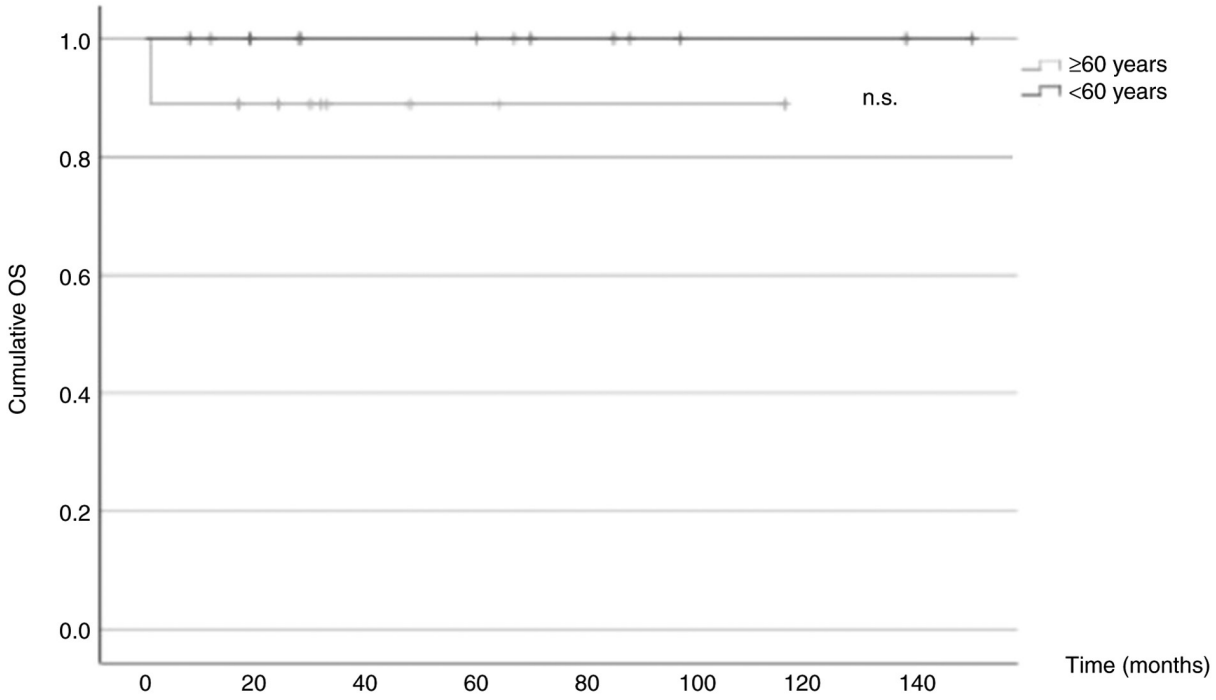

Figure 2. Kaplan-Meier curve of OS. OS, overall survival; n.s., not significant.

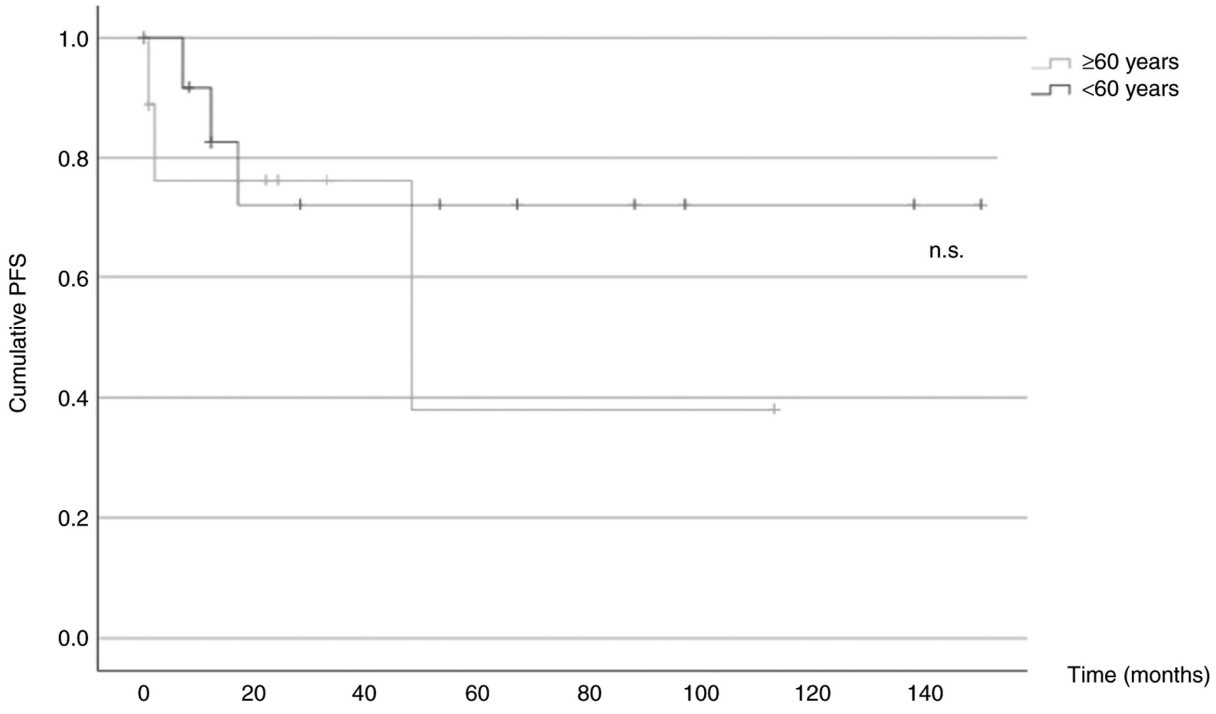

Figure 3. Kaplan-Meier curve of PFS. PFS, progression-free survival; n.s., not significant.

PFS. A total of 5/22 patients (22.7%) experienced disease progression, with 2/9 patients (22.2%) in the older group and 3/13 patients (23.1%) in the younger group. Kaplan-Meier curves were plotted, and a log-rank test was performed to assess any significant differences between the 2 groups (95% confidence interval, 36.1-115.5 in the older cohort vs. 74.6-148.9 in the younger cohort). The results revealed a nonsignificant P-value of 0.485 (Fig. 3).

Discussion

In total, 22 patients were included in the present analysis, of whom five were female. An overlap of men was expected, as there is a higher prevalence of CML in men than women (8), however not to such a high extent. In the present study, the relatively small sample size likely caused this shift. Moreover, all the patients in the present study were diagnosed in the chronic

phase. As a CML diagnosis is typically made in the chronic phase (8), no difference in the two groups was to be expected in this regard.

The median LDH level at diagnosis was 457 U/l in the younger group and 413 U/l in the older group; however, the median LDH level at the start of imatinib therapy was lower compared with their respective median LDH at diagnosis, with a median level of 428 U/l in the younger group and 385 U/l in the older group. Moreover, when comparing the median WBC level at diagnosis with that at the start of imatinib therapy, both groups demonstrated a lower median WBC level at the start of imatinib therapy. The median WBC at diagnosis was 61.45 G/l in the younger group and 38.51 G/l in the older group. In comparison, the median WBC at the start of imatinib therapy was 51.69 G/l in the younger group and 30.25 G/l in the older group. Overall, the WBC at diagnosis ranged from 12.73-421.94 G/l and the WBC at the start of therapy start ranged from 11.08-156.55 G/l. These findings were expected as most patients with newly diagnosed CML receive hydroxyurea before the start of TKI therapy which leads to a reduction in the levels of WBC, reticulocytes and LDH (9). Hydroxyurea is a chemical agent which suppresses bone marrow activity, initiates megaloblastosis and produces antitumour effects (9). It can be useful in the primary management of CML until the BCR-ABL1 gene is confirmed. The medication is usually started if patients suffer from symptoms and/or when the leucocyte count is very high. To reduce the risk of hyperviscosity syndrome, hydroxyurea is administered until the TKI is started (9).

Similar to the present research, a study by Castagnetti *et al* (10) assessed the differences in patients with CML between those classed as 'young adults' (18-29 years old), 'adults' (30-59 years old) and 'elderly' (>60 years old) by promoting several multicentric prospective clinical studies over a time span of 40 years. The authors collected data on the hematologic characteristic of patients before the start of any treatment and the study reported that the young adults had a median WBC level at diagnosis of 61 G/l (range, 15-880 G/l), the adults had a median WBC level at diagnosis of 57 G/l (range, 13-780 G/l) and the elderly had a median WBC level at diagnosis of 59 G/l (12-544 G/l). These results indicate that the maximum WBC levels decline with age, a finding that was also demonstrated in the present study, where patients in the younger group had WBC levels at diagnosis ranging from 14.77-421.94 G/l and older patients had WBC levels at diagnosis ranging from 12.73-195,42 G/l.

Spleen size was categorized into 2 groups: Normal and enlarged. In the younger group, 76.9% of spleens were enlarged (n=10), whereas only 15.4% (n=2) were of normal size. Furthermore, one patient had no record of spleen size (7.7%) and there were no splenectomies performed in this group. By contrast, 55.6% of the spleens in the older group were of normal size (n=5) and only 22.2% (n=2) were enlarged. Additionally, one patient had no record of spleen size (11.1%) and one patient underwent a splenectomy (11.1%) prior to CML diagnosis. The aforementioned study by Castagnetti *et al* (10) also assessed the differences in spleen size among young adults (18-29 years old), adults (30-59 years old) and the elderly (>60 years old). The study reported that 71% of the young adults had enlarged spleens, followed by 63% of the adults and 55% of the elderly. These results support the findings of the present study of an increased number of enlarged spleens in the younger patient cohort (<60 years).

In the present study, 59.01% of all patients went into remission. A total of 8 (61.5%) were in the younger group, compared with 5 (55.6%) in the older group; however, this difference was not statistically significant. In-line with this finding, a study by Saussele *et al* (11) reported that age was not a relevant marker for remission rate in the TKI era. Another study by Cortes *et al* (12) evaluated the effects of age on prognosis in patients with CML and divided their study group into patients aged ≥60 and <60 years. The study reported that there was no significant difference in remission rates between the two age groups. However, a marked difference between the study by Cortes *et al* and the present study is that Cortes *et al* treated their patients with imatinib after failed interferon-α therapy. The authors suggested that the association between CML therapy and older age in regard to prognosis notably diminished, whereas allogeneic transplantation or interferon-α therapy are associated with numerous side effects in elder patients. Therefore, the generally well-tolerated modern treatment with imatinib and higher-generation TKIs could be the reason for the lack of differences in remission rates between different age groups.

Furthermore, of the 13/22 (59.1%) patients that went into remission in the present study, most achieved CMR 4.5 (younger group, 46.2%; older group, 33.3%). Moreover, one patient in both groups achieved CMR 4 (younger group, 7.7%; older group, 11.1%). Additionally, in both groups there was 1 patient who achieved CMR 3. In the aforementioned study by Cortes *et al* (12), no difference in remission rates was reported between the two age groups (<60 and ≥60 years old); however, there was a difference in remission depth. A total of 44% of the older patient group had attained complete cytogenetic remission in comparison with the younger group (56%). However, a 10-year observation of patients in the randomized CML-study IV, who were distributed into four different age groups (16-29, 30-44, 45-59 and ≥60 years), reported that there were no significant differences in CMR 4 (13).

In the present study, 27.3% of patients had to end the therapy due to side effects, such as severe nausea, joint pain, bloating, lack of concentration, fatigue, exanthema, oedema, pruritus, muscle cramping and wound healing disorder (younger group, 23.1%; older group, 33.3%). Only 1/9 (11.1%) patients in the older group died, and none in the younger group. Adattini *et al* (14) assessed the efficacy and safety of first-line imatinib treatment in patients with CML with a mean age of 55 years. The study reported side effects comprising anaemia, superficial oedema, leukopenia, neutropenia, thrombocytopenia, fatigue, muscle cramps and infection as the most frequent. In the study, all 89 included patients experienced at least one adverse effect associated with imatinib treatment.

Additionally, in the present study, 22.7% of patients had to end imatinib therapy due to disease progression (younger group, 23.1%; older group, 11.1%). There was also no significant difference between the PFS of the two age groups. Progression of disease can occur due to several reasons, such as mutations of the BCR-ABL gene, development of resistances or a low cytogenetic response (15). In the study by Adattini *et al* (14), 31% of all patients had to discontinue their

treatment with imatinib due to poor response. Furthermore, the study analysed the probability of having to switch to a second- or third-generation TKI, resulting in a 15% chance of switching therapy within 12 months, 27% within 2 years and 46% within 5 years upon initiation of imatinib therapy. In the study by Castagnetti *et al* (10), which compared young adults (18-29 years old), adults (30-59 years old) and the elderly (>60 years old), the probability of disease progression at 8 years was 16% among the young adults, 5% among the adults and 7% among the elderly. Another study by Gugliotta *et al* (15) assessed age differences in patients treated with imatinib and divided 559 included patients into two groups (<65 and ≥65 years old). The PFS for the patient group of <65 years old was 90%, whereas patients aged ≥65 years had an PFS of 75%. However, after excluding the deaths unrelated to CML progression, the PFS was 93 and 91% for patients aged <65 and ≥65 years, respectively. The results of the present study revealed no significant difference between the younger and older patients regarding PFS, which is in-line with the literature.

In the present study cohort, 1/22 (4.5%) patients died at the age of 83, and this was not due to CML. These findings lead to a 10-year overall survival rate of 100% in the younger group and 90% in the older group. This difference in OS was not statistically significant. Cortes *et al* (12) also reported that age had no impact on either achieving response or survival. Moreover, the study by Castagnetti *et al* (10) reported an 8-year survival rate of 93% in the young adult group, 95% in the adult group and 89% in the elderly cohort. These findings suggest that there is no significant difference in OS between older and younger patients, when investigating CML-related deaths. Furthermore, imatinib is still among the preferred first-line therapy options for CML treatment, as in comparison with higher-generation TKIs such as nilotinib and dasatinib, no significant differences in OS have been reported (16,17).

The present study has certain limitations. As it was retrospective, there was a risk of selection bias and the influence of confounding factors, meaning that the study population could be biased toward a particular subgroup. Therefore, the results may not reflect the true population, which makes it difficult to generalize the findings to broader groups. Another limitation is the small sample size, as it was performed at a single centre. Variations in entry dates and differences in follow-up durations may have also affected the results. Additionally, the statistical approach of the study was not designed to determine the strength of associations. Notably, both a small sample size and selection bias exacerbate the impact of each other: A small sample size increases the risk that any biases in the selection of participants will distort the findings, and the limited sample may be disproportionately affected by these biases, reducing the robustness of the conclusions of the study. For future research, larger studies are needed to enable subgroup analyses and account for confounding factors such as co-existing health conditions and other clinical characteristics. Moreover, real-world data from multiple centres should be collected and further investigated in meta-analyses, which help to gain more representative and reliable conclusions.

In conclusion, the present study demonstrated that, in a real-world setting of imatinib treatment in patients with BCR-ABL-positive CML, age had no significant impact on remission rates, remission depth, PFS and OS. With a 10-year-survival rate of 100% for patients aged <60 years and 90% for patients aged ≥60 years, the treatment outcomes of patients with CML in the study cohort were good. Furthermore, the results revealed that, in-line with previous studies, the impact of age as a factor has diminished in the modern era of TKI treatment, due to their high efficacy and good tolerability. However, further studies with larger patient groups and the inclusion of newer TKIs are needed to gain further comprehensive insights.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

Conceptualization was performed by RG, GK, MP and JS; methodology by RG, GK, MP and JS; validation by RG and JS; formal analysis by RG and JS; investigation by RG and JS; resources were provided by MP and JS; data curation by RG and JS; writing-original draft preparation by RG and JS; writing-review and editing by RG, GK, MP and JS; visualization by RG and JS; supervision by GK, MP and JS; project administration by RG and JS and funding acquisition by MP and JS. RG and JS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board and the Ethics Committee of Lower Austria (approval no. GS4-EK-4/825-2022) and was performed according to the Declaration of Helsinki. Due to the retrospective nature of the study, the Commission for Scientific Integrity and Ethics at the Karl Landsteiner University of Health Sciences waived the requirement for informed consent.

Patient consent for publication

Not applicable.

Competing interests

JS declares honorarium payments from Abbvie, Amgen, Angelini, Gilead, Janssen, Kite, Merck, Merck Sharp & Dohme, Miltenyi, Novartis, Pfizer, Roche and Servier as an invited speaker or expert consulting not related to CML. The other authors declare that they have no competing interests.

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