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First-line imatinib in elderly patients with chronic myeloid leukaemia from the CAMELIA registry: Age and dose still matter

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ABSTRACT

We retrospectively evaluated the role of age and dosage in 372 CML patients (170 women, 202 men) treated with first-line imatinib (IMA) from the records of the CAMELIA registry. The median follow-up of the patients was 82.3 (18.0–177.3) months. The treatment results of 80 elderly patients aged over 65 years at diagnosis were compared in analysis "A" with those of 292 younger patients and in analysis "B" with those of 90 patients younger than 40 and 202 patients aged 40–64. The elderly patients had statistically adverse values of the Sokal, ELTS, and ECOG scores and Charlson comorbidity index in both analyses (p from = 0.012 to ≤ 0.001). Despite a more frequent use of a daily dose lower than 400 mg – in 31 elderly patients (38.8%) than in 45 younger ones (15.4%) ($p < 0.001$), there were no statistically significant differences in the achievement of optimal haematological, cytogenetic, and molecular responses according to the ELN criteria in both the analyses, A and B. The comparisons of overall survival with CML-related death (OS_{CML}) and event-free survival (EFS) were insignificant inanalysis A (p = 0.07 and 0.396, respectively) but progression-free survival (PFS) differed significantly (p = 0.007). In analysis B OS_{CML} and PFS differed significantly (p = 0.027 and 0.003) but EFS was similar (p = 0.351). Elderly patients with a sustained dose of IMA of 400 mg/day have insignificantly better OS, PFS, and EFS compared to patients treated with a lower dosage of IMA. The results in the treatment of the elderly CML patients were comparable with those of the younger ones in terms of the probabilities of the achievement of optimal ELN responses. However, the results for the survival probabilities were influenced by age and the IMA dosage.

1. Introduction

The results of treatment in patients with chronic myeloid leukaemia (CML) have been dramatically improved by the discovery of tyrosine kinase inhibitors (TKI). The overall survival (OS) of patients treated with imatinib (IMA) achieved 90% and 83% at five and 10 years, respectively [1,2]. Epidemiological data on the age of CML patients at diagnosis differ, with a reported median age range between 52 and 64 years [3–5]. The prevalence of CML has been continually on the increase and the achievement of a plateau is expected in 30–40 years [6]. The patient's age is a part of the calculation of prognostic risk scores – Sokal, Hasford, and the EUTOS Long-term Survival Score (ELTS). Several studies have already confirmed that in the era of TKI age is losing its negative prognostic importance, not only for the achievement of an optimal therapeutic response, but also for the survival of patients [7–11]. The results of the CML treatment of elderly patients may also be influenced by the different biological behaviour of the disease, a worse overall condition of the patient's health, comorbidities and associated medication, and, often, a reduced dosage of TKI. There are fewer reports on studies that evaluated the analysis of the treatment of very young patients with CML. However, the results of the studies are inconsistent because only some described worse responses in young patients as a result of the more aggressive behaviour of CML or worse compliance of very young patients [12–15].

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On the evidence of the studies in phases I and II, the optimal dose of IMA in the first line for patients with CML-CP (chronic phase) was set at 400 mg of IMA once a day [16–19]. This dosage was also used in the IRIS study. In comparison with real-life practice, the IRIS study, however, did not include patients aged > 70 years; the median age of the patients was 50 years [2].

In other CML studies too the age median of patients ranged between 50 and 55 years. According to German authors, CML patients older than 65 years have as much as a 3.8 times lower chance of being included into a clinical study [20]. The obvious cause was often the presence of serious comorbidities, because it is known that only 25% of patients older than 65 years do not have other comorbidities [21].

Though IMA is relatively well tolerated, a portion of patients in clinical practice requires a reduction in the IMA dose because of undesirable effects. A reduction applies more often to patients of greater age, who suffer more often from associated diseases and worse renal and liver functions and whose other medication may also interfere with TKI [22,23].

The present analysis aimed to evaluate, in real clinical practice, the importance of age (< 65 and ≥65 years) at the time of a CML diagnosis for the achievement of a therapeutic response and the categories of survival commonly used to evaluate the success of TKI treatment in CML (overall survival OS, progression-free survival PFS, and event-free survival EFS) in CML patients treated in the first line with IMA. At the same time, these results were evaluated in relation to the dose of IMA that was administered, as there are not many papers available reporting the long-term results of treatment in CML patients with a sustained reduction in their IMA dose.

2. Methods

2.1. Patients

The present analysis included 372 patients (170 women, 202 men) suffering from CML in the chronic phase (CP 95.2%) or accelerated phase (4.8%), diagnosed in the years 2010–2016 and treated in the first line with IMA. The data in the database of the CAMELIA (Chronic MyEloid LeukemIA) registry was evaluated retrospectively in March 2018. Four haematological centres in the Czech Republic (Hradec Kralove, Olomouc, Pilsen, and Prague) cooperated in the analysis. The age median of the whole cohort at diagnosis was 54 years (18–88 years). The analysis included those patients using IMA in the first line of treatment minimally for a period of 18 months (18 M) in order to evaluate therapeutic responses. Two analyses were performed: analysis A, in which the patients were divided according to their age at diagnosis into two groups: age < 65 years (292 patients; 122 women and 170 men) and age ≥65 years (80 patients; 48 women and 32 men) and analysis B, in which the patients were divided into three groups: age < 40 years (90 patients; 34 women and 56 men); age > 40 years and < 65 years (202 patients; 88 women and 114 men); and age ≥65 years (the same patients as in analysis A). The characteristics of the cohorts are presented in Table 1. The CAMELIA registry and data collection were approved by all the local Ethics Committee boards; the patients signed informed consents.

2.2. Definition of treatment responses and the endpoints

All the centres evaluated optimal clinical responses in accordance with the recommendations of the European LeukemiaNet (ELN) from 2009 and 2013 [24,25].

The cytogenetic response was assessed according to the number of mitoses of Ph+ cells detected in the bone marrow; a minimum of 20 mitoses was required for a valid analysis; conventional cytogenetic method G-banding was used. A complete cytogenetic response (CCyR) was defined as the absence of Ph+ mitoses in the bone marrow. The molecular response and its depth were assessed according to the BCR-ABL1 transcript level, which was assessed by means of a quantitative real-time polymerase chain reaction method using a reverse transcriptase (Q-RT-PCR). The result was expressed as a ratio of BCR-ABL1 to ABL (or to another control gene) × 100% and was converted to the International Scale (IS). Major molecular response (MMR) was defined as ≤0.1% of the BCR-ABL1 transcript level. All the centres participated in ELN or the national external quality control programme for BCR-ABL1 Q-RT-PCR.

OS was defined as the time from diagnosis to death from any cause, irrespective of the discontinuation of IM. OS_{CML} was defined as the time to death as a result of CML only (deaths from other causes were considered as competing risks). PFS was defined from the time of the initiation of IMA until progression to the accelerated (AP) or blastic (BC) phases, or death from any cause. EFS was defined in the same manner as the PFS described above, with the addition of failure according to ELN (i.e. a less complete haematological response (CHR) by 3 M, no cytogenetic response (CyR) by 6 M, a less than complete cytogenetic response (CCyR) by 18 M, or loss of the response), TKI treatment change, and adverse events leading to a sustained discontinuation of the therapy.

CCI (the Charlson comorbidity index) was calculated by the summation of weight scores for 19 medical conditions and was calculated at the time of the diagnosis of CML [26]. For the purpose of our analysis, patients were classified into two CCI groups (CCI 0–2 and CCI ≥ 3). Performance status was evaluated according to the scale of the Eastern Cooperative Oncology Group (ECOG) and patients were classified according to their functional impairment [27].

2.3. Statistics

The comparison of quantitative variables was performed using a non-parametric Mann-Whitney test; qualitative variables were compared using Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method and log-rank test for the comparison

of the age groups and the Grey test in the event of competitive risks. The level of statistical significance was set to 0.05. The patients who underwent allogeneic transplantation using haematopoietic cells (HSCT) were censored at transplant.

2.4. Follow-up and treatment

The median of the follow-up time (FU) of the whole cohort was 82.3 months (M) (range 18.0–177.3 M). The follow-up of the patients belonging to various age groups differed (see Table 1). The differences were statistically significant both in analysis A ($p < 0.001$, Mann-Whitney test) and analysis B ($p < 0.001$; Kruskall-Wallis test; also for the difference between the group ≥65 years and the groups aged > 40 and < 65 after adjustment for multiparametric comparisons).

The cohort included CML patients treated in the first line with IMA. For initial cytoreduction hydroxyurea was allowed. Patients previously treated with interferon were not included into the analysis. The median of the average daily dose of IMA in the group of younger patients was 400 mg/day (range 225.9–634.8 mg/day) and in elderly patients identically 400 mg/day (range 133.3–544.7 mg/day). In our cohort a reduced dose of IMA was administered at some point to 45 younger (15.4%) and 31 elderly patients (38.8%) ($p < 0.001$). The reason for the reduction of the dose in the course of therapy was the toxicity of IMA, especially haematological, which was manifested in 102 patients (27.4%) of the whole cohort: 70 younger (24.0%) and 32 elderly patients (40%) ($p = 0.007$). The initial reduction of the dose was only performed in six younger (2.1%) and 8 elderly patients (10.1%). A dose of IMA > 400 mg/day was used in 48 younger (16.4%) and three elderly patients (3.8%) ($p < 0.001$) (see Table 2). The higher doses were administered primarily because of a suboptimal response and the impossibility of using another TKI.

In order to evaluate therapeutic responses, the cohort of patients

Table 1
Characteristics of patients (baseline demographic and haematological characteristics).

Age group		Total	< 40 years	40–64 years	≥65 years	p-value
Patients, N		N = 372	N = 90	N = 292	N = 80	
Follow-up, Month (M)	Median and range	82.3 (18–177.3)	104.3 (19.3–177.3)	90.8 (18.0–173.3)	57.4 (18.1–165.3)	
Gender, N (%)	Female	170 (45.7)	34 (37.8)	122 (41.8)	48 (60.0)	
	Male	202 (54.3)	56 (62.2)	170 (58.2)	32 (40.0)	
Sokal score	Low	135 (36.3)	43 (47.8)	85 (42.1)	7 (8.8)	< **0.001**
	Intermediate	126 (33.9)	24 (26.7)	63 (31.2)	39 (48.8)	
	High	103 (27.7)	21 (23.3)	53 (26.2)	29 (36.3)	
	Not available	8 (2.2)	2 (2.2)	1 (0.5)	5 (6.3)	
ELTS score	Low	200 (53.8)	54 (60.0)	121 (59.9)	25 (31.3)	< **0.001**
	Intermediate	91 (24.5)	21 (23.3)	45 (22.3)	25 (31.3)	
	High	73 (19.6)	13 (14.4)	35 (17.3)	25 (31.3)	
	Not available	8 (2.2)	2 (2.2)	3 (0.5)	5 (6.3)	
ECOG performace score	0	151 (40.6)	38 (42.2)	90 (44.6)	23 (28.8)	**0.012**
	1	106 (28.5)	26 (28.9)	54 (26.7)	26 (32.5)	
	2	22 (5.9)	3 (3.3)	11 (5.4)	8 (10.0)	
	3	5 (1.3)	0 (0.0)	1 (0.5)	4 (5.0)	
	4	3 (0.8)	0 (0.0)	1 (0.5)	2 (2.5)	
	Not available	85 (22.9)	23 (25.5)	45 (22.3)	17 (21.3)	
Charlson comorbidityindex	0–2	292 (78.5)	89 (98.9%)	164 (81.2%)	39 (48.8)	< **0.001**
	3–4	50 (13.4)	0 (0.0%)	24 (11.9%)	26 (32.5)	
	5–6	11 (3.0)	0 (0.0%)	2 (1.0%)	9 (11.3)	
	7+	2 (0.5)	0 (0.0%)	0 (0.0%)	2 (2.5)	
	Not available	17 (4.6)	1 (1.1%)	12 (5.9%)	4 (5.0)	
Median and range of parameters						
Leukocytes (10^9 /l)		95 (3.7–631.4)	168 (3.7–542.2)	340 (3.8–631.4)	58 (6.3–562.2)	**0.002**
Platelets (10^9 /l)		368 (36–3308)	435 (90–1725)	340 (36–3308)	415 (109–2279)	0.078
Haemoglobin (g/l)		123 (13–170)	118 (57–170)	124 (13–167)	124 (77–170)	0.362
Palpable spleen (cm)		0 (0–26)	4 (0–25)	0 (0–25)	0 (0–26)	< **0.001**

ELTS: EUTOS long-term survival score, ECOG: Eastern Cooperative Oncology Group.

Table 2
Patient treatment and status at the last check-up.

Age group	< 40 years (N = 90)	40–64 years (N = 202)	≥65 years (N = 80)
• **First-line treatment (N, %)**			
Imatinib 400 mg permanently	199 (68.1)		46 (57.5)
Imatinib at any time < 400 mg	45 (15.4)		31 (38.8)
Imatinib at any time > 400 mg	48 (16.5)		3 (3.7)
• **Second-line treatment (N, %)**	37 (41.1)	80 (39.6)	26 (32.5)
Dasatinib/Nilotinib	14 (37.8)/9 (24.3)	42 (52.5)/27 (33.8)	15 (57.7)/10 (38.5)
HSCT	9 (24.3)	4 (5.0)	0 (0.0)
Interferon	2 (5.4)	3 (3.8)	0 (0.0)
Chemotherapy	0 (0.0)	2 (2.5)	0 (0.0)
Other (HU, sine therapy)	3 (8.1)	2 (2.5)	1 (3.8)
• **Third-line treatment (N, %)**	18 (20.0)	45 (22.3)	6 (7.5)
Dasatinib/Nilotinib/Imatinib	3 (16.7)/5 (27.8)/4(22.2)	9 (20.0)/14 (31.1)/12 (26.7)	1 (16.7)/4 (66.7)/1 (16.7)
HSCT	4 (22.2)	7 (15.6)	0 (0.0)
Interferon	1 (5.6)	0 (0.0)	0 (0.0)
Other (HU, sine therapy)	1 (5.6)	3 (6.7)	0 (0.0)
• **Current treatment (N, %)**	83 (92.2)	172 (85.1)	59 (73.8)
Imatinib	56 (67.5)	117 (68.0)	44 (74.6)
Dasatinib/Nilotinib/Ponatinib	8 (9.6)/9 (10.8)/0 (0.0)	28 (16.3)/17 (9.9)/1 (0.6)	6 (10.2)/8 (13.6)/0 (0.0)
HSCT	10 (12.0)	6 (3.5)	0 (0.0)
Interferon	0 (0.0)	2 (1.2)	0 (0.0)
Other (HU, sine therapy)	0 (0.0)	1 (0.6)	1 (1.7)
• **Death, N (%)**	7 (7.8)	28 (13.9)	18 (22.5)
CML – related death	4 (4.4)	15 (7.4)	5 (6.3)
CML – unrelated death	3 (3.3)	13 (6.4)	13 (16.3)

HSCT: Haematopoietic stem cell transplantation, HU: hydroxyurea.

was divided into three groups according to the IMA dose employed: a group permanently treated with a dose of 400 mg daily, a group to which a reduced dose of IMA < 400 mg daily was administered at some point during treatment, and finally a third group to which an IMA dose > 400 mg daily was administered at some point during treatment without a reduction below it.

At the time of the evaluation of the cohort, treatment with IMA was being received by 217 (69.1%) patients, 173 of them younger (67.8%) and 44 elderly (74.6%). The necessity of using other lines of treatment was comparable in both groups. Initiation of the second line of TKI therapy was indicated in 117 younger (40.1%) and 26 elderly patients (32.5%), and third-line treatment was started in 63 younger (21.6%) and six elderly patients (7.5%) (see Table 2).

In our cohort 32 patients (16 young adults; 16 adults) underwent HSCT (see Table 2). In seven cases (21.9%) early HSCT was indicated as the treatment option for high-risk patients and in 25 patients (78.1%) it was indicated after the failure of IMA or another TKI.

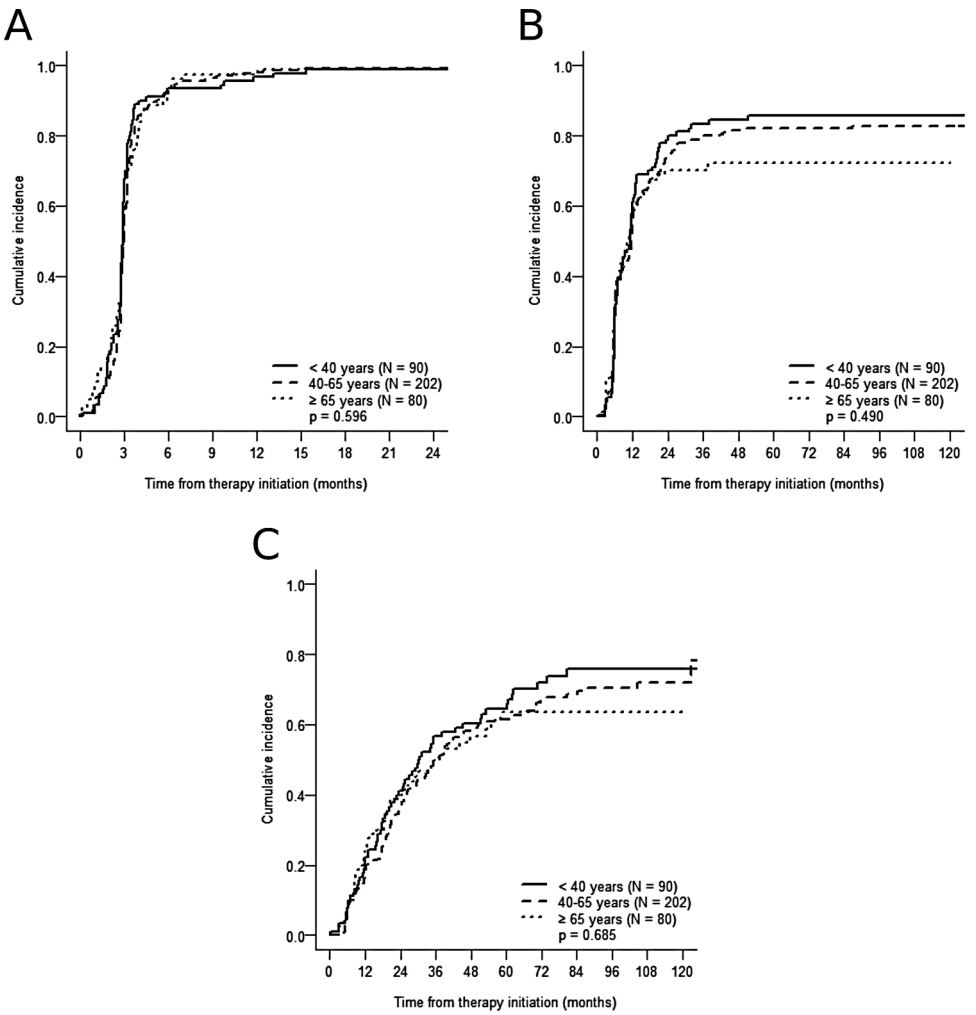

Fig. 1. Cumulative incidence of complete haematological (A), complete cytogenetic (B), and major molecular responses (C) according to age group (< 40 years; 40–64 years; ≥65 years).

3. Results

3.1. Response to therapy

3.1.1. Analysis A

In no time period was the importance of age (< 65 years vs ≥65 years) confirmed in our cohort for the achievement of optimal responses according to the ELN criteria. CHR at 3 M therapy was achieved in 181 younger (92.3%) and 45 elderly patients (91.8%) (p = 0.765), CCyR at 6 M in 92 younger ones (36.5%) and 21 elderly ones (31.3%) (p = 1.000), CCyR at 12 M in 126 younger ones (45.5%) and 28 elderly ones (36.4%) (p = 0.679), MMR at 12 M in 45 younger ones (16.2%) and 14 elderly ones (18.2%) (p = 0.476), and MMR at 18 M treatment in 47 younger (26.4%) and 19 elderly patients (32.8%) (p = 0.224). The median time to achieve CHR, CCyR, and MMR was identical in both age groups: for CHR the median time was 2.9 M vs. 3.0 M, for CCyR 11.8 M vs.10.3 M, and for MMR 34.5 M vs. 35.4 M, again without proof of a statistically significant difference according to age. In the evaluation of the cumulative incidence of the achievement of CHR, CCyR, and MMR, we did not record any significant statistical differences between both groups (p = 0.857; p = 0.319; p = 0.786).

3.1.2. Analysis B

In this analysis younger patients were divided into very young and adult groups (age < 40 years vs. 40–64 years vs ≥65 years). CHR at 3 M therapy was achieved in 55 young adults (91.7%), in 126 adults (92.6%), and in 45 elderly patients (91.8%) (p = 0.844), CCyR at 6 M in 27 young adults (34.6%), in 65 adult ones (37.4%), and in 21 elderly ones (31.3%) (p = 1.000), CCyR at 12 M in 41 young adults (47.1%), in 85 adult ones (44.7%), and in 28 elderly ones (36.4%) (p = 0.423), MMR at 12 M in 14 young adult ones (16.1%), in 31 adult (16.3%) ones, and in 14 elderly ones (18.2%) (p = 0.760), and MMR at 18 M treatment in 17 young adults (34.7%), in 30 adult ones (23.3%) and in 19 elderly patients (32.8%) (p = 0.128). In the evaluation of the cumulative incidence of the achievement of CHR, CCyR, and MMR no confirmation was obtained of any significant statistical difference between the three groups (p = 0.596; p = 0.490; p = 0.685) (see Fig. 1).

3.2. Long-term outcomes

Of the whole cohort, 53 patients died (14.2%): seven young adults (7.8%), 28 adult patients (13.9%), and 18 elderly ones (22.5%). However, the occurrence of deaths connected with CML was comparable in both groups: four young adults (4.4%), 15 adults (7.4%), and five elderly patients (6.3%). In the group of younger patients (< 65 years), in 10 patients the cause was progression of CML and nine patients died because of complications connected with HSCT.

The occurrence of death after HSCT was comparable in the groups of young adults and adults (37.5% vs. 43.5%). The causes of death after HSCT were the following: progression to AP/BC in two patients, transplant-related (GvHD, infection) in nine patients, non-CML-related in two patients. The OS of the transplant patients were significantly

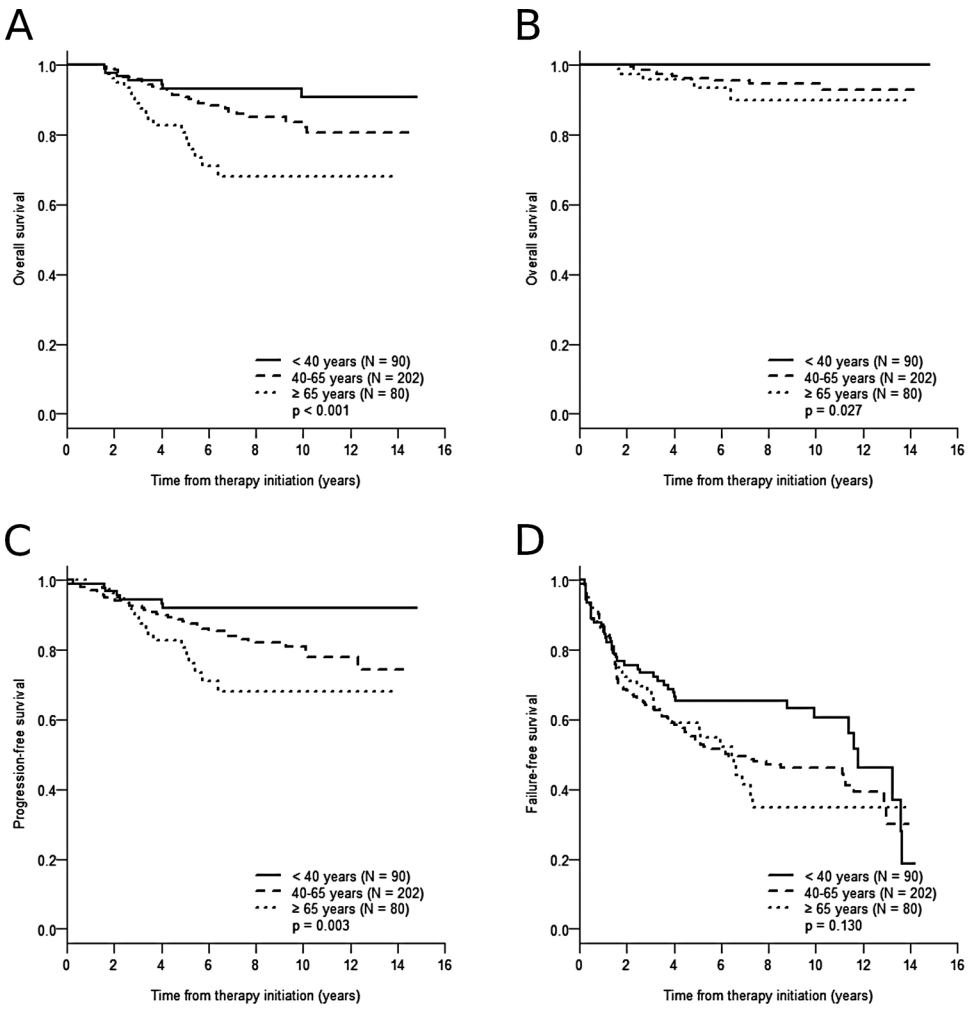

Fig. 2. Outcome stratified by age group (< 40 years; 40–64 years; ≥65 years). (A) overall survival (B) overall survival with death related to chronic myeloid leukaemia. (C) progression-free survival (D) failure-free survival.

worse when compared with the patients treated with TKI only (92.3% vs. 61.2%; p < 0.001) (see Fig. S1, Supplementary materials). In the elderly group no HSCT was performed; all the patients died because of CML. In elderly patients the more frequent cause of death was co-morbidity: 13 elderly (16.0%) vs. 16 younger patients (5.5%) (see Table 2).

Clear trends were observed in the assessment of 10-year survival probabilities: for patients in the age group < 40 years, ≥40 to < 65 years, and ≥65 years OS was 90.6, 83.7, and 68.1%; OS_{CML} was 100, 94.6, and 89.8%; PFS was 92.1, 80.8, and 68.1%, and EFS was 46.0, 36.7, and 29.3%. In a comparison of survival probabilities according to Kaplan and Meier significant differences were observed in OS (p < 0.001), OS_{CML} (p = 0.027), and PFS (p = 0.003), but not in EFF (p = 0.351) (see Fig. 2).

The effect of CCI on OS was also demonstrated in the group of younger patients, where in dependence on CCI there was 10-year OS in the subgroup CCI 0–2 OS 87.1% vs. 70.4% in the subgroup with CCI ≥ 3 (p = 0.018). Nevertheless, the effect of CCI on OS was not found in the elderly patients, where OS in patients with CCI 0–2 was 62.5% vs. 73.4% in patients with CCI ≥ 3 (p = 0.224)) (see Fig. S2, Supplementary materials).

3.3. Prognostic significance of imatinib dose

In the evaluation of the whole cohort in relation to the therapeutic dose of IMA, we demonstrated that the best OS_{CML} was achieved in the group of patients treated with a sustained dose of IMA 400 mg daily. With the sustained use of a dose of IMA 400 mg daily, 10-year OS_{CML} was 96.8% (95% CI:94.3–99.4%), with a reduced IMA dose at any time during therapy < 400 mg, OS_{CML} was 94.4% (95% CI: 87.9 − 10.0%), and with doses IMA > 400 mg at any time during therapy, 89.2% (95% CI: 80.3–98.2%) (p = 0.018).

PFS and EFS at 10 years with a permanent dose of IMA 400 mg daily were 85.7% (95% CI: 80.8–90.6%) and 43.1% (95% CI: 36.2–50.0%); with a reduced dose of IMA < 400 mg/day they were 77.1% (95% CI: 66.1–88.0%) and 40.9% (95% CI:27.6–54.2%). With doses of IMA > 400 mg/day at any time during therapy 10-year PFS was 72.1% (95% CI: 58.9–85.3%) and EFS 9.4% (95% CI: 1.2–17.6%). The differences were statistically significant both for PFS (p = 0.011) and EFS (p < 0.001) in dependence on the IMA therapeutic dose used (see Fig. 3). The results for OS, OS_{CML}, PFS, and EFS according to age division and the IMA dose used are presented in Fig. 3.

4. Discussion

The first study confirming the fact that in the new era of TKI age had lost its negative prognostic importance was the paper of Cortes in 2003 [7]. In his analysis, CCyR was achieved by 79% of elderly (≥60 years) and 86% of younger patients (< 60 years). In 2011, the team Gruppo Italiano Malattie Ematologiche dell'Adulto (GINEMA) CML Working Party evaluated the importance of age in 559 CML patients treated with IMA in the first line [8,9]. The achievement of CCyRat 6 M and MMR at

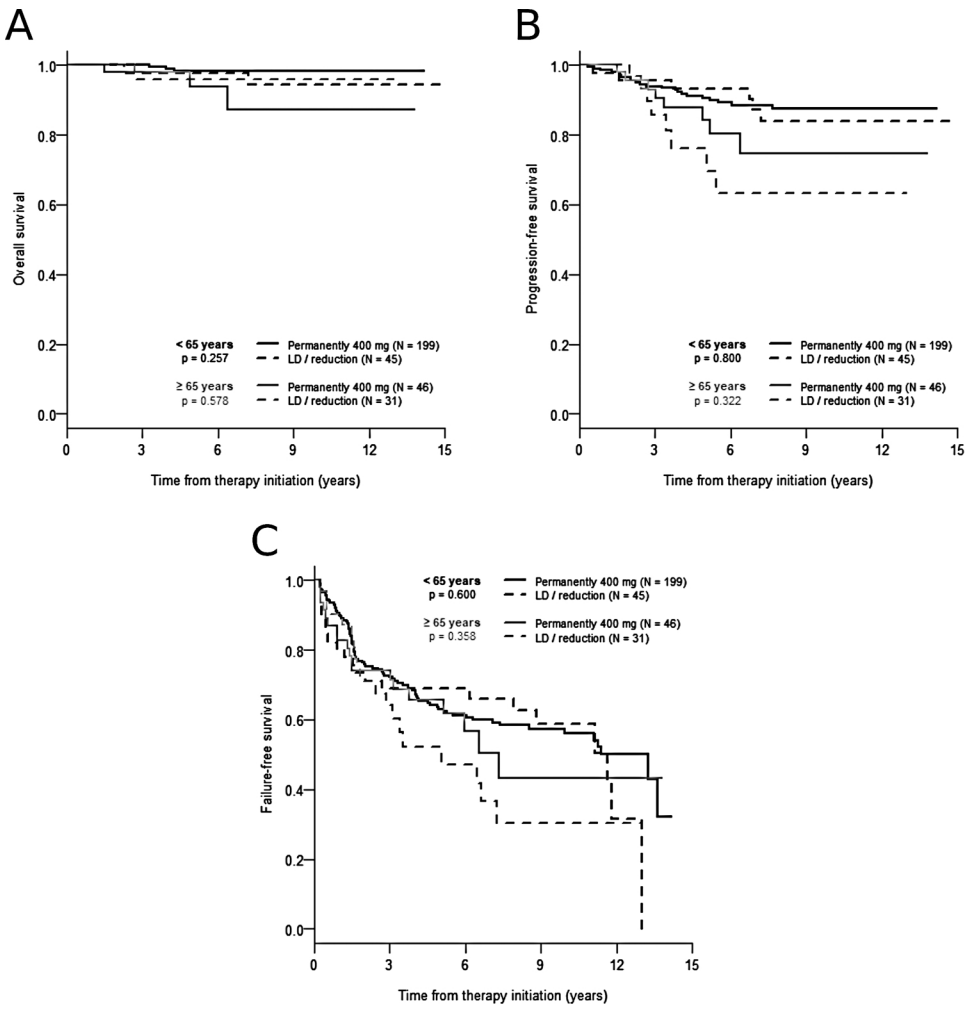

Fig. 3. Outcome stratified by age and imatinib dose group (imatinib permanently 400 mg and imatinib < 400 mg at any time): (A) overall survival with death related to chronic myeloid leukaemia (B) progression-free survival (C) failure-free survival.

12 M was identical in both groups (69% vs. 67% and 58% vs. 59%, respectively). Six-year OS with CML-related death was also comparable in both groups (94% vs. 96%; p = 0.380). These results are in agreement with both our analyses, as we did not observe a difference in the achievement of optimal responses in the sense of CCyR and in MMR between the groups.

At the end of the GINEMA study 74% of the younger patients and 65% of the elderly ones were still being treated with IMA, which are again results similar to our analysis, where 67.8% of the younger and 74.6% of the elderly patients in our cohort remained on IMA. This fact represents further evidence in favour of a very good therapeutic effect of IMA in the first line. Other lines of treatment were represented in all age groups comparably except HCST. We can thus state that elderly patients were not discriminated against in terms of acceptance to another line of therapy because of their age. However, the time of observation was significantly shorter in the elderly patients in our study. There are two possible explanations. The shorter observation time might be caused by the significantly shorter OS of elderly patients. Another less likely reason might have been a slower introduction of IMA in first-line treatment at the beginning of our study period. On the other hand, despite the short observation time the elderly patients achieved favourable results comparable with those of the younger patients.

Younger patients had a lower risk significantly more frequently according to their Sokal and ELTS scores (43.8% vs. 8.8%, p < 0.001; 40.1% vs. 18.8%, p = 0.003), which was very probably caused by the composition of the calculations themselves. In agreement with the GINEMA results, at the time of their CML diagnosis our cohort of elderly patients also showed statistically lower values of leukocytes and a less enlarged spleen in comparison with the younger patients, especially young adults. We assume that the elderly patients were thus displayed symptoms earlier and were checked by physicians more frequently, including blood count assessment. Another cause might be a different biological behaviour of the disease – a more indolent course of CML in the elderly.

Higher CCI values and the occurrence of worse ECOG in the group of patients aged ≥ 65 years were expected. The importance of CCI at higher ages for OS and EFS was confirmed by Breccia [10]. In his study, however, the patients were of a greater age (≥75) and their division according to CCI was different, into a group without comorbidities (CCI - 0) and one with CCI ≥ 1. The median OS in these groups was 40.8 M and 20.16 M, respectively. In Saußele's paper, the impact of CCI on OS was assessed within the framework of the CML IV study. No effect of CCI on the therapeutic response was found, but the great importance of CCI for OS (p < 0.001) was confirmed [28]. Our analysis demonstrated an effect of CCI on OS of borderline statistical significance (p = 0.052). Surprisingly, we only demonstrated the importance of CCI for OS in the group of younger patients (p = 0.018) and not in the group of elderly ones. We assume that comorbidities may play a more important role in the younger ones, while in elderly patients their greater age plays a more important role.

Some published analyses also focused on the toxicity of IMA therapy

and confirmed a higher occurrence of toxicity in elderly patients [8,11]. The cause was primarily a higher rate of occurrence of haematological toxicity. According to Latagliata et al., there was an occurrence of haematological toxicity of the degree 3/4 in 25% of elderly vs. 9.1% younger patients in the 117 CML patients who they analysed. In our cohort too, a higher representation of haematological toxicity was observed in the elderly patients (17.5% in the elderly vs. 6.5% in the younger ones). A higher risk of the development of cytopenias in elderly patients may be connected with polypharmacy, a lower reserve of bone marrow, and possible dysplastic changes in the marrow at a greater age. However, our study was not aimed at a detailed analysis of the toxicity of treatment with IMA.

Our analysis has confirmed that in real-life clinical practice the treatment is rarely commenced with doses of IMA lower than the recommended 400 mg daily. In our cohort the initial lower doses were used only in six younger patients (2.1%) and seven elderly patients (8.8%). The more frequent reduction of doses in elderly patients can be explained by physicians' fear of the toxicity of the treatment in this fragile population. However, reduction of the dose in the course of IMA therapy was twice as frequent in percentage terms, in 23 elderly patients (28.8%), as in 37 younger ones (12.7%) ($p < 0.001$).

In the evaluation of the whole cohort, regardless of age, the administration of lower doses of IMA did not influence the results of OS, OS_{CML}, PFS, and EFS in comparison with the patients receiving a permanent dose of IMA of 400 mg daily. The achievement of a good therapeutic effect even at lower IMA doses can be explained by highly variable inter-individual pharmacokinetics or concomitant medication, which may influence plasma and subsequently intracellular levels of IMA. There are several reports on the achievement of higher levels of IMA in women and elderly patients. The possible explanation usually includes the lower weight of women and changes in the distribution volume, reduced albumin, and worsening renal function, which result in an increase in α-acid glycoprotein, all associated with a greater age [29–35].

The worst therapeutic results were observed in patients treated with a dose of IMA > 400 mg. This group of patients, however, also included the patients with an accelerated phase of CML and apparently also the patients with an aggressive biological behaviour of the disease who did not respond optimally to IMA therapy. Prior to the availability of the second and third generations of TKI, an increase in the IMA dose was the only therapeutic option for IMA failure or suboptimal response management, primarily in elderly patients, whereas in younger ones, HSCT might have been indicated.

Our study has demonstrated a comparable treatment response according to the ELN criteria in elderly patients when compared with younger ones, despite the higher risk and lower IMA dosage used in this fragile comorbid population [36,37]. However, favourable responses to treatment were not sufficiently transformed into improvements in survival probabilities, especially when elderly patients aged over 65 were compared with younger patients aged less than 40 years (analysis B). For some statistical comparisons our study may be of limited power as a result of the lower number of patients in evaluated groups and shortened duration of the observation. On the other hand, it may be the result of age and the negative influence of a lower IMA dosage.

5. Conclusion

Our retrospective study from real-life practice has confirmed that IMA therapy in elderly patients with CML gives comparable therapeutic responses to those achieved in younger patients, in spite of the significantly unfavourable values of prognostic scores, more frequent comorbidities, and more frequently administered lower dose of IMA. However, when compared with younger patients of an age less than 40 years the negative impact of greater age and a lower IMA dosage became more obvious, particularly in survival analyses. Elderly patients should be managed with the utmost care and with an effort to maintain a standard IMA dosage.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.04.011.

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