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ORIGINAL ARTICLE

Ten-year outcome of chronic-phase chronic myeloid leukemia patients treated with imatinib in real life

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Abstract

Imatinib, the first BCR/ABL kinase inhibitor approved for the treatment of chronic myeloid leukemia (CML), has changed the long-term outcome of patients affected by this disease. The aim of our analysis was to report, after a median follow-up of 10.2 years (range 5.8–14.8), the long-term outcome, efficacy, and safety of imatinib treatment (frontline and after interferon failure) in a single institution cohort of 459 patients with CML in chronic phase treated outside of clinical trials. The 10-year overall survival of the whole cohort was 77.1%, while the 10-year probability of dying due to CML and other causes was 7.8% and 16%, respectively. The prognostic value of the *BCR-ABL1* ratio at 3 months (⩽ 10%) and of complete cytogenetic response and major molecular response at 1 year was confirmed also in the real-life practice. The EUTOS long-term survival score better stratified the baseline risk of dying of CML compared with other risk scores. Two hundred thirty-six (51.4%) patients achieved a deep molecular response during imatinib treatment after a median time of 4.57 years, and 95 (20.6%) had a stable deep molecular response maintained for at least 2 consecutive years. Imatinib was associated with a low rate of serious cardiovascular events and second neoplasia. This 10-year real-life follow-up study shows that imatinib maintains efficacy over time and that long-term administration of imatinib is not associated with notable cumulative or late toxic effects.

Keywords Chronic myeloid leukemia · Long-term follow-up · Imatinib · Real-life experience

Introduction

The treatment of chronic myelogenous leukemia (CML) has drastically changed since the introduction of imatinib, the first-generation tyrosine kinase inhibitor (TKI). Imatinib was commercialized in 2001, initially in interferon-resistant and/or interferon-intolerant chronic-phase (CP) CML patients and then for first-line treatment since 2003. Despite the advent of treatment-free remission (TFR) strategies, CML patients are expected to receive treatment with TKIs for a prolonged time period. Data on the long-term efficacy and toxicities in this setting are crucial in understanding the occurrence of events after long-time treatment. Recently, an update of the IRIS trial reported the 10-year follow-up and outcome of CML patients treated with imatinib frontline [1]. However, no real-life experiences on the very long–term follow-up (up to 10 years) of CML patients treated with imatinib outside of clinical trials have so far been published. The aim of our study was to provide a comprehensive and detailed analysis of the long-term outcome of CML patients as a useful reference for the baseline decision-making process in the selection of front-line treatment. This analysis focuses on the very long–term (10.2 years) outcome, efficacy, and toxicities of patients with CP-CML treated with imatinib frontline or after interferon failure at a single institution. Compared with sponsored studies, real-world data may better define the clinical course of patients who discontinued the drug for events related to resistance or side effects.

Patients and methods

Our analysis included a series of 459 adult patients treated with branded imatinib frontline or after interferon (IFN)

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failure. All patients included were in chronic phase, genetically determined as Philadelphia-positive (Ph+) and/or *BCR-ABL1*+ and uniformly diagnosed and treated at the Sapienza University between 2000 and 2016. Diagnostic criteria were assessed according to the ELN criteria [2], and the risk scores were defined following the Sokal [3], Euro [4], Eutos [5], and Eutos long-term survival (ELTS) [6] stratifications. Complete cytogenetic response (CCyR), major molecular response (MMR = *BCR-ABL1*^{IS} < 0.1%) and deep molecular responses (DMR) (MR$^{4.0}$ = *BCR-ABL1*^{IS} < 0.01%; MR$^{4.5}$ = *BCR-ABL1*^{IS} < 0.0032%; MR$^{5.0}$ = *BCR-ABL1*^{IS} < 0.001) were defined according to the standardized criteria [7] and according to the International Scale (IS) [8]. Early molecular response (EMR) was considered a level of *BCR-ABL1* transcript < 10% at 3 months [2]. In the definition of molecular responses rate, we excluded atypical transcripts not quantifiable with RQ-PCR. Cytogenetics was performed at the local laboratory by chromosome banding analysis of at least 20 marrow cell metaphases at diagnosis, at 3 months, 6 months, and 12 months; thereafter, it was repeated every 3 months until the achievement of CCyR only in patients who did not achieve it within the first year of treatment. A qualitative assessment of *BCR/ABL1* transcript was performed at diagnosis, while a quantitative evaluation was carried out every 3 months until an achievement of a MMR, and then every 6 months. All responses were calculated from imatinib starting. The baseline performance status of all patients was assessed using the Eastern Cooperative Oncology Group (ECOG) score [9]. Severity of cardiovascular events was defined according to the Common Terminology Criteria for Adverse Events (CTCAE). Overall survival (OS) was calculated from the date of imatinib treatment start until death at any time for any reason; progression-free survival (PFS) was calculated from the date of imatinib treatment start until progression to accelerated phase (AP) or blast phase (BP) at any time; event-free survival (EFS) was calculated from the date of imatinib treatment start until death, progression to AP or BP, failure on imatinib, or imatinib treatment discontinuation for any cause. Resistance to imatinib was retrospectively defined according to the current ELN criteria [7]; intolerance was considered a condition that due to the severity and/or receptiveness of one or more drug-related side effects determined a therapy discontinuation. Cumulative incidence (CI) rate of death was defined as the probability that the event (CML-related or CML-unrelated death) occurred during a specific period of time (10 years) [10]. Time to response was calculated from the date of treatment start until the first achievement of cytogenetic and/or molecular response; cumulative incidence of responses was assessed considering competing risks defined by AP, BC, and death. Probabilities of OS, PFS, and EFS were calculated with the Kaplan-Meier (KM) method [11], and the differences between KM curves were performed using the long-rank test [12]. Statistical significance was considered for p values < 0.05 [13]. Death was classified as CML related and CML unrelated (death due to other causes). CML-unrelated deaths were defined if a progression to AP and BP did not occur and a patient had at least a CCyR within 6 months before death. The cumulative incidence of CML-related deaths was calculated according to the competing risk [14, 15] of CML-unrelated deaths.

Results

Patients' characteristics

The baseline characteristics of the patients are summarized in Table 1. A predominance of female gender was observed (54.8%). The median age of the population was 55.1 years (range 18.8–91.2). Twenty-eight percent of patients were older than 70 years at diagnosis. Three hundred twenty-eight (71.5%) patients received imatinib frontline, while 131 (28.5) patients started imatinib after IFN failure. The median time of prior IFN treatment was 5.6 years (range 2.4–8.9). The incidence of e14a2 transcript was 65.6%. According to the prognostic scores calculated at diagnosis prior to any therapy, high-risk patients were 9% by Sokal, 5.9% by Hasford, 2.3% by Eutos, and 7% by ELTS score. The initial dose of imatinib was 400 mg daily, 800 mg daily, or other doses in 88.2%, 11.7%, and 3.1% of patients, respectively. Forty-two (9.2%) patients had a history of cardiovascular disease, and 21 (4.6%) patients had a previous solid tumor before starting imatinib. All patients were followed until death or until the last follow-up scheduled for December 2016, and the median follow-up was 10.2 years (range 6.6–13.8).

Outcome

The 10-year OS of the whole cohort was 77.1% (CI 95% 73.1–81.5); the 10-year probability of dying due to CML and other causes was 7.8% (CI 95% 5.1–10.3) and 16% (CI 95% 11.5–18.8), respectively (Fig. 1). The 10-year OS of patients who never developed resistance or intolerance and, therefore, received only imatinib was 77.9% (CI 95% 72.6–82.4), while the 10-year OS of patients who, after receiving imatinib, started a 2TKI due to intolerance or resistance was 77% (CI 95% 67.5–84.1) (p = 0.38) (Fig. 2). The 10-year PFS was 93.1% (CI 95% 88.6–95.7), while the 10-year EFS was 55% (CI 95% 50–59.6), considering any reason for treatment discontinuation: intolerance (10.4%), lack of cytogenetic response (17.5%), no achievement of major molecular response over time (MMR) (22.6%), lack of molecular response (6.1%), evolution in blast phase (13.7%), death (29.7%) (Fig. 3a, b). Stratifying all patients in 4 groups according to age (18–35, > 35–< 50, > 50–< 65, and > 65 years), no differences were found in the 10-year CI of death due to CML (p =

Table 1 Patient characteristics at baseline

N patients	459
Age median (range)	55.1 (range 18.8–91.2)
Age < 50 years *N*/%	167 (36.3)
Age 50–70 years *N*/%	164 (35.7)
Age > 70 years *N*/%	128 (28)
Gender *N*/%	
Male	207 (45.2)
Female	252 (54.8)
Previous treatment with IFN *N*/%	
Yes	131 (28.5)
No	328 (71.5)
Sokal score *N*/%	
Low	235 (51.2)
Intermediate	183 (39.9)
High	41 (9)
Hasford score *N*/%	
Low	267 (58.2)
Intermediate	165 (35.9)
High	27 (5.9)
ELTS score	
Low	315 (68.7)
Intermediate	112 (24.4)
High	32 (7)
Eutos score *N*/%	
Low	448 (97.7)
High	11 (2.3)
Type of transcript *N*/%	
e14a2	301 (65.6)
e13a2	147(32.1)
e14a2+e13a2	9 (2)
Others	2 (0.4)
Initial dose of imatinib mg/die	
400	405 (88.2)
800	40 (11.7)
Others	14 (3.1)
Previous history of cardiovascular diseases *N*/%	
Yes	42 (9.2)
No	417 (90.8)
Previous history of solid tumor *N*/%	
Yes	21 (4.6)
No	438 (95.4)

0.472), whereas a difference was observed if all other causes of death were considered ($p < 0.001$) (Fig. 4). According to gender, no differences were observed in terms of 10-year OS ($p = 0.474$) and 10-year PFS ($p = 0.556$). The e13a2 type of transcript (detected in 32.1% of patients) at baseline had a negative impact on the 10-year PFS ($p = 0.035$), but not on the 10-year OS ($p = 0.151$) (Fig. 5a, b). The ELTS score ($p < 0.001$), compared with Sokal ($p = 0.003$) and Hasford ($p = 0.039$) score, better stratified the baseline risk of patients in terms of 10-year CI of CML-related deaths (Fig. 6).

Comparison between imatinib frontline and after IFN

The 10-year OS in patients treated with imatinib after IFN and imatinib frontline was 75.3% (CI 95% 66.9–81.9) and 77.8% (CI 95% 72.2–82.5) ($p = 0.468$), respectively. No difference was also found between the two groups in terms of 10-year PFS (87.5%, CI 95% 80.4–92.2 vs 92.7%, CI 95% 88.8–95.3; $p = 0.051$) and 10-year EFS (56.7%, CI95% 47.7–64.6 vs 54.5%, CI 95% 48.4–60.1; $p = 0.385$) (Fig. 7). The 10-year probability of dying due to CML was 5.9% (CI 95%; 3–8.7%) and 12.2% (CI 95%; 6.6–17.9) in patients treated with imatinib frontline and after IFN ($p = 0.016$), respectively. Conversely, no difference was observed as for the 10-year probability of dying due to other causes between the two groups (16.3%, CI 95% 11.7–20.9 vs 12.4%, CI 95% 6.7–18.2; $p = 0.280$). We found that the group of patients who was previously treated with IFN and had the e13a2 transcript at baseline showed a worse 10-year OS ($p = 0.016$) and PFS ($p = 0.001$) compared with patients treated with imatinib frontline having e13a2 or e14a2 and patients treated with imatinib second line having e14a2 at diagnosis (Fig. 8).

Responses

Patients achieving a CCyR at 3, 6, and 12 months were 56.2%, 70.3%, and 73%, respectively. The median time to achieve a CCyR was 107 days (range 28–190). The rate of 3-month CCyR according to the Sokal score stratification was 79%, 55.1%, and 34.1% ($p = 0.002$) for low-, intermediate-, and high-risk patients, respectively. The incidence of 12-month CCyR was higher in low- and intermediate-risk patients compared with high risk ($p < 0.001$). Among patients who achieved a CCyR at 12 months, only 12.8% never reached a MMR, while, considering patients who had not achieved a CCyR at 12 months, 25.8% of them never reached a MMR during imatinib ($p = 0.005$). One-hundred eighty-four patients (40%) were evaluable for molecular response at 3 months. Among them, patients achieving an EMR at 3 months were 85.4%. A MMR at 6 and 12 months was observed in 38.3% and 57.1% of patients, respectively. Among patients who had not achieved a MMR at 12 months, 42.7% never reached a MMR during imatinib treatment. Comparing patients who started imatinib frontline and after IFN, no difference was found in terms of cumulative incidence of CCyR at 12 months (79.2% vs 87.6%; $p = 0.052$), EMR (82.3% vs 78.4%; $p = 0.064$) and MMR at 6 months (42.1% vs 37.6%; $p = 0.068$) and 12 months (58.7% vs 54.9%; $p = 0.081$). After a median time of 10.2 years (range 5.8–14.8), 83 (18.1%) patients achieved as their best molecular response a MMR after a median time of 2.4 years (range IQ 1.36–4.01), 162 (35.3%)

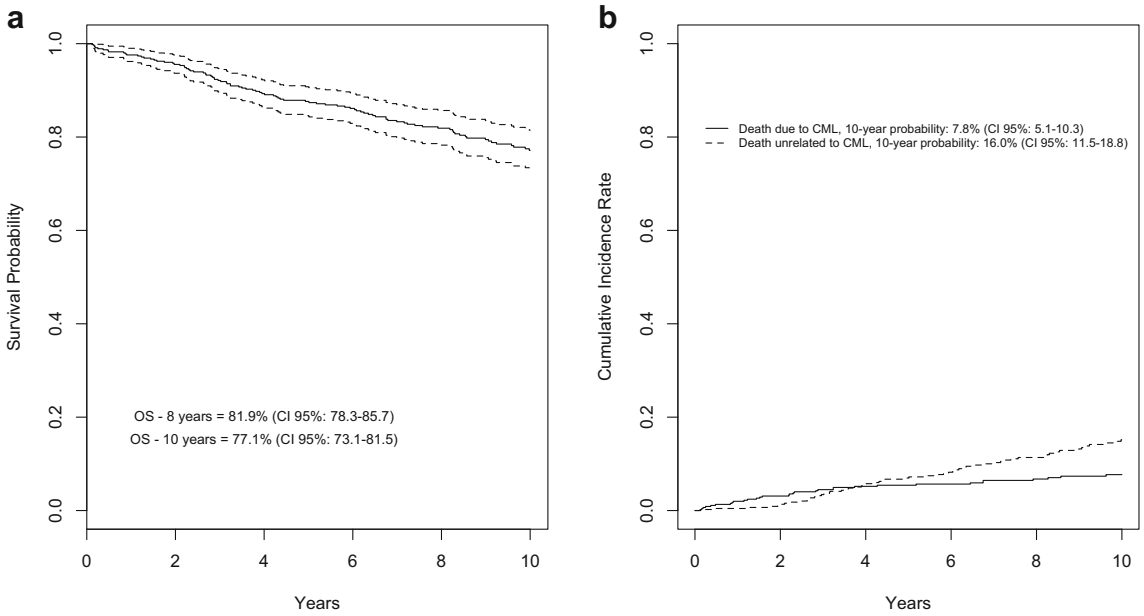

Fig. 1 **a** 10-year overall survival. **b** 10-year cumulative incidence of death due to CML or to other reasons

patients a $MR^{4.0}$ after a median time of 4.57 years (range IQ 2.08–7.33), and 74 (16.1%) patients a $MR^{4.5}$ after a median time of 8.23 years (range IQ 4.14–11.53), and 60 (13.1%) patients never achieved a MMR during the treatment (Table 2). One hundred seventy-two (52.4%) of 328 patients who had received imatinib frontline and 64 (52%) of 123 patients who had started imatinib after IFN failure ($p = 0.24$) achieved a DMR as their best molecular response. Among 236 patients who achieved a DMR, 95 (40.2%) had a sustained DMR (a DMR maintained for at least 2 consecutive years and a previous imatinib treatment of at least 5 years) and therefore considerable as potential candidates for drug discontinuation

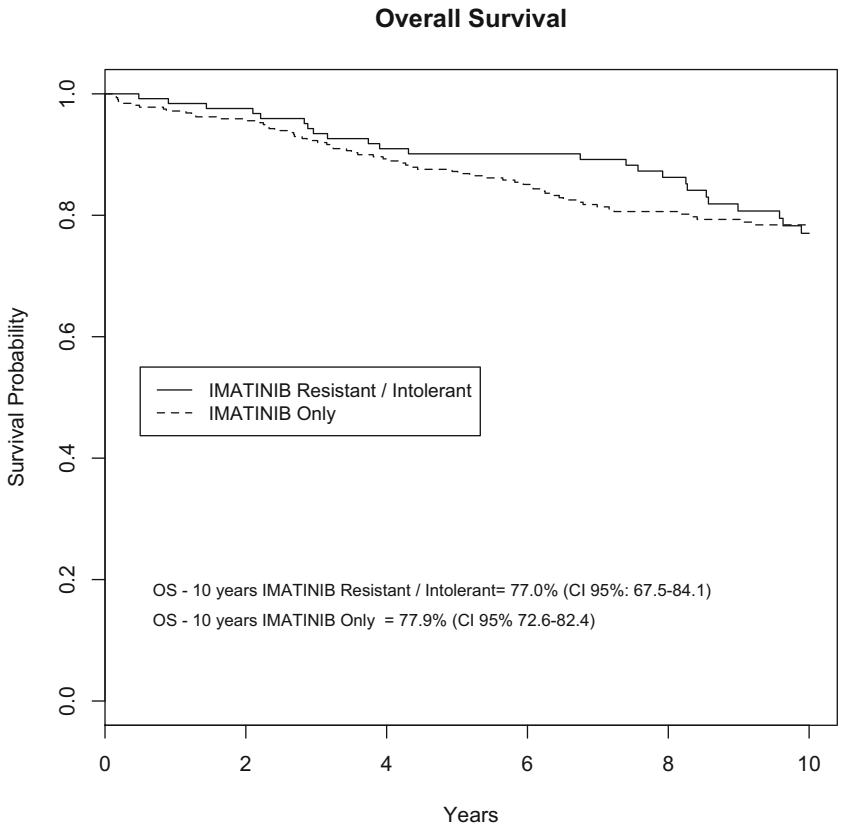

Fig. 2 10-year overall survival of patients treated with imatinib only and of patients who initially started imatinib and then switched to a 2TKI after resistance or intolerance to imatinib

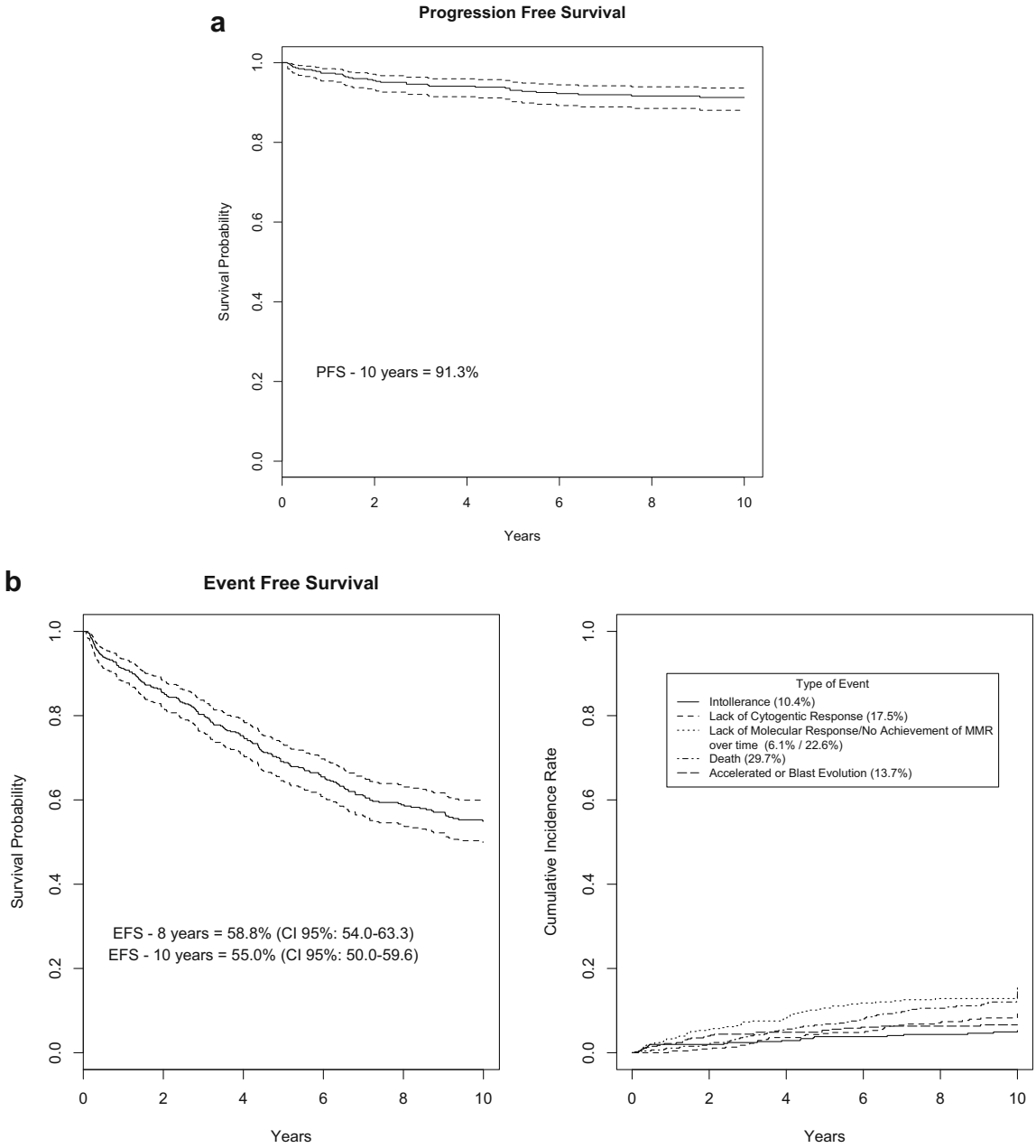

Fig. 3 **a** 10-year progression-free survival. **b** 10-year event-free survival and 10-year cumulative incidence of events causing discontinuation of treatment

according to the ESMO guidelines [16]. In this group, no difference was found between patients who started imatinib frontline and after IFN (53% vs 47%; $p = 0.34$) and patients who had > 70 years and < 70 years ($p = 0.13$). Of this group, 50 patients discontinued the treatment: 14 relapsed in a median time of 4 months, with a treatment-free remission (TFR) rate of 72% after 12 months. Fourteen patients received IFN, but apparently, no differences in the relapse rate were observed compared with patients who had received only imatinib. The e13a2 transcript did not impact on molecular response achievement (EMR at 3 months and MMR at 12 months) (79.4% vs 84.2%, $p = 0.17$ and 55.5% vs 59.1%, $p = 0.22$) nor on timing of response (median time 125 vs 110 days; $p = 0.32$ and 16 and 13 months; $p = 0.18$) compared with patients with e14a2 transcript. The e13a2 transcript affected the CCyR achievement at 12 months (76.2% vs 89.6%; $p = 0.011$) only in the cohort of patients who had started imatinib after IFN failure, but not in the cohort of patients treated with imatinib frontline (84.6% vs 86.9%; $p = 0.067$) compared with e14a2. One patient showed at diagnosis the atypical e6a2 transcript; he achieved a disappearance of transcript by qualitative molecular PCR (qT-PCR) after 18 months of therapy, and he is still on imatinib maintaining the response. Another patient presented the e14a3 transcript at baseline; he did not achieve

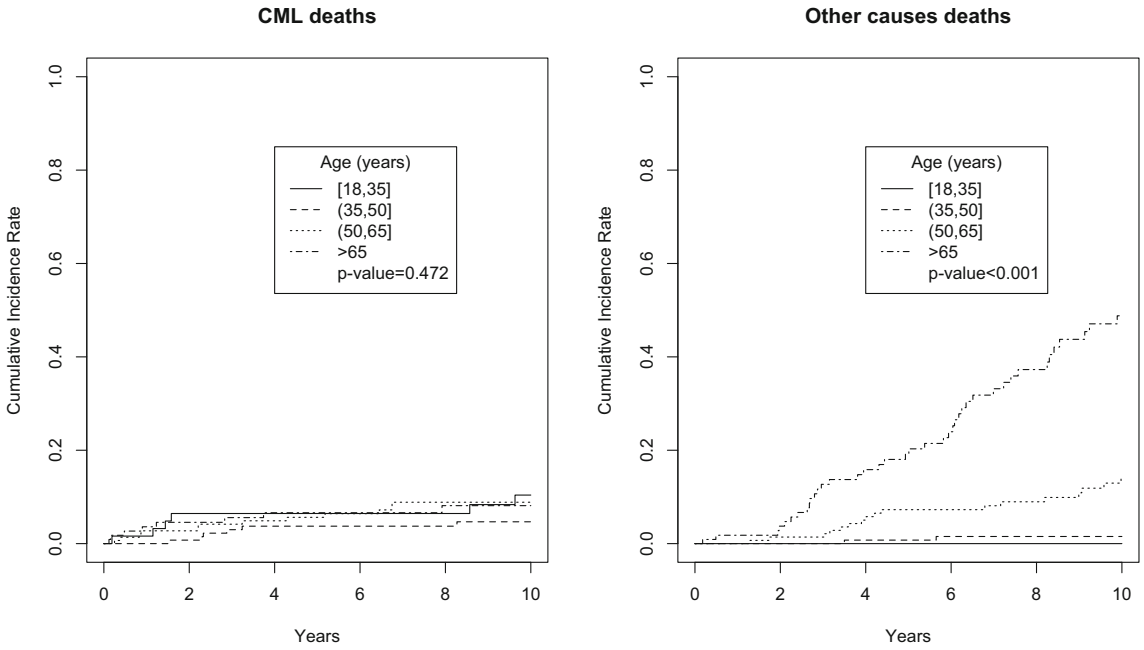

Fig. 4 10-year cumulative incidence of death due to chronic myeloid leukemia and due to other causes according to age

a negative qT-PCR with imatinib but responded to dasatinib which is still ongoing. The achievement of a CCyR at 3 and 12 months was related to a significantly better 10-year OS ($p < 0.001$) and 10-year PFS ($p < 0.001$). The achievement of an EMR at 3 months and a MMR at 12-months was associated with a significant advantage in terms of 10-year OS ($p = 0.006$ and $p = 0.032$, respectively) and 10-year PFS ($p = 0.004$ and $p = 0.009$, respectively) (Fig. 9a, b). Furthermore, both in the group of patients that received imatinib frontline and in the group of patients who had started imatinib after IFN failure, the achievement of EMR was associated with a better 10-year OS ($p = 0.001$ and $p = 0.0014$, respectively) and PFS (0.0032 and 0.0027, respectively). Also, the achievement of a MMR at 12 months was a favorable prognostic factor on 10-year OS ($p < 0.001$ and 0.001) and PFS ($p < 0.001$ and $p = 0.0023$) when the two groups were analyzed separately.

Rates of progression and outcome after progression

Eighteen patients (3.9%) with a median age of 52.7 years (range 25.8–82) and a median duration of imatinib of 16 months (range 3–59) experienced a blast crisis (BC, 10 lymphoid and 8 myeloid). Among this cohort, 16 (88.8%) patients had been treated with imatinib first line, while only 2 (11.2%) had received imatinib after IFN failure ($p = 0.031$). All progressions to BC occurred within the first 5 years and a further risk of progression to BC was 0% up to 10 years of follow-up. After progression, 10 (55.5%) patients died of the disease or due to complications related to intensive treatment. Eight patients responded to intensive chemotherapy and started dasatinib treatment; 5 achieved a MMR and 3 a DMR. The 3-year OS of these patients was 43.5% (CI 95% 32.5–53.3).

Treatment failure

One-hundred twenty-eight patients (27.9%) switched to second generation inhibitors (2TKIs) after a median time of treatment of 3.48 years (range IQ 1.47–5.89); 23 (17.9%) patients were intolerant, while 105 (82.1% or 22.8% of the whole cohort) were resistant. Among the resistant patients, 29 (27.6%) had received IFN before imatinib, while 76 (72.4%) had started imatinib frontline ($p = 0.02$). The most frequent causes of intolerance were skin toxicities (43.4%), muscle cramps (26%), and recurrent conjunctivitis (17.3%). Only 1 patient (4.3%) included in the intolerant group had not achieved a MMR at the time of discontinuation. Among resistant patients, 42 (46.2%) had not reached a CCyR at 12 months and 81 (77.1%) had never achieved a MMR during imatinib. Twenty-four (22.8%) resistant patients had achieved at least a MMR with imatinib ($n = 17$ MMR; $n = 7$ $MR^{4.0}$) but had lost it after a median time of 14 months (range 6–22). Among the group of patients who developed resistance to imatinib, 57 started dasatinib (3 patients at 80 mg, 3 at 140 mg, and 51 at 100 mg), 45 started nilotinib (3 patients at 600 mg and 41 at 800 mg), and 3 were treated with bosutinib (1 patient at 500 mg, 1 at 400 mg, and 1 at 300 mg) as second line. After a median time of 5.4 years (range 2.8–6.6), 24 (22.8%), patients achieved as their best molecular response a MMR after a median time of 13 months (range 6–24), 35 (33.3%) patients a $MR^{4.0}$ after a median time of 19 months (range 12–32), and 25 (23.8%) patients a $MR^{4.5}$ after a median

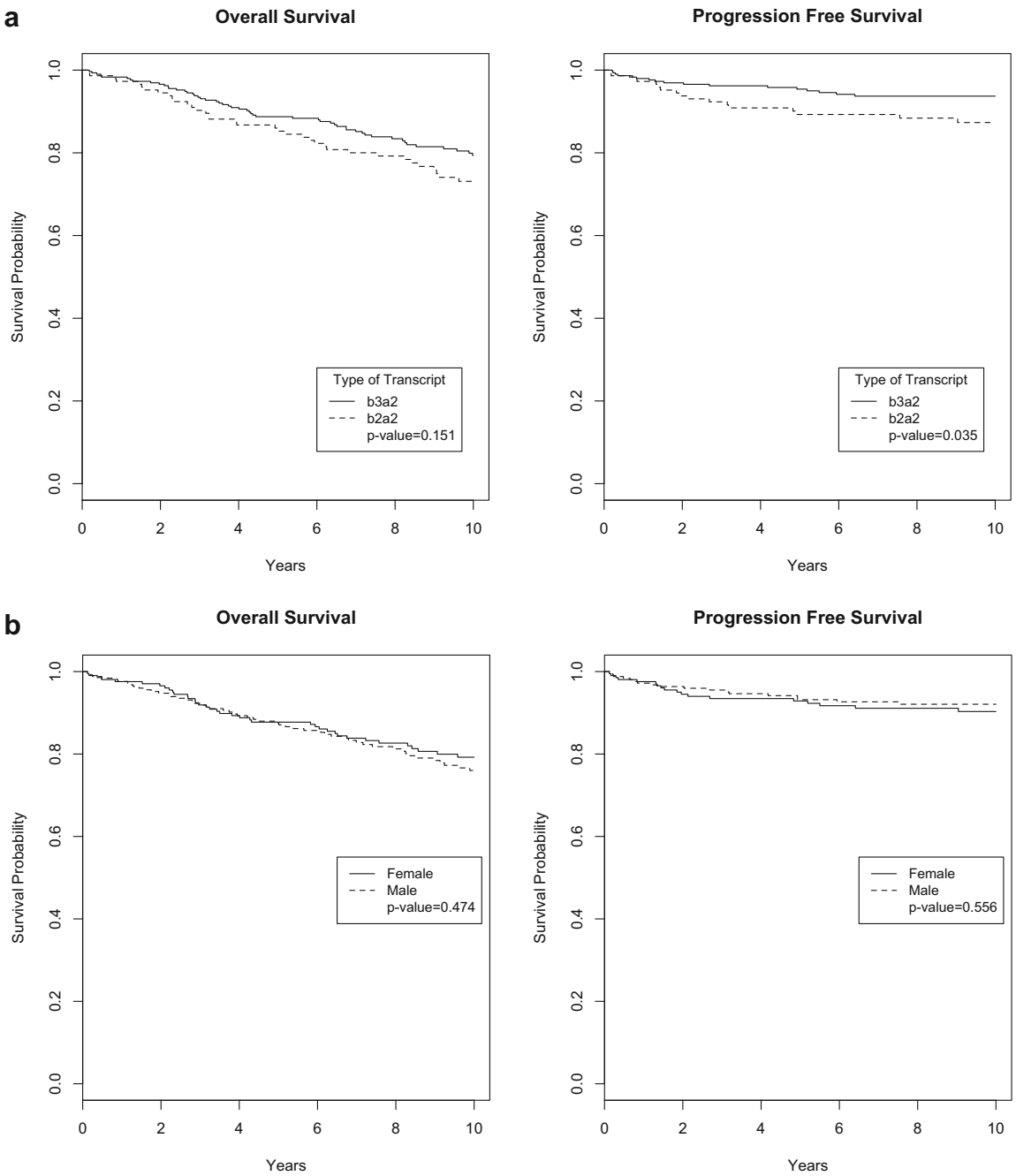

Fig. 5 **a** 10-year overall survival and 10-year progression-free survival according to type of transcript at baseline. **b** 10-year overall survival and 10-year progression-free survival according to gender

time of 26 months (13–48), and 21 (20.1%) patients never achieved a MMR during the treatment and switched to a third-line therapy. Three patients after a median duration of 2TKI treatment of 13 months (range 3–26) experienced a lymphoid BC; 2 of them died for disease progression, and one patient underwent allogenic transplant and is still alive. Among the intolerant patients, 11 started dasatinib (2 at 80 mg and 9 at 100 mg), 11 started nilotinib (5 patients at 600 mg and 6 at 800 mg), and 1 was treated with bosutinib (400 mg). After a median time of 6.8 years (range 1.8–7.6), 5 (21.7%) patients maintained as their best molecular response a MMR, 8 (34.8%) patients achieved a $MR^{4.0}$ after a median time of 13 months (range 8–16), 7 (30.4%) patients reached a $MR^{4.5}$ after a median time of 17 months [13–22], and 3 (13.1%) patients obtained a $MR^{5.0}$ after a median time of 22 months [17–26]. The 5-year OS and PFS after starting a 2TKI was 85.2% (CI 95% 73.5–94.3) and 85.8% (CI 95% 79.2–92.8), respectively.

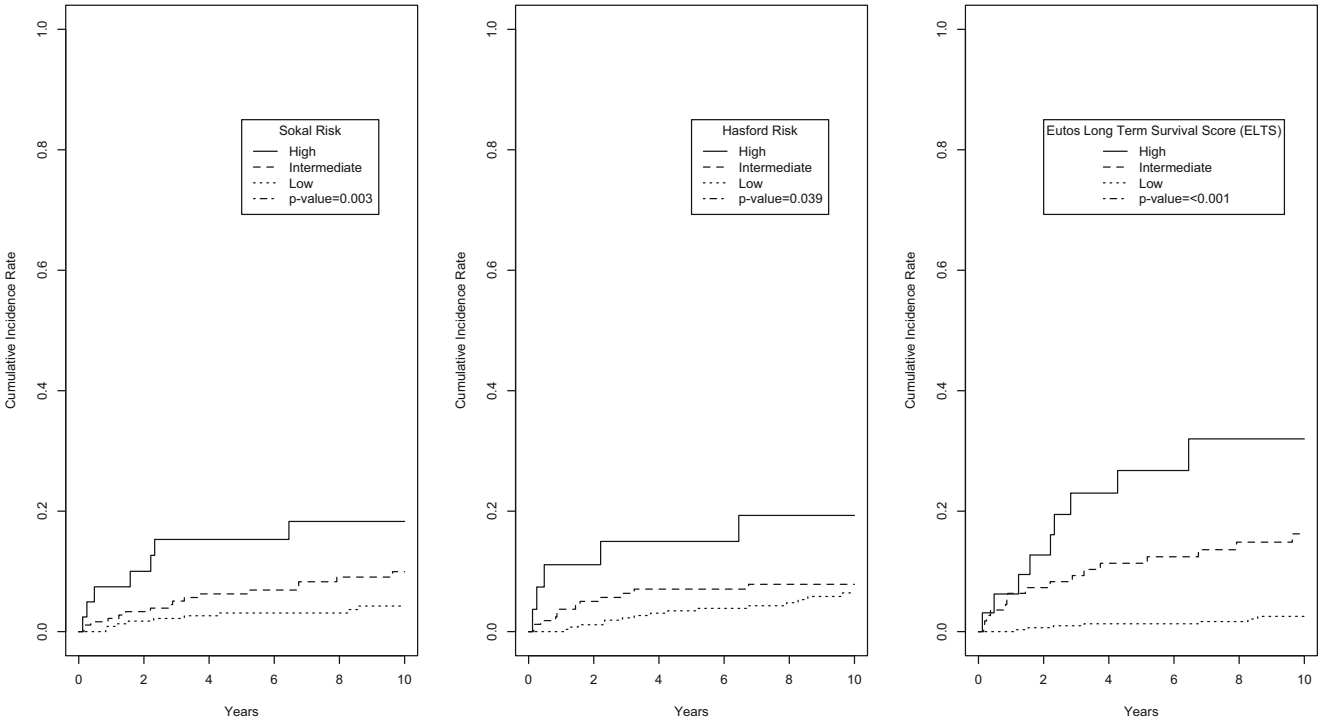

Fig. 6 10-year cumulative incidence of death according to Sokal risk score, Hasford risk score, and EUTOS long-term survival score

Long-term toxicities and deaths

We focused on the long-term safety of imatinib with a particular attention to severe cardiovascular (CV) events and development of solid tumors. In 17 patients (3.7%), a grade 3/4 CV event occurred during treatment. Among them, 4 (23.6%) experienced a myocardial infarction and 2 patients died, 2 (11.8%) had a heart failure that required hospitalization, 3 (17.6%) had a stroke causing 2 deaths, 3 (17.6%) an atrial fibrillation resolved only after specific therapy, 3 (17.6%) a

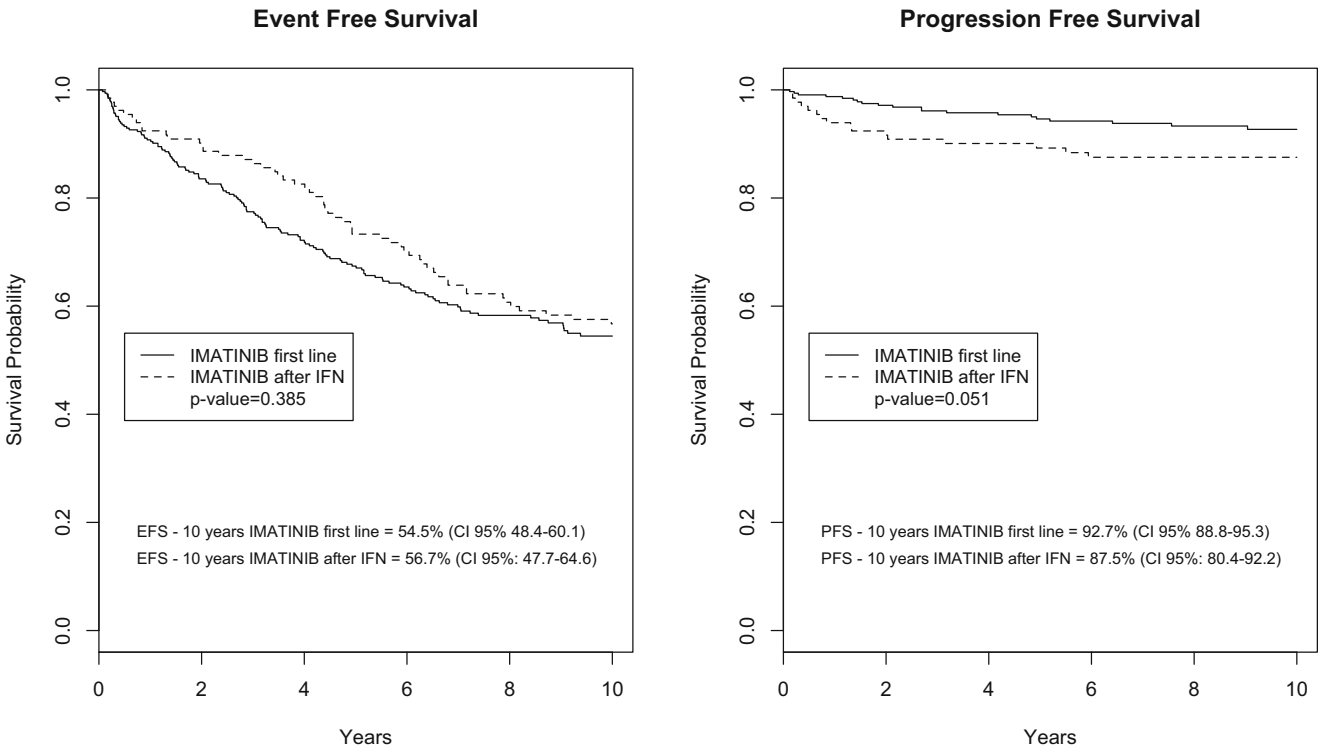

Fig. 7 10-year event-free survival and 10-year progression-free survival in imatinib frontline and after IFN groups

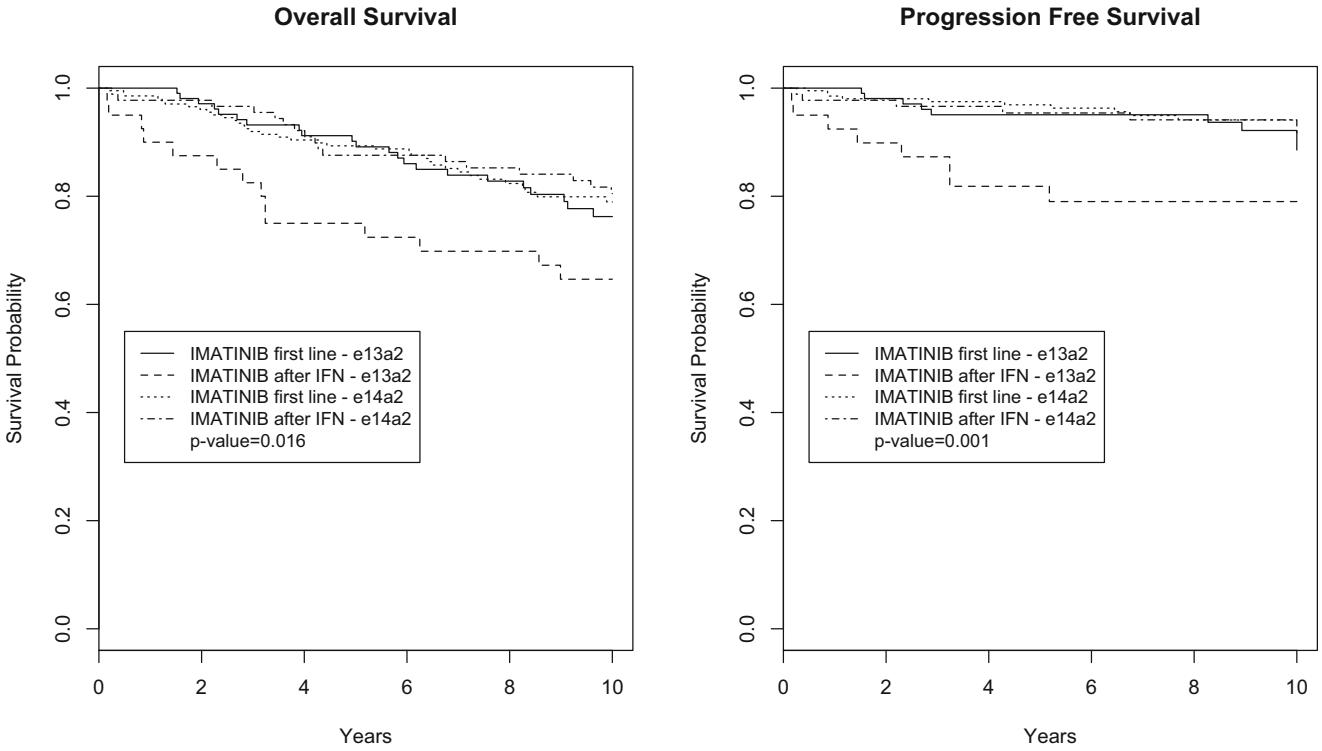

Fig. 8 10-year OS and 10-year PFS according to type of transcript at baseline in imatinib frontline and after IFN

venous thrombotic event that required anticoagulant treatment, and 2 (11.8%) a peripheral arterial occlusive event with 1 pulmonary embolism. Thirty-nine patients (8.5%) developed a solid tumor during the course of treatment: the most frequent sites involved were prostate (25.6%), gastrointestinal (20.5%), bladder (12.8%), lung (10.3%), and breast (10.3%). In the whole population, we observed 51 (11.1%) deaths. Forty-one deaths (80.4% of deaths and 8.9% of all patients) were classified as CML unrelated, and 10 deaths (19.6% of deaths, 2.1% of all patients) as CML related. The main reasons of CML-unrelated deaths were CV events (25.4%) and malignancies (21.8%) (Table 3).

Discussion

This study is the final comprehensive report of a retrospective analysis including 459 chronic-phase Ph+ and/or *BCR-ABL1*+

Table 2 Response rates after a 10-year follow-up

Cytogenetic response		Median time of achievement CCyR[1]
CCyR[1] at 3 months	56.3%	107 days (range 28–190)
CCyR[1] at 6 months	70.3%	
CCyR[1] at 12 months	73%	
Molecular response		Median time of achievement EMR[2]
EMR[2] at 3 months	85.4%	121 days (range 27–142)
MMR[3] at 6 months	38.3%	
MMR[3] at 12 months	57.1%	
Molecular response rate after 10-year follow-up		Median time of achievement MMR[3], MR 4.0, and MR 4.5
No MMR[3]	13.1%	2.4 years (range IQ 1.36–4.01)
MMR[3]	18.1%	4.57 years (range IQ 2.08–7.33)
MR 4.0	35.3%	8.23 years (range IQ 4.14–11.53)
MR 4.5	16.1%	
sDMR[4]	20.6%	

CCyR complete cytogenetic response, *EMR* early molecular response, *MMR* major molecular response, *sDMR* sustained deep molecular response

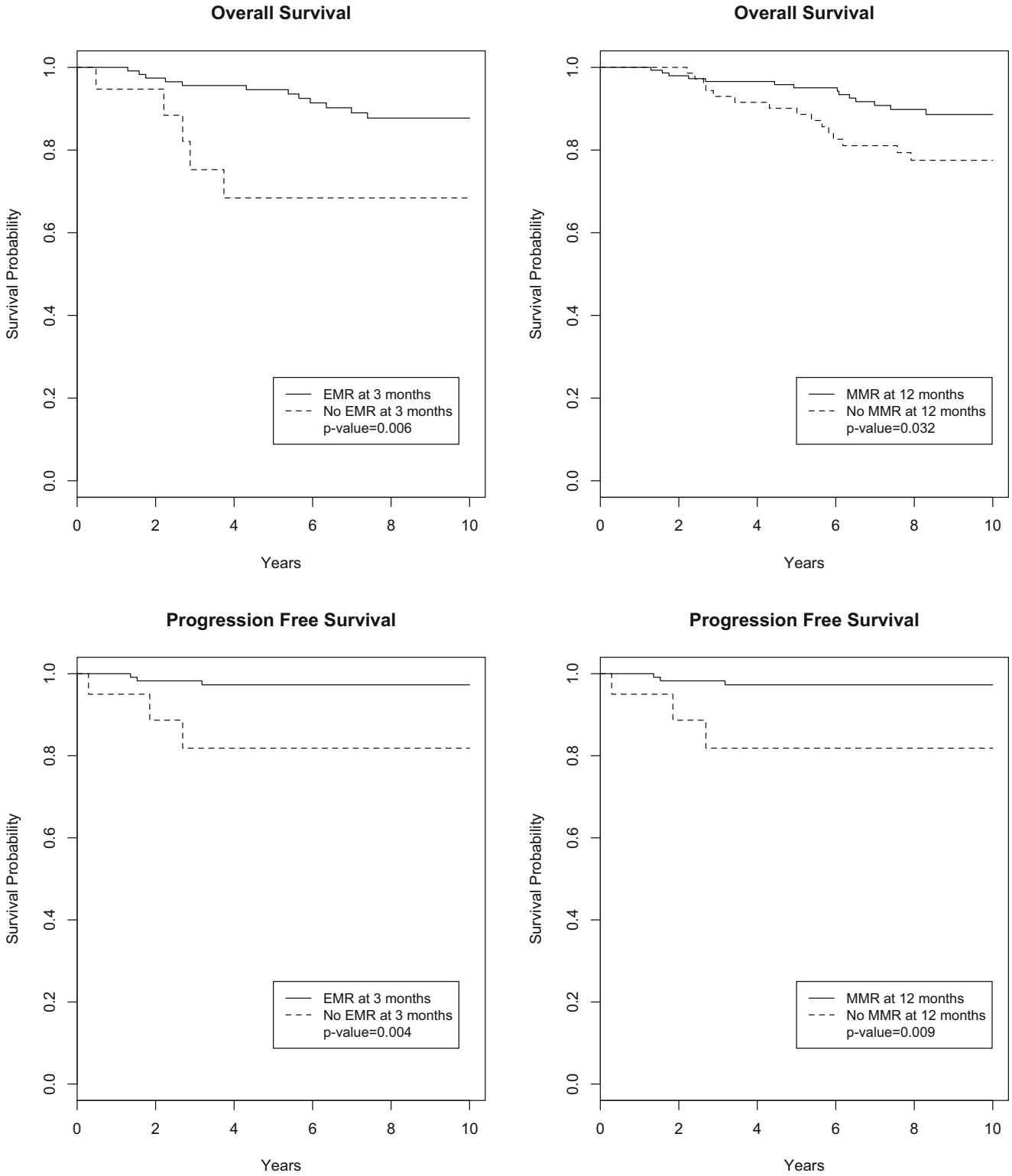

Fig. 9 **a** 10-year overall survival according to the achievement of early molecular response at 3 months and major molecular response at 12 months. **b** 10-year progression-free survival according to the achievement of early molecular response at 3 months and major molecular response at 12 months

adult CML patients with a 10-year follow-up followed and treated at a single institution. The long-term follow-up reported demonstrates robust results in terms of outcome, responses, and toxicities of imatinib-treated CML patients outside the setting of company-sponsored studies. A recent update of the IRIS trial has shown that the estimated OS rate at 10 years with first-line imatinib therapy was 83.3% and that patients who had a response to imatinib were unlikely to die from

Table 3 10-year toxicities and causes of death

Long-term toxicities			
Secondary tumors	39 (8.5%) patients	**Grade 3/4 cardiovascular events**	17 (3.7%) patients
Prostate cancer *n* (%)	10 (25.6)	Cardiac insufficiency *n* (%)	2 (11.8)
Colon cancer *n* (%)	8 (20.5)	Myocardial infarction *n* (%)	4 (23.6)
Bladder cancer *n* (%)	5 (12.8)	Cerebral stroke *n* (%)	3 (17.6)
Breast cancer *n* (%)	4 (10.3)	Atrial fibrillation *n* (%)	3 (17.6)
Lung cancer *n* (%)	4 (10.3)	Venous thrombotic event *n* (%)	3 (17.6)
Thyroid cancer *n* (%)	3 (7.7)	Peripheral arterial occlusive *n* (%)	2 (11.8)
Kidney cancer *n* (%)	2 (5.2)		
Skin cancer *n* (%)	2 (5.2)		
Vocal cords cancer *n* (%)	1 (2.4)		
Deaths			
CML[1] related	10 (19.6% of deaths) patients	**CML[1] unrelated**	41 (80.4% of deaths) patients
Blast crisis	10 (100%)	**Cardiovascular *n* (%)**	14 (34.2)
LBC[2]	8 (80%)	Cardiac insufficiency *n* (%)	5 (35.8)
MBC[3]	2 (20%)	Myocardial infarction *n* (%)	3 (21.4)
		Cerebral stroke *n* (%)	3 (21.4)
		Cardiac arrhythmias *n* (%)	3 (21.4)
		Secondary tumors *n* (%)	12 (29.2)
		Prostate cancer *n* (%)	4 (33.4)
		Colon cancer *n* (%)	3 (25)
		Breast cancer *n* (%)	2 (16.6)
		Lung cancer *n* (%)	2 (16.6)
		Bladder cancer *n* (%)	1 (8.4)
		Other causes *n* (%)	11 (26.8)
		Septic shock *n* (%)	3 (27.3)
		Pneumonia *n* (%)	2 (18.2)
		Terminal kidney insufficiency *n* (%)	4 (36.3)
		Cerebral bleeding *n* (%)	2 (18.2)
		Unknown *n* (%)	4 (9.8)

CML chronic myeloid leukemia, *LBC* lymphoid blast crisis, *MBC* myeloid blast crisis

CML [1]. Furthermore, in a retrospective analysis that included only CML patients treated with imatinib after IFN failure, the MDACC group showed a 10-year OS rate of 68% and an EFS rate of 51% suggesting a major change in the natural course of CML after IFN failure [17]. In our study, the 10-year OS of the whole cohort was 77.1%; comparing the 10-year OS of patients treated with imatinib after IFN (75.3%) and imatinib frontline (77.8%), considering only the impact of imatinib therapy, we did not find any significant difference. Imatinib was effective even in CML patients resistant to IFN and determined similar outcomes compared with patients treated frontline. Furthermore, in our large series of patients, the 10-year probability of dying due to disease (7.8%) was lower than dying due to other causes (16%) confirming that life expectancy of CML patients treated with imatinib is near to that of the normal population. Focusing on the prognostic factors, which potentially may affect the long-term outcome of CML patients, we observed that the ELTS score calculated at baseline better predicted the 10-year risk of disease-related death compared with the other specific prognostic scores, as previously reported [16]. In fact, compared with other scores, patients who were classified at baseline as high risk according to the ELTS stratification [18, 19] had a considerable higher 10-year probability risk of dying due to CML compared with patients who belonged to low- and intermediate-risk score ($p < 0.001$). Therefore, the ELTS score allowed a more precise stratification of the risk of death at diagnosis in this subset of patients and, based on these results, its use in the clinic practice should be recommended. Although better and faster cytogenetic and molecular responses were reported in CML patients with the e14a2 transcript [20–22], only few studies have shown a difference in terms of outcome. Castagnetti et al. reported that the 7-year OS (90% and 83%, $p = 0.017$), PFS (89% and 81%, $p = 0.005$), and failure-free survival (71% and 54%, $p < 0.001$) were significantly better in patients with the e14a2 transcript treated frontline with imatinib compared with those who harbored the e13a2 transcript at baseline [23]. In our analysis, the e13a2 transcript negatively affected only the 10-year PFS ($p = 0.035$) but no difference in terms of OS was found comparing the e14a2 and e13a2 groups ($p = 0.151$). Compared with other reports (20–23), in our series, the e13a2 transcript had no impact on both the molecular response achievement and on the timing of response compared with patients carrying the e14a2 transcript. According to our results, also age was not an independent prognostic factor on CML patients outcome; indeed, the 4 age groups (18–35, >

35–< 50, > 50–< 65, and > 65 years) showed no significant difference considering the 10-year cumulative incidence of death due to CML ($p = 0.472$). Several studies have reported on outcome of elderly patients [24–26]; the French group showed that the 7-year estimated OS of elderly CML patients (> 70 years) treated with imatinib was 80.8% [22] reporting a high level of sustained responses to imatinib. We observed a 10-year OS of 73.4% and 79.4% in elderly (> 65 years) and younger CML patients (< 65 years) ($p = 0.467$), respectively. These data confirm the concept that imatinib is a very effective treatment also for older patients allowing high survival rate and holding a safe toxicity profile regardless of baseline comorbidities and that older age per se must not be a limiting factor for treating patients with imatinib. Several studies have shown that the EMR at 3 months has a positive impact on the subsequent possibility of achieving a DMR and a significantly prolonged OS [27–30]. However, data about the correlation between the achievement of a MMR within the first year of imatinib treatment and a better outcome are still controversial. We observed that not only the achievement of an EMR at 3 months but also a MMR at 12 months were associated with a significant advantage in terms of 10-year OS ($p = 0.032$) and 10-year PFS ($p = 0.009$). Furthermore, among the group of patients who did not achieve a MMR at 12 months, only 28.5% (compared with 84.7% in the group of patients who achieved a MMR at 12 months; $p < 0.001$) obtained a subsequent DMR during imatinib, confirming that the achievement of a MMR at 12 months is associated with a subsequent achievement of DMR. One of the present most relevant endpoints of treatment is the achievement of a DMR as a prerequisite for a possible discontinuation of TKI administration. In the GIMEMA trial [31], the 6-year CI of DMR in CML-patients treated with imatinib frontline was 61%; in our study, the 10-year CI of DMR was 51.4%. Furthermore, in the whole population, we observed that 95 (20.6%) patients treated with imatinib for more than 5 years had a sustained DMR (DMR maintenance for more than 2 years); these patients were therefore potentially eligible for treatment discontinuation according to the recent ESMO guidelines [16]. Among this group of patients, 83% and the 87% had achieved an EMR at 3 months and a MMR at 12 months, respectively; therefore, reaching molecular responses at these specific time-points can predict potential achievement of a sustained DMR that is now considered a prerequisite to discontinue TKIs.

In our cohort of 459 patients after a median follow-up of 122 months, 39 (8.5%) patients developed a secondary solid tumor. These data are important for two reasons: the incidence of secondary malignancy development observed in our CML population is not significantly higher compared with that in the age- and sex-matched Italian population [32]; our data confirm the main findings of three large clinical trials of CML patients treated with TKIs (MD Anderson Cancer Center trial [33] German CML study IV [34], and Novartis global database [35]) in which the overall incidence of second malignancies was similar to that of the general population. In two of these studies, higher standardized incidence ratios (SIR) for some cancer types were observed: kidney, melanoma, and endocrine tumors in the MD Anderson study [33] and non-Hodgkin lymphomas in the German CML study IV [34]. In our cohort of patients, the heterogeneity of the malignancies observed precluded a proper evaluation of the SIR for different types of cancer.

We also focused on the long-term toxicity of imatinib in terms of serious CV events (grade 3–4). Clinical trials that followed a large number of patients prospectively for a long period of time did not show an increased risk of CV events in patients who received imatinib [1, 36, 37]. For instance, the long-term follow-up of patients on imatinib in the IRIS study showed that CV events were rare (1.7%) [1]. Furthermore, retrospective analysis of 6 imatinib trials, including 2327 patients with a median exposure to imatinib of 2.4 years, documented a congestive heart failure incidence of 0.2% [38]. Also in our population, the long-term incidence of grade 3–4 CV events was low (3.7%). Based on available data from clinical studies and real-life data, it appears therefore that imatinib has little clinical impact on cardiac function and potential occurrence of arterial occlusive events.

In conclusion, the results of this single-center study show that imatinib administered in the real-life setting to CML patients for a median follow-up of more than 10 years consistently provides high rates of remission, profound responses. and overall survival, and is associated with a very safe long-term toxicity profile.

Authors' contribution MB designed the study, wrote and revised the manuscript; MM collected data and wrote the manuscript; DAF and FE analyzed data; ES, LR, RL, and SCR followed patients; DD and GC performed molecular analysis; RF critically revised the paper and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments.

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