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ORIGINAL ARTICLE

Secondary malignancies in chronic myeloid leukemia patients after imatinib-based treatment: long-term observation in CML Study IV

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Treatment of chronic myeloid leukemia (CML) has been profoundly improved by the introduction of tyrosine kinase inhibitors (TKIs). Long-term survival with imatinib is excellent with a 8-year survival rate of ~88%. Long-term toxicity of TKI treatment, especially carcinogenicity, has become a concern. We analyzed data of the CML study IV for the development of secondary malignancies. In total, 67 secondary malignancies were found in 64 of 1525 CML patients in chronic phase treated with TKI ($n = 61$) and interferon-α only ($n = 3$). The most common malignancies ($n \geqslant 4$) were prostate, colorectal and lung cancer, non-Hodgkin's lymphoma (NHL), malignant melanoma, non-melanoma skin tumors and breast cancer. The standardized incidence ratio (SIR) for all malignancies excluding non-melanoma skin tumors was 0.88 (95% confidence interval (0.63–1.20)) for men and 1.06 (95% CI 0.69–1.55) for women. SIRs were between 0.49 (95% CI 0.13–1.34) for colorectal cancer in men and 4.29 (95% CI 1.09–11.66) for NHL in women. The SIR for NHL was significantly increased for men and women. An increase in the incidence of secondary malignancies could not be ascertained. The increased SIR for NHL has to be considered and long-term follow-up of CML patients is warranted, as the rate of secondary malignancies may increase over time.

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INTRODUCTION

Treatment of chronic myeloid leukemia (CML) has been profoundly improved by the introduction of tyrosine kinase inhibitors (TKIs). Long-term survival with imatinib is excellent with a 5-and 8-year survival rate of 90% and 88%, respectively.[1,2] The life expectancy of patients who achieve complete cytogenetic remission is not different from that of the general population,[3,4] and is influenced mostly by comorbidities.[5]

The increased life expectancy requires closer long-term observation of potential side effects. The development of secondary malignancies is regarded as a common risk of antineoplastic therapies. An increased rate of secondary malignancies compared with the general population has been reported in patients with Hodgkin's lymphoma,[6,7] chronic lymphocytic leukemia[8,9] and other lymphoproliferative diseases,[10] as well as in polycythemia vera[11] and essential thrombocythemia.[12,13]

An increased rate of secondary malignancies has also been described in patients who had received allogeneic stem cell transplantation[14–18] for various hematologic diseases. Exposure to radiotherapy,[19,20] chemotherapy and immunosuppression, either disease or treatment related,[21] have been suggested as risk factors for secondary malignancies.

TKIs have also been discussed as risk factors for malignancies. Preclinical data demonstrated an interaction of imatinib with DNA repair mechanisms.[22] In studies with rats, neoplastic changes occurred in kidneys, urinary bladder, urethra, preputial and clitoral glands, small intestine, parathyroid glands, adrenal glands and non-glandular stomach.[23]

Another TKI effect that may be relevant for the development of malignancies is the inhibition of T-lymphocytes and dendritic cells. It has been shown that imatinib inhibits the effector function of T-lymphocytes and impairs the differentiation of peripheral blood progenitor cells into dendritic cells.[24]

These effects may facilitate the development of lymphatic malignancies during long-term exposure to imatinib.

In CML, data on the incidence of secondary malignancies are contradictory (see Supplementary Table 1). An increased rate of prostate cancer was found in a French cohort of 189 CML patients treated with imatinib.[25] However, data from the Novartis registries

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of more than 9500 patients did not confirm this observation, but they were not obtained from randomized trials.[26]

Analyses of patient cohorts from multiple phase I and II trials at the MD Anderson Cancer Center, who were treated with TKI for CML and other myeloproliferative neoplasms, showed a risk of secondary malignancies that was lower than expected in the general population.[27] In line with this is the analysis from Poland of 221 CML patients under imatinib treatment (median of 61 months) with no increase of secondary malignancies.[28]

In contrast, two other studies demonstrated an higher incidence in CML patients: (1) an analysis of the US-American SEER database found a significantly higher observed/expected ratio of secondary malignancies in the imatinib era of 1.48 versus 1.06 in the pre-imatinib era;[29] (2) a study that crosslinked the Swedish CML register to the Swedish Cancer registry found a standardized incidence ratio (SIR) of 1.52 for a patient cohort from the imatinib era;[30] and (3) in a cohort of 1038 Czech and Slovakian CML patients treated with TKI, the age-adjusted incidence rate of secondary malignancies was found to be 1.5-fold higher than that of the general population, but the difference was not statistically significant.[31]

However, CML itself has been discussed as a risk factor for solid cancers and hematologic malignancies. The acquired translocation t(9;22) at diagnosis of CML and additional chromosomal changes/mutations as a sign of clonal evolution during the course of disease show the potential of genetic instability in CML. Therefore, progenitors may already have the capacity to enforce themselves as distinct cells with enhanced malignancy resulting in solid cancers/hematologic malignancies before or later than CML.[32] Two epidemiological studies that analyzed cancer registries for patients with CML in Sweden[31,33] and patients with myeloproliferative neoplasms including CML in Denmark[34] showed an increased risk of secondary malignancies in CML patients.

To further elucidate the risk for the development of secondary malignancies in chronic-phase CML patients under treatment, we analyzed data from the CML Study IV after a median treatment duration of >5 years.

PATIENTS AND METHODS

Patients

CML study IV is a randomized 5-arm trial that compares imatinib 400 mg vs imatinib 800 mg vs imatinib 400 mg in combination with interferon-α vs imatinib 400 mg in combination with low-dose cytarabine and vs imatinib 400 mg after interferon failure.

The study was conducted as previously published.[1]

Inclusion criteria allowed the history of primary cancer if the disease was in stable remission without impact on study procedures. A total of 102 malignancies were reported in 92 patients before the diagnosis of CML. If relapses occurred within 5 years after diagnosis of primary cancer, they were not considered for further analysis.

Median follow-up for all patients after diagnosis of CML was 67.5 months (range, 0.12–124 months). Analysis was done according to intention-to-treat principle, that is, for patients on primary imatinib and after switch of therapy based on failure or intolerance.

Statistical analysis

SIRs[35] were calculated from the age-specific rates from the German reference population, obtained from the Robert Koch Institute.[36] Patients <15 years of age were excluded from the study and the groups 15–19 years and >85 years of age were not considered as >30 patient years were observed. As usual, non-melanoma skin cancer was not considered.[36] The 95% confidence intervals (CIs) were calculated with 'Mid-P exact test' using the modification of Miettinen[37] as previously described.[38] Overall survival and progression-free survival as defined by the ELN (European LeukemiaNet) criteria[39] were calculated using the Kaplan–Meier method.[40] Cumulative incidences of second malignancies were estimated under the presence of the competing risk of death.[41] Unless otherwise specified, date of diagnosis was considered as starting point for all time-to-event analyses. If one type of malignancy occurred more than once in a patient it was counted as one case according to the IACR (International Association of Cancer Registries).[42]

If not specified otherwise, all computations were done with SAS 9.2 (SAS Institute, Cary, NC, USA) or R 3.0.1.[43]

Ethics

The protocol followed the Declaration of Helsinki and was approved by the ethics committee of the 'Medizinische Fakultät Mannheim der Universität Heidelberg' and by local ethics committees of participating centers. Written informed consent was obtained from all patients before they entered the study.

RESULTS

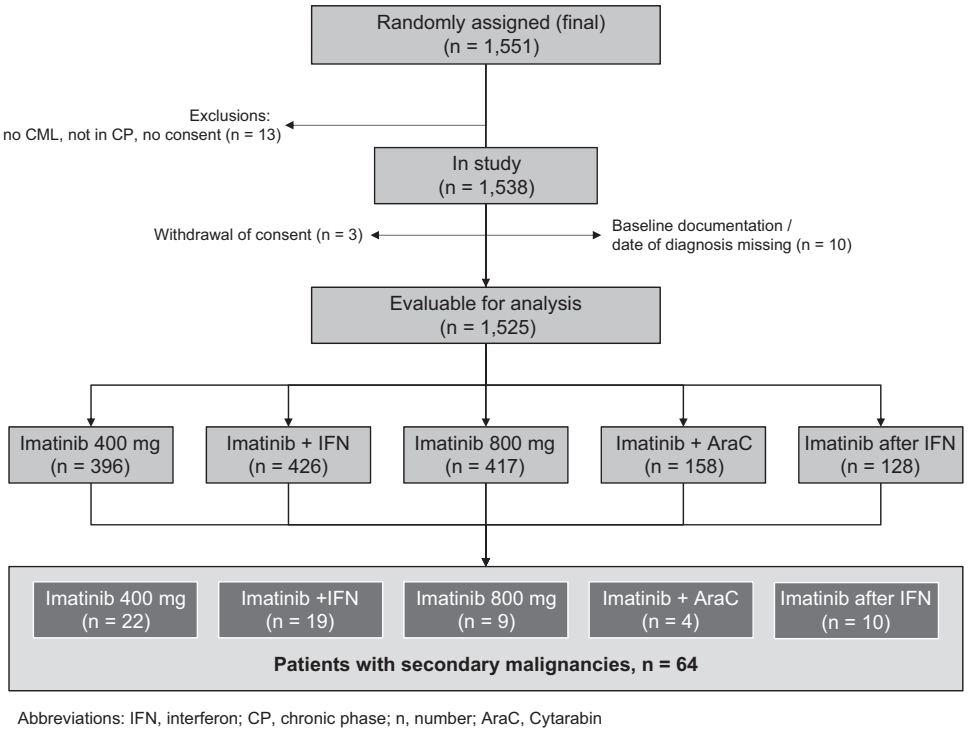
Patient characteristics

From February 2002 to March 2012, 1551 CML patients in chronic phase were randomized; 1525 were evaluable. Patient characteristics are described in Table 1 and Figure 1.

Table 1. Patient characteristics of available patients and patients with secondary malignancies

Characteristic	*Patients who developed secondary malignancies* (n = *64*)	*Total cohort* (n = *1525*)
Age at diagnosis of CML, years	65 (30–88)	52 (16–88)
Age at diagnosis of secondary malignancy, years	66 (31–88)	—
Time to secondary malignancy, years	2.4 (0.1–8.3)	—
Follow-up after diagnosis of secondary malignancy, months	46.8 (0–104.6)	—
Median overall survival, months	Not reached	Not reached
Patients with history of cancer, *n*	12	92
Malignancy was metastases or recurrence of primary malignancy, *n*	5	—
Time from primary cancer to secondary malignancy, years	Range 5–19	—
Treatment for CML	n *(%)*	n *(%)*
Imatinib 400 mg	22 (34)	396 (26)
Imatinib+IFN	19 (30)	426 (28)
Imatinib 800 mg	9 (14)	417 (27)
Imatinib+AraC	4 (6)	158 (10)
IFN-standard	10 (16)	128 (8)
Of this, IFN only	3	15

Abbreviations: AraC, Cytarabin; CML, chronic myeloid leukemia; CP, chronic phase; IFN, interferon.



Abbreviations: IFN, interferon; CP, chronic phase; n, number; AraC, Cytarabin

Figure 1. Consort statement of the CML study IV and occurrence of secondary malignancies per recruitment arm.

Secondary malignancies

In total, 67 secondary malignancies in 64 (4.2%) patients were found after a median follow-up of 67.5 months. Of these patients, 26 were female (41%). The median age of these 64 patients at diagnosis of CML was 65 years (range, 30–88 years), and the median age at diagnosis of the first secondary malignancy after diagnosis of CML was 66 years (range, 31–88 years). The median time from diagnosis of CML to secondary malignancy was 2.4 years (range, 0.1–8.3 years).

So far, cumulative incidences of secondary malignancies among the five therapy arms are similar; the 5-year cumulative incidence varied between 1.9 and 6.3% (see Figure 1).

Two patients with secondary malignancy had been switched to second-generation TKIs (dasatinib: 1, nilotinib: 1) because of imatinib failure 3 days and 3 years, respectively, before the diagnosis of the secondary malignancies. In addition, one patient received allogeneic stem cell transplantation (>4 years before diagnosis of secondary malignancy).

Twelve of the patients with primary cancer before CML diagnosis developed malignancies under TKI treatment. Six of these patients had metastases or recurrence of the first malignancy 5–19 years after diagnosis of the primary cancers (two patients with breast cancer and one patient with cancer of unknown origin, prostate rectal and renal cell cancer).

The types of malignancies were: prostate ($n=9$, 13%), colorectal ($n=6$, 9%), lung ($n=6$, 9%), non-Hodgkin's lymphoma (NHL; $n=7$, 10%), malignant melanoma ($n=5$, 7%), skin tumors (basalioma $n=4$ and squamous cell carcinoma $n=1$, 7%), breast ($n=5$, 7%), pancreas ($n=4$, 6%), kidney ($n=4$, 6%), chronic lymphocytic leukemia ($n=3$, 4%), head and neck ($n=2$, 3%), biliary ($n=2$, 3%), sarcoma ($n=2$, 3%), and esophagus, stomach, liver, vulva, uterus, brain and cancer of unknown origin (each $n=1$, 1%, see Table 2).

Three patients had more than one malignancy while receiving TKI. One patient developed a leiomyosarcoma and later a liposarcoma, one patient had a NHL that recurred (recurrence after 7 years) and one patient had prostate cancer and developed a NHL.

Outcome of patients with secondary malignancies

Of the 64 patients, 8 were in complete cytogenetic remission, 31 in major molecular remission at the time of diagnosis of the secondary malignancy. Two had progression of CML before diagnosis of the secondary malignancy, and one of these regained a remission before diagnosis of secondary malignancy (Table 2).

After diagnosis of secondary malignancies, CML treatment was continued without modification in 36 patients (56%). After a median follow-up time of 46.8 months (range 0–105 months) from time of diagnosis of the secondary malignancy, 26 patients had died. Of these patients, 22 died from the secondary malignancy, 2 from other causes (cerebellar infarction, infection) and 2 from unknown causes. Progression of CML was not a cause of death in any case. With a 4-year-survival of 57% (95% CI 43–70%, median overall survival 6.5 years), the overall survival and progression-free survival was significantly reduced in patients who developed secondary malignancies (Figures 2a and b).

Statistical analysis

Cumulative incidences. Cumulative incidence of secondary malignancies in patients >50 years of age was significantly higher than in patients $\leqslant 50$ years old ($P<0.001$): at 6 years the cumulative incidence was 8.1% (95% CI 9.2–10.5%) and 0.8% (95% CI 0.3–1.9%), respectively (Figure 3).

No significant differences were found between males and females (cumulative incidence 4.6% (95% CI 3.2–6.5%) vs 5.2% (95% CI 3.4–7.5%)) and EUTOS (European Treatment and Outcome Study)[44] high- vs low-risk patients at 6 years.

SIRs for secondary malignancies (without non-melanoma skin tumors) in the CML population in comparison with the general German population were 0.88 (95% CI 0.63–1.20) in men and 1.06 (95% CI 0.69–1.55) in women (38 and 24 patients observed vs 43.0 and 22.7 patients expected in the matched German population, Figures 4a and b).

Table 2. Incidence, treatment and outcome of secondary malignancies in the German CML IV study (cases: $n = 67$)

Secondary malignancy	*Cases*, n				*Remission status of CML at time of secondary NPL*, n					*Treatment of secondary NPL*						*Change of CML therapy*	*Outcome*		
	Male	*Female*	*Total*	%	n	*MMR*	$MR^{4.0}$	$MR^{4.5}$	*CCyR*	*Less than CCR*	*OP*	*RTx*	*CTx*	*AHT*	*Rituximab*	*Observe*	*None*		*Death*	*Remission*	*Stable disease*
Prostate	9	0	9	13	9	3		3	2	1	6	3	2	2					3	6	
Colorectal	3	3	6	9	6	1	1		1	3	4	2	2						2	4	
Lung	4	2	6	9	6	1			2	3	4	2	2						5	1	
Non-Hodgkin's lymphoma	4	3	7	10	7	1	1	3		2		3	1		1	2				2	5
Melanoma	2	3	5	7	5	1		2		2	5									5	
Skin, non-melanoma	2	3	5	7	5	1		2	1	1	5									5	
Breast	0	5	5	7	5	1				4	2	3	2	2					3	2	
Pancreatic	2	2	4	6	4	1				3	3		1				1		3	1	
Renal	2	2	4	6	4	1	1	1		1	2		1				1		3	1	
Chronic lymphatic leukemia	2	1	3	4	3	1				2											3
Head and neck	2	0	2	3	2	2					2									2	
Hepatobiliary	1	1	2	3	2	2					1		2						2		
Sarcoma	2	0	2	3	2	2					1 (2)									2	
Esophagus	1	0	1	1	1					1		1							1		
Stomach	1	0	1	1	1					1						1			1		
Liver	1	0	1	1	1					1						1			1		
Vulva	0	1	1	1	1				1										1		
Uterus	0	1	1	1	1				1		1									1	
Brain	1	0	1	1	1					1	1	1	1						1		
Cancer of unknown origin	1	0	1	1	1		1				1	1	1						1		
Total	40	27	67	100	67	18	4	11	8	26	37	17	15	4	1	2	4	0	27	32	8

Abbreviations: AHT, antihormone therapy; CCyR, complete cytogenetic remission; CML, chronic myeloid leukemia; CTx, chemotherapy; MMR, major molecular remission; MR, molecular remission; none, no tumor-specific therapy; NPL, neoplasia; observe, observation; OP, operation; RTx, radiotherapy.

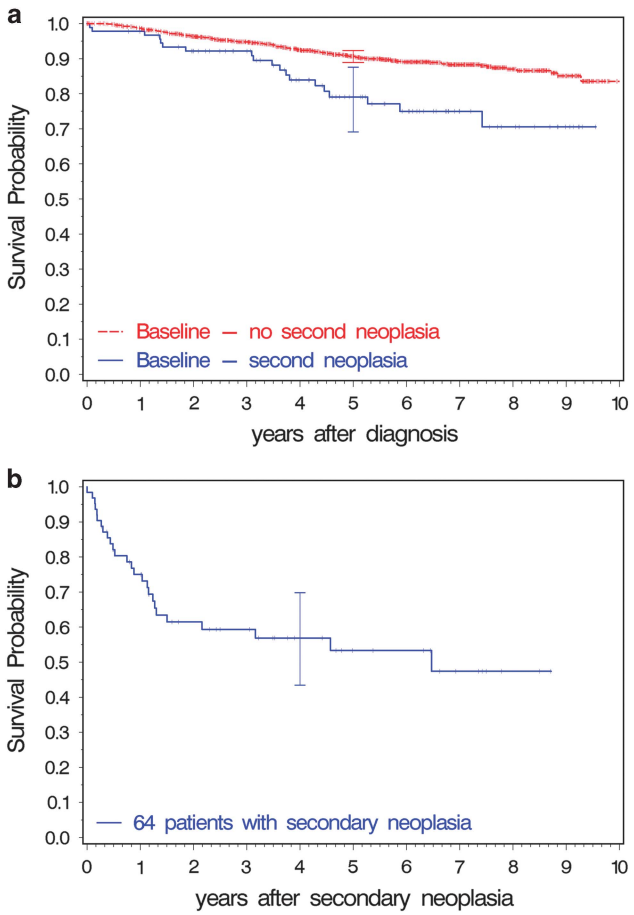


Figure 2. Probability of survival with or without the appearance of secondary malignancies. (**a**) Overall survival from time of diagnosis of CML. (**b**) Progression-free survival from time of diagnosis of secondary malignancy.

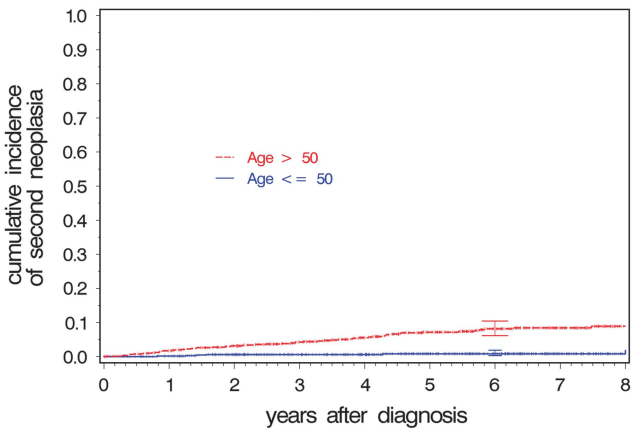


Figure 3. Cumulative incidence of all secondary malignancies according to age $\leqslant 50$ vs >50 years.

Cancer subtypes. Regarding the subtypes of secondary malignancies, the numbers for prostate cancer, colorectal cancer, breast cancer, malignant melanoma, pancreas and kidney cancer in CML patients were not statistically significantly different from expected numbers of the general population. The SIRs were between 0.49 (colorectal in male) and 3.33 (kidney cancer in female) (Figure 4).

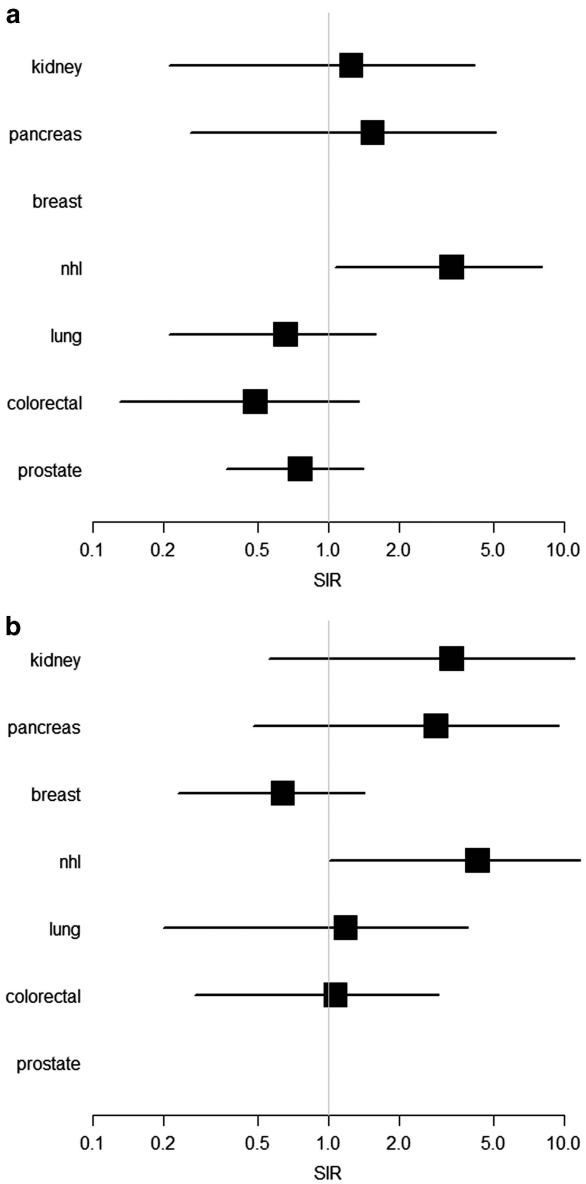


Figure 4. SIRs of secondary malignancies within CML study IV for men and women compared with normal population for different tumor types. (**a**): SIRs of men (**b**) and SIRs of women.

The number of cases of NHL however was significantly higher in the CML IV cohort than the expected number in the matched German population. The SIR for male was 3.33 (95% CI 1.06–8.04) and 4.29 for female (95% CI 1.09–11.66) (see Table 3 and Figure 4b).

DISCUSSION

Overall, our data do not support an increased risk for secondary malignancies in CML patients treated with imatinib as the SIR of men and women were similar to that of general population. However, looking at subtypes of malignancies we found a significant increase of the SIR for NHL for both sexes.

These data are in contrast to analyses of population-based registries in Denmark[34] and Sweden[33] that found an increased risk for secondary malignancies in CML patients. The observation timeframes for both studies were between 1970 and 2007 and between 1977 and 2008, respectively, and therefore mostly from

Table 3. Standardized incidence rates of secondary malignancies (excluding non-melanoma skin cancer)

	Male			*Female*		
	CML IV	*Matched German population*	*Observed/expected (95% confidence interval)*	*CML IV*	*Matched German population*	*Observed/ expected (95% confidence interval)*
Overall, *n*	38	43.0	0.88 (0.63–1.20)	24	22.7	1.06 (0.69–1.55)
Age >50 years, *n*	37	40.6	0.91 (0.65–1.24)	20	20.5	1.02 (0.65–1.54)
Age <50 years, *n*	1	2.4	0.42 (0.02–2.06)	4	2.2	1.82 (0.58–4.39)
Secondary malignancy type (types with only one occurence were not shown)						
Prostate, *n*	9	11.8	0.76 (0.37–1.40)			
Colorectal, *n*	3	6.1	0.49 (0.13–1.34)	3	2.8	1.07 (0.27–2.92)
Lung, *n*	4	6.1	0.66 (0.21–1.58)	2	1.7	1.18 (0.20–3.89)
NHL, n	4	1.2	3.33 (1.06–8.04)	3	0.7	4.29 (1.09–11.66)
Breast, *n*				5	7.8	0.64 (0.23–1.42)
Pancreas, *n*	2	1.3	1.54 (0.26–5.08)	2	0.7	2.86 (0.48–9.44)
Kidney, *n*	2	1.6	1.25 (0.21–4.13)	2	0.6	3.33 (0.56–11.01)

Abbreviations: CML, chronic myeloid leukemia; NHL, non-Hodgkin's lymphoma.

the pre-TKI era. Both studies did not report on the specific treatment, but one can conclude that most commonly hydroxyurea and interferon-α were given to the patients during most of the time period. Knowing that BCR-ABL itself is a mutant driver of malignancy, this could explain the discrepancy of the studies.

The data from the SEER database contrast the above observations as in their study secondary malignancies in the pre-imatinib era were less common than in the imatinib era.[29]

A recent analysis of 868 CML patients from the Swedish CML registry diagnosed between 2002 and 2011 that were crosslinked to the Swedish Cancer registry showed a 50% overall increased risk of second malignancies compared with the normal population.[30] This is in line with the study by Rebora *et al.*[33] A possible explanation of the differences to our analyses is that we have a very well-described patient population with very good remission rates under imatinib-based treatments.[45] Therefore, the BCR-ABL effect as described above may play a less important role in the CML IV trial cohort and may contribute to lower incidence rates of secondary malignancies.

In line with our observation is the study by Voglova *et al.*[31] The age-adjusted incidence rate of secondary malignancies in their cohort of 1038 Czech and Slovakian CML patients treated with TKI was 1.5-fold higher than the normal population, but the difference was not statistically significant.[31]

Subtypes

There are several studies showing an increasing risk for subtypes of different cancers under TKI treatment. Verma *et al.*[27] reported on secondary malignancies in patients with different myeloproliferative neoplasms including CML. They found a smaller number of secondary neoplasms than expected but an increased risk of melanoma, kidney and endocrine cancers.

In our study the increased rate of prostate cancer, the most common malignancy we found, was not statistically significant. This corresponds to data from the Novartis registries of clinical trials and adverse event reports of more than 9500 patients and more than 1 20 000 patient years and is in contrast to Roy *et al.*[25]

The increased frequency of NHL in our study was statistically significant. It must be considered that two of the seven cases occurred in patients who had already developed a secondary malignancy: in one case the documented NHL was a recurrence after 7 years, and the other case was a NHL in a patient with a previously documented prostate cancer. Another reason for the increased number of NHL cases may be that three of the seven cases were low-grade lymphomas that are easily missed in the general population but found in a monitored study cohort. We could not demonstrate a sex difference in appearance of NHL as this was shown by Radivoyevitch *et al.*[46]

Prevalence

In addition, a high number of patients (92 out of 1525, 6.0%) with malignancies that were diagnosed before the CML diagnosis were randomized to our study. In an analysis of the SEER database, Brenner *et al.*[47] found that 14% of patients with CML had a malignancy before CML was diagnosed. Usually, in official publications like from the German Robert Koch Institute, cancer prevalence is reported as a period prevalence, for example, 5-year prevalence instead of point prevalence. Thus, no number for comparison exists directly. However, the cancer prevalence in our patient population seems to be high and a potential influence on the pathogenesis of CML can be discussed.

The diagnosis of secondary malignancies had a significantly unfavorable impact on overall survival and progression-free survival compared with other study patients of our trial. Remarkably, the cause of death in all these patients was not related to CML as no progression was observed.

Observation data from other disease entities, for example, Hodgkin's lymphoma, indicate a long latency time between time after start of exposure to a risk factor and risk of secondary malignancies. The relative risk increased from 2.2 after 5 years to 10.9 after 20 years.[7] Peaks for the rate of secondary malignancies were 5 to 9 years after chemotherapy and remained raised for ⩾25 years.[6] Therefore, longer follow-up of CML patients is warranted. In summary, there is no consistent distribution of malignancies in the different reports.[25–27,31,33,34] The risk of secondary malignancies is increased in population-based studies of CML patients,[27,34] but not increased in case–control studies of CML patients who are treated with TKI.[27,28,31] So far, it is impossible to dissect patient selection in the observed patient populations from the impact of CML treatment on the risk of secondary malignancies.

Therefore, it is speculative if secondary malignancies occur after long exposure to TKI. Ideally, long-term follow-up on large cohorts of CML patients under treatment is warranted. As analyses of cancer registries often do not integrate complete data on treatment, a solution could be a registry on CML trial patients after end of study.

CONFLICT OF INTEREST

BH has received honoraria from Bristol-Myers Squibb (BMS) and research funding from Novartis; SWK honoraria and research funding by Novartis; MCM honoraria and research funding from Novartis, BMS, ARIAD and Pfizer; MP honoraria from BMS and consultancy from Novartis; AH honoraria from Novartis, BMS, ARIAD, consultancy from Novartis and research funding from Novartis, ARIAD and Pfizer; RH research funding from Novartis and BMS and SS honoraria from Novartis, BMS, Pfizer, ARIAD and research funding from Novartis and BMS. The other authors declare no conflict of interest.

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Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)