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Incidence of second malignancies during treatment of chronic myeloid leukemia with tyrosine kinase inhibitors in the Czech Republic and Slovakia

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Tyrosine kinase inhibitors (TKI) have completely changed the prognosis of patients with Ph+ chronic myeloid leukemia (CML). The occurrence of a second malignancy (SM) in CML patients successfully treated with TKI may significantly affect their prognosis.

In a retrospective study of 1,038 patients with CML treated at 10 centers in the Czech Republic and Slovakia between 2000 and 2009, SM was detected in 35 (3.37%) patients after TKI therapy was initiated. The median intervals from the diagnosis of CML and from the start of TKI therapy to the diagnosis of SM were 58 months (range 2 – 214) and 32 months (range 1 – 102), respectively. The observed age-standardized incidence of SM after the start of TKI therapy was 8.95 / 1,000 person-years.

Comparison of the incidence of SM in CML patients with population data was performed only for patients from the Czech Republic. The age-standardized incidence rate of all malignant tumors except non-melanoma skin cancers was 6.76 (95% CI: 6.74; 6.78) / 1,000 person-years in 2000 – 2007 while the incidence rate of SM in 708 CML patients from the Czech Republic treated with TKI was 9.84 (95% CI: 6.20; 13.48) / 1,000 person-years, i.e. 1.5-fold higher, although the difference was statistically insignificant. The distribution of SM types in CML patients treated with TKI was similar to that in the age-standardized general Czech population. The median overall survival (OS) of patients treated with TKI who also developed SM (57 months) was shorter than the OS of patients treated with TKI but not suffering from SM (median OS not reached, log rank test $p<0.001$). Prospective long-term population-based studies in CML patients treated with TKI as first-line therapy are needed to determine the relationship of SM to TKI therapy.

Key words: chronic myeloid leukemia; tyrosine kinase inhibitor; incidence; second malignancy

Tyrosine kinase inhibitors (TKI) have significantly changed the prognosis of patients with Ph+ chronic myeloid leukemia (CML). The estimated overall survival (OS) of patients with Ph+ chronic phase CML treated with imatinib in the IRIS study was 86% at 7 years according to intention-to-treat analysis [1]. When death from other causes than CML was ruled out, the rate increased to 94% [1]. The occurrence of a second malignancy (SM) in a patient successfully treated for primary malignancy can be a serious complication. SM may also be related to the treatment of a primary malignancy. Reports about the occurrence of SM during the course of CML are also known from the era that preceded the use of TKI [2, 3]. There are conflicting data on the incidence of SM in CML patients during treatment with TKI [4, 5, 6, 7] but most reports did not find increased incidence of SM after TKI therapy in CML patients. In a single center, SM was registered in 6 patients treated for CML with TKI between 2000 and 2007. This observation, together with limited literature on the topic, led us to the decision to initiate a retrospective study in order to evaluate the incidence and types of SM in a larger group of CML patients from the CML registries CAMELIA and INFINITY.

Material and methods

In the Czech Republic and Slovakia, the treatment of CML with TKI is concentrated in large hematology centers. These maintain two independent registries of patients with CML. Both registries (CAMELIA and INFINITY) participate in the WP4 and European Treatment and Outcome Study (EUTOS) for Chronic Myeloid Leukemia project of the European

LeukemiaNet. Definitions for the diagnosis of Ph+ CML were according to the WHO classification of myeloid malignancies [8]. Staging of solid tumors was in accordance with the TNM or tumor-specific staging systems [9].

The patients gave informed consent to collection of their data approved by local ethics committees. Data on the incidence of solid tumors in the population were obtained from the National Cancer Registries [10].

Neither registry has a separate database on SM. Therefore, we performed retrospective search for patients with SM in centers participating in both registries. The centers were requested to review documentation of all registered Ph+ CML patients treated with TKI between 2000 and 2009, and to provide the following additional data for patients who developed a second malignancy: type and localization of SM, date of diagnosis of SM, additional previous treatment of CML, including chemotherapy or radiotherapy, treatment of SM, status of patients and cause of death. The CML registries served as a source of basic characteristics of patients and diseases: age, sex, date of diagnosis of CML, phase of CML at diagnosis, cytogenetics and type of BCR-ABL1 transcript, CML treatment, and time period between the diagnoses of CML and SM.

Survival of the patients was evaluated as of December 31, 2009 or the date of death according to the Kaplan-Meier method [11]. Statistical significance was calculated using the log rank test [12]. Age standardization of cancer incidence was performed according to the standard methodology [13], with 95% confidence intervals being used. The age standard corresponded to the age distribution of patients at the start of TKI therapy was as follows: 15 – 39 years 22%, 40 – 49 years 20%, 50 – 59 years 31%, 60 – 69 years 20%, and 70 or more years 7%. Comparison of cancer incidence between populations was performed by the Mantel-Haenszel test [13].

Results

A total of 1,038 patients with CML were treated with TKI between January 1, 2000 and December 31, 2009 (832 imatinib only, 192 imatinib and subsequent second-generation TKI, 14 second-generation TKI only). The patients' demographic characteristics are shown in Table 1. SM developed in 43 patients (4.14%) after the diagnosis of CML (Table 2). Patients with basal cell carcinoma as SM, other malignancies prior to CML and with SM before the start of TKI therapy were excluded from further analysis.

A detailed analysis was performed in a group of 35 patients with CML and SM after the initiation of TKI therapy (3.37% of 1,038 patients) (Tables 3, 4). The median age of these 35 patients (23 male, 12 female) was 58 years (range 32 – 74) at the time of CML diagnosis and 65 years (range 33 – 80)

Table 1. Demographics of the patients and disease characteristics

		No. of patients	*%*
All patients		1038	100
Registry	CAMELIA	720	69.4
	INFINITY	318	30.6
Country	Czech Republic	708	68.2
	Slovak Republic	330	31.8
Sex	Male	544	52.4
	Female	494	47.6

Age (years)	*Mean*	*Median*	*Ranges*
CML diagnosis	50	52	15 – 89
Start of TKI	51	53	17 – 89

Follow-up (months)	*Mean*	*Median*	*Ranges*
From diagnosis	60	51	1 – 246
From start of TKI	44	41	1 – 112

		No. of patients	*%*
TKI in the first-line therapy of CML	IM only	515	49.6
	IM followed by DA/NI	88	8.5
	DA/NI	14	1.3
	TKI in 1st line in total	617	59.4
TKI therapy after the failure or intolerance of other previous therapy	IM only	317	30.5
	IM followed by DA/NI	104	10.0
	DA/NI	-	-
	TKI in 2nd line in total	421	40.6

IM = imatinib, DA = dasatinib, NI = nilotinib

Table 2. Patients according to second malignancy and their treatment of CML

	TKI in 1st line		TKI in 2nd line[2]		All patients	
	No. of patients	*%*	*No. of patients*	*%*	*No. of patients*	*%*
Without SM or with other skin tumors (C44) as SM	597	57.5	398	38.4	995	95.9
SM after CML and other malignancies before CML	3	0.3	1	0.1	4	0.4
SM after CML diagnosis and before the start of TKI	2	0.2	2	0.2	4	0.4
SM after CML and after the start of TKI with risk factors[1]	1	0.1	4	0.4	5	0.5
SM after CML and after the start of TKI without risk factors[1]	14	1.3	16	1.5	30	2.8
All patients	617	59.4	421	40.6	1,038	100

[1]Risk factors for SM: allogeneic stem cell transplantation, high dose chemotherapy, therapy for other malignancies before the diagnosis of CML
[2]TKI as second-line CML treatment after failure or intolerance of previous therapy
CML = chronic myeloid leukemia, TKI = tyrosine kinase inhibitors

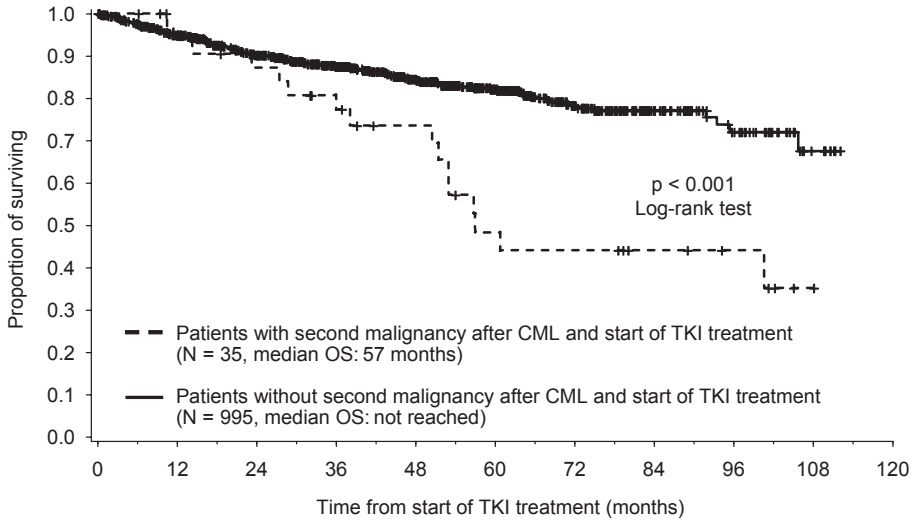

Figure 1. Overall survival from start of TKI therapy (OS_{TKI}) in patients with and without second malignancy

at the time of SM diagnosis. The median intervals from the diagnosis of CML and start of TKI therapy to the diagnosis of SM were 58 months (range 2 – 214) and 32 months (range 1 – 102), respectively.

Table 3. Characteristics of patients with second malignancies after diagnosis of CML and after start of TKI

		Number of patients	*%*
Sex	Male	23	65.7
	Female	12	34.3
Phase of disease at CML diagnosis	Chronic	32	91.4
	Accelerated	1	2.9
	Blastic	2	5.7
Type of BCR-ABL1 transcript	b3a2	24	68.,6
	b2a2	9	25.6
	b2a3	1	2.9
	Unknown	1	2.9
TKI treatment	first-line	15	42.9
	second-line	20	57.1
Treatment response at SM diagnosis	CCgR	19	54.3
	less then CCgR or relapse	12	34.3
	Unknown	4	11.4
Age (years)	*Mean*	*Median*	*Range*
at CML diagnosis	57	58	32 – 74
at the start of TKI	59	61	32 – 76
at SM diagnosis	62	65	33 – 80
Interval (months)	*Mean*	*Median*	*Range*
from CML to SM	65	58	2 – 214
from the start of TKI to SM	37	32	1 – 102

CCgR = Complete cytogenetic response

Imatinib (IM) was used as first-line therapy in 14 patients and dasatinib in one patient. Eight of the patients were shortly (< 2 months) pretreated with hydroxyurea. In 20 patients, IM was used as second-line therapy following other treatments.

One patient suffered from multiple malignancies aside from CML. CML was diagnosed at the age of 60 and he subsequently developed renal carcinoma, prostate adenocarcinoma and glioblastoma.

At the date of evaluation, 19 patients were alive, 16 died; SM caused the death in 11 of the patients; one patient died due to progression of CML; two patients died because of infectious complications related to therapy; in two patients, the cause of death was directly related to neither CML nor SM.

The median OS from the start of IM treatment (OS_{IM}) of 35 patients who were treated with TKI and who developed SM was 57 months. The median OS of 995 patients without SM was not reached (Figure 1). The difference in the OS of CML patients treated with IM with and without SM was statistically significant (log rank test, p= 0.001).

The crude incidence rates of SM after the start of TKI therapy were 9.27 / 1,000 person-years in all patients, 8.63 / 1,000 person-years in patients with first-line TKI therapy and 9.82 / 1,000 person-years in patients with second-line TKI therapy. To avoid the influence of different age structures in the analyzed groups, age-standardized incidence rates were also calculated. As a standard for age-standardized rate calculations, the age distribution of patients at the start of TKI therapy was used: 15 – 39 years 22%, 40 – 49 years 20%, 50 – 59 years 31%, 60 – 69 years 20%, 70 and more years 7%. The age-standardized incidence rates of SM were 8.95 (95% CI: 5.96; 11.94) / 1,000 person-years in all patients, 9.08 (95% CI: 4.46; 13.70) / 1,000 person-years

Table 4. Patients with second malignancies after diagnosis of CML and after start of TKI

Patient	Sex[1]	Age at CML [years]	CML treatment (drugs)[2]	Time from dg. CML to start of TKI [months]	TKI treatment before SM [months]	Type of SM	Site of SM	Age at SM [years]	Therapy of SM[3]	OS_{SM}[4] [months]	OS_{CML}[4] [months]	Status (cause of death[5])
1	M	68	HY,IFN,IM	15.6	97.1	Carcinoma	Lung	77	R	3.5	116.2	SM
2	M	49	CHT,IM,DA*	1.0	57.0	Papillocarcinoma	Kidney	54	n.k.	0.0	58.0	sepsis
3	F	73	HY,IM	1.6	8.5	Adenocarcinoma	Pancreas	74	CH	1.9	12.0	SM
4	M	55	HY,DA	1.0	23.5	Carcinoma	Bladder	57	S	3.9	28.4	SM
5	M	36	HY,BU,IFN,IM*	140.6	43.0	Seminoma	Testis	52	S,CH,R	7.4	191.0	CML
6	M	43	HY,BU,IFN,IM,SCT*	112.4	101.5	Carcinoma	Anus	61	S	3.4	217.3	*alive*
7	M	55	HY,IFN,IM,DA,NI	33.6	37.7	Carcinoma	Colon	61	S,R	63.5	134.8	*alive*
8	F	65	HY,IM,DA,NI	0.5	10.1	Myelofibrosis	Hematopoietic tissue	66	n.k.	0.2	10.8	*alive*
9	F	62	HY,IM	50.7	23.1	Carcinoma	Lung	68	CH	12.8	86.7	SM
10	F	72	HY,IM	41.0	13.3	Carcinoma	Uterus	76	R	9.8	64.2	other
11	M	74	HY,IFN,AraC,IM	17.3	52.0	Adenocarcinoma	Vater's papilla	80	S	1.0	70.3	SM
12	F	32	HY,IM,SCT*	0.4	14.9	Carcinoma in situ	Cervix uteri	33	S	63.5	78.9	*alive*
13	M	52	HY,IFN,IM	56.3	33.3	Adenocarcinoma	Prostate	59	H	5.6	95.3	*alive*
14	M	62	HY,IFN,IM	16.7	92.0	Carcinoma	Lung	71	S	2.1	110.9	*alive*
15	M	46	HY,IFN,IM,DA	11.3	42.5	Adenocarcinoma	Lung	50	CH,R	14.2	68.0	SM
16	F	49	HY,IM	0.7	9.2	Carcinoma	Breast	50	S,R,H	44.8	54.6	*alive*
17	M	71	HY,IM	1.0	9.6	Carcinoma	Larynx	72	S,R	4.7	15.2	SM
18	M	54	IFN,CHT,IM*	23.9	96.5	Adenocarcinoma	Lung	64	S,CH	11.4	131.8	*alive*
19	M	71	HY,IFN,IM	19.3	36.3	B-CLL	Hematopoietic tissue	76	CH	65.8	121.4	*alive*
20	M	41	HY,IFN,AraC,IM	106.0	28.4	Adenocarcinoma	Appendix	52	S,CH	9.7	144.0	SM
21	M	57	IM	0.3	5.8	B-CLL	Hematopoietic tissue	58	n.k.	0.2	6.3	*alive*
22	M	63	HY,IFN,AraC,IM	13.1	74.5	Carcinoma	Prostate	71	R	14.5	102.1	*alive*
23	M	42	IFN,AraC,IM	40.4	28.7	Adenocarcinoma	Colon	48	S,CH	51.3	120.4	*alive*
24	F	40	IFN,AraC,IM	42.8	46.7	Carcinoma	Pancreas	48	S,CH	6.3	95.7	SM
25	M	67	IM	0.9	0.7	Adenocarcinoma	Rectum	67	n.k.	8.5	10.1	*alive*
26	F	58	IFN,IM	69.4	72.5	Carcinoma	Breast	70	H	6.6	148.5	*alive*
27	F	51	IFN,IM,DA	9.9	54.0	Carcinoma	Breast	56	S,CH	6.7	70.6	sepsis
28	F	68	HY,IM	0.2	32.1	Pheochromocytoma	Adrenal gland	71	S	0.0	32.4	*alive*
29	M	69	HY,IM	1.5	2.3	Carcinoma	Stomach	69	CH,R	16.1	19.9	*alive*
30	F	32	IFN,IM	117.1	33.6	Carcinoma	Uterus	45	S	3.2	153.9	*alive*
31	M	53	HY,IFN,IM	9.4	8.8	Carcinoid	Small intestine	55	S	32.8	51.0	*alive*
32	F	64	IM	1.1	6.3	Carcinoma	Breast	65	CH	5.2	12.6	SM
33	M	69	IM	2.3	20.9	Carcinoma	Lung	71	none	11.0	34.3	*alive*
34	M	68	HY,IM	0.7	23.8	Adenocarcinoma	Lung	70	n.k.	4.9	29.4	SM
35	M	59	HY,IFN,IM	32.4	47.3	Melanoma	Skin	65	CH	4.1	83.8	other

[1] F = female, M = male

[2] HY = hydroxyurea, INF = interferon, BU = busulphan, AraC = cytosinarabinosid, SCT = allogeneic stem cell transplantation, IM = imatinib, DA = dasatinib, NI = nilotinib, * = CML treatment with increased risk for SM development

[3] S = surgery, CH = chemotherapy, R = radiotherapy, H = hormonal therapy, n.k. = not known

[4] OS_{SM} = overall survival from diagnosis of second malignancy, OS_{CML} = overall survival from diagnosis of CML

[5] SM = death related to second malignancy, CML = death related to chronic myeloid leukemia, sepsis = infectious complications of treatment, other = other cause of death

Table 5. Incidence of SM after diagnosis of CML and after start of TKI

Group of patients	Number of patients / number of SM (proportion of patients with SM)	Person-years of follow-up since start of TKI treatment	Crude incidence of SM per 1,000 person-years	Age- standardized incidence per 1,000 person-years (95% CI)
All patients	1,038 / 35 (3.37%)	3,775	9.27	8.95 (5.96; 11.94)
All patients treated with TKI in 1st line	617 / 15 (2.43%)	1,738	8.63	9.08 (4.46; 13.70)
All patients treated with TKI in 2nd line	421 / 20 (4.75%)	2,037	9.82	8.80 (4.90; 12.70)
Patients treated with TKI for 2 or more years	699 / 26 (3.72%)	3,263	7.97	7.83 (4.79; 10.87)
TKI for 2 or more years in 1st line	374 / 6 (1.60%)	1,419	4.23	4.85 (0.92; 8.77)
TKI for 2 or more years in 2nd line	325 / 20 (6.15%)	1,844	10.84	9.74 (5.41; 14.07)
Patients from the Czech Republic (CZ)	708 / 29 (4.10%)	2,722	10.66	9.84 (6.20; 13.48)
CZ patients treated with TKI in 1st line	411 / 12 (2.92%)	1,207	9.94	10.15 (4.40; 15.91)
CZ patients treated with TKI in 2nd line	297 / 17 (5.72%)	1,515	11.22	9.64 (4.87; 14.40)

in patients with first-line TKI therapy, and 8.80 (95% CI: 4.90; 12.70) / 1,000 person-years in patients with second-line TKI therapy (Table 5).

The incidence rates of SM in 699 patients treated with TKI for two or more years were as follows: crude rate 7.97 / 1,000 person-years (4.23 and 10.84 / 1,000 person-years in first- and second-line treatment, respectively), age-standar-dized rate 7.83 (95% CI: 4.79; 10.87) / 1,000 person-years [4.85 (95% CI: 0.92; 8.77) and 9.74 (95% CI: 5.41; 14.07) per 1,000 person-years in first- and second-line treatment, respectively; see Table 5].

Since recent detailed data about the incidence of tumors in the entire population were only available for the Czech Republic [10], the comparison of incidence rates of SM in CML patients with population data was performed only for patients from the Czech Republic. The age-standardized incidence rate of all malignant tumors excluding other skin tumors (C00 – C97 excluding C44) in the entire population of the Czech Republic aged 15 years or more is 6.76 (95% CI: 6.74; 6.78) / 1,000 person-years (data from 2000 – 2007). The incidence rates of SM in our group of 708 CML patients from the Czech Republic treated with TKI were 9.84 (95% CI: 6.20; 13.48) / 1,000 person-years, 10.15 (95% CI: 4.40; 15.91) and 9.64 (95% CI: 4.87; 14.40) / 1,000 person-years in the first- and second-line TKI therapy, respectively (see Table 5). Although the observed incidence of SM in CML patients treated with TKI was 1.5 times higher compared with the incidence of malignancies in the whole population of the Czech Republic, the difference was not statistically significant (Mantel-Haenszel test [13]).

Discussion

SM are serious complications in CML patients and can significantly affect their prognosis. SM have been a leading cause of death among long-term survivors of Hodgkin's lymphoma [14, 15]. SM are usually considered to be late sequelae of chemo- and/or radiotherapy. They may arise from the clonal selection of cells that have accumulated transforming genetic lesions induced by chemo- and radiotherapy [14]. DNA repair defects (also known to play a role in the pathogenesis of CML) are assumed to increase the susceptibility to treatment-related cancers [15]. Multiple other factors may influence the risk of SM, such as lifestyle factors (tobacco, alcohol, diet, etc.), environmental exposures (contaminants, occupation, etc.), host factors (genetics, immune function, hormonal etc.), and combinations of influences, including gene-environment and gene-gene interactions [15]. Hereditary susceptibility to cancers might explain the development of metachronous tumors throughout life.

The occurrence of SM in CML patients was described also in the pre-imatinib era. In the Czech Republic, Chrobák reported SM in 3 of 95 CML patients treated with busulfan [2]. Controversy exists as to leukemogenicity of hydroxyurea when used for treatment of myeloproliferative disorders [16, 17]. In an Italian study comparing long-term follow-up of interferon-α versus conventional chemotherapy in CML, second malignancies were slightly more frequent in chemotherapy patients (4 of 104, or 4%) than in interferon-α patients (2 of 218, or 1%) [3]. Eight SM developed in 208 (3.8%) patients who underwent stem cells transplantation for CML according to an

EBMT analysis [18]. Several case reports about simultaneous or subsequent development of CML and other hematological malignancies were published [19-24].

The incidence of SM in CML patients during the treatment with IM and/or second generation TKI is not known. Roy observed unexpected occurrence of SM of the urogenital tract in CML patients treated with interferon-α followed by imatinib [4]. In Roy's analysis, SM developed in 6 (3.2%) of 189 patients, with prostate adenocarcinoma being recorded in 3 of them and bladder cancer in one of them. All 6 patients were pretreated with interferon-α [4]. An epidemiological analysis of SM among 9,518 patients treated in Novartis-sponsored clinical trials and spontaneous adverse reports from approximately 124,000 patient-years of treatment showed no evidence of an increase in the overall incidence of malignancies or bladder, kidney or prostate tumors in patients treated with imatinib, as compared to that of the age-adjusted general population [5]. No localization of SM was predominant in our patients. Our patients developed a broad spectrum of second solid tumors or hematological malignancies, histologically most frequently carcinomas. Consistent with the distribution of malignancies within the Czech population, women participating in our study most commonly developed breast carcinoma while men were most frequently affected by lung cancer, colorectal cancer and prostate carcinoma [25].

SM in 67 (4.07%) patients out of 1,647 CML patients treated with first- and second-generation TKI in one center was reported by Verma et al. [6]. The most commonly observed tumors in his study were skin cancers (31% of all SM), other tumors were diagnosed in 2.8% of patients treated with TKI. The proportion of patients with SM and spectrum of SM in our study were very similar to those in Verma's study.

SM were documented in 28 of 957 patients (rate 1.1 / 100 person-years) with an observed/expected ratio of 1.27 (95% CI: 0.84; 1.84) in the Imatinib Long-Term Effects (ILTE) study [7]. The ILTE study showed that CML patients on imatinib did not appear to have substantially higher SM rates than the general population. The incidence rate of SM in our study of 1,038 CML patients was 1.5 times higher than the age-standardized incidence of tumors in the general population of the Czech Republic. However, the difference was not statistically significant.

The slightly higher incidence of SM in CML patients treated with TKI in our study might be probably influenced by the centralization of care for CML patients in the Czech Republic and Slovakia, foundation of CML registries and more careful registration of toxicity of new drugs.

The incidence of the majority of tumors increases with age. Imatinib significantly prolongs the overall survival of CML patients. CML patients live longer than before. Even this fact might be one of the factors that contribute to the development of SM.

The significance of CML characteristics (genomic instability, long-term presence of residual BCR-ABL1 transcript in many patients) in SM development has not been clarified. Genomic instability in CML in widely discussed in the literature. BCR-ABL has been shown to induce endogenous reactive oxygen species (ROS) that result in chronic oxidative DNA damage, double-strand breaks (DBS) in S and G_2/M cell-cycle phases, and mutagenesis [26]. BCR-ABL-mediated ROS generation in combination with aberrant regulation of DNA repair pathways contributes to a mutation phenotype in CML cells and results in genomic instability leading to point mutations and cytogenetic abnormalities [26].

Direct relationship between the development of SM and IM has not yet been demonstrated. Even our study did not provide data that would clearly point to a possible relationship between SM and TKI. To clarify the incidence of SM in CML after TKI therapy, studies in larger populations of patients with CML are required. Population-based registries have an advantage compared to patient registries in studies because they can, when aimed at toxicity, follow-up larger populations of CML patients for a long time. Population-based registries have been used successfully to evaluate which SM occur in excess after first primary malignancies and to provide a valuable starting point for nested case-control studies that evaluate treatment effects in detail [15].

The overall survival of CML patients evaluated from the date of CML diagnosis is dependent on the curability of SM. Patients with CML suffering from SM that is well responsive to treatment or completely curable show long-term survival that corresponds to the response to the CML treatment.

In conclusion solid tumors and hematological malignancies may occur concomitantly with or consequently after the diagnosis of CML. We observed a slightly higher incidence of SM in CML patients treated with TKI compared with the incidence of malignancies in the entire population of the Czech Republic. However, the difference was not statistically significant. The most common type of SM in our group of patients was carcinoma, with no predominant location. SM in patients with CML is a serious complication that affects their survival depending on its curability. The relationship between SM and the treatment of CML with TKI is unknown. Longer follow-up of a larger number of CML patients treated with TKI as first-line therapy in population-based registries may determine the incidence of SM more precisely and clarify the relationship between the development of SM and TKI. Prospective collection of data on SM was started in the CAMELIA and INFINITY registries in 2008.

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