Incidence of second primary malignancies and related mortality in patients with imatinib-treated chronic myeloid leukemia

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ABSTRACT

The majority of patients with chronic myeloid leukemia are successfully managed with life-long treatment with tyrosine kinase inhibitors. In patients in chronic phase, other malignancies are among the most common causes of death, raising concerns on the relationship between these deaths and the off-target effects of tyrosine kinase inhibitors. We analyzed the incidence of second primary malignancies, and related mortality, in 514 chronic myeloid leukemia patients enrolled in clinical trials in which imatinib was given as first-line treatment. We then compared the observed incidence and mortality with those expected in the age- and sex-matched Italian general population, calculating standardized incidence and standardized mortality ratios. After a median follow-up of 74 months, 5.8% patients developed second primary malignancies. The median time from chronic myeloid leukemia to diagnosis of the second primary malignancies was 34 months. We did not find a higher incidence of second primary malignancies compared to that in the age- and sex-matched Italian general population, with standardized incidence ratios of 1.06 (95% CI: 0.57–1.54) and 1.61 (95% CI: 0.92–2.31) in males and females, respectively. Overall, 3.1% patients died of second primary malignancies. The death rate in patients with second primary malignancies was 53% (median overall survival: 18 months). Among females, the observed cancer-related mortality was superior to that expected in the

age- and sex-matched Italian population, with a standardized mortality ratio of 2.41 (95% CI: 1.26 – 3.56). In conclusion, our analysis of patients with imatinib-treated chronic myeloid leukemia did not reveal a higher incidence of second primary malignancies; however, the outcome of second primary malignancies in such patients was worse than expected. Clinicaltrials.gov: NCT00514488, NCT00510926.

Introduction

The availability and the extensive use of tyrosine kinase inhibitors targeting the BCR-ABL protein in patients with chronic myeloid leukemia (CML) has reduced the rate of progression from chronic phase to advanced phase.[1] As a consequence, at least 50% of deaths occur in patients in chronic phase, or in remission,[2] raising concerns on the relationship of such deaths with the off-target effects of tyrosine kinase inhibitors.[3] Although most of the attention is focused on cardiovascular adverse events,[4] other malignancies are the most common cause of death in patients in chronic phase or in remission.[2]

Imatinib was the first tyrosine kinase inhibitor developed for the treatment of CML and is the most extensively studied. However, it is still unclear whether its immunomodulatory properties[5-11] may affect anti-cancer immune surveillance in the long-term, or whether its off-target activity may influence oncosuppressive pathways. Of note, regardless of the underlying mechanisms, neoplastic alterations have been described in multiple tissues of rats exposed to imatinib.[12] Several studies, mainly referring to imatinib-treated patients, have investigated the risk of second primary malignancy (SPM) in CML,[13-20] with sometimes contrasting results. Indeed, in comparisons with the general population, some epidemiological studies of unselected CML patients reported higher incidences of SPM[18,21] while similar incidences were found in three large analyses of patients enrolled in clinical trials.[14,17,20]

Moreover, it is still debated whether CML patients *per se*, regardless of the treatment used, might be at higher risk of SPM,[21-24] a condition that might be now unveiled by the increased survival of patients.

For all these reasons, it is important to retrieve addition-

Table 1. Characteristics of the patients at diagnosis of chronic myeloid leukemia.

	All patients	Patients with SPM	Patients without SPM	*P*
Patients, N (%)	514	30 (5.8)	484 (94.2)	
Males, N (%)	309 (60)	17 (57)	292 (60)	
Females, N (%)	205 (40)	13 (43)	192 (40)	
Age, years, median (range)	52 (18 – 84)	60 (35 - 77)	51 (18 – 84)	**0.002**
Sokal score, N (%)				
Low	200 (39)	7 (23)	193 (40)	
Intermediate	204 (40)	20 (67)	184 (38)	
High	110 (21)	3 (10)	107 (22)	0.008
EUTOS score, N (%)				
Low	476 (93)	30 (100)	446 (92)	
High	38 (7)	0	38 (8)	0.15
ELTS score, N (%)				
Low	282 (55)	15 (50)	267 (55)	
Intermediate	160 (31)	13 (43)	147 (30)	
High	72 (14)	2 (7)	70 (14)	0.23
ECOG performance status ≥ 1, N (%)	108 (21)	10 (33)	98 (20)	0.088
Transcript type, N (%)				
b2a2	185 (36)	11 (37)	174 (36)	
b3a3	267 (52)	16 (53)	251 (52)	
b2a2/b3a2	56 (11)	3 (10)	53 (11)	
other	6 (1)	0	6 (1)	0.98
Clonal cytogenetic abnormalities, N (%)*	17 (5)	1 (4.8)	16 (5)	1
Variant translocations, N (%)*	26 (5.1)	3 (10)	23 (4.7)	0.18
Deletion 9q, N (%)*	55 (11)	6 (20)	49 (11)	0.13
Prior hydroxyurea treatment, N (%)	238 (46)	9 (30)	229 (47)	0.088
Imatinib high doses, N (%)	126 (25)	9 (30)	117 (24)	0.51
Prior malignancies, N (%)	25 (4.9)	-	-	-
Follow-up, months, median, (range)	74 (3-99)	-	-	-

*Of evaluable patients. The statistically significant difference observed for Sokal score probably reflects the higher median age of patients with SPM, resulting in a higher proportion of intermediate Sokal risk patients in this group. In addition, no significant statistical difference between patients with or without SPM was observed regarding values of hemoglobin, white blood cells, eosinophils, basophils, blasts, platelets, and spleen (*data not shown*). SPM: second primary malignancies; CML: chronic myeloid leukemia; EUTOS: EUropean Treatment Outcome Study; ELTS: EUTOS Long-Term Survival; ECOG: Eastern Cooperative Study Group.

al data on the potential carcinogenic role of tyrosine kinase inhibitors,[12] on the incidence of other malignancies, and on their outcome.[13-20]

We report here on the malignancies observed in a cohort of 514 evaluable patients with newly diagnosed, chronic phase CML, treated first-line with imatinib in three multicenter national studies.

Methods

We performed a retrospective analysis of 559 patients enrolled in three prospective clinical trials with imatinib front-line in 62 Italian institutions of the *Gruppo Italiano Malattie Ematologiche dell'Adulto* (GIMEMA) CML Working Party. Detailed inclusion criteria have been published previously.[25-28] Briefly, patients were at least 18 years old, with a diagnosis of Philadelphia chromosome/*BCR-ABL*-positive CML in early chronic phase (6 months or less from diagnosis to starting imatinib; only hydroxyurea allowed). All the patients provided written informed consent before enrollment. The studies were reviewed and approved by the Internal Review Board of all the participating Institutions, and performed in accordance with the Declaration of Helsinki. For the purpose of the present analysis, a specific survey was conducted in all Centers with a request to review the clinical records of all the enrolled patients. Overall, 52/62 (84%) Institutions replied to the survey, and each Center reported on all its patients; overall, data were collected on 514/559 (92%) patients, 309 (60%) males and 205 (40%) females. Detailed data on all malignancies, prior to and after the diagnosis of CML, were collected, including: site, histology type, date of diagnosis, therapy (surgery, chemotherapy, radiotherapy, other), and outcome. Cancers were classified according to the International Classification of Diseases, version 10 (ICD-10). We excluded non-melanoma skin cancers (ICD-10: C-44) from the analysis, because of the possible under-reporting of such neoplasms, and acute leukemias/myelodysplastic syndromes, considering their possible relationship with CML.

Prior malignancies were defined as malignancies diagnosed before CML, other malignancies denote all malignancies, including relapses of prior malignancies, diagnosed after CML. SPM, the focus of this analysis, are *de novo* malignancies diagnosed after CML (thus excluding relapses of prior malignancies).

Descriptive statistics were used for SPM incidence and mortality. Means were compared with the *t*-test and frequencies with the χ^2 test or Fisher exact test, as appropriate. Cumulative incidences and survival curves were estimated according to the Kaplan-Meier method. For comparison with the general population, we calculated the standardized incidence ratio (SIR) and standardized mortality ratio (SMR), which are based on the ratio between observed cases and expected cases in the general reference population in the same period, matched by sex and age (5-year age classes were considered). We reported the overall ratios (for subjects aged 20-84 years), rather than those for specific age subgroups, to avoid selection biases.

Data on cancer incidence and mortality in the general Italian population were taken in March 2016 from the AIRTUM (*Associazione Italiana Registri TUMori*) database ITACAN (AIRTUM ITACAN: *Tumori in Italia*, Versione 2.0; http://www.registritumori.it), which covers 51% of the Italian general population, and reports cancer incidence and mortality rates derived from real, observed cancer cases. Times to events (patient-years) were calculated from the date of diagnosis of CML to the date of diagnosis of the SPM, death, or last contact, whichever came first, for incidence; and to the date of death or last contact, for mortality.

Results

Patients

Data from 514 patients, 309 (60%) males and 205 (40%) females, were analyzed. The median age at CML diagnosis was 52 (range, 18-84) years. The median follow-up from diagnosis of CML to death, or last contact, whichever came first, was 74 (range, 3-99) months. The total patient-years for the incidence calculation were 3011.1 (males and females: 1806.3 and 1204.8 patient-years, respectively). The total patient-years for the mortality calculation were 3077.7 (males and females: 1849.4 and 1228.3 patient-years, respectively). The characteristics of the whole cohort of patients and of patients with or without SPM are summarized in Table 1; age at CML diagnosis was significantly higher in patients with SPM than in patients without SPM (60 and 51 years, respectively; P=0.002).

Malignancies in the follow-up

Overall, other malignancies were observed in 35/514 (6.8%) patients (Tables 2 and 3). Four patients had a relapse of a malignancy diagnosed before CML (2 bladder cancers, 1 renal cancer, and 1 breast cancer), and another patient developed multiple myeloma from a pre-existing monoclonal gammopathy of undetermined significance.

Table 2. Malignancies observed in the follow-up and related mortality.

Malignancy type	All malignancies observed/deaths, N	Second primary malignancies observed/deaths, N
Colon	4 / 4	4 / 4
Prostate	3 / 0	3 / 0
Breast	3 / 0	2 / 0
Central nervous system	2 / 2	2 / 2
Pancreas	2 / 2	2 / 2
Bladder	2 / 1	-
Liver	2 / 1§	2 / 1§
Non-Hodgkin lymphoma	2 / 1	2 / 1
Thyroid	2 / 0	2 / 0
Bile duct	1 / 1	1 / 1
Esophagus	1 / 1	1 / 1
Lung	1 / 1	1 / 1
Kidney	1 / 1	-
Soft tissues	1 / 1	1 / 1
Urethra	1 / 1	1 / 1
Bowel	1 / 0	1 / 0
Endometrium	1 / 0	1 / 0
Stomach	1 / 0	1 / 0
Multiple myeloma	1 / 1	-
Ovary	1 / 1	1 / 1
Rectum	1 / 0	1 / 0
Testis	1 / 0	1 / 0
TOTAL, n	35 / 19	30 / 16
% of all patients (N=514)	6.8 / 3.7	5.8 / 3.1

§The other patient died due to progression of CML to blast phase. Treatment for other malignancies included chemotherapy in 14 patients, radiotherapy in nine patients, surgery in 19 patients, and hormonal therapy in one patient

SPM were, therefore, diagnosed in 30/514 (5.8%) patients (17/309 males, 5.5%; 13/205, 6.2%, females). The estimated 7-year cumulative incidence of SPM was 6.3% and 8.5% in males and females, respectively (Figure 1A). In these patients, the median time from CML diagnosis to SPM diagnosis was 34 (range, 3-80) months, and the median age at SPM diagnosis was 65 (range, 38-79) years. The most frequent SPM were colon cancers (n=4), prostate cancers (n=3), breast cancers (n=2), central nervous system cancers (n=2), pancreatic cancers (n=2), liver cancers (n=2), non-Hodgkin lymphomas (n=2), and thyroid cancers (n=2). No difference in the incidence of SPM was observed between patients initially treated with high-dose imatinib (800 mg) *versus* standard-dose imatinib (400 mg): 9/126 (7.1%) *versus* 21/388 (5.4%), respectively (P=0.51); moreover, no patient with SPM received treatment with second-generation tyrosine kinase inhibitors or underwent allogeneic stem cell transplantation. At the time of SPM diagnosis, all patients were in complete hematologic remission, 28/30 were in complete cytogenetic remission

Table 3. Details of malignancies observed during the follow-up of patients with chronic myeloid leukemia.

ID	Age at CML Dx (years)	Sex	Prior HU	OM	Age at OM Dx (years)	Time CML Dx - OM Dx (months)	Time IM - OM Dx (months)	IM Dose (mg)	CCyR	OM therapy	OM outcome	Follow-up CML Dx – Last contact/death (months)	PM	Age at pM Dx (years)	Therapy of pM	Status of pM at CML Dx	Time pM Dx – relapse (months)
1	53	F	No	Bile duct cancer	56	37	36	400	Yes	S	Death	44					
2	35	F	No	Breast cancer	38	25	25	400	Yes	S, CHT	CR	73					
3	50	F	Yes	Breast cancer	54	51	51	800	Yes	S, CHT	CR	84					
4	53	F	No	Colon cancer	53	3	3	400	No	No/palliation	Death	4					
5	60	F	Yes	Colon cancer	60	3	3	800	No	S, CHT	Death	27					
6	63	F	Yes	Colon cancer	65	22	21	800	Yes	S	Death	27					
7	64	M	Yes	Colon cancer	68	44	43	400	Yes	No/palliation	Death	50					
8	77	M	No	DLBCL	79	10	9	400	Yes	S, RT, CHT	CR	74					
9	54	F	No	Endometrial cancer	61	78	76	400	Yes	S	CR	78					
10	56	M	No	Esophageal cancer	58	23	23	400	Yes	RT, CHT	Death	37					
11	61	M	Yes	Gastric cancer	65	48	44	400	Yes	S	CR	91					
12	77	F	No	Hepatocarcinoma	79	13	13	400	Yes	No/palliation	Stable *	73					
13	69	M	No	Hepatocarcinoma	72	34	34	400	Yes	CHT	Death	41					
14	60	M	No	Glioblastoma	63	26	26	400	Yes	S	Death	28					
15	61	M	No	High-grade glioma	64	33	33	400	Yes	S, RT, CHT	Death	39					
16	64	F	No	Leiomyosarcoma	65	7	7	800	Yes	No/palliation	Death	8					
17	57	M	No	Lung cancer	60	36	36	400	Yes	RT, CHT	Death	41					
18	64	M	Yes	Mantle cell lymphoma	65	6	5	400	Yes	CHT	Death	11					
19	65	F	Yes	Ovarian cancer	71	63	61	800	Yes	S, CHT	Death	85					
20	70	M	No	Pancreatic cancer	72	11	10	400	Yes	No/palliation	Death	15					
21	60	F	No	Pancreatic cancer	67	80	80	800	Yes	No/palliation	Death	82					
22	75	M	No	Prostatic cancer	77	10	9	400	Yes	S	CR	72					
23	69	M	No	Prostatic cancer	74	42	42	800	Yes	S	CR	87					
24	54	M	No	Prostatic cancer	60	62	61	400	Yes	S	CR	87					
25	52	F	No	Rectal cancer	58	71	70	400	Yes	S	CR	84					
26	58	M	No	Small bowel cancer	65	79	78	400	Yes	S	CR	79					
27	35	M	Yes	Testis cancer	38	35	34	800	Yes	S	CR	84					
28	39	F	Yes	Thyroid cancer	42	30	29	400	Yes	S, RT	CR	80					
29	50	M	No	Thyroid cancer	52	25	25	800	Yes	S, RT	CR	79					
30	72	M	No	Urethral cancer	78	61	61	400	Yes	RT, CHT	Death	65					
31	57	M	Yes	Bladder cancer	59	27	25	400	Yes	S	CR	87	Bladder cancer	51	S	CR	105
32	72	M	No	Bladder cancer	79	83	82	800	Yes	No/palliation	Death	86	Bladder cancer	70	CHT, RT	CR	117
33	54	F	Yes	Breast cancer	59	59	58	800	Yes	S, CHT	CR	82	Breast cancer	46	S, RT, CHT, H	CR	156
34	79	M	Yes	Multiple myeloma	81	18	15	400	Yes	CHT	Death	46	MGUS	78	No	Stable	36
35	74	M	Yes	Renal cancer	77	25	24	400	Yes	RT, CHT	Death	48	Renal cancer	74	S	CR	28

* The patient subsequently died from progression of CML to blast phase. ID: identification; CML: chronic myeloid leukemia; DX: diagnosis; OM: other malignancy; pM: prior malignancy; DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; MGUS: monoclonal gammopathy of undetermined significance; HU: hydroxyurea; IM: imatinib; S: surgery; CHT: chemotherapy; RT: radiotherapy; H: hormone therapy; CR: complete remission; CCyR: complete cytogenetic response.

and 27/30 had a major molecular response.

Other malignancies were the second cause of death in this cohort (19/514; 3.7%), while death from progression of CML to advanced phase was the first cause (25/514; 4.8%). As expected, patients who developed a SPM had a significantly lower overall survival rate compared to patients without a SPM (7-year overall survival: 43.6% *versus* 89.9%; $P<0.001$; Figure 1B). In detail, considering only the patients with SPM, 16/30 (53%) died because of the SPM. The median overall survival after diagnosis of the SPM was 18 months (Figure 1C) and the median age at death of patients with these malignancies was 66 (range, 53-84) years. All four patients with colon cancer died within 2 years of diagnosis (after 1, 5, 6, and 24 months).

Comparison with the general population

We then compared the incidence of SPM, and the related mortality, with that reported in the Italian general population, matched by sex and age (Table 4).

In Italy, the standardized incidence of malignancy between 20 and 84 years of age is 7.6/1.000 and 5.2/1.000 person-years in males and females, respectively. In males, we observed 17 SPM, and the SIR was 1.06 [95% confidence interval (CI): 0.57 – 1.54]. In females, we observed 13 SPM, which resulted in a SIR of 1.61 (95% CI: 0.92 – 2.31).

In Italy, the standardized mortality for malignancy between 20 and 84 years of age is 3.5/1.000 and 1.9/1.000 person-years in males and females, respectively. In our cohort, 9/309 (2.9%) males died of a SPM, and the SMR was 1.26 (95% CI: 0.53 – 1.99); 7/205 (3.4%) females died of a SPM, resulting in a statistically significantly higher SMR (2.41; 95% CI: 1.26 – 3.56).

Discussion

The assessment of SPM risk is particularly complex: large cohorts of patients, long follow-up, accurate and comprehensive data collection, and a proper reference population are required for a good estimation of the risk. In this context, the analysis of both clinical trials and epidemiological registries, although with distinct drawbacks, provides essential information.

In our cohort of 514 patients with chronic phase CML treated in clinical trials with front-line imatinib, with a median follow-up of 74 months, 30 (5.8%) patients had a SPM. A higher age at CML diagnosis was the only baseline factor significantly associated with SPM; reasonably, it justifies the higher proportion of intermediate-Sokal risk patients observed in this group. Of note, no CML-related characteristic was linked to the occurrence of SPM.

The incidence of SPM among patients with chronic phase CML was not significantly increased compared to that in the age- and sex-matched Italian population. These data confirm the main findings of three large analyses of CML patients treated with tyrosine kinase inhibitors in clinical trials (German CML study IV,[20] MD Anderson Cancer Center trial,[17] and Novartis global database[14]) in which the overall incidence of SPM was similar to that of the general population. Of note, this conclusion was consistent despite the important differences of these studies regarding patients' characteristics (including epidemiological aspects), treatments received, and follow-up. Two of these analyses found higher SIR for some cancers types: non-Hodgkin lymphomas in the German CML study IV;[20] melanoma, kidney and endocrine tumors in the MD Anderson Cancer Center analysis.[17] Unfortunately, in our study, the relatively low number and the heterogeneity of the malignancies observed precluded a proper evaluation of the SIR for different types of cancer.

In contrast to these data, analysis of the epidemiological CML Swedish Registry on 868 unselected CML patients treated with tyrosine kinase inhibitors[18] showed an overall increased SIR for other malignancies (1.52; 95% CI: 1.13 – 1.99); the SIR maintained a statistical significance in females (1.81; 95% CI: 1.18 – 2.66). It is worth noting that

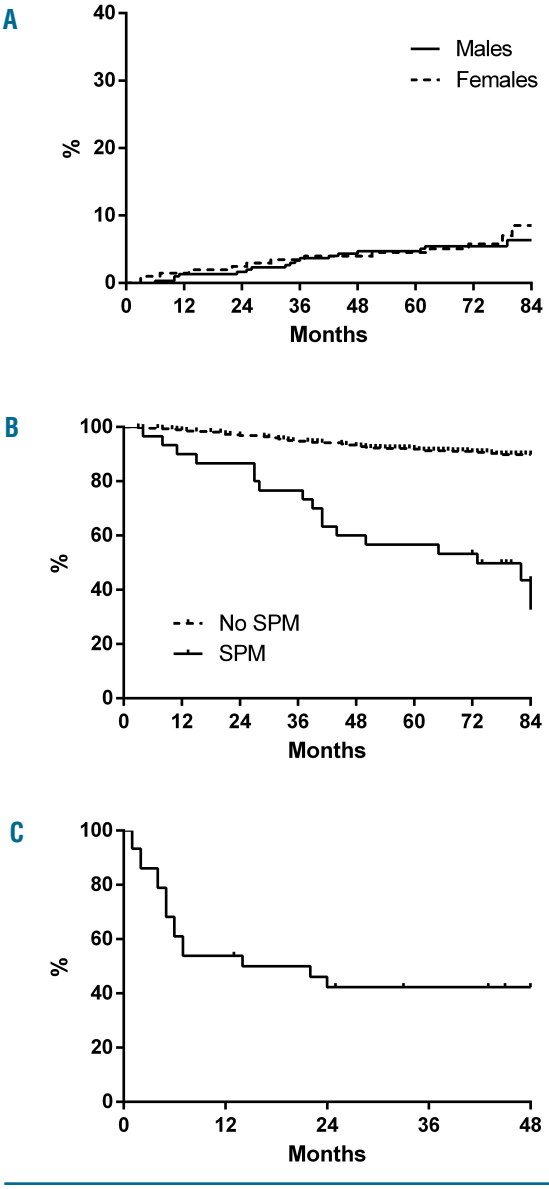

Figure 1. Cumulative incidence of second primary malignancies and overall survival of patients with or without second primary malignancies. (A) Cumulative incidence of SPM in 514 patients (309 males; 205 females); the estimated 7-year cumulative incidence was 6.3% and 8.5% in males and females, respectively; (B) Overall survival (OS) from CML diagnosis: 7-year OS was 43.6% in patients with SPM (n=30) and 89.9% in patients without SPM (n=484); $P<0.001$. (C) OS from SPM diagnosis (n=30): the median OS was 18 months, and the estimated 4-year OS was 42.3%

we observed a trend for an increased SIR in females (1.6; lower 95% CI: 0.92).

In our study, progression of CML to advanced phase and other malignancies were the most common causes of death (4.8 and 3.7%, respectively). The death rate in patients with SPM was particularly high (53%), with a relatively short median overall survival (18 months from diagnosis of the SPM). Of note, in females, the mortality from SPM was significantly superior to that expected in the Italian age-matched female population, with a SMR of 2.41 (95% CI: 1.26 – 3.56).

Despite the limitations due to the small number of patients, some factors favoring the high mortality observed for SPM can be hypothesized. For example, the therapeutic approach to SPM in patients with CML may be less intensive (6/30 patients received only palliative care) or the biological behavior of the SPM may be more aggressive, as a consequence of CML itself, or because of imatinib. With regards to the latter point, it should be remembered that in a breast cancer model in mice, treatment with imatinib was associated with an increased malignant behavior compared to control conditons.[29] Moreover, tyrosine kinase inhibitors could enhance, or facilitate, the progression of SPM through the inhibition of ABL, which is a downstream effector of the epinephrine receptors that might have a tumor-suppressor role in breast, prostate, and colorectal cancers[30-32] (interestingly, all our patients with a colon cancer died) or through impairment of the immune system,[6-11] potentially affecting anti-tumor surveillance. An in-depth evaluation of immunological mechanisms might be particularly intriguing in view of the potential use of new molecules enhancing the immune system against cancer.

In conclusion, the prevalence of CML is increasing steadily and this, together with the aging of patients, means that the number of subjects at risk of developing SPM is increasing. However, the fact that an increased incidence was not detectable in the majority of the cohorts analyzed so far does not support the fear that chronic treatment with tyrosine kinase inhibitors, in particular imatinib, cause more SPM compared to those occurring in the general population. Despite these reassuring results, large studies with a long follow-up (e.g. using data from CML registries) are warranted to properly investigate the incidence of specific types of SPM, and to fully address mortality due to SPM. This could help to improve patients' management through early diagnosis of SPM and treatment optimization in conjunction with oncologists. Furthermore, the comparison of the incidence of SPM (and their outcomes) in patients treated with different tyrosine kinase inhibitors may provide important clues on the potential role of each inhibitor.

Table 4. Second primary malignancies: comparison of incidence and mortality with those in the Italian general population, matched by sex and age*.

Sex	Patient-years	SPM (N)	Expected SPM	SIR	95% CI
M	1806.3	17	16.1	1.06	(0.57; 1.54)
F	1204.8	13	8.1	1.61	(0.92; 2.31)
		Deaths (N)	**Expected deaths**	**SMR**	**95% CI**
M	1849.4	9	7.2	1.26	(0.53; 1.99)
F	1228.3	7	2.9	**2.41**	**(1.26; 3.56)**

* Five-year age classes were considered. We report the overall (20-84 years) ratios, rather than those for specific age subgroups, to avoid selection biases. SPM: second primary malignancies; SIR: standardized incidence ratio; SMR: standardized mortality ratio.

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