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RESEARCH ARTICLE

Second cancers in MPN: Survival analysis from an international study

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Abstract

One out of ten patients with Philadelphia-negative myeloproliferative neoplasms (MPN) develop a second cancer (SC): in such patients we aimed at assessing the survival impact of SC itself and of MPN-specific therapies. Data were therefore extracted from an international nested case-control study, recruiting 798 patients with SC diagnosed concurrently or after the MPN. Overall, 2995 person-years (PYs) were accumulated and mortality rate (MR) since SC diagnosis was 5.9 (5.1-6.9) deaths for every 100 PYs. A "poor prognosis" SC (stomach, esophagus, liver, pancreas, lung, ovary, head-and-neck or nervous system, osteosarcomas, multiple myeloma, aggressive lymphoma, acute leukemia) was reported in 26.3% of the patients and was the cause of death in 65% of them (MR 11.0/100 PYs). In contrast, patients with a "non-poor prognosis" SC (NPPSC) incurred a MR of 4.6/100 PYs: 31% of the deaths were attributed to SC and 15% to MPN evolution. At multivariable analysis, death after SC diagnosis was independently predicted (HR and 95% CI) by patient age greater than 70 years (2.68; 1.88-3.81), the SC prognostic group (2.57; 1.86-3.55), SC relapse (1.53; 10.6-2.21), MPN evolution (2.72; 1.84-4.02), anemia at SC diagnosis (2.32; 1.49-3.59), exposure to hydroxyurea (1.89; 1.26-2.85) and to ruxolitinib (3.63; 1.97-6.71). Aspirin was protective for patients with a NPPSC (0.60; 0.38-0.95). In conclusion, SC is a relevant cause of death competing with MPN evolution. Prospective data are awaited to confirm the role of cytoreductive and anti-platelet drugs in modulating patient survival after the occurrence of a SC.

1 | INTRODUCTION

Philadelphia-negative myeloproliferative neoplasms (MPN) are chronic bone marrow disorders associated with a variable prognosis depending on the occurrence of vascular events and the transformation into myelofibrosis, myelodysplasia or acute myeloid leukemia. In addition to these incident events, recent studies consistently reported that MPN patients are also prone to an increased risk of developing second cancers (SC).[1-5] Blood and solid cancers occur in about 17% of patients with MPN, often preceding the diagnosis of MPN: melanoma, prostate cancer and non-MPN blood cancers have been diagnosed in excess as compared with control population in North Europe registry studies.[6]

We recently published the results from a nested case–control study with 647 MPN patients with SC and 1234 matched controls (MPN patients without SC) recruited from European LeukemiaNet (ELN) centers and reported that the exposure to cytoreductive drugs, such as hydroxyurea and ruxolitinib, increases the occurrence of non-melanoma skin cancers.[7]

In the present study, we re-examined this large database with the following two purposes: (a) to evaluate the prognosis of MPN patients

TABLE 1 Characteristics of MPN patients with a second cancer (SC)

	N (%) Total = 798
Characteristics at MPN diagnosis	
MPN diagnosis	
PV	275 (34.5%)
ET	396 (49.6%)
MF	127 (15.9%)
Age, mean ± SD	63.4 ± 12.1
Male gender	419 (52.5%)
JAK2 V617 mutation	603 (75.6%)
CV risk factors (smoke, hypertension, dislipidemia, diabetes, alcohol, obesity)	569 (71.3%)
Characteristics at SC occurrence	
Age, mean ± SD	68.9 ± 11.3
HB (g/dl), median (Q1, Q3)	13.2 (11.9, 14.5)
WBC (10^9/l), median (Q1, Q3)	7.6 (5.9, 10.1)
HCT (%), median (Q1, Q3)	41.0 (36.3, 44.7)
PLT (10^9/L), median (Q1, Q3)	409.0 (282.0, 556.0)
Splenomegaly (n = 21 missing)	164 (20.6%)
Prognostic groups[a]	
Non-poor prognosis SC (NPPSC)	**587 (73.6%)**
Melanoma	36 (4.5%)
Non-melanoma skin cancer	164 (20.6%)
Breast cancer	101 (12.7%)
Colorectal cancer	69 (8.6%)
Prostate/urinary tract cancer	153 (19.2%)
Kidney cancer	7 (0.9%)
Endocrine cancer	13 (1.6%)
Kaposi sarcoma	1 (0.1%)
Duodenal neuroendocrine tumor	1 (0.1%)
CLL	18 (2.3%)
Indolent NHL	24 (3.0%)
Poor prognosis SC (PPSC)	**209 (26.2%)**
Ovary/uterus cancer	29 (3.6%)
Upper gastrointestinal tract cancer	27 (3.4%)
Liver/pancreas cancer	18 (2.3%)
Respiratory tract trachea bronchus lung	69 (8.6%)
Head & neck cancer	20 (2.5%)
Cerebral cancer	3 (0.4%)
Osteosarcoma	1 (0.1%)
Muscle sarcoma	1 (0.1%)
Liposarcoma	2 (0.3%)
MM/WD	19 (2.4%)
Aggressive NHL	10 (1.3%)
T-cell lymphomas	8 (1.0%)
ALL/Burkitt lymphoma	2 (0.3%)
Treatments before/at SC occurrence	
Hydroxyurea	552 (69.2%)
Ruxolitinib	33 (4.1%)
Interferon	29 (3.6%)
Pipobroman	30 (3.8%)
Busulfan[b]	20 (2.5%)
Aspirin	607 (76.1%)
Major events after SC occurrence	
Thrombosis	86 (10.8%)
Arterial	44 (5.5%)
Venous/Splanchnic	42 (5.3%)
Major bleeding	39 (4.9%)
MPN evolution	63 (7.9%)
SC relapse	108 (13.6%)
Death	178 (22.3%)

Note: For two patients, SC type was not available.
[a]Based on classification of Zheng et al.[8]
[b]Five patients were treated with both hydroxyurea and busulfan.

with SC and (b) to establish whether cytoreductive and antiplatelet therapies have any impact on the survival of such patients.

2 | METHODS

Details of this multicenter international nested case-control study (MPN-K Study, *ClinicalTrials.gov: NCT03745378*) have been reported elsewhere.[7] Each center reported patients diagnosed with MPN (according to PVSG, 2008 and 2016 WHO) in the years 2000 to 2016 and concurrently or subsequently reporting a solid or blood cancer. Index date was the date of SC diagnosis. The present paper reports the data of all the 798 patients with a SC diagnosis enrolled in the MPN-K study that included 647 patients with and 151 patients without matched controls.

Patients were grouped into two prognostic classes based on the 5-year relative survival from cancer diagnosis.[8] The "poor prognosis" SC group (PPSC) included cancers in the stomach, esophagus, liver, pancreas, lung, ovary, head-and-neck, nervous system, osteosarcomas, multiple myeloma, aggressive lymphoma, acute leukemia; the "non-poor prognosis" SC group (NPPSC) included melanoma, non-melanoma skin cancer, kaposi sarcoma, chronic lymphocytic leukemia, indolent non-Hodgkin's lymphoma and cancers in breast, colorectal, prostate/urinary tract, kidney, duodenal, endocrine and neuroendocrine system.

The study requested centers to provide the date and cause of death as well as treatments for MPN since MPN diagnosis, treatments for SC, MPN evolution and SC relapse during follow-up.

2.1 | Statistical methods

Descriptive statistics were used to summarize the characteristics of MPN patients with SC. Categorical variables were presented as a number and percentage, while continuous variables were presented as a mean and SD (SD).

Survival after SC diagnosis was estimated by the Kaplan-Meier method and was compared in PPSC and NPPSC using the log-rank test. Age and gender-adjusted survival curves were estimated by a Cox proportional-hazard model.

Cumulative incidence function (CIF) of cause-specific mortality adjusted for age and gender was estimated with the competing-risk method and stratified by prognostic group. A multivariable Cox proportional-hazard model was fitted to estimate the Hazard Ratio (HR) of death, as well as the corresponding 95% confidence interval (CI). This was associated with the occurrence of thrombosis before/at diagnosis of MPN and during follow-up in the whole cohort and stratified by prognostic group. Adjustments were made for patient characteristics at MPN diagnosis (age, sex, typology of MPN, cardiovascular risk factors, *JAK2V617F* mutation) but also for MPN evolution (myelofibrosis, acute leukemia, myelodysplasia), thrombosis and treatments during follow-up. Adjustments were further made for patient characteristic at SC diagnosis (hemoglobin levels (HB), platelet count (PLT), leukocyte count (WBC), splenomegaly), for SC relapse during the follow-up and for vascular events preceding (thrombosis) or following (bleeding or thrombosis) SC diagnosis. Causes of death were considered as multiple "competing" outcomes, and cause-specific CIFs were accordingly estimated by the competing risk method.

For all hypotheses tested, two-tailed P-values less than 0.05 were considered to be significant.

Analyses were performed using STATA software, release 13 (StataCorp LP, College Station TX, USA).

3 | RESULTS

3.1 | Study population

The study included 798 MPN patients with a SC (Table 1). Neoplasms occurred most frequently in the prostate, the breast, the skin (basal cell carcinoma) and the lymphoid tissue. The PPSC were reported in 209 cases (26%): 68 cancers occurred in the lung and 47 in the stomach, esophagus or head&neck, while 39 SC were aggressive lymphoproliferative disorders. Chemotherapy was prescribed for the treatment of SC in 78 (9.8%) of the patients.

3.2 | Survival analysis

Overall 2995 person-years (PYs) were accumulated and 178 deaths occurred (median: 3.0, interquartile range 1.0-3.4), with a mortality rate (MR) of 5.9 deaths for every 100 PYs (95% CI: 5.1-6.9).

During the follow-up, 108 (13.5%) relapsed their SC and the major cause of death was SC itself in 78 (43.8%). The MPN evolution caused 21 deaths (11.8%), infection 23 deaths (12.9%) and

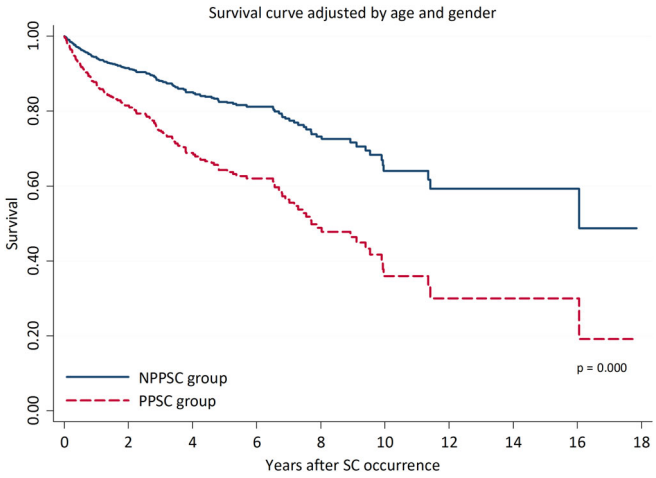

FIGURE 1 Survival curves adjusted for age and gender stratified by prognostic groups (NPPSC, non-poor prognosis SC, PPSC, poor-prognosis SC) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Multivariable Cox proportional-hazard model for predictors of all-cause mortality

	HR (95% CI)	*P*
Prognostic group		
NPPSC	1.00 (Ref.)	
PPSC	2.57 (1.86-3.55)	.000*
Age at SC > 70	2.68 (1.88-3.81)	.000*
Male gender	1.14 (0.83-1.57)	.425
MPN diagnosis		
PV/ET	1.00 (Ref.)	
MF	1.13 (0.74-1.73)	.568
CV risk factors	0.84 (0.59-1.19)	.321
JAK2 mutation	0.99 (0.68-1.45)	.966
PLT at SC < 150 × 10^9/L	1.44 (0.89-2.33)	.134
HB at SC < 10 g/dL	2.32 (1.49-3.59)	.000*
WBC at SC < 10 × 10^9/L	0.76 (0.54-1.05)	.098
Splenomegaly at SC	1.22 (0.84-1.76)	.290
Thrombosis before SC	0.92 (0.53-1.59)	.764
Thrombosis after SC	0.95 (0.59-1.53)	.838
Bleeding after SC	0.66 (0.34-1.30)	.230
Hydroxyurea	1.89 (1.26-2.85)	.002*
Ruxolitinib	3.63 (1.97-6.71)	.000*
Aspirin	0.77 (0.53-1.11)	.160
Relapse of SC	1.53 (1.06-2.21)	.023*
MPN evolution	2.72 (1.84-4.02)	.000*

Abbreviations: HB, hemoglobin levels; NPPSC, non-poor prognosis SC; PLT, platelet count; PPSC, poor-prognosis SC; WBC, leukocyte count.
*Significant associations with mortality (*p*-values < 0.05).

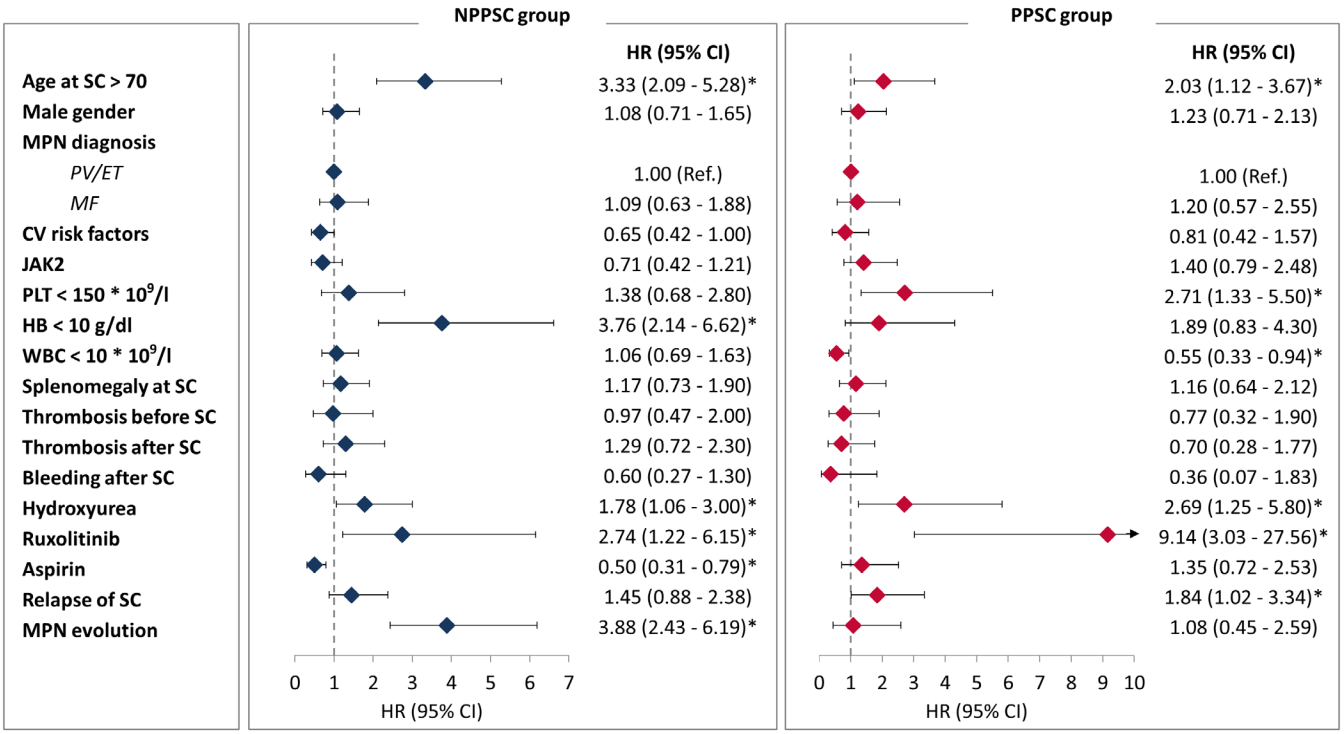

FIGURE 2 Multivariable Cox proportional-hazard model for predictors of all-cause mortality stratified by prognostic group (HB, hemoglobin levels; NPPSC, non-poor prognosis SC; PLT, platelet count; PPSC, poor-prognosis SC; WBC, leukocyte count) [Color figure can be viewed at wileyonlinelibrary.com]

cardiovascular disorders 11 deaths (6.2%). Other causes of death were reported for 17 patients (9.6%) and the cause of death was not reported for 28 patients (15.7%).

The MR was much poorer in PPSC (11.0 vs 4.6 deaths per 100 PYs; $P < .01$) with only 36% (vs 64%) alive at 10 years from diagnosis (Figure 1). In particular, respiratory cancers incurred a dismal MR of 23.9/100 PYs, corresponding to 44% 5-year and 17% 10-year survival.

During the follow-up from SC diagnosis 7.9% of the patients experienced an evolution of their MPN into myelofibrosis, myelodysplasia or acute myeloid leukemia. And, MR was significantly poorer in MF patients (10.4/100 PYs vs 5.7 PV and 4.9 ET; $P = .004$) and the prognosis of patients with NPPSC was effected by MPN evolution (Figure S1).

Fifteen years after SC occurrence, the CIF of SC-related mortality was 16%, while by MPN evolution was 6% and by other causes 19%. In the subgroup with PPSC, however, the cumulative mortality incidence caused by SC was 32% vs 1% by MPN vs 17% by other causes.

Among the 33 patients who had been treated with ruxolitinib, 16 died during follow-up: SC was the cause of death for eight of them (50%), infection for three patients (18.8%) and cardiovascular events for two of them (12.5%), while none died of MPN evolution. Other causes of death were reported for one patient (6.3%) and no cause of death was reported for two (12.5%).

3.3 | Multivariable analysis

Multivariable analysis of survival after SC diagnosis (Table 2) confirmed the predictive power of the type of SC (ie, PPSC) and its clinical behavior (ie, relapse), as well as clinical evolution of MPN and anemia. However, the analysis also pointed out that exposure to hydroxyurea or Ruxolitinib since MPN diagnosis was independently associated with a poorer outcome after SC diagnosis. The HR reported for hydroxyurea (2.69; 1.25-5.80) and ruxolitinib (9.19; 3.03-27.56) in the PPSC group were statistically significant also in the subgroup of patients with NPPSC (Figure 2).

In the subgroup of patients with NPPSC aspirin was independently associated with a 50% reduction of risk of death (HR 0.50; 0.31-0.79; = .003).

4 | DISCUSSION

SCs are a major issue occuring in over 8% of overall cancer patients: more than half of whom die of their second primary malignancy.[9] The risk of second primary malignancies is particularly high in patients with primary lymphoid neoplasms,[9] but is also significantly increased in myeloid neoplasms.[5] In particular, cancers in the upper gastrointestinal tract, nose, lung, kidney, skin, endocrine gland and nervous system are significantly increased in MPN patients as compared with the general population.[5] The genetic basis of multiple primary cancers is not well-known, however, the *JAK2V617F* mutation was associated with both solid and lymphoid neoplasms, and the rs2736100_C SNP of *TERT* has been proved to increase the risk of solid cancers in MPN patients.[10-15] In MPN patients, cyotoreductive drugs have been implicated in the development of non-melanoma skin cancers, but not of other cancers.[7]

This study reported the survival outcomes of 798 cases of SC occuring a median of 9 years after MPN diagnosis, and retrieved from an international multi-country study. Survival was shown to be dismal, as only in the 26% of the patients who had a PPSC (stomach, esophagus, liver, pancreas, lung, ovary, head-and-neck or nervous system, osteo-sarcomas, multiple myeloma, aggressive lymphomas and acute leukemias). Five-year survival of lung cancer patients, however, was not inferior to the rates reported for non-MPN patients.[16] The reported survival of patients incurring a PPSC was significantly reduced by elderly status (ie, age over 70 years), thrombocythopenia, leukocytosis, but also by exposure to cytoreductive drugs such as hydroxyurea (HR 2.69) or ruxolitinib (HR 9.14).

In patients with NPPSC cytoreductive drugs were independent predictors of survival after SC diagnosis, despite adjustment for initial MPN diagnosis, MPN evolution during the follow-up as well as for anemia, thrombocytopenia and leukocytosis at SC diagnosis.

The association of exposure to hydroxyurea and ruxolitinib with patient survival after SC diagnosis, regardless of MPN status and of cytopenias at SC diagnosis, was clinically relevant. We suppose that actively treated patients may have received a less aggressive treatment for their SC or poorly tolerated SC-targeted chemotherapy. However, we investigated also further hypotheses for ruxolitinib, since the association with survival was impressive. Ruxolitinib has been tested in patients with colorectal cancer,[17] multiple myeloma,[18] breast cancer,[19] lung cancer,[20,21] and other neoplasms in small phase 1-2 studies. They were often early interrupted and did not report any detrimental or beneficial effect of the drug onto patient survival. However, co-harboring of *JAK2* and *PDL1/PDL2* genes by the same 9p24.1 region allowed us to hypothesize some interaction of *JAK2* inhibition with *PDL1* expression and cancer immunosurveillance. However, in breast cancers, a high *JAK2* expression was associated with a higher degree of tumor infiltration by lymphocytes and a significantly lower risk of recurrence.[22] However, 9p24.1 amplifications reported in lymphomas, triple-negative breast cancers and lung cancers resulted in both increased *JAK2* and *PDL1* expression.[23] Based on these premises, one would expect that *JAK2* inhibition might also reduce *PDL1* expression, which has been proved in triple-negative breast cancer with 9p24.1 amplification.[24] However, inhibition of *STAT3* pathway has been proven both to reduce the tumor infiltrating lymphocytes and response to checkpoint inhibitors,[25] and to interfere with the lymphocyte tumor-inhibitory Th1 pathway.[22] Since immunosurveillance is a major driver of survival in solid cancers,[26] we hypothesize that exposure to ruxolitinib in patients with SC might have favored cancer progression in a subgroup of SC patients. We therefore suggest caution in the use of checkpoint inhibitors concurrently with ruxolitinib in MPN patients developing SC. However, further studies are warranted to explore the biologic and clinical reasons for the interaction of ruxolitinib with SC prognosis documented by the present study.

Arterial thrombosis may herald SC in MPN patients,[27] but in our analysis had no impact on the prognosis of SC either before and after diagnosis of SC. However, aspirin was a strongly protective agent in the subset of NPPSC, where cause of death was equally distributed between MPN evolution, SC and other causes. However, a modest reduction of cancer-specific mortality in aspirin users has been widely demonstrated especially for colon cancer but also for breast cancer, hepatocellular carcinoma and other malignant neoplasms.[28,29]

Note, MPN was the principal cause of death in 11.8% of patients incurring NPPSC, moreover, infections were a relevant cause of death, which may be partially related to MPN itself. Furthermore, NPPSC do not lead to a dismal survival, therefore, MPN patients with a NPPSC should be cared for carefully with regard to their MPN, and vascular events diligently prevented.

The limited number of patients treated with ruxolitinib in the present retrospective study may hamper the clinical validity of the very high HR reported for the drug. Therefore, larger controlled studies are awaited in the next years. Also, future prospective studies targeting germinal and acquired genetic factors predisposing individuals to MPN and to multiple primary cancers are awaited, in order to personalize MPN-directed therapies. Moreover, the impact of previous and/or ongoing exposure to cytoreductive and antiplatelet drugs in patients harboring a SC needs to be confirmed by prospective studies.

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CONFLICT OF INTEREST

TB has been a speaker and consultant for Novartis and he has received research grant from AOP Orphan. VDS has received consulting and lecture fees from Amgen, Celgene, Novartis, and institutional research grants from Bayer and Novartis. MLF has been a member of advisory board for Novartis and she has received travel grants from the company. MFM has been a speaker and consultant for Novartis. MM has received honoraria for advisory boards and lectures at sponsored meetings from Celgene, Amgen, Janssen, Gilead, Novartis. AMV has been a speaker for Novartis, Celgene, and Shire and participated to advisory boards of Celgene, Incyte, Novartis. The remaining authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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