Second Malignancies in Philadelphia-negative Myeloproliferative Neoplasms–Single-center Experience

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Abstract. *Aim: The aim of this work was to retrospectively analyze patients with Philadelphia-negative myeloproliferative neoplasms through evaluation of frequency and characteristics of second malignancies (other than acute leukaemia and myelodysplastic syndrome). Patients and Methods: Records of 172 patients were reviewed; an analysis was performed on data from 66 patients treated with hydroxyurea, 105 patients treated with other cytoreductive therapy, and 25 patients without treatment. Results: A higher occurrence of second malignancies was found in the group treated with hydroxyurea (7.6%; other cytoreduction: 1.2%; without therapy: 0). After a median follow-up of 89 months in the hydroxyurea group, 13 patients developed second cancer during hydroxyurea therapy, located on the skin (68.75%) and other sites (31.25%). Conclusion: The incidence of second malignancies during hydroxyurea therapy in our cohort patient was significantly higher than the incidence of malignancies in the Czech population of corresponding age.*

Philadelphia-negative myeloproliferative neoplasms (MPN) are a group of disorders with a high frequency of thrombotic and haemorrhagic complications. The clinical manifestation of these diseases ranges from no symptoms to life-threatening episodes. Cytoreduction is indicated in high-risk patients (1-4). In these cases, anagrelide, hydroxyurea and other cytoreductive therapies are used. However, several reports, have raised concerns on long-term safety of these drugs (5, 6). In 1998, the was a concern regarding the long-term safety of hydroxyurea treatment: it was reported that 13% of patients with essential thrombocythaemia treated with hydroxyurea developed myelodysplastic syndrome, acute myeloid leukaemia or solid tumours (7). Most of these patients carried a 17p deletion. This chromosome abnormality, which is due to an unbalanced translocation or to monosomy 17 or to i(17q), is associated with tumor protein p53 (*TP53*) mutation (7, 8). Hydroxyurea, also known as hydroxycarbamide, is a non-alkylating hydroxylated urea analogue. Hydroxyurea inactivates ribonucleoside diphosphate reductase, an enzyme converting ribonucleotides into deoxyribonucleotides, which are building blocks for DNA synthesis and repair (9). By depleting intracellular pools of deoxyribonucleotides, hydroxyurea acts as a cytotoxic and antineoplastic S-phase-specific agent which mainly inhibits DNA synthesis, while RNA and protein synthesis are less affected (9, 10). Hydroxyurea is an effective therapeutic agent for patients with MPN, such as the polycythaemia vera, essential thrombocythaemia and primary myelofibrosis, as well as for patients with sickle cell disease. Hydroxyurea is considered to be the first choice for treatment of these disorders as underlined at the European LeukemiaNet consensus conference (1), although it has been formally approved only in some countries for this indication. According to the Czech Collaborative Group for Philadelphia-negative myeloproliferative disease, hydroxyurea is preferentially intended for patients aged 65 years and over, due to the undefined potential for increasing the risk of leukaemia (3, 4). Hydroxyurea can effectively reduce leukocyte and platelet counts in patients with MPN. The effect on erythropoiesis requires a prolonged administration, with regard to the red cell lifespan (9).

The short-term toxicity of hydroxyurea includes transient and reversible myelosupression; however, long-term risks have not been yet defined. Cutaneous side-effects are very common in a long-term therapy and include alopecia, xerosis, atrophy of the skin and subcutaneous tissue, hyperpigmentation of skin and nails, oral and malleolar ulcerations, and solar hypersensitivity (5, 11-13). To our knowledge, a complete description of these skin toxicities other than leg ulcers is still lacking in the literature. Painful cutaneous ulcers are among

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the most common and troublesome side-effects of hydroxyurea therapy (5, 12), often leading to drug discontinuation; the reported incidence ranges from 5-10% of treated patients (5). Currently, the occurrence of skin ulcers or other unacceptable mucocutaneous manifestations during hydroxyurea treatment is classified as treatment intolerance (14). Patients undergoing long-term hydroxyurea therapy have an increased risk of developing both squamous cell and basal cell carcinoma, typically in sun-exposed areas but also in the oral mucosa (15-18). The possibility that hydroxyurea is leukaemogenic has been a matter of controversy, especially with regard to MPN. However, the same hydroxyurea target involved in DNA synthesis (rubonucleotide reductase) is also involved in DNA repair. Thus, hydroxyurea has the potential to be mutagenic, just like other agents interfering with DNA repair (9). Due to its ability to cause DNA damage, block DNA repair and impede *TP53* gene activation, hydroxyurea creates an environment favourable for the development of gene mutations, particularly those involving chromosome 17 (9). Hydroxyurea potentiates the effects of UV radiation and causes solar hypersensitivity and skin cancer (9). Nevertheless, the risk of developing leukaemia or other malignancies following hydroxyurea exposure has not been clearly confirmed. According to a literature review on the use of hydroxyure therapy in sickle cell anaemia in adults, hydroxyurea therapy is not associated with leukaemia, and the authors of that review provided no evidence that hydroxyurea contributes to the occurrence of skin neoplasms (19).

Patients and Methods

This work is a retrospective analysis of patients with Philadelphia-negative MPN with the evaluation of frequency and characteristics of second malignancies (other than acute leukaemia or myelodysplastic syndrome). The analysis included all patients with Philadelphia-negative MPN treated at the Department of Haematology at the University Hospital Brno, Czech Republic between 1993 and 2012. MPN diagnosis was established predominantly according to the WHO criteria (20); only a few patients were diagnosed by the Polycythaemia Vera Study Group criteria (21). A total of 172 patients were monitored. Medical history was taken for all patients, followed by physical examination, complete blood cell count, and blood chemistry before treatment initiation. The identification of cancer cases was obtained from individual chart records. Particular attention was given to the documentation of any neoplastic events, all of which were histologically confirmed. All tumours except acute leukaemia and myelodysplastic syndrome were recorded. For each patient, the period at risk started from the date of MPN diagnosis to the end of follow-up (31 December 2012), second tumour occurrence, or death. The project was conducted in accordance with institutional guidelines after being approved by the local Ethics Committee (approval number 25/09/2013).

Statistical methodology. Frequency tables and descriptive statistics (median and range) were used to describe the monitored patients and their tumours. Standard non-parametric methods were used to test differences between groups of patients. Comparisons between patients with and without second tumour were performed using the Mann–Whitney test; comparison of proportion of patients was assessed using the maximum likelihood (ML) chi-square test. All analyses were performed at the 0.05 level of significance.

Observations over all treated years for all patients were pooled into a single sample, followed by the calculation of incidence of second tumours from all patient-years. The incidence in our set was compared using the one-sample binomial test with the incidence of malignancies in the Czech population, which was obtained from the Czech National Cancer Registry (CNCR). Only data on persons of corresponding age were used for the comparison. Occurrence of any second tumour and second skin cancer was evaluated separately. Kaplan–Meier curves were drawn for the time from MPN diagnosis to the occurrence of second malignancy for different therapies and for the cumulative dose of hydroxyurea to the occurrence of second tumour according to patient age. The difference between the curves was evaluated by the log-rank test (Mantel–Cox). A multivariate logistic regression was performed to evaluate the role of potential relevant confounders (hydroxyurea vs. other treatment, patient age, length of follow-up, dosage of hydroxyurea) as independent risk factors for second malignancies.

Results

Records of 172 patients monitored due to Philadelphia-negative MPN in one haematological Center between 1993 and 2012 were reviewed. These patients included 97 patients with ET, 35 with primary myelofibrosis and 40 with polycythaemia vera. Within the group of patients with MPN, 66 were treated with hydroxyurea, 105 received other therapy (anagrelide, ruxolitinib, interferon alpha) and 25 had no cytoreductive therapy. Twenty-four patients were treated with combination or sequential treatment with more than one drug. The median age at the time of MPN diagnosis was 55 years; the median age was higher (64 years) in the group of patients treated with hydroxyurea. The median follow-up after MPN diagnosis was 66 months; the follow-up period was longer (median=89 months) in the group of patients treated with hydroxyurea compared to other groups. Basic characteristics of patients are shown in Table I.

Fifteen patients (8.7%) developed different second cancers 13 of them (19.7%) had received therapy with hydroxyurea, two patients (2.0%) were administered anagrelide; no cancer developed in patients treated with ruxolitinib (three patients only) and interferon-alpha (five patients only). The occurrence of second skin cancer was assessed separately; all cases of skin cancer were recorded in the hydroxyurea-treated group (9/66, 13.6%). The occurrence of tumors in different groups depending on the type of treatment is shown in Table II. Three patients of these 13 had another cancer or recurrence of previous tumour during hydroxyurea treatment. One patient was diagnosed with the same histological type of skin cancer in three different locations; this clinical manifestation was evaluated as one tumour. Thus, the total

Table I. *Characteristics of patients diagnosed with Philadephia-negative myeloproliferative neoplasm (MPN).*

Factor	HU treatment (N=66)	Other cytoreductive therapy (N=105)	Without cytoreductive therapy (N=25)	All patients (N=172)
Gender				
Female	37 (56.1%)	63 (60%)	17 (68%)	103 (59.9%)
Male	29 (43.9%)	42 (40%)	8 (32%)	69 (40.1%)
MPN diagnosis				
ET	33 (50%)	64 (61%)	14 (56%)	97 (56.4%)
PMF	13 (19.7%)	24 (22.9%)	4 (16%)	35 (20.3%)
PV	20 (30.3%)	17 (16.2%)	7 (28%)	40 (23.3%)
Age at time of MPN diagnosis, years	64 (23-83)	53 (14-78)	52 (19-83)	55 (14-83)
WBC count at MPN, $\times 10^9$/l	10.7 (6.53-19.2)	9.8 (5.02-34.1)	8.5 (4.56-22.76)	9.9 (4.56-34.1)
Haemoglobin level at MPN, g/l	154.5 (84.9-215)	144.5 (110-226)	142.5 (108-189)	147 (84.9-226)
Haematocrit at MPN, 0-1	0.46 (0.25-0.66)	0.43 (0.33-0.7)	0.41 (0.32-0.59)	0.435 (0.25-0.7)
Platelet count at MPN, $\times 10^9$/l	816 (243-1721)	874 (319-2100)	519 (158-863)	815 (158-2100)
Follow-up after MPN, months	89 (3-254)	66 (0-254)	48 (0-217)	66 (0-254)

MPN: Myeloproliferative neoplasm, ET: essential thrombocythaemia, PV: polycythaemia vera, PMF: myelofibrosis, WBC: white blood cell. Values are given by medians and range unless otherwise indicated.

number of diagnosed second malignancies was 16 in patients treated with hydroxyurea, and two in patients on anagrelide therapy. Table III shows the histological type and site of second malignancies.

The comparison of characteristics of patients with second tumours according to the type of cytoreductive therapy reveals the differences between the group of patients treated with hydroxyurea and other groups; some of them may be due to a low number of patients (Table IV). The group of patients with second cancer treated with hydroxyurea consists of people at an older age not only at the time of MPN diagnosis (median age=67 years), but even at the time of diagnosis of a second cancer (median age=73 years). The duration of cytoreductive therapy until the occurrence of second cancer is comparable between the two groups of patients.

The incidence of second malignancies in the group of patients with Philadelphia-negative-MPN treated with hydroxyurea was compared with the incidence of malignancies in the general Czech population. Due to the age characteristics of the monitored group of patients with MPN treated with hydroxyurea, the incidence was compared with data on the general Czech population aged 40 years and over. Data from years 2000-2010 were obtained from the Czech National Cancer Registry. In our patient cohort, we found statistically significantly higher incidence rates of both all secondary tumours and skin tumours ($p<0.001$).

Due to a clearly higher incidence of second malignancies in the group of patients treated with hydroxyurea, this group of patients was subjected to a detailed analysis. The basic characteristics of patients treated with hydroxyurea are shown in Table V. The comparison of the group of patients on hydroxyurea with all second malignancies and skin cancer with the group of patients without second tumours did not show any statistically significant differences in sex and MPN type.

Table II. *Occurrence of second cancer during the cytoreductive therapy in patients with myeloproliferative neoplasm (MPN).*

Therapy	No. of patients with MPN	No. of patients with second cancer		
		Total	Skin cancer	Other second cancer
Hydroxyurea	66	13 (19.7%)	9 (13.6%)	4 (6.1%)
Anagrelide	100	2 (2.0%)	0	2 (2.0%)
Ruxolitinib	3	0		
Interferon alpha	5	0		
No cytoreductive therapy	25	0		
Total	172*	15 (8.7%)	9 (5.2%)	6 (3.5%)

*Patients may be treated with more than one different drug.

Further analysis of patients on hydroxyurea therapy at the time of MPN diagnosis represents the comparison of age, duration of hydroxyurea therapy, average annual dose and cumulative dose of hydroxyurea (Table VI). Patient age and even the duration of therapy do not appear to be statistically significant parameters when comparing individual groups. The average and maximal annual doses of hydroxyurea were a statistically significant parameter in our group when compared with groups of patients with skin cancer ($p=0.026$ for the average annual dose, $p=0.011$ for the maximal annual dose). The cumulative dose of hydroxyurea until diagnosis of secondary cancer or the end of follow-up does not seem to be a statistically significant

Table III. *Histological type and site of second tumours by therapy.*

Histological type of tumour therapy	Site	HU		Other cytoreductive	
		N_{tum}	%	N_{tum}	%
Squamous cell carcinoma (including *in situ*)	Skin	5	31.25		
Basal cell carcinoma	Skin	3	18.75		
Malignant melanoma	Skin	3	18.75		
Adenocarcinoma	Colon	1	6.25	2	100.0
	Prostate	1	6.25		
Renal cell carcinoma chromophobe	Kidney	1	6.25		
Small cell cancer	Lung	1	6.25		
Neuroendocrine tumour	Small intestine	1	6.25		
Total		16	100.0	2	100.0

HU: Hydroxyurea, N_{tum}: number of tumors.

Table IV. *Characteristics of patients with second cancer at the time of diagnosis Philadelphia-negative myeloproliferative neoplasm (MPN).*

Factor	HU therapy (N=13)	Other cytoreductive therapy (N=2)
Gender		
Female	6 (46.2%)	1 (50%)
Male	7 (53.8%)	1 (50%)
MPN diagnosis		
ET	7 (53.8%)	
PMF	3 (23.1%)	1 (50%)
PV	3 (23.1%)	1 (50%)
Age at MPN diagnosis, years	67 (53-78)	51.5 (46-57)
WBC count at MPN, $\times 10^9$/l,	10.7 (8.07-18.9)	11.6*
Haemoglobin level at MPN, g/l	162 (122-201)	141 (130-152)
Haematocrit at MPN, 0-1	0.47 (0.34-0.63)	0.43 (0.39-0.46)
Platelet count at MPN, $\times 10^9$/l	635 (371-1380)	1321.5 (1053-1590)
Follow-up after MPN, months	111 (35-215)	77 (26-128)
Age at the time of diagnosis of secondary malignancies, years	73 (59-82)	57 (56-58)
Time from MPN to second cancer, months	54 (21 -166)	66 (10-122)
Time on cytoreductive treatment until second cancer, months	58 (5-155)	59 (7-112)
Follow-up after diagnosis of second cancer, months	51 (0-81)	11 (6-16)

*Missing data for one patient, HU: hydroxyurea, ET: essential thrombocythaemia, PMF: primary myelofibrosis, PV: polycythaemia vera, Values are median and range unless otherwise indicated.

parameter with regard to the occurrence of any second tumors. However, in some cases of multiple second tumors, the cumulative dose appears to be much higher when compared with the group of patients with a single second tumour. The statistical comparison of these groups was not performed due to the low number of cases.

The probability of occurrence of second tumours with respect to the time from MPN diagnosis (Figure 1) was estimated by the Kaplan–Meier method, the comparison of patients on hydroxyurea treatment and other cytoreductive therapies shows the 10-year estimates of 71% and 99% of patients without any second tumour (p=0.006), respectively. Multivariate analysis (Table VII) shows the significantly higher risk of second malignancy in patients treated with hydroxyurea compared those treated with other cytoreductive drugs (odds ratio=7.2, p=0.022). Patient age and duration of follow-up were not statistically significant (p=0.181 and p=0.149, respectively).

Furthermore, we evaluated the influence of dosage of hydroxyurea until the occurrence of second malignancies in the subgroup of patients treated with hydroxyurea. After the cumulative dose of 2,000 g of hydroxyurea 68% and 77% patients were reported without any second tumor and skin cancer, respectively. The Kaplan–Meier curves were also

Table V. *Basic characteristics of patients treated with hydroxyurea, comparison of patients with second cancer and patients treated with hydroxyurea without second cancer.*

N_{pt} ($\%_{pt}$)	All second malignancies		Skin cancer		All patients (N_{pt}=66)
	With tumour (N_{pt}=13)	Without tumour (N_{pt}=53)	With tumour (N_{pt}=9)	Without tumour (N_{pt}=57)	
Gender	p=0.423		p=0.452		
Male	7 (53.8%)	22 (41.5%)	5 (55.6%)	24 (42.1%)	29 (43.9%)
Female	6 (46.2%)	31 (58.5%)	4 (44.4%)	33 (57.9%)	37 (56.1%)
Diagnosis	p=0.804		p=0.541		
ET	7 (53.8%)	26 (49.1%)	6 (66.7%)	27 (47.4%)	33 (50.0%)
PMF	3 (23.1%)	10 (18.9%)	1 (11.1%)	12 (21.1%)	13 (19.7%)
PV	3 (23.1%)	17 (32.1%)	2 (22.2%)	18 (31.6%)	20 (30.3%)

Npt: Number of patients, ET: essential thrombocythaemia, PMF: primary myelofibrosis, PV: polycythaemia vera.

Table VI. *Comparison of hydroxyurea (HU) therapy between patients with and without second tumours.*

	All second malignancies				Skin cancer	
	Without tumour (N_{pt}=53)	With tumour (N_{pt}=13)	With one tumour (N_{pt}=9)	With two tumours (N_{pt}=4)	Without tumour (N_{pt}=57)	With tumour (N_{pt}=9)
Age at the time of MPN diagnosis*	p=0.151				p=0.115	
Median (range)	61 (23-83)	67 (53-78)	65 (53-77)	69 (66-78)	61.5 (23-83)	67 (53-78)
Age at the time of start HU therapy	p=0.337				p=0.242	
Median (range)	63 (23-84)	67 (53-79)	66 (53-79)	67 (67-78)	63 (23-84)	68 (53-79)
Duration of HU therapy (years)†	p=0.198				p=0.530	
Median (range)	6 (1-17)	5 (1-12)	4 (1-6)	6 (4-12)	6 (1-17)	5 (1-12)
Average annual dose of HU (g)†	p=0.098				p=0.026	
Median (range)	175 (21-903)	232 (94-449)	155 (94-406)	361 (221-449)	168 (21-903)	280 (107-449)
Maximal annual dose of HU (g)†	p=0.065				p=0.011	
Median (range)	187 (21-1005)	280 (94-675)	179 (94-498)	506 (280-675)	187 (21-1005)	406 (107-675)
Cumulative dose of HU (g)†	p=0.567				p=0.243	
Median (range)	861 (27-11733)	1262 (94-2691)	928 (94-1560)	2164 (1698-2691)	861 (27-11733)	1394 (107-2691)

*Missing information of date of diagnosis in one patient without tumour; †until diagnosis of second cancer or the end of follow-up (31.12.2012). N_{pt}: Number of patients, MPN: myeloproliferative neoplasm.

used to express the estimated probability of cumulative dose of hydroxyurea with respect to occurrence of second malignancies according to the patient's age (Figure 2). This figure shows a significantly higher risk of occurrence of second malignancies in patients aged 60 years and over who were administered the same or even a lower cumulative dose of hydroxyurea compared to younger patients (aged under 60 years), p=0.023.

Multivariate analysis in patients with hydroxyurea treatment (Table VIII) showed that the maximal annual dose of hydroxyurea is a statistically significant parameter for risk of skin tumors (p=0.002). Patient age and cumulative dose of hydroxyurea were not statistically significant (p=0.071 and p=0.061, respectively).

Table VII. *Multivariable regression model for the occurrence of all second tumours.*

	OR (95% CI)	p-Value
ET	1.216 (0.265-5.584)	0.801
PMF	1.813 (0.347-9.463)	0.481
Female	0.714 (0.2-2.551)	0.605
HU therapy	7.194 (1.322-39.148)	0.022
Follow-up after MPN	1.008 (0.997-1.018)	0.149
Age at time of MPN diagnosis	1.036 (0.984-1.09)	0.181
Intercept	0.002 (0-0.074)	0.001

ET: Essential thrombocythemia, PMF: primary myelofibrosis, HU: hydroxyurea, MPN: myeloproliferative neoplasm; OR: Odds ratio; 95% CI: 95% confidence interval.

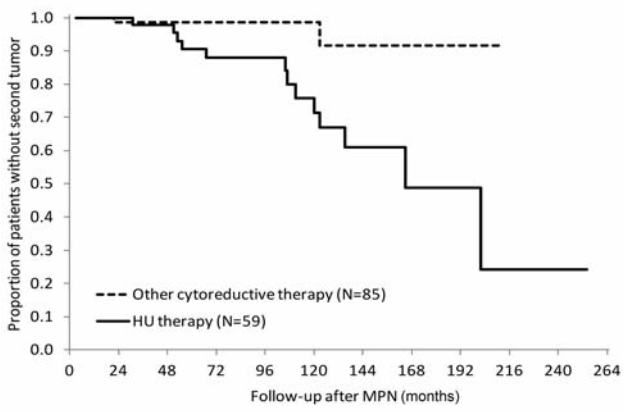

Figure 1. *Kaplan–Meier curves relating the time from diagnosis of myeloproliferative neoplasm (MPN) with the occurrence of second malignancy: comparison of patients on hydroxyurea (HU) and other cytoreductive therapy, p=0.006.*

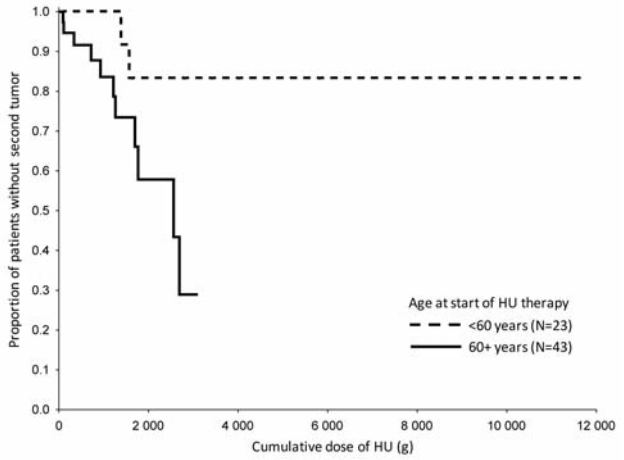

Figure 2. *Kaplan–Meier curves relating the cumulative dose of hydroxyurea (HU) with the occurrence of second malignancy: comparison of patients aged under 60 years and those aged 60 years and over, p=0.023.*

Table VIII. *Multivariate regression model for the occurrence of all second and skin tumours in patients treated with hydroxyurea (HU).*

	All tumours		Skin tumours	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age at time of MPN diagnosis (years)	1.054 (0.993-1.118)	0.085	1.074 (0.994-1.16)	0.071
Maximal annual dose of HU (g)	1.011 (1.004-1.019)	0.004	1.015 (1.005-1.024)	0.002
Cumulative dose of HU (g)	0.999 (0.998-1)	0.058	0.999 (0.998-1)	0.061
Intercept	0.002 (0-0.191)	0.007	0 (0-0.067)	0.005

OR:Odds ratio; 95% CI: 95% confidence interval.

Discussion

A longer life expectancy of patients with Philadelphia-negative MPN leads us to consider the potential adverse effects of long-term treatment of these patients. Long-term side effects of hydroxyurea are widely discussed in the literature, but a consensus has not been yet reached in this area.

In the present work, patients with Philadelphia-negative MPN were found to have a higher incidence rate of second malignancies in a group exposed to hydroxyurea therapy. Second malignancies were very rare in the anagrelide-treated group and not observed at all in patients without cytoreductive treatment. The involvement of the wide spectrum of MPN patients in different stages of diseases and with different type of management (including those without cytoreductive therapy) showed that the development of cancer could actually be a consequence of hydroxyurea therapy. However, as the follow-up of patients on hydroxyurea therapy is longer than that of other groups, a more prolonged monitoring could show an increase in the number of neoplastic events, possibly in all groups.

Our findings of a higher incidence of skin tumors during treatment with hydroxyurea are consistent with published data (11, 12) mainly in sun-exposed areas; but most data are only presented as case reports (15-18). Hydroxyurea has the potential to be mutagenic, just like other agents that interfere with DNA repair in human cells. It is also a definite promoter of cancer in humans since it potentiates UV radiation in the induction of basal and squamous cell skin carcinoma (9). In our study, the most commonly reported secondary tumor was skin cancer (11/172 in all groups, 11/66 hydroxyurea group); all skin carcinomas were observed in the group of patients treated with hydroxyurea.

In the prospective study of Finazzi *et al*., second malignancies were rarely found after treatment with hydroxyurea-alone, and were not observed in patients without myelosupressive therapy (6); however, the sequential use of busulphan and hydroxyurea significantly increases the risk of a second malignancy. In contrast, our patients with second tumors treated with hydroxyurea were not previously exposed to other cytoreductive drugs.

The incidence of second malignancies during the hydroxyurea therapy in our cohort of patients was significantly higher than cancer incidence rates in the general Czech population. Multivariate analysis showed a seven-fold higher risk of second malignancies in patients treated with hydroxyurea rather than with other cytoreductive drugs.

A higher incidence of second tumors observed in the group of patients treated with hydroxyurea led to a detailed analysis of this group of patients. Average and maximal annual doses of hydroxyurea were statistically significantly higher in patients with second skin cancer when compared with the group of patients without second tumor. Surprisingly, the cumulative dose of hydroxyurea was not statistically significant with respect to the occurrence of second tumors. However, further analysis suggested that the cumulative dose is probably relevant in a small group of patients who developed more second malignancies; differences between the group of patients with a single tumor and the group of patients with multiple tumors are apparent. These findings led us to the hypothesis that a higher dose of hydroxyurea over a certain time period is a more important factor for higher risk of second tumors than the cumulative dose. This could be one reason for the low incidence of secondary skin cancer in patients treated with hydroxyurea for sickle cell anaemia, as published by Lanzkron *et al*. (19), hydroxyurea doses are usually lower compared to those for MPN therapy. With regards to the recurrence of second tumors, the cumulative dose plays a role before the diagnosis of the first second malignancy. However, the evaluated number of patients is too small and definite conclusions cannot be drawn based on this analysis.

The weak point of this work involves not only the small number of patients included, but also the use of retrospective data. The analysis of prospective data in a larger study group of patients studied would definitely lead to more reliable conclusions which might then be used in practice. The comparison of incidence of second malignancies in our cohort with the incidence in the general Czech population, although of the appropriate age, is not quite correct. The comparison with patients with MPN on therapy other than hydroxyurea would be ideal. Of course, we have such a group of patients (treated with anagrelide), but these patients are much younger and thus the general Czech population was preferred.

In our opinion, patients on long-term hydroxyurea treatment may face an increased risk of developing skin cancer, particularly squamous cell carcinoma, on sun-exposed areas. However, larger studies of hydroxyurea-treated patients should be performed in order to detect the real incidence of second malignancies. Patients treated with hydroxyurea in the long-term should be monitored by dermatologists. Intolerance to therapy should be considered in patients who develop skin cancer during hydroxyurea therapy, and those patients be offered another therapeutic alternative. Only a continuous long-term monitoring of these patients and reporting all patients who develop second cancer can ensure the definition of any possible long-term risks. Larger studies of hydroxyurea-treated patients should be performed with the aim of establishing the real incidence of second tumors.

Conflicts of Interest

The Authors do not have any conflict of interest regarding this study.

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