Malignancies in Wegener's Granulomatosis: Incidence and Relation to Cyclophosphamide Therapy in a Cohort of 293 Patients

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ABSTRACT. ***Objective.*** To describe the incidence of malignancies in a cohort of Danish patients with Wegener's granulomatosis (WG) and to investigate the cancer risk associated with cyclophosphamide (CYC) therapy in WG.

Methods. In total, 293 patients diagnosed with WG between 1973 and 1999 were studied. Cancer incidence in the cohort was assessed through 2003 by linkage to the Danish Cancer Registry and compared to that of the general population by calculation of standardized incidence ratios (SIR). Analyses were stratified according to treatment with low cumulative CYC doses (≤ 36 g) and high doses (> 36 g, corresponding to treatment with 100 mg CYC/day for > 1 year).

Results. Fifty cancers occurred during 2121 person-years of followup (SIR of cancer of 2.1, 95% CI 1.5–2.7). Significantly increased SIR were observed for acute myeloid leukemia (AML; SIR 19.6, 95% CI 4.0–57), bladder cancer (SIR 3.6, 95% CI 1.2–8.3), and non-melanoma skin cancers (SIR 4.7, 95% CI 2.8–7.3). Leukemias and bladder cancers were diagnosed 6.9–18.5 years after initiation of CYC therapy. The risk of these malignancies was not increased for patients who never received CYC or for patients treated with cumulative CYC doses ≤ 36 g. In contrast, high risks of AML (SIR 59.0, 95% CI 12–172) and bladder cancer (SIR 9.5, 95% CI 2.6–24) were observed for patients treated with cumulative CYC doses > 36 g.

Conclusion. Treatment with high cumulative CYC doses implies a substantial risk of late-occurring, serious malignancies in WG. Patients with WG should be monitored for development of cancer for several decades after cessation of CYC therapy. These findings emphasize the need for development of new treatment regimens in WG. (First Release Oct 15 2007; J Rheumatol 2008;35:100–5)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS CYCLOPHOSPHAMIDE
BLADDER CANCER ACUTE MYELOID LEUKEMIA SKIN CANCER

Wegener's granulomatosis (WG) is a potentially lethal disorder characterized by granulomatous inflammation of the respiratory tract, necrotizing vasculitis affecting small- to medium-size vessels, glomerulonephritis, and the presence of circulating antineutrophil cytoplasmic antibodies (ANCA)[1,2]. Treatment of patients with active WG is typically initiated by a prolonged phase of aggressive, remission-inducing immunosuppression followed by a phase of less intensive maintenance therapy aiming at preventing vasculitis relapse[3]. Since the late 1970s, standard therapy for induction of remission has consisted of oral cyclophosphamide (CYC) at 1–2 mg/kg/day in combination with corticosteroids at an initial dose of 1 mg/kg/day[1,4,5]. Between 75% and 90% of patients treated according to this regimen will achieve complete remission of their disease[1,4,6].

The carcinogenic effects of CYC were recognized decades ago[7]. Subsequent studies of patients with hematologic malignancies revealed a high risk of acute myeloid leukemia (AML) and bladder cancer following treatment with CYC, and the risk of secondary malignancies was shown to be dependent upon the cumulative dose of CYC received[8-10]. A dose-dependent increased risk of malignancies was also reported for CYC-treated patients with rheumatoid arthritis (RA)[11,12]. Varied assessments have been published regarding the incidence of cancer in WG[1,13-16], and the relationship between cumulative CYC dose and risk of selected malignan-

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cies has been investigated in a few WG studies[14,15,17]. Two groups found a more than 30-fold increased incidence of bladder cancers among WG patients as compared to the general population[1,15], while others reported a standardized incidence ratio (SIR) of bladder carcinomas of < 5.0[13,16]. The incidence of hematologic neoplasias was not increased in a cohort of patients with ANCA-positive vasculitides described by Westman, *et al*[16]. In contrast, Hoffman and coworkers observed an 11-fold increase in non-Hodgkin's lymphomas among patients with WG[1], and Knight, *et al* found SIR for lymphomas and leukemias of 4.2 and 5.7, respectively, in a register-based investigation of WG patients[13]. For skin cancers, SIR of 7.3 and 10.4 have been reported[13,16]. Several groups have noted a particularly high incidence of selected malignancies among WG patients treated with cumulative CYC doses > 100 g[14,15,17]. The results of a nested case-control study from Sweden suggested a direct dose-response relationship between CYC dose and risk of bladder cancer in WG[17], while the cumulative CYC dose did not emerge as a statistically significant predictor of bladder cancer in a WG study from the US National Institutes of Health (NIH)[15]. To date, the effects of different cumulative CYC doses on the overall cancer risk in WG have not been systematically analyzed. Our aim was to describe the incidence of malignancies in a cohort of 293 Danish patients with WG followed for a median of 6.0 years and to investigate the risk of malignancies associated with low and high cumulative CYC doses in WG.

MATERIALS AND METHODS

The hospital discharge register was used to identify patients discharged from Danish hospitals with a diagnosis of WG. This register was established in 1977 and contains information on about 99% of all admissions to non-psychiatric hospital departments in Denmark[18]. A search for the medical records was performed for all patients identified in the hospital discharge register. Available medical files were reviewed, and patients who retrospectively met the classification criteria for WG[19] were included in the study. Patients with incomplete or missing medical files were excluded from further analyses. Sufficient clinical information could be retrieved for 293 patients with WG. The following basic clinical data were recorded in all cases: sex, age at diagnosis, year of diagnosis, and cumulative dose of CYC. If the cumulative CYC dose could not be determined with certainty, the CYC dose was recorded as "uncertain/unknown." A total of 200 patients received CYC as an oral dose of 1–2 mg CYC/kg/day in combination with prednisolone at an initial dose of 1 mg/kg/day. Nineteen patients received CYC as intravenous pulses of 0.75 g/m^2/month in combination with corticosteroids. Thirty-three patients were treated with both intravenous and oral CYC during their course of illness. Among patients with a known cumulative CYC dose, 51 were switched to maintenance therapy with either azathioprine (AZA) or methotrexate (MTX) in standard doses after achievement of complete remission. These patients were all diagnosed with WG after 1994. No patient received anti-tumor necrosis factor (TNF) therapy, and no patient was treated with CYC prior to the diagnosis of WG.

To obtain information on malignancies, the cohort was linked to the files of the Danish Cancer Registry, which has collected information on all cancer diagnoses in Denmark since 1943. Malignancies are coded according to the Danish version of the International Classification of Diseases, 7th Revision (ICD-7)[20] and, since 1978, according to the International Classification of Diseases for Oncology (ICD-O-1)[21]. The cohort was also linked to the Central Population Register to obtain dates of death and emigration. Followup for cancers started at the date of WG diagnosis and continued until date of death or emigration, if applicable, or until December 31, 2003.

Multiplication of person-years under observation for the WG patients by the appropriate national cancer incidence rates for men and women separately in 5-year age groups and 5-year calendar time periods yielded the expected number of cancers in the cohort. The SIR, calculated as the observed number of cancers divided by the expected number of cancers, was determined for all cancer types, and corresponding 95% confidence intervals were calculated assuming a Poisson distribution of the observed number of cancers. Exact Poisson limits were used when the observed number was < 10. Otherwise, Byar's approximation was used. Analyses were stratified by time since the WG diagnosis and by cumulative doses of CYC therapy. For the latter analyses, we defined a cumulative CYC dose of 36 g, roughly corresponding to the cumulative dose received after treatment with 100 mg CYC daily for 1 year, as an arbitrary, but clinically relevant cutoff level between a "low-dose CYC" and a "high-dose CYC" group. Patients treated with unknown/uncertain doses of CYC were excluded from the dose-response analyses (n = 47).

We finally investigated whether maintenance treatment with a disease modifying antirheumatic drug (DMARD) affects the risk of cancer after therapy with CYC. In this analysis, followup started 1 year after the WG diagnosis, since the majority of patients were switched to maintenance treatment within a year following initiation of CYC therapy (exact start date of maintenance treatment was not available in all cases). A total of 171 patients with a known cumulative CYC dose were followed for more than 1 year. These patients were divided into 2 groups: patients treated with CYC and corticosteroids only (n = 120), and patients treated with MTX or AZA after CYC (n = 51). SIR of different malignancies were subsequently calculated as described.

RESULTS

Descriptive data are summarized in Table 1. The median age of the 293 patients at the time of WG diagnosis was 59.0 years (range 14–88 yrs), and the median duration of followup was 6.0 years (range 0–28 yrs). Fifty cancers occurred during 2121 person-years of followup, corresponding to a cancer rate of

Table 1. Descriptive data for 293 Danish patients with WG.

Characteristic	No.	%
Sex		
Male	156	53.2
Female	137	46.8
Age at diagnosis, yrs		
14–19	9	3.1
20–39	44	15.0
40–59	98	33.5
60–79	134	45.7
80+	8	2.7
Year of diagnosis		
1973–74	2	0.7
1975–79	14	4.8
1980–84	29	9.9
1985–89	58	19.8
1990–94	81	27.6
1995–99	109	37.2
Cumulative dose of CYC		
No CYC	41	14.0
Uncertain/unknown dose	47	16.0
1–36 g	129	44.0
> 36 g	76	25.9

CYC: cyclophosphamide.

23.6 per 1000 person-years and an overall SIR of cancer of 2.1 (95% CI 1.5–2.7). SIR of different cancer types are listed in Table 2. We observed significantly increased SIR of bladder cancer, non-melanoma skin cancer, and leukemia (all AML). Among non-melanoma skin cancers, increased SIR were found for both squamous cell carcinomas and basal cell carcinomas. Most of the skin cancers occurred in sun-exposed areas, typically in the facial region (SIR for basal cell carcinomas of the face = 4.4, 95% CI 1.7–9.0, n = 7; SIR for squamous cell carcinomas of the face = 18.5, 95% CI 6.0–43.0, n = 5). SIR of selected cancers according to time from the WG diagnosis are shown in Table 3. Bladder cancers occurred after a median latency period of 11.7 years (range 6.9–18.5 yrs, n = 5), while the 3 cases of AML developed after 7.0, 9.0, and, 16.0 years, respectively. The risk of non-melanoma skin cancer was increased during all latency periods except during the first year following the WG diagnosis.

No excess of cancer was observed among patients who never received CYC (Table 3). In contrast, the overall cancer risk was significantly increased for the CYC-treated patients. The risk of non-melanoma skin cancer was significantly increased in both the "low-dose CYC" and the "high-dose CYC" group, while the risks of bladder cancer and AML were significantly increased only for patients treated with cumulative CYC doses > 36 g. Nine of the 19 cancers observed in the "high-dose CYC" group occurred in patients who had received 36–72 g CYC, corresponding to a treatment duration between 1 and 2 years with CYC at 100 mg/day (SIR 2.5, 95% CI 1.2–4.8). Two of 4 bladder cancers and 1 of 3 leukemias were seen in this group. The remaining 10 malignancies developed in patients treated with > 72 g CYC (SIR 2.3, 95% CI 1.1–4.2).

There was no significant difference between the cumulative CYC dose received by patients treated with CYC and corticosteroids only (median cumulative CYC dose 35 g, range 0.6–260 g) and the cumulative CYC dose received by patients treated with CYC plus other DMARD (median cumulative CYC dose 23 g, range 0.5–332 g; p = 0.49, Wilcoxon 2-sample test). Table 4 shows SIR of selected cancers calculated for the patients of the 2 groups. Although the confidence intervals are broad and overlap, the SIR of bladder cancer and non-melanoma skin cancer tended to be higher for patients switched to MTX or AZA following CYC therapy than for patients who did not receive maintenance therapy after CYC.

DISCUSSION

To our knowledge, this is the first systematic investigation of overall cancer risk associated with different cumulative CYC doses in WG. In agreement with previous estimates, we found a 2-fold increased overall risk of cancer in our cohort[1,13,16]. Increased SIR were observed for bladder cancer, non-melanoma skin cancer, and AML. The highest SIR, 19.6, was observed for AML. The risk of developing AML was significantly increased from the fifth to the ninth year of followup. This finding is in agreement with observations by Baker, *et al*, who studied patients with RA subjected to longterm oral CYC

Table 2. Standardized incidence ratios (SIR) of different cancers in a cohort of 293 Danish patients diagnosed with WG between 1973 and 1999 and followed throughout 2003.

Site of Cancer (modified ICD-7 code[21])	Observed*	SIR	95% CI
All sites (140–205)	50	2.1	1.5–2.7
Buccal cavity and pharynx (140–148)	0	—	0.0–7.8
Digestive organs (150–159)	4	0.8	0.2–2.1
Colon (153)	2	1.1	0.1–3.9
Rectum (154)	1	1.0	0.0–5.8
Liver, not specified as primary (156)	1	3.8	0.1–21
Respiratory system (160–164)	5	1.5	0.5–3.4
Breast (170)	4	1.5	0.4–3.8
Female genital organs (171–176)	1	0.7	0.0–3.7
Male genital organs (177–179)	4	2.4	0.7–6.2
Kidney (180)	1	1.7	0.0–9.5
Bladder (181)	5	3.6	1.2–8.3
Malignant melanoma (190)	1	1.7	0.0–9.2
Non-melanoma skin (191)	19	4.7	2.8–7.3
Squamous cell carcinoma	6	11.5	4.2–25
Basal cell carcinoma	13	3.8	2.0–6.5
Brain and nervous system (193)	1	1.7	0.0–9.3
Non-Hodgkin's lymphomas (200, 202, 205)	0	—	0.0–6.8
Hodgkin's disease (201)	0	—	0.0–65
Leukemia (204)	3	5.9	1.2–17
Acute myeloid leukemia	3	19.6	4.0–57
Other specified sites (192, 194–197, 203)	0	—	0.0–7.5
Metastases and unspecified sites (198–199)	2	3.0	0.4–11

* Number of observed cancer cases.

Table 3. Standardized incidence ratios (SIR) of selected malignancies according to time from vasculitis diagnosis and cumulative cyclophosphamide (CYC) dose in a cohort of 293 Danish patients diagnosed with WG between 1973 and 1999 and followed throughout 2003.

	All Cancers			Bladder Cancer			Non-Melanoma Skin Cancer			Acute Myeloid Leukemia		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Latency, yrs												
< 1	3	1.1	0.2–3.3	0	—	0.0–21	0	—	0.0–8.8	0	—	0.0–210
1–4	17	1.9	1.1–3.1	0	—	0.0–6.6	7	4.8	2.0–10	0	—	0.0–64
5–9	14	1.9	1.0–3.1	2	4.6	0.5–17	6	4.6	1.7–10	2	42.5	5.1–153
10+	16	3.2	1.8–5.2	3	12.9	2.7–38	6	6.9	2.5–15	1	32.8	0.8–183
CYC dose, g*												
No CYC	3	0.9	0.2–2.5	0	—	0.0–20	2	3.5	0.4–13	0	—	0.0–159
1–36	17	1.8	1.1–2.9	1	1.7	0.0–9.4	6	3.9	1.4–8.4	0	—	0.0–63
> 36	19	2.4	1.4–3.7	4	9.5	2.6–24	7	5.2	2.1–11	3	59.0	12–172

* Patients with unknown/uncertain cumulative CYC doses were excluded from the dose-response analyses (n = 47). Obs: Number of observed cancer cases.

Table 4. Standardized incidence ratios (SIR) of selected malignancies according to induction therapy with cyclophosphamide (CYC) and corticosteroids only or induction therapy with CYC followed by maintenance treatment with either methotrexate or azathioprine in a cohort* of Danish patients with WG.

	All Cancers			Bladder Cancer			Non-Melanoma Skin Cancer			Acute Myeloid Leukemia		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
CYC only, n = 120	23	2.0	1.3–3.0	2	3.0	0.4–10.8	7	3.7	1.5–7.6	2	27.8	3.1–100
CYC + maintenance treatment, n = 51	12	2.9	1.5–5.1	3	13.8	2.8–40	6	8.5	3.1–19	1	39.7	0.5–221

* Patients with unknown/uncertain cumulative CYC doses and patients who were followed < 1 year were excluded from analysis. Obs: Number of observed cancer cases.

therapy and found a mean latency between first CYC administration and development of hematologic malignancies of 7.0 years[11]. Similarly, Radis, *et al* found 5 hematologic malignancies among 119 CYC-treated patients with RA, and these neoplasias occurred after 4.3–8.8 years of followup[12]. In contrast to others[1,13], we did not detect an increased risk of non-Hodgkin's lymphomas among our patients with WG. However, it should be emphasized that our study did not have the statistical power to rule out excess risks of specific malignancies.

Like other groups investigating the cancer risk associated with CYC therapy[1,9-11,13,15,16], we found an increased SIR of bladder cancer in our cohort. The observed SIR of bladder cancer (SIR 3.56) is of the same magnitude as those reported in 2 Swedish WG studies (SIR of 4.1 and 4.8)[13,16]. It is, however, much lower than the 30-fold increased incidence of bladder cancer described in a cohort of WG patients followed at the NIH[1,15]. In the NIH cohort, 36% of the patients had received a cumulative CYC dose < 50 g, 29% had received 50–100 g, and 35% were treated with > 100 g CYC[15]. In our study, 76% of the patients with known cumulative CYC doses received < 50 g, 16% were treated with 50–100 g, and only 8% received > 100 g CYC. The higher incidence of bladder carcinomas among the NIH patients might therefore reflect that these patients generally received higher cumulative doses of CYC than the patients in our study. Sixty percent (3/5) of the observed bladder carcinomas occurred after more than 9 years of followup, confirming that bladder carcinomas develop with a substantial latency following treatment with CYC[1,9-13,15].

The risk of non-melanoma skin cancer was increased from 1 year after the diagnosis of WG and remained significantly increased throughout followup. It could be speculated that the close temporal relationship between development of WG and the occurrence of skin cancers was a consequence of shared pathogenetic pathways for these diseases. However, as no case of skin cancer was observed during the first year of followup, we find it more plausible to assume that the short latency between institution of treatment and the occurrence of these malignancies reflects the well known risk of skin cancer associated with intense immunosuppressive therapy[16,22-24].

Our data demonstrate a disturbingly high relative risk of serious malignancies for patients treated with cumulative CYC doses of more than 36 g. Thus, a cumulative CYC dose > 36 g was associated with a 9.5-fold increased SIR of bladder cancer and a 59-fold increased SIR of AML. In contrast, the SIR of these life-threatening malignancies were not increased for patients treated with lower cumulative doses of CYC. Together, these findings substantiate that administration of oral CYC at a standard dose of 100 (to 150) mg/day for more than (9 to) 12 months is associated with a markedly increased risk of cancer morbidity in WG[16,17]. That a proportion of the observed bladder cancers and leukemias developed in patients subjected to treatment with 36–72 g confirms that CYC-induced malignancies do not necessarily occur in the patients treated with the highest cumulative doses of CYC[9,10,15,17].

Recently, anti-TNF-therapy was shown to increase the risk of cancer among CYC-treated WG patients beyond that observed for patients treated with CYC only[25]. In accord with this finding, our data indicate that DMARD maintenance therapy may cause a further increase in the risk of skin cancers and bladder carcinomas among CYC-treated patients with WG. However, due to the relatively small number of patients available for the analysis, further studies are needed to determine the cancer risk associated with DMARD therapy following CYC treatment in WG.

It has been suggested that WG *per se* might be associated with an increased incidence of cancers of the urinary tract and hematopoietic system[13,26-28]. Although our study was not designed to address this issue, several lines of circumstantial evidence indicate that the increased risk of bladder cancer and AML observed among our patients was related to therapy with CYC and not to the underlying vasculitis disorder. First, the latencies observed between the diagnosis of WG and the occurrence of these malignancies are compatible with a CYC-related pathogenesis[8,9,15]. Second, risks of bladder cancer and AML were most pronounced for the patients of the "high-dose CYC" group. Third, while hematologic malignancies associated with autoimmune disorders are typically lymphoproliferative[29-32], treatment with alkylating agents is a well known risk factor for development of both myeloid neoplasms and bladder cancer[8,9]. Finally, no cases of AML or bladder cancer were seen among patients who did not receive CYC.

The strengths of our investigation include high validity of the WG diagnoses, information on cumulative CYC dose for the majority of patients, and high quality of the cancer data. We used the hospital discharge register to identify patients with WG, while the exact dates of the WG diagnoses, i.e., start dates of followup, were obtained from patients' medical files. In most cases, the registration date in the hospital discharge register and the date of diagnosis were closely related in time, and only a few patients were diagnosed with WG before registrations in the hospital discharge register began in 1977. Thus, a potential survival bias is expected to have only a minor influence on the results and would be in the direction to underestimate any true effect.

We confirm an increased incidence of malignancies among patients with WG and show that treatment with high cumulative CYC doses implies a substantial risk of late-occurring cases of bladder cancer and AML. Thus, patients with WG should undergo longterm followup with periodic urinalyses after CYC therapy, and should undergo a comprehensive urologic evaluation in case of persistent hematuria, as per the newly published EULAR recommendations[33]. Recent studies show that mycophenolate mofetil and MTX can induce remission in WG patients intolerant to CYC[34] and in patients with early WG[6], respectively. Our data emphasize the relevance of such efforts to develop new treatment regimens for induction of remission in WG.

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