Cyclophosphamide: As bad as its reputation?

Long-term single centre experience of cyclophosphamide side effects in the treatment of systemic autoimmune diseases

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Summary

OBJECTIVES: Despite new treatment modalities, cyclophosphamide (CYC) remains a cornerstone in the treatment of organ or life-threatening vasculitides and connective tissue disorders. We aimed at analysing the short- and long-term side-effects of CYC treatment in patients with systemic autoimmune diseases.

METHODS: Chart review and phone interviews regarding side effects of CYC in patients with systemic autoimmune diseases treated between 1984 and 2011 in a single university centre. Adverse events were stratified according to the "Common Terminology Criteria for Adverse Events" version 4.

RESULTS: A total of 168 patients were included. Cumulative CYC dose was 7.45 g (range 0.5–205 g). Gastro-intestinal side effects were seen in 68 events, hair loss occurred in 38 events. A total of 58 infections were diagnosed in 44/168 patients (26.2%) with 9/44 suffering multiple infections. Severity grading of infections was low in 37/58 cases (63.8%). One CYC-related infection-induced death (0.6%) was registered. Amenorrhoea occurred in 7/92 females (7.6%) with 5/7 remaining irreversible. In females with reversible amenorrhoea, prophylaxis with nafarelin had been administered. Malignancy was registered in 19 patients after 4.7 years (median, range 0.25–22.25) presenting as 4 premalignancies and 18 malignancies, 3 patients suffered 2 premalignancies/malignancies each. Patients with malignancies were older with a higher cumulative CYC dose. Death was registered in 28 patients (16.6%) with 2/28 probably related to CYC.

CONCLUSIONS: Considering the organ or life-threatening conditions which indicate the use of CYC, severe drug-induced health problems were rare. Our data confirm the necessity to follow-up patients long-term for timely diagnosis of malignancies. CYC side-effects do not *per se* justify prescription of newer drugs or biologic agents in the treatment of autoimmune diseases.

Key words: cyclophosphamide; side effect; autoimmune disease; scleroderma; vasculitis; systemic lupus erythematosus

Introduction

Cyclophosphamide (CYC) is used to treat organ or life-threatening anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides and connective tissue diseases such as systemic lupus erythematosus (SLE) or scleroderma (SSc). Despite new immunosuppressive drugs and biologic agents CYC remains a cost-effective option to control disease. Accordingly, the current French recommendations for treatment of granulomatosis with polyangiitis (GPA) still propose the use of CYC in defined situations [1]. In contrast to published data, we found a very positive side-effect profile of CYC. If correctly indicated and administered in standardised fashion CYC appears to be well tolerated. To substantiate this perception we decided to analyse the side effects over a long time period which, in addition to short term side effects, also allows judging the carcinogenic effects in patients with severe autoimmune diseases.

Clinical side effects of CYC comprise nausea, vomiting, anorexia, bone marrow suppression, infection, infertility, teratogenicity, pneumonitis and malignancies such as lympho-proliferative disorders, urothelial and skin cancer [2–4]. Most of these side effects are short in duration and only few are organ or even life-threatening. Notably, many of these can be prevented if adequate measures are taken: Cumulative dose can be drastically reduced if CYC is administered in form of IV pulses instead of oral medication. Systematic addition of 2-mercaptoethansulfonat-natrium (mesna) prevents bladder cancer [5], and pretreatment with gonadotropin releasing agents such as nafarelin or freezing of sperm may preserve fertility [6]. As a rather surprising fact, these recommendations are ignored in recent studies published in high ranking journals [7]. In order to better evaluate the risk/benefit profile of CYC as well as the benefit/costs of different immunosuppressive strategies, we set out to analyse the data of our own patients over a time period of 27 years. The study is retrospective in nature; however, in addition to chart reviews all patients or their general practitioners were contacted in order to collect and complement the data.

Patients and methods

Medical charts of all patients treated with CYC between April 1984 and December 2011 in the Department of Rheumatology, Clinical Immunology and Allergology at the University Hospital of Bern, Switzerland, were reviewed, interviews by telephone or e-mail correspondence with patients and their general practitioners were additionally performed.

Diagnoses were based on the American College of Rheumatology (ACR) criteria for rheumatoid arthritis (RA), SLE, Le Roy criteria for SSc, Dalakas criteria for polymyositis/dermatomyositis, Sharp criteria for mixed connective tissue disease (MCTD), Criteria from the European-American-Consensus-Conference from 2002 for Sjögren syndrome, Mac Adam criteria for polychondritis and Chapel Hill Consensus Conference of 1992 or current ACR criteria for vasculitis.

The following parameters were recorded: disease manifestation, immuno-suppressive medication, laboratory data, short- and long-term adverse effects of CYC, cumulative CYC dosage, route of administration, and mortality. Each adverse event was stratified according to the "Common Terminology Criteria for Adverse Events" version 4 (Grade 1 [mild] through 5 [death related to adverse event]) [8]. Regarding infections we assessed the time interval between the last CYC cycle and infection. We then calculated the effect of GC therapy and concomitant immunosuppressive therapy, lymphocyte count and prophylaxis with TMP-SMX within one month prior to infection. If TMP-SMX prophylaxis status was not known, it was considered as not given. Co-morbidities favouring infections such as diabetes, renal insufficiency, alcohol abuse and neoplasia were noted.

Intravenous (IV) CYC pulses were given at doses of 0.6–1 g/m^2 of body surface in 3–4 weekly intervals, and daily oral CYC was prescribed at 1–2 mg/kg/day to be taken as a single morning dose. Oral CYC was often prescribed until 1999 and thereafter only if IV pulses did not result in remission of disease activity. In these situations mesna was prescribed in a dose equal to the CYC dose. All IV-patients received a pre- and post-CYC fluid bolus of a total of two liters, a pre- and post-CYC dose of Mesna to prevent bladder toxicity and antiemetics. After 2003 SLE treatment followed the Euro-Lupus-Nephritis-Trial (500 mg each for 6 times, at 2 week intervals) [9].

182 patients were treated with CYC, 14 of these were excluded from further analysis due to missing information on cumulative CYC dosage and insufficient data regarding follow up. The characteristics of the 168 patients analysed are displayed in table 1. In brief: CYC was prescribed to induce remission of vasculitis in 89 patients (ANCA associated and RA vasculitis) or to control connective tissue diseases in 69 patients (SLE and scleroderma (SSc). Six small- /medium-sized vessel vasculitides could not be classified. Route of CYC administration was oral (PO) in 13 patients, PO and IV in a sequential manner in 27 patients and IV only in the remaining 126 patients. Median cumulative CYC dosage was 7.45 g (range 0.5–205 g).

Statistical analysis

Influencing factors for infection, malignancy, infertility and death were analysed using multivariate regression analysis (IBM SPSS Statistics version 21).

Results

We registered a total of 162 adverse events consisting of nausea in 63 (37.5%), vomiting in 23 (13.6%), hair loss in 38 (22.6%), cytopenia in 38 patients (22.6%) and haemorrhagic cystitis in one patient. Nausea and vomiting was the reason for switching from IV to PO CYC application in one patient, and it was the reason for termination of CYC in another. Cytopenia was characterised as lymphopenia in 36 patients and thrombopenia in another two patients. In 27 patients lymphopenia was associated with infection. Severity of nausea, vomiting, hair loss and cytopenia was classified as mild to moderate (grade 1 to 2) in in all but one event. One patient developed haemorrhagic cystitis during oral CYC treatment (at times before standard mesna prophylaxis). Severity of haemorrhagic cystitis was graded 3. All of these side effects were temporary in nature and normalised and healed, respectively, without sequelae.

Infections

58 infections in 44 patients were reported (table 2). There were nine patients with more than one infection: 7 patients suffered 2 infections, 1 patient suffered 4 infections and another patient suffered 5 infections. 15 of the 58 infections (25.9 %) were of bacterial, 11 (18.9%) of viral and 5 (8.6%) of fungal origin; the causative agent was not identified in the remaining 27 (46.6%) infections. Prophylaxis for Pneumocystis jirovecii pneumonia (PJP) with TMP-SMX was prescribed in 20 cases (34.5%).

Pneumonia occurred in 18 patients. 2 were caused by *Pneumocystis jirovecii* and 2 by *Haemophilus influenza*. One patient suffered from pneumonia of unknown origin twice, finally with fatal outcome. The two patients suffering from PJP had no prior prophylaxis with TMP-SMX. Their lymphocyte counts were 0.5 G/l and 0.3 G/l respectively at the time of infection. Concomitant prednisone doses of 50 mg and 5 mg, respectively, plus 15 mg of weekly methotrexate SC in the latter patient were given 1 month prior to infection.

In two cases of upper airway infection the underlying agents were identified as *Staphylococcus aureus* and *Streptococcus species*, respectively. Viral infections comprised Herpes Zoster (8 patients) and Cytomegalovirus (CMV) (2 patients). Urinary tract infections of any cause were noted in 6 cases, 3 caused by *Escherichia coli*. Candidosis in 5 patients was oral in 4 and vaginal in one. One case of severe aphthous stomatitis of unknown agent was treated with both antifungal and antiviral therapy and healed.

Sepsis was noted in three patients with two patients having bacterial, catheter-related sepsis induced by *Coagulase negative Staphylococcus*. One patient suffering lethal septicaemia of unknown origin three months after the last CYC dose had concomitant treatment with azathioprine and a lymphopenia of 0.33 G/l. Furthermore he suffered from prostatic cancer yet had no tumour related immune-

suppressing therapy. He had not received TMP-SMX prophylaxis. One of the patients with Coagulase negative Staphylococcus catheter-related infection had no other concomitant immunosuppressive treatment besides CYC. She had a lymphopenia of 0.3 G/l and suffered from malnutrition because of rapidly progressive systemic sclerosis. The second patient with coagulase negative staphylococcus catheter-related infection was under glucocorticoid treatment (prednisone equivalent 10 mg daily) and hydroxychloroquine 200 mg daily. She had a mild lymphopenia of 0.94 G/l.

At time of infection, lymphocyte counts for the entire infection group showed a median value of 0.63 G/l (range 0.18–3.44) and for the subgroups showing median values for bacterial infections of 0.63 G/l (range 0.18–11.8), for viral infections a median of 0.29 G/l (range 0.05–1.07), for fungal infections a median of 0.64 G/l (range 0.52–2.86), and within the group of unknown origin the median value was 0.43 G/l (range 0.3–3.44).

In 49 (84.5%) cases of infection, patients received additional immunosuppressive medication. This consisted of GC in 34 cases, GC plus any other type of immunosuppressive medication (IS) in 14 cases and one patient receiving IS without GC (i.e., azathioprine). In the group of patients receiving only additional GC medication one month prior to infection, we registered lower lymphocyte counts at time of infection, a shorter duration between last CYC and infection and a higher median dosage of GC compared to the group with GC plus IS. Median values for "GC only" versus "GC plus IS" were: lymphocyte counts 0.54 versus 0.92 G/l, time from last CYC to infection 15 versus 30 days, GC dosage preceding infection 17.5 versus 10 mg/d. The severity of infections showed a median of two in each group.

Vasculitis or connective tissue disease (CTD) revealed similar rates of infection in each group with 32.2% in vasculitis (22/69 patients) and 34.8% in CTD (31/89 patients).

Co-morbid conditions possibly favouring infection were diabetes mellitus in 7 patients, renal insufficiency in 6, preexistant neoplasia in 1 patient and splenectomy in another. None of the 2 patients with alcohol abuse suffered infection.

Grading of side effects is summarised in table 3.

Reproductive system

Details are given in table 4. A total of 7/92 (7.6%) women suffered amenorrhoea at a median age of 35 years of age (range 21–50) after a mean cumulative CYC dose of 14.4 g (range 6–40). Amenorrhoea was irreversible in 5/7 and reversed in 2/7 women within 2 years after CYC induction. The latter two patients had been treated prophylactically with nafarelin, an analogon of gonadotropine-releasing-hormone (GnRH) started together with the first cyclophosphamide pulse. Their cumulative CYC dosages were 7.25 g for SLE at the age of 21 years and 14.4 g for eosinophilic granulomatosis with polyangiitis (eGPA) at 25 years of age, respectively.

In the other five women irreversible amenorrhoea developed after a median cumulative CYC dose of 34.5 g (range 6–40) at a median age of 39 years (range 34–50) treated

Table 1: Patient characteristics.				
Diagnosis		**Number of patients [%]**	**Median age at diagnosis, years (range)**	**Gender**
				Female	**Male**
All patients		168	52.7 (7.5–86)	92 (54.7%)	76 (45.2%)
Vasculitis		89		38	51
ANCA associated		51	51.6	22	29
GPA		34	51.1	15	19
MPA		4	50.7	1	3
eGPA		4	55.2	1	3
Others		9	68.2	5	4
Cryoglobulinaemic vasculitis		2	52.1	1	1
Henoch-Schönlein purpura		1	53.9	1	
RA associated vasculitis		15	53.3	10	5
Panarteritis nodosa		9	68.5	1	8
Behçet's disease		3	34.0	1	2
Other small-/medium-sized vessel vasculitis		6	62.0	2	4
Giant cell vasculitis		1	77.4		1
Cogan's syndrome		1	49.7		1
Polychondritis		1	39.8	1	
Connective tissue diseases		69		47	22
SLE		28	39.5	25	3
SSc	Diffuse	20	54.8	14	14
	Limited	8			
Sjögren syndrome		4	53.4	4	
Inflammatory muscle disease		2	46.0		2
Mixed connective tissue disease		2	22.9	2	
Undifferentiated connective tissue disease		5	49.1	2	3
Autoimmune eye disorders		1	49.1	2	
Others		8	59.5	3	4
GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; eGPA = eosinophilic GPA; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.					

for miscellaneous autoimmune diseases (small vessel vasculitis, systemic lupus erythematosus, granulomatosis with polyangiitis, scleroderma and undifferentiated polyarthritis).

Azoospermia was reported in 1/76 (1.3%) male patient with Behçet's vasculitis after a cumulative CYC dose of 40 g at 33 years of age.

Severity of secondary sterility was classified as grade 3.

Pre-/malignancy

For details see table 5. We registered 22 pre-/malignancies in 19 patients (12 male, 7 female) with 3 patients suffering 2 pre-/malignancies each. Median age at tumour diagnosis was 60.75 years (range 43.5–85.5 years). Median time from first dose CYC to tumour diagnosis was 56 months (range 3–267 months). Median cumulative dose at time of malignancy was 10.6 g (range 1.95 to >100 g).

Actinic keratosis, classified as skin premalignancy was diagnosed in 4 cases, 9 of the 18 malignancies were 9 skin cancers, 8 basaliomas and 1 squamous cell carcinoma (mean age 76, range 57–85). All skin pre-/malignancies were successfully treated. Interval between the start of CYC therapy and diagnosis of skin cancer was less than four years in two of these patients.

The GPA patient suffering from B-cell lymphoma at the age of 83.5 years had received a cumulative CYC dose of 70 g. The neoplasm was diagnosed 22.25 years after the first CYC dose. He died two months after diagnosis of lymphoma. A chronic myelomonocytic lymphoma (CMML) suspected in a 86.5 year old female with RA vasculitis occurred only 4 months after initiation of CYC. She died 3 months after having received a cumulative CYC dose of 2.3 g. One SLE patient suffering acute myeloid lymphoma (AML) at the age of 57 is in remission more than 3 years after diagnosis.

The patient with the adrenal carcinoma had developed multiple metastases, however, is in remission more than nine years after diagnosis. The patient with kidney tumour died of septicaemia three years after diagnosis. The patient with seminoma has so far been cured by semicastration and chemotherapy. The urothelial carcinoma was diagnosed 1.08 years after CYC induction only. The chondrosarcoma was detected three months after the first dose of CYC in an anti-Hu syndrome. As this rare syndrome is typically associated with malignancy, the chondrosarcoma is considered part of the disease and not caused by CYC [10].

Table 2: Infections.

IS = immunosuppressive medication; TMP-SMX= trimethoprime-sulfamethoxazole; **Infection type**	No	GC only 1 month before infection	GC plus IS 1 month before infection	Prophylaxis with TMP-SMX	Days last CYC to infection median (range)	Lymphopenia*		Grade**				
						Global (<1.1 G/l)	≤0.3 G/l	1, 2	3	4	5	
Bacterial infections (total)	*15*	*10*	*5*	*8*								
Hidradenitis	1		1		14	1		1				
Laryngitis/Pharyngitis	3	3	1	1	25 (14–90)	2		3				
Urinary tract	3	2	2	1	30 (13–72)	1			1	2		
Bronchial contamination	1	1			20			1				
Pneumonia	4	2		2	67.5 (15–120)	3	1		3	1		
(out of "Pneumonia": PCP)	*2*	*1*	*1*		*(15– 120)***	*1*	*1*		*2*			
Gastrointestinal infection	1	1		1	9	1			1			
Catheter-related infection	2	1	1	1	28.5 (27–30)	1	1		2			
Fungal infection (total)	*5*	*4*	*2*	*1*	*17 (13–90)*							
Candida-Stomatitis/Glossitis	4	3	2	1	22 (13–90)	3		4				
Vaginal	1	1			17	1		1				
Viral infections (total)	*11*	*5*	*3*	*4*	*14.5 (10–150)*							
CMV-Infection	2	2					2		2			
Herpes zoster	8	2	3	3	14,5 (10–150)	3	2	7	1			
Gastrointestinal infection	1	1		1			1	1				
Undetermined type (total)	*27*	*15*	*5*	*7*	*24 (9–120)*							
Infection unknown localization	2	2		1	14	1	1	2				
Agranulocytosis	1	1		1			1	1				
Upper respiratory tract	1	1			12	1		1				
Bronchitis	1	1			14	1		1				
Pneumonia	14	5	2	4	24 (14–120)	9		10	2	1	1	
Urinary tract infection	3	2	1	1	62 (24–100)	2		2	1			
Gastroenteritis	1	1	1		37			1				
Perichondritis	1	1	1			1		1				
Stomatitis	2				19.5 (14–25)	1	1	2				
Otitis	1	1			70	1		1				
All	*58*	*34*	*15*	*20*		*34*	*10*	*38*	*15*	*4*	*1*	

* Lymphocyte count unknown in 2 patients with pneumonia, 1 patient with laryngitis/pharyngitis and 1 patient with gastrointestinal infection;
** Grade not known for 1 patient with pneumonia, 1 patient with gastrointestinal infection, 1 patient with perichondritis, 1 patient with herpes zoster and both patients with CMV-infection, was the reason for stopping CYC therapy in one CMV-patient;
*** Patient had stopped TMP-SMX 3 months before the infection, after completing CYC therapy.

Mortality

Twenty-eight patients (16.6%) had died, 4 deaths were infection-related (1 died 3 months after completed CYC therapy, 3 died more than 6 years after completed CYC therapy), 10 disease-related (8 SSc, 1 GPA with renal failure, 1 rheumatoid arthritis), 11 other causes (2 myocardial infarction, 4 heart failure, 1 pulmonary embolism, 1 respiratory failure, 1 cardiac arrest, 1 visceral perforation, 1 assisted suicide), 3 of unknown cause.

One patient with lethal respiratory failure due to infection had a total treatment period of 6 months IV CYC for rapid progressive systemic sclerosis (cumulative CYC dosage of 5.5 g). He concomitantly suffered prostatic cancer.

Statistics

Statistical analysis revealed no relevant influence of either age, sex, type of disease, type of co-medication, co-morbidities or cumulative CYC dosage on incidences of infection, malignancy, infertility or death. In particular there was no statistical correlation between the infection and the 1–month-preceding lymphocyte count or medication including glucocorticoids. Overall regression analysis failed to give valuable data because of the small sample size within each group.

Table 3: Grading of adverse events.

Adverse events	Number (%)	Female	Male
Grade 1 or 2			
Infections	38		
Nausea	63 (37.5)	33	30
Vomiting	23 (13.6)	16	7
Hair loss	38 (22.6)	26	12
Cytopenia	38 (22.6)	19	19
Amenorrhoea	7 (7.6)		
Grade 3			
Secondary sterility	6	5	1
Infections	15		
Haemorrhagic cystitis	1 (0.5)		1
Grade 4			
Infections	4		
Grade 5			
Infection	1		

Table 4: Characteristics of patients with amenorrhoea.

	Amenorrhoea[1]		Reversible amenorrhoea[1]		Irreversible amenorrhoea[1]		No amenorrhoea[2]
	N = 7		N = 2		N = 5		N = 42
Median age (range)	35 (21–50)		23 (21–25)		37 (34–50)		35 (8–50)
Median cumulative CYC dose, g (range)	14.4 (6–40)		10.8 (7.25–14.4)		24.45 (6–40)		7.35 (0.5–122.4)
GnRh-analogon			yes		no		no
Single patients			age (years)	dose (g)	age (years)	dose (g)	
			21	7.25	34	36	
			25	14.4	35	40	
					39	6	
					43	34.5	
					50	7.3	

[1] Age and cumulative CYC dose at onset of amenorrhoea.
[2] females <50 years of age

Table 5: Pre-/malignancies.

		All	Male	Median time CYC to tumour, months	Median time CYC to tumour, years	Median cumulative CYC dose, g
Premalignancy		**4**	**1**	**3**		
Actinic keratosis		4	1	3	63 (24–76)	5.25 (2–6.33)	30.6 (6–100)
Malignancies		**16**	**4**	**12**		
Skin*		9	2	7	60 (24–117)	5 (2–9.75)	10.6 (3.9–70)
Urothelial carcinoma		1		1	13	1.08	9.1
Haematologic**		4	2	2	39.5 (4–267)	3.3 (0.3–22.25)	14 (2.3–70)
Others***		4	2	2	82 (3–192)	6.8 (0.25–16)	9.1 (2–16)
All		**22**	**7**	**15**	**56 (3–267)**	**4.7 (0.25–22.25)**	**10.6 (2–100)**

* 8 basaliomas, 1 squamous cell carcinoma;
** 1 suspected CMML, 1 secondary AML on myelodysplastic syndrome, 1 smouldering myeloma and 1 diffuse B-cell-lymphoma;
***1 kidney-tumour, 1 seminoma, 1 chondrosarcoma and 1 adrenal carcinoma.

Discussion

CYC, even in the era of an evolving number of biologics, still plays an important role in treating autoimmune diseases. This is illustrated by the recent French recommendations to treat ANCA-associated vasculitides, but also by a comparative work from the European Vasculitis Study Group [11]. In this study CYC was added to the new biologic to induce remission and not only used as control medication. Considering the demand for cost-effectiveness one has to take into account that a standard induction therapy by a currently used biologic amounts to costs more than 10 times higher when compared to CYC.

Our retrospective analysis of 168 patient charts complemented by phone interviews with patients and/or their treating physicians confirms a positive side effect profile of CYC in the treatment of systemic autoimmune diseases. Most side effects were mild and transient, very few were severe in nature [12, 13]. In discussing severe side effects of a drug, one has to judge them in the context of severity and prognosis of the disease itself. CYC is used for the treatment of organ or life-threatening autoimmune diseases. It may, therefore, be difficult in a given case to precisely determine respective roles of disease and drug. The fact that only one patient died as a probable consequence of treatment, but 11 patients as an undisputable consequence of their immune disease clearly argues for a decisive role of the disease in the majority of fatal cases, at least in our cohort.

The following side effects need to be discussed in more detail: Amenorrhoea, infection, malignancy and death. Regarding amenorrhoea, our data confirm a well-known age-dependency [14–16]. The two patients with transient amenorrhoea were at least nine years younger than the five with persisting amenorrhoea. Based on their family planning they were treated with GnRH, as has recently been published with conflicting results [17, 18]. We cannot distinguish the effect of age from the effect of GnRH. Very recent data showed that antimullerian hormone levels remained higher in a patient cohort treated with GnRH as compared to a group without, indicating preservation of ovarian function by GnRH [19]. Despite some contradicting data, we suggest usage of GnRH starting together with the first infusion of CYC.

Regarding infections, we calculated effects of GC prescription, TMP-SMX prophylaxis, lymphocyte counts and combination therapies on incidence and outcome. Although we found descriptive differences, they did not reach statistical significance. On the one hand one may argue that populations were too small to reach statistical significance. On the other one may conclude that the signals are indeed very small and, therefore, do not become clinically relevant. Published data show a negative effect of glucocorticoids if prescribed beyond six months and at doses as low as 5 mg per day [20]. Another study reported a negative impact of IV glucocorticoids and/or immunosuppressants as long-term risk factors for infections [21]. In conclusion, our findings together with published data prompt us to continue monitoring lymphocyte counts and to reduce GC doses as soon as clinically feasible.

Data unanimously show increased risks for non-melanoma skin cancer, leukaemia and urinary tract cancer [22, 23]

with delays up to 18.5 years. Remarkably, a cumulative dose of 36 g (corresponding to 100 mg/day over 1 year) did not result in a significant increase of malignoma formation [23]. An analysis of a cohort of 535 vasculitis patients showed an increase only in non-melanoma skin cancer [24]. This finding may primarily be explained by the lower cumulative CYC doses used today. An intriguing difference in malignoma incidence was suggested regarding GPA versus microscopic polyangiitis [22], strongly arguing for a contributing effect of the underlying autoimmune disease.

In our cohort we found a rather wide spectrum of malignoma, a wide range in cumulative CYC doses and a wide range in time intervals between initiation of CYC treatment and diagnosis of the neoplastic diseases. In line with published data, 13 of 19 tumours were premalignancies or basaliomas/squamous epithelial carcinomas of the skin. Remarkably, 2 of these developed within 4 years. We registered a total of four haematological and lymphoproliferative malignomas. Two of the patients were diagnosed at an age beyond median life expectancy. Of note, no bladder cancer was diagnosed, a fact which may be related to the consequent prescription of mesna even if CYC is taken as an oral medication. The other malignomas such as adrenal carcinoma or seminoma do not have a clear association with CYC.

A weakness of the study is its retrospective nature. Although we recovered many previously lost data by phone interviews, it is likely that we missed patients and side effects. Yet, there is no obvious bias in data acquisition. Percentages, types and severity of side effects would probably not have changed. An advantage of our study is that we report data of a single academic centre. This allows judgement of standard operation procedures and may underline certain published recommendations. Finally, in contrast to randomised controlled trials which study well characterised, however, highly selected patients, retrospective studies report on everyday situations, including patients with unfavourable disease profiles at very high treatment risks.

In summary, we could confirm our hypothesis that CYC – used in the recommended doses and administered in standardised fashion – shows a surprisingly positive side-effect profile. The data strongly argue for an individualised and differentiated use of either CYC or one of the newer drugs/biologic agents. The fact that malignoma were diagnosed after short intervals and at low cumulative doses asks for a vigilant eye on the development of any kind of neoplastic disease throughout the whole patient history, in particular in situations of lasting remission.

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