Zoster after Cyclophosphamide for Systemic Lupus Erythematosus or Vasculitis: Incidence, Risk Factors, and Effect of Antiviral Prophylaxis

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ABSTRACT. Objective. To assess the incidence and the risk factors for zoster in patients exposed to intravenous cyclophosphamide (CYC) for systemic vasculitis or systemic lupus erythematosus (SLE), as well as the protective effect of prophylaxis by valacyclovir (VCV).

Methods. This retrospective study included all adults treated by intravenous CYC for SLE or systemic vasculitis between 2011 and 2015 at Toulouse University Hospital, France. Zoster occurrence was recorded using medical chart review, laboratory data, and patient interviews. Univariate Cox models were computed to assess the risk factors for zoster and the protective effect of prophylaxis by VCV.

Results. The cohort consisted of 110 patients (81 systemic vasculitis and 29 SLE). During a mean followup of 3.4 years after CYC initiation, 10 cases of zoster occurred, leading to an overall incidence of 27.9/1000 patient-years (95% CI 15.2–50.6); it was 59.4/1000 patients (95% CI 27.5–123.6) during the year after CYC initiation. Four patients experienced persistent postherpetic neuralgia. Probable risk factors were lymphopenia < 500/μl at CYC initiation (HR 5.11, 95% CI 0.94–27.93) and female sex (HR 4.36, 95% CI 0.51–37.31). The incidence was higher in patients with SLE (HR as compared with systemic vasculitis patients = 2.68, 95% CI 0.54–13.26). None of the 19 patients exposed to VCV during the followup developed zoster.

Conclusion. The incidence of zoster is high in systemic vasculitis and in patients with SLE exposed to intravenous CYC. CYC may favor postherpetic neuralgia. Prophylaxis by VCV should be considered, particularly in cases of lymphopenia < 500/μl at CYC initiation and during the year after.

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Immunocompromised patients are at risk for varicella-zoster-virus (VZV) reactivation[1,2]. The incidence of zoster in this population is between 2- and 10-fold higher than in the general population[2]. This setting includes patients with autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel diseases, or systemic vasculitis[2,3,4,5,6]. Further, the increased risk of zoster in these patients when treated with corticosteroids, biologics, or nonbiologic immunosuppressive drugs is demonstrated[7].

Patients with SLE are particularly at risk of developing zoster[2,5], with an incidence ranging from 6.4 to 37.7/1000 patient-years (PY) in observational studies[8,9,10,11]. Age-, sex-, and treatment-adjusted relative risk has been estimated to be 2.45 (95% CI 1.77–3.40) compared to the general population[12]. Exposure to corticosteroids[12,13], exposure to immunosuppressive drugs including oral and

intravenous cyclophosphamide (CYC)[13,14], renal impairment, and lymphopenia have been described as main risk factors for zoster in these patients[13].

In contrast, few data are available on zoster occurrence in patients with systemic vasculitis. However, it is a concern in granulomatosis with polyangiitis (GPA) patients[15,16]. A single study assessed its incidence, derived from the Wegener's Granulomatosis Etanercept Trial (WGET), and it was estimated to be 45.0/1000 PY (95% CI 27.0–70.0)[17]. The association of corticosteroids and CYC seems a strong risk factor for zoster in patients with GPA[15]. Kidney failure may also be associated with an increased zoster incidence in these patients[17].

Intravenous CYC is a strong immunosuppressive drug still indicated in the treatment of severe flares of SLE[18,19] and systemic vasculitis[20], in association with corticosteroids. Exposure to CYC increases the risk of severe infection, particularly during the year after the first exposure[21,22].

However, no study has been focused on the risk of zoster in systemic vasculitis and patients with SLE exposed to pulse intravenous CYC. The suspected risk factors (lymphopenia, kidney failure) need to be confirmed in this population. Moreover, the efficacy of antiviral prophylaxis to prevent zoster occurrence, demonstrated in stem cell transplantation[23,24], is unknown in this population.

The aims of our study were to describe the incidence of zoster in patients exposed to pulse intravenous CYC for systemic vasculitis or SLE, to describe the cases of zoster in this population, and to assess the risk factors for zoster as well as the protective effect of prophylaxis by valacyclovir (VCV).

MATERIALS AND METHODS

Design. We conducted an observational, retrospective, monocentric study at Toulouse University Hospital, a French 2986-bed tertiary hospital.

Patients. We selected all the patients who were prescribed pulse intravenous CYC over 5 years, between January 1, 2011, and December 31, 2015, from the hospital pharmacy database. Medical charts were reviewed and diagnoses ascertained using international criteria[25,26]. Patients meeting inclusion criteria were those who were adults (≥ 18 yrs of age), were treated for SLE or systemic vasculitis, had no previous exposure to CYC, and were followed at Toulouse University Hospital.

Outcomes. Zoster occurrence was searched using the following sources: medical chart reviews, VZV PCR at the Virology Department of Toulouse University Hospital, and phone interviews with the patients and/or their general practitioners.

Zoster characteristics, time of occurrence from CYC and other immunosuppressive drugs, and zoster complications were described. Postherpetic neuralgia was defined as the persistence of dermatomal pain at least 90 days after the acute zoster rash appearance[27].

Statistical analyses. The incidence estimates of zoster during the overall followup and during the first year after the first pulse of CYC were calculated with their 95% CI intervals.

Risk factors for zoster occurrence during the year after the first exposure to CYC were assessed using Cox models. Covariables were the following: age (≥ 50 vs < 50 yrs, 50 yrs being the median age in our cohort, and being close to the mean age of zoster occurrence in France[28]), sex, the presence of diabetes mellitus, active cancer, renal failure at CYC initiation (defined by an estimated glomerular filtration rate < 60 ml/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration formula[29]), lymphopenia at CYC initiation (defined as a lymphocyte count < 1000/μl), the cumulative dose of CYC, the exposure to immunosuppressive drugs other than corticosteroids and CYC, and prophylaxis with VCV. Because of the expected low number of zoster events, only univariate analyses were computed.

All analyses were computed using the SAS V9.3TM software (SAS Institute).

Ethical issues. This study is in accordance with the Declaration of Helsinki. According to French law, patients were informed of data collection and of the possibility to refuse it during their hospital stay. Patients were reminded of this during phone interviews. The study was registered to the French national committee on data privacy (Commission Nationale de l'Informatique et des Libertés – CNIL, No. 2096181).

RESULTS

Selection of the population. Out of 360 patients treated with intravenous CYC during the study period, 161 were treated for SLE or systemic vasculitis. Fifty-one patients were further excluded (26 because of followup out of Toulouse University Hospital and 25 previously treated by CYC). No patient refused to participate. Eventually, 110 patients were included in the analyses: 29 with SLE and 81 with systemic vasculitis, including 68 with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV; 26 with GPA, 20 with microscopic polyangiitis, 11 with eosinophilic granulomatosis with polyangiitis, and 11 with unclassified AAV), 5 with polyarteritis nodosa, 7 with unclassified vasculitis and 1 cryoglobulinemic vasculitis. An interview of the patients and/or of their general practitioners, in addition to medical chart and laboratory testing review, was possible for 87 patients.

Patients' characteristics. Patients' characteristics at the time of first exposure to CYC are detailed in Table 1. Mean age was 55.7 years, and 54.5% were women. In comparison with systemic vasculitis patients, SLE patients were younger, were more frequently female, had less frequent baseline kidney failure, had more frequent lymphopenia, and had been more frequently exposed to corticosteroids and immunosuppressive drugs before the exposure to CYC.

Among the 12 patients who had a history of zoster, 8 were women and 4 had SLE. No patient had been vaccinated against VZV in the cohort at the time of exposure, nor thereafter during the followup.

The mean number of CYC pulses was 5.5 (range 1–9). The mean cumulative dose of CYC was 5605 ± 3214 mg (range 780–27,320; 8 missing values) and was comparable between SLE and vasculitis patients (5227 and 5748 mg, respectively). All patients were exposed to corticosteroids concomitantly to CYC. The mean exposure to corticosteroids was 2.6 years, and was higher in patients with SLE (4.1 vs 2.0 yrs in patients with vasculitis). Because of the retrospective design, we could not calculate the cumulative dose exposure to corticosteroids. During the year after the first exposure to CYC, 87.3% of the patients were exposed to another immunosuppressive drug (10.9% to ≥ 2 immunosup-

Table 1. Patients' characteristics at CYC initiation. Values are n (%) unless otherwise specified.

Characteristics	Whole Cohort, n = 110	Systemic Vasculitis, n = 81	SLE, n = 29
Female	60 (54.5)	37 (45.7)	23 (79.3)
Age, yrs, mean ± SD	55.7 ± 18.8	62.2 ± 15.4	37.3 ± 15.0
Medical history			
Diabetes	8 (7.3)	8 (9.9)	0
Cancer	6 (5.5)	6 (7.4)	0
Varicella [a]	71 (100)	49 (100)	22 (100)
Zoster [b]	12 (14.6)	8 (14.0)	4 (16.0)
Kidney failure [c]	52 (49.5)	41 (53.2)	11 (39.3)
Lymphopenia [c]			
< 1000/μl	36 (34.3)	22 (28.6)	14 (50.0)
< 500/μl	9 (8.6)	4 (5.2)	5 (17.9)
Previous treatments			
Corticosteroids	40 (36.4)	20 (24.7)	20 (69.0)
Other immunosuppressive drugs	26 (23.6)	9 (11.1)	17 (58.6)
AZA	10 (9.1)	5 (6.2)	5 (17.2)
MMF	13 (11.8)	1 (1.2)	12 (41.4)
MTX	8 (7.3)	4 (4.9)	4 (13.8)
RTX	1 (0.9)	0	1 (3.4)
CSA	1 (0.9)	0	1 (3.4)
BEL	2 (1.8)	0	2 (6.9)
Treatments received in the year after CYC			
Plasmapheresis	20 (18.2)	20 (24.7)	0
Corticosteroids	110 (100)	81 (100)	29 (100)
Other immunosuppressive drugs	96 (87.3)	69 (85.2)	27 (93.1)
AZA	55 (50.0)	41 (50.6)	14 (48.3)
MMF	20 (18.2)	6 (7.4)	14 (48.3)
MTX	4 (3.6)	3 (3.7)	1 (3.4)
RTX	26 (23.7)	25 (30.9)	1 (3.4)
BEL	1 (0.9)	0	1 (3.4)

[a] Missing values in 39 patients. [b] Missing values in 28 patients. [c] Missing values in 5 patients. CYC: cyclophosphamide; SLE: systemic lupus erythematosus; AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; RTX: rituximab; CSA: cyclosporine; BEL: belimumab.

pressive drugs). Patients with SLE were more frequently exposed to mycophenolate mofetil (MMF) and less frequently exposed to rituximab (RTX) than the vasculitis patients (Table 1).

The mean followup from the first CYC pulse was 3.4 years (SD 1.7), corresponding to 355.9 PY. The mean followups were similar between SLE and vasculitis patients (3.3 ± 1.6 and 3.5 ± 1.7 yrs, respectively). Twelve patients (including 11 patients with systemic vasculitis) died during the followup: 4 sepsis (including 1 associated with alveolar hemorrhage and 1 associated with digestive ischemia complicating vasculitis), 2 intracranial bleeds, 1 B cell lymphoma, 1 prostate cancer, 1 respiratory distress due to vasculitis lung involvement, 1 refractory epilepsy complicating a cerebral vasculitis, and 2 unknown causes.

Exposure to VCV. Nineteen (17.2%) patients were exposed to VCV during the followup, given orally 500 mg once or twice a day. Two patients had a history of zoster, 5 had SLE and 16 started VCV concomitantly to CYC treatment. The mean duration of exposure to corticosteroids in these 19 patients was 3.6 years, and the mean cumulative dose of CYC was 5914 mg. Of note, 20.5% of the patients exposed to a high cumulative dose of CYC (> 3000 mg, which was the median cumulative dose of CYC in the cohort) were exposed to a prophylaxis with VCV, in contrast with 10.3% of the patients exposed to a lower cumulative dose of CYC. During the year after CYC, 15 of these patients were exposed to azathioprine, 3 to RTX, and 1 to MMF. Because of the retrospective design of the study, we could date precisely VCV withdrawal in 7 patients only; the mean duration of exposure was 396 days. No adverse drug reaction related to VCV was observed.

Incidence and description of zoster cases. Ten patients (9.1%) developed a zoster during the followup. The characteristics of these 10 cases of zoster are described in Table 2. Seven were treated for systemic vasculitis. Nine occurred in women and the mean age was 63 years. Only 1 patient had a previous history of zoster. Six cases occurred during the year after the first exposure to CYC (Table 2 and Figure 1). Seven patients were exposed to a prednisone-equivalent daily dose ≤ 15 mg at the time of zoster occurrence. Three patients were hospitalized for zoster management (Patients 3, 5, and 8 in Table

Table 2. Characteristics of the 10 zoster cases that occurred during the followup.

Patient	Sex; age, yrs	Potential Risk Factors	Disease	Time from First CYC Exposure, mos	Cumulative CYC Dose at Time of Zoster, mg	Other Exposures after CYC	Exposure at the Time of Zoster	Location	Treatment	Evolution
1	F; 75	Diabetes, RF[a], lymph.[b]	MPA	67.7	NA	CS, AZA	–	Eye	VCV, 1 g × 2/d, PO, 7 days	Favorable
2	F; 87	–	GPA	66.3	4440	CS, AZA	–	Thorax	VCV, PO, 7 days	Postherpetic neuralgia
3	F; 27	RF[a], lymph.[b]	SLE	1.7	2760	CS	CYC, CS	Lumbar, extensive	ACV, 1.5 g/d IV, 5 days; then VCV 1 g × 3/d, PO, 10 days	Favorable
4	F; 67	Zoster, RF[a], lymph.[b]	MPA	26.9	3840	CS, MMF	MMF	Thorax	VCV, 1 g/d, PO, 10 days	Favorable
5	F; 76	RF, lymph.[b]	ANCA-associated vasculitis	42.9	1320	CS, MMF, tacrolimus	MMF, tacrolimus, CS	Lower limb	ACV, 200 mg × 5/d, PO, 7 days	Favorable
6	F; 62	RF[a]	GPA	4.2	7560	CS	CS	Thorax	VCV, 500 mg × 3/d, PO, 7 days	Ophthalmic zoster
7	M; 67	–	Unspecified vasculitis	0.8	1840	CS	CYC, CS	Thorax	VCV, 1 g × 2/d, PO, 7 days	Postherpetic neuralgia
8	F; 75	RF[a], lymph.[b]	SLE	4.4	3000	CS, MMF	CS, MMF	Thorax	ACV, 500 mg × 2/d, IV, 7 days	Postherpetic neuralgia
9	F; 71	–	MPA	1.5	3120	CS	CYC, CS	Thorax	ACV, PO, 10 days	Postherpetic neuralgia
10	F; 26	Lymph.[b]	SLE	9.3	1000	CS, MMF	MMF, CS	Thorax	VCV, 1 g × 3/d, PO, 7 days	Favorable

[a] Renal failure: glomerular filtration rate < 60 m/min (CKD-EPI creatinine equation) at first CYC infusion. [b] Lymphopenia < 1000/μl at first CYC infusion. ACV: acyclovir; AZA: azathioprine; CS: corticosteroids; CYC: cyclophosphamide; GPA: granulomatosis with polyangiitis; IV: intravenous; MMF: mycophenolate mofetil; MPA: microscopic polyangiitis; NA: not available; PO: *per os*; VCV: valacyclovir; RF: renal failure; SLE: systemic lupus erythematosus; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; ANCA: antineutrophil cytoplasmic antibodies; lymph.: lymphopenia.

2). One patient (Patient 3 in Table 2) had a lumbar zoster extensive to the thigh, with favorable outcome after antiviral treatment. No bacterial infection complicating cutaneous lesions and no visceral dissemination was observed. One patient had a recurrence with herpes zoster ophthalmicus developing 15 months after the first episode, and 4 patients had postherpetic neuralgia.

The overall incidence of zoster after exposure to CYC was 27.9/1000 PY (95% CI 15.2–50.6); it peaked during the year after CYC initiation with an incidence of 59.4/1000 patients (95% CI 27.5–123.6).

The incidence of zoster in patients with SLE was 34.5/1000 PY (95% CI 11.8–96.6); it peaked with 111/1000 PY (95% CI 38.5–280.6) during the year after CYC initiation. The incidence in patients treated for systemic vasculitis was 26.0/1000 PY (95% CI 12.6–52.7); it was 40.5/1000 PY (95% CI 13.9–112.5) during the year after CYC initiation.

Factors associated with zoster. The results of univariate analyses are shown in Table 3. There was an increased risk of zoster in case of lymphopenia < 500/μl at CYC initiation (HR 5.11, 95% CI 0.94–27.93) and in women (HR 4.36, 95% CI 0.51–37.31). The incidence was 2.7-fold higher in patients with SLE compared with systemic vasculitis patients (HR 2.68, 95% CI 0.54–13.26).

None of the 19 patients exposed to VCV during the followup developed zoster.

DISCUSSION

The incidence of zoster in this cohort was 6-fold higher (14-fold higher when considering the year after CYC initiation) than in the French general population in 2015 (estimated to be 4.19/1000 inhabitants)[30,31].

This cohort study demonstrated the high incidence of zoster after intravenous CYC for systemic vasculitis or SLE, particularly during the year after CYC initiation and for patients with SLE. The cases of zoster were not extensive, but 30% of the patients were hospitalized and 40% had postherpetic neuralgia. Comparative analysis strongly suggested that female sex and lymphocyte count < 500/μl at CYC initiation were risk factors, and that prophylaxis by VCV was protective.

The incidence of zoster in patients with SLE in our cohort (34.5/1000 PY) was close to the incidence observed in the previously quoted nationwide Taiwanese SLE cohort (37.7/1000 PY), in which 22% of patients were treated with CYC[12]. Other retrospective studies found a lower incidence of zoster in SLE, ranging from 6.4 to 22.0/1000 PY. However, only 1–15% of the

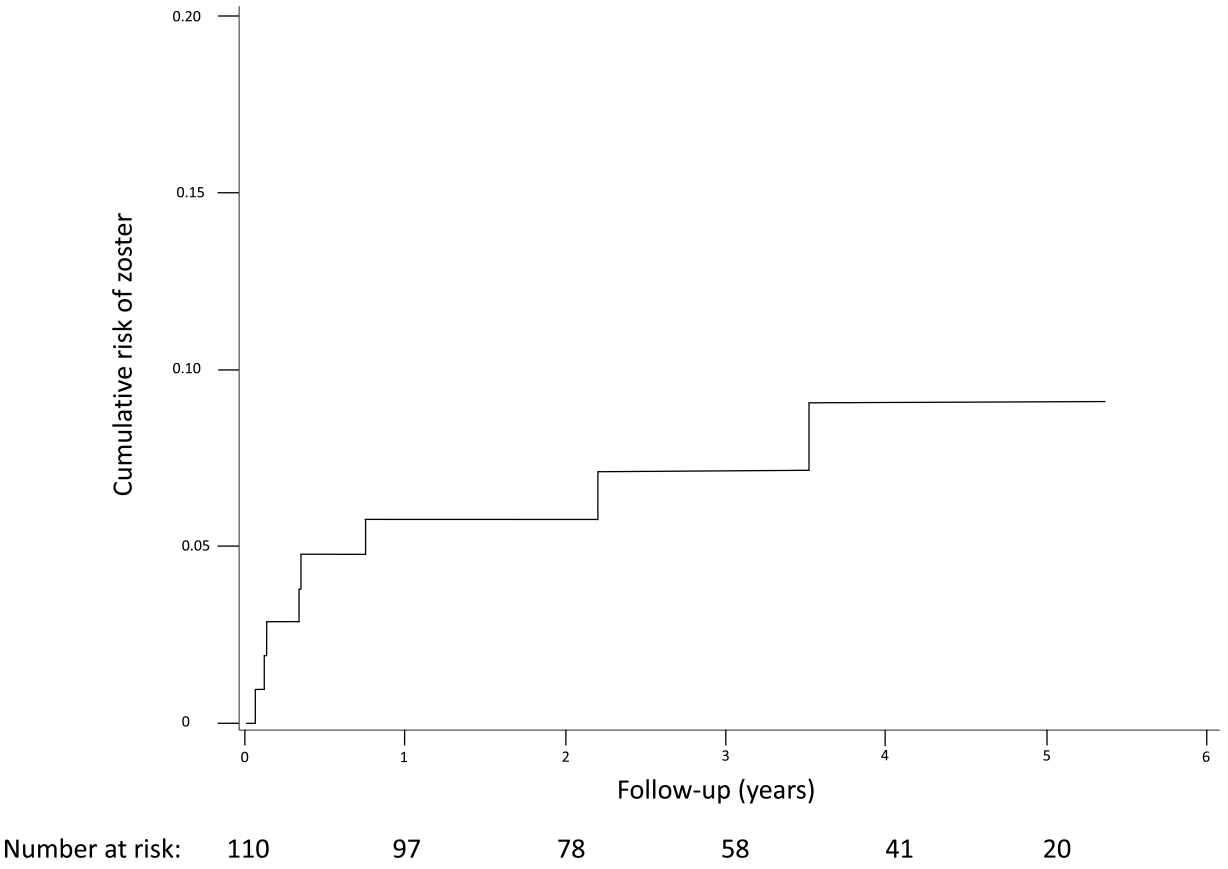

Figure 1. Cumulative probability of zoster after cyclophosphamide initiation.

included patients had been exposed to CYC in these cohorts[9,10,11].

Very few data exist regarding the incidence of zoster in systemic vasculitis. It was 26/1000 PY in our study, which is lower than the results from the WGET trial (45/1000 PY)[17]. Of note, 73% of the 180 patients with GPA included in the WGET trial had been exposed to CYC before the trial and 70% during the trial; 49% were also treated with etanercept, which may increase the risk of VZV reactivation[32]. The trend of an increased incidence of zoster in patients with SLE as compared with systemic vasculitis patients in our study could be partly explained by a higher frequency of lymphopenia in SLE and/or by a higher rate of exposure to immunosuppressive drugs prior to CYC initiation.

Six of the 10 cases of zoster occurred during the year after the first exposure to CYC, and 2 occurred more than 5 years after. Cohort studies led to contradictory results regarding the time of zoster occurrence in patients with SLE: some suggested that the risk of developing VZV reactivation is higher during the first year after SLE diagnosis[33,34], while others suggested a higher incidence after years of inactive disease[8,9,10,35,36]. Similarly, studies in patients with systemic vasculitis suggested a higher risk of zoster when the disease is in complete remission[16,17,37]. However, CYC seems a strong risk factor for short-term severe infection and of zoster in these patients, as demonstrated in our study[22,38,39,40,41]. Of note, the short mean followup in our study (3.4 yrs) prevented us from estimating the longterm risk of zoster.

The rarity of disseminated zoster is in accordance with the literature, with a frequency of 10.9% of the cases of zoster observed in the SLE series by Kahl[8]. No local complication was observed in our cohort, in contrast with the study of Borba, *et al*, in which 11.7% of SLE patients with zoster had bacterial complications independent of disease activity, lymphopenia, and exposure to immunosuppressive drugs[10]. There were 30% of our patients who were hospitalized for zoster management. This is higher than the rate estimated for all immunocompromised patients in France (11.0%)[28]. However, the rate of hospitalization for zoster in patients with SLE is increasing, probably because of the complexity of SLE treatments and better access to specialist physicians[42]. Interestingly, the rate of postherpetic neuralgia was higher in our study (40%) than in previous SLE and GPA cohorts (ranging from 14% to 28%)[9,10,16,17]. Consequently, this finding suggests that exposure to CYC could be a risk factor for postherpetic neuralgia.

Table 3. Univariate analysis of factors associated with occurrence of zoster in the year after exposure to pulse intravenous CYC for systemic vasculitis or SLE (n = 110). Values are n (%) unless otherwise specified.

Variables	Without Zoster Occurrence, n = 104	With Zoster Occurrence, n = 6	HR (95% CI)	p
SLE vs vasculitis	26 (25.0)	3 (50.0)	2.68 (0.54–13.26)	0.23
Age ≥ 50 yrs	65 (62.5)	4 (66.7)	1.26 (0.23–6.90)	0.79
Females	55 (52.9)	5 (83.3)	4.36 (0.51–37.31)	0.18
Antecedents				
Diabetes	8 (7.7)	0	–	–
Cancer	6 (5.8)	0	–	–
Renal failure at CYC initiation [a]	49 (49.5) [b]	3 (50.0)	1.01 (0.20–5.01)	0.99
Lymphopenia at CYC initiation				
< 1000/μl	33 (33.3) [b]	3 (50.0)	1.89 (0.38–9.35)	0.44
< 500/ μl	7 (7.1) [b]	2 (33.3)	5.11 (0.94–27.93)	< 0.06
Exposure to IS before CYC	24 (23.1)	2 (33.3)	1.58 (0.29–8.65)	0.59
Concomitant exposure to CS	104 (100)	6 (100)	–	–
CYC cumulative dose > 3 g [c]	69 (71.9) [d]	4 (66.7)	0.73 (0.13–4.01)	0.72
Prophylaxis by valacyclovir	19 (18.2)	0	–	–

[a] Renal failure: glomerular filtration rate < 60 ml/min at first CYC infusion. [b] Missing values in 5 patients. [c] Median value of CYC cumulative dose in the cohort. [d] Missing values in 8 patients. CS: corticosteroids; CYC: cyclophosphamide; IS: immunosuppressive drugs (excluding corticosteroids); SLE: systemic lupus erythematosus.

Our study suggests that female sex and lymphopenia < 500/μl at CYC initiation are risk factors for zoster. The incidence of zoster is higher among women in the general population[43,44,45]. However, data are conflicting in patients with SLE[11,12,36] and GPA[16,17,41]. The finding that lymphopenia would be a strong risk factor for zoster development in patients with SLE and vasculitis is in accordance with previous literature[36,40,46]. Our study suggests that strong attention should be paid to lymphocyte count < 500/μl at CYC initiation. Because of the retrospective design, we could not measure lymphocyte subtypes and therefore their effect on zoster occurrence. A study in patients with AAV has demonstrated that a low CD4+ lymphocyte count is more predictive of infection occurrence than the total lymphocyte count[41].

Older age is a risk factor for zoster in the general population[45], but was not a risk factor for zoster in previous SLE and AAV cohorts[5,13,38,39,41]. This result is confirmed by our study. Nearly half of our population had a baseline renal failure. This was not a risk factor for zoster in our cohort. Literature shows discrepant results in SLE[8,9,12,36], while renal involvement was associated to zoster occurrence in the WGET trial[17].

Similarly, a higher cumulative dose of CYC was not associated with a higher risk of zoster in our study. Findings are conflicting in previous SLE cohorts[13,22]. In a prospective trial in patients with GPA comparing pulse intravenous and oral CYC (leading to higher cumulative doses), there was a 3-fold higher occurrence of zoster in patients exposed to oral CYC[47]. Of note, in our study, 20.5% of patients exposed to a cumulative dose of CYC > 3000 mg had prophylaxis with VCV, as compared with 10.3% of the patients exposed to a lower cumulative dose. This may have contributed to the finding of no influence of the cumulative dose of CYC on zoster occurrence.

Most importantly, no patient with prophylaxis developed zoster (including 2 with a previous history of zoster). Even if time-varying exposure could not be performed, this finding strongly suggests the efficacy of such prophylaxis in preventing zoster in systemic vasculitis and SLE patients treated with pulse intravenous CYC.

Our study has limitations, mainly due to the retrospective design. First, an underrecording of zoster cannot be ruled out but seems unlikely. Indeed, we used several sources to identify the outcome, and recall bias is unlikely for zoster. Second, some covariable values were missing, and we could not calculate the cumulative dose of corticosteroids. Similarly, we could not record the exact dates of withdrawal for all patients exposed to VCV, preventing time-varying analyses. Third, some variables that may have influenced the outcome occurrence, such as CD4+ lymphocyte count or serum γ-globulin level, were not available (both at baseline and at the time of zoster occurrence). Fourth, because two-thirds of the zoster cases occurred early after CYC initiation, we could not assess the effect of the exposure to other immunosuppressive drugs after CYC in this cohort (immortal time bias). Fifth, because of lack of statistical power, we could not conduct multivariate analyses. Similarly, because of the absence of zoster occurrence in patients exposed to prophylaxis with VCV, we could not compute any HR for this association, but this finding strongly suggests that such prophylaxis has a strong protective effect in this setting. Lastly, none of our patients had been vaccinated against VZV. Some studies showed that inactivated vaccine may be an efficient alternative prophylaxis strategy in patients having autoimmune diseases[48,49]. However, patients with SLE and

systemic vasculitis are generally exposed to intravenous CYC urgently owing to severe flare, often at the disease onset in case of renal involvement. In the cases in which vaccination cannot be done before immunosuppressive drug exposure, prophylaxis by VCV is an effective option.

The incidence of zoster is high in patients with systemic vasculitis and SLE exposed to pulse intravenous CYC. Exposure to CYC may favor postherpetic neuralgia. In patients not vaccinated against VZV, prophylaxis with VCV should be considered, particularly in women, in case of lymphopenia < 500/μl at CYC initiation and during the year after.

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