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Vasculitis

Long-term risk of malignancies in ANCA-associated vasculitis

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ABSTRACT

Objectives: Patients with anti-neutrophil cytoplasmic antibodies-associated vasculitis (AAV) have an increased malignancy risk, largely attributed to immunosuppressive therapy. Given the latency period for malignancy development, data on long-term incidence in large AAV cohorts remain limited. This study aimed to assess the cumulative malignancy incidence in patients with AAV from European Vasculitis Society (EUVAS) clinical trials (1995-2012).

Methods: We analysed 848 patients with AAV from 17 European countries. Data were collected via questionnaires sent to the principal investigators of 7 EUVAS trials. Standardised incidence ratios (SIRs) were calculated using national malignancy databases.

Results: At a median follow-up of 8 years (IQR: 2.2-8.8 years), 135 patients experienced 153 malignancies. The overall SIR was 1.40 (95% CI: 1.18-1.64), primarily driven by nonmelanoma skin cancer (NMSC; SIR: 3.52; 95% CI: 2.6-4.7). Excluding NMSC, the SIR was 1.17 (0.96-1.4). The most common malignancies were NMSC (62 cases), prostate (11.1%), and lung (9.8%). The incidence of first malignancy was 2.01 per 100 person-years (95% CI: 1.70-2.39). Cumulative malignancy incidence was 10.8% at 5 years, 19% at 10 years, and 38.2% at 20 years. Patients diagnosed before the age of 40 years had a 30-fold increased risk of NMSC (SIR: 30; 95% CI: 6.03-87.65). Cyclophosphamide use for >6 months, azathioprine duration, and age >65 years were independent risk factors. The diagnosis of malignancy predicted worse survival (log-rank = 9.2; P = .002).

Conclusions: Patients with AAV have a significantly increased risk of NMSC, particularly younger individuals, while solid tumour risk is not significantly elevated. Prolonged cyclophosphamide and azathioprine use were associated with malignancy development.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Summarise the state of scientific knowledge on this subject before you did your study and why this study needed to be done.

- The survival of patients with anti-neutrophil cytoplasmic antibodies-associated vasculitis (AAV) has improved due to earlier diagnosis and the use of immunosuppressive therapy. However, concerns remain regarding the long-term malignancy risk associated with these treatments.
- Studies have shown that patients with AAV have up to twice the malignancy incidence compared with the general population, with a notably higher risk for nonmelanoma skin cancer (NMSC), leukaemia, and bladder malignancy.
- Given the shift in treatment paradigms for AAV and the relatively short follow-up periods in previous studies, extended follow-up is essential to better assess the long-term malignancy risk in patients with AAV.

WHAT THIS STUDY ADDS

Summarise what we now know as a result of this study that we did not know before.

- The cumulative incidence of malignancies was 10.8% at 5 years, 19% at 10 years, 24.3% at 15 years, and 38.2% at 20 years.
- NMSC was the most frequently observed malignancy (30.1%), followed by prostate cancer (11.1%) and lung cancer (9.8%).
- Patients who developed malignancies had a significantly reduced survival compared with those without malignancies (log-rank = 7.7; P = .005).
- Among patients with AAV, the standardised incidence ratio (SIR) for NMSC was significantly elevated at 3.52 (95% CI: 2.6-4.7).
- The overall SIR for all malignancies was 1.4 (95% CI: 1.18-1.64), primarily driven by NMSC. When excluding NMSC, the SIR was 1.17 (95% CI: 0.96-1.4).
- Key predictors of malignancy included cyclophosphamide use for more than 6 months, azathioprine use, total treatment duration, and older age.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

Summarise the implications of this study.

- This study suggests that patients with AAV do not have an overall increased risk of malignancy, except for NMSC, which remains significantly elevated.
- Findings support reconsidering the duration of cyclophosphamide treatment, potentially limiting its use to less than 6 months.
- Given the high incidence of NMSC, particularly in younger patients, it is crucial to emphasise preventive measures such as routine dermatologic screening and strict sun protection advice.

INTRODUCTION

The survival of patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) has significantly increased over the past decades due to earlier diagnosis and immunosuppressive treatment. However, the use of immunosuppressants, initially including corticosteroids, cyclophosphamide, and azathioprine, has led clinicians to become increasingly concerned about side effects, not only in the short term, such as infections and metabolic disorders, but also in the long term, that is, the risk for malignancy. Indeed, several studies have shown increased malignancy incidence in patients with AAV. Reported incidence of malignancy in immunosuppressive-treated patients with AAV has been globally twice that of the general population [1–3]. In a Swedish cohort of 195 patients with AAV diagnosed between 1997 and 2010, followed for a median of 8 years, the authors reported an overall standardised incidence ratio (SIR) for malignancy of 2.8 (SIR of 1.8 if squamous cell malignancy was excluded). Among non–skin malignancies, the higher risk was found for bladder and pancreatic malignancies [4]. Data from a Danish registry including 293 patients with granulomatosis with polyangiitis (GPA) diagnosed between 1973 and 1999, followed for a mean length of 9.7 years, showed a SIR for all site malignancies of 1.9 (95% CI: 1.5-2.4). In this cohort, myeloid leukaemia (SIR, 13.3), bladder malignancy (SIR, 5.5), and nonmelanoma skin cancer (NMSC), (SIR, 4.0) were the most common types of malignancy [5].

Randomised clinical trials (RCTs) in an attempt to improve outcomes for patients with AAV have been designed and performed within a European network, ‘European Vasculitis Society’ (EUVAS) starting in 1993. As the follow-up within RCTs was limited to 18 months, a 5-year follow-up of the first 4 RCTs within EUVAS was conducted [6]. This study included 535 patients from Non-renal Wegener’s Granulomatosis Treated Alternatively with Methotrexate (NORAM), Cyclophosphamide versus Azathioprine for Early remission phase of vasculitis trial (CYCAZAREM), Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis (MEPEX), and Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis (CYCLOPS) [7–10] and showed an increased rate of malignancies compared with the general population, with an overall SIR of 1.58 (95% CI: 1.17-2.08). However, the increased risk was mainly driven by an increased risk of NMSC (SIR: 2.78; 95% CI: 1.56-4.59) [11]. This study’s relatively short follow-up could have accounted for the lower malignancy detection rate compared with previous observational studies. Therefore, extending the follow-up of these study participants seemed appropriate to better apprehend malignancy risk as a function of time since disease diagnosis.

By extending the time of follow-up, death becomes a competing event for malignancy incidence and should, therefore, be accounted for in this prognostic study. Moreover, other factors may also confound the association between vasculitis and malignancy. Indeed, malignancy risks in vasculitis will vary according to treatment, disease subtype, and severity [4,5]. Immunosuppressive therapy impairs the immune system’s ability to detect and eliminate malignant cell clones and may also exert direct mutagenic effects. Various treatment regimens have been linked to differing cancer incidence rates, with high-dose cyclophosphamide being the most frequently associated, particularly with an increased risk of NMSC, leukaemia, and bladder malignancies [12].

When selecting immunosuppressive therapies for AAV, it is crucial to balance disease control with long-term safety considerations. During remission induction therapy, treatment typically consists of pulsed cyclophosphamide or rituximab in combination with high-dose corticosteroids. For those patients with pulmonary haemorrhage or severe renal impairment, plasma exchange might be considered. Patients with non-organ-threatening disease may be successfully treated with a less toxic induction regimen of either methotrexate or mycophenolate mofetil alongside corticosteroids. Maintenance therapy generally includes azathioprine, methotrexate, or rituximab, with gradual corticosteroid tapering to minimise long-term adverse effects.

Other potential causes of the increased malignancy risk are that a dysfunctional immune system linked with autoimmunity

could amplify the susceptibility to specific malignancies [13,14]. Furthermore, vasculitis could manifest as a paraneoplastic phenomenon. Lastly, a coincidental correlation attributable to detection bias, where patients with vasculitis seek medical attention and undergo closer monitoring, might contribute to certain accounts of malignancy associated with vasculitis [15].

This study aimed to analyse the cumulative incidence of malignancy in an extended follow-up of patients from EUVAS prospective RCTs. Additionally, we sought to evaluate SIRs of overall and subgroup-specific malignancies, considering factors such as sex, age, clinical diagnosis, ANCA type, kidney function, and duration of immunosuppressive therapy. Furthermore, we aimed to assess malignancy-related mortality and identify risk factors for malignancy in AAV.

METHODS

The present study comprised patients with a newly diagnosed AAV entered into EUVAS RCTs (NORAM, CYCAZAREM, MEPEX, CYCLOPS, International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE), Rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS), and Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis (MYCYC)) 1995-2012. Patients were recruited from 74 centres in 17 countries in Europe. EGPA (Eosinophilic Granulomatosis with Polyangitis) patients and patients younger than 18 years were excluded from this study. Diagnosis of GPA and microscopic polyangiitis (MPA) was made according to the criteria adapted from the American College of Rheumatology criteria (1990) and the Chapel Hill consensus definitions (1994) for GPA and MPA [16,17].

All studies were approved by the local ethics committees, and all patients gave written informed consent. Patients were well-characterised at trial entry, including the type and duration of induction and maintenance therapy. EUVAS trials followed standardised diagnostic and disease-stage criteria, with demographic, clinical, and laboratory data entered into a central database. Baseline assessments included ANCA type, C-reactive protein levels, full blood count, and plasma or serum creatinine. Disease activity was measured using the Birmingham Vasculitis Activity Score, and estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease-EPI equation [18].

Long-term follow-up data on patient outcomes were collected from questionnaires to the principal investigators of the original RCTs. Questionnaires were designed to collect data on cumulative duration and type of immunosuppressive therapy, end-stage kidney failure, malignancies, comorbidities, patient survival, and causes of death if appropriate [19]. Questions on malignancies were related to type, diagnosis date, and localization. Trial adverse event report forms were reviewed (within the original RCT) for possible additional malignancies. The study baseline was defined at the date of trial entry.

Continuous variables were presented as mean and SD and, in the case of nonnormal distribution, as the median and IQR. Categorical variables are expressed as counts and frequencies. For comparisons of baseline characteristics between patients with versus without a diagnosed malignancy during follow-up, Student's t test was used, or Kruskal–Wallis test, chi-squared test, or Fisher's exact test was also used when appropriate. For all statistical analyses a 2-tailed $P < 0.05$ was considered significant, and 95% CI was calculated.

The main outcome was assessed using time-to-event analyses. Estimation of survival rates was presented as Kaplan–Meier graphs. Survival rates were compared using the log-rank test. Risk factors were analysed using competing-risks regression based on Fine and Gray proportional subhazards model, with azathioprine, cyclophosphamide, and age included as covariates.

Malignancies were coded according to the 10th International Classification of Diseases. For patients with multiple malignancies only the 2 first registered malignancies were considered.

SIRs were calculated to compare malignancy incidence in the study cohort with the general population, adjusting for country, sex, age, and calendar year. SIRs were derived as the ratio of observed to expected malignancies, with expected cases determined using person-years at risk multiplied by general population malignancy rates from the GLOBOCAN 2020 database (1995-2016) compiled by the International Agency for Research on Cancer [20]. Poisson distribution was used to estimate 95% CIs for SIRs.

SIRs were further analysed based on age, sex, European region (Central east, Northern east, Southern east, and West), trial, diagnosis, ANCA type, recruitment period, baseline eGFR, and follow-up duration.

All estimations were performed using the statistical analysis software SPSS Statistics 26, except the relative survival analysis, which was done with STATA 16. The remaining graphs were designed with GraphPad Prism 9.

Patients were not directly involved in the design, recruitment, or conduct of this study. However, the research question was informed by clinical priorities and concerns raised by patients in routine practice. The results of this study will be shared with patient communities through appropriate channels, including patient advocacy groups and public summaries.

RESULTS

Baseline clinical variables

Eight hundred forty-eight patients with AAV (56% GPA, 44% MPA) were included. Men were overrepresented (56%); mean age at randomisation in the RCTs was 58.04 ± 14.20, and most participants were living in the north-east European region (47.6%).

In our study, 135 patients were diagnosed with 153 malignancies. A first malignancy was diagnosed after a median follow-up of 6.26 years (IQR: 2.91-9.88 years) in 135 (15.9%) patients. Overall, the incidence rate of the first event of malignancy in the 848 patients was 135 cases/6699.93 person-years, that is, 2.01 per 100 person-year (95% CI: 1.70-2.39).

The mean age at malignancy diagnosis was 69 ± 11 years. Patients diagnosed with malignancies were older at randomisation in the RCTs, with a mean age of 62 ± 12 years compared with 57 ± 14 years in those without malignancies during follow-up ($P < .001$). The majority of patients diagnosed with malignancy were men (61%), and GPA was the most prevalent type of AAV, affecting 59% of those with a malignancy diagnosis. No other statistically significant differences in baseline clinical variables were identified between those who developed malignancy or not (Table 1).

Incidence of malignancy

Figure 1 illustrates the cumulative incidence of malignancy over a median of 7.96 total years of follow-up. The cumulative

Table 1
Characteristics of patients at entry into the RCTs with respect to the development of a malignancy or not

		No malignancies n = 713 (84.1%)	Malignancies n = 135 (15.9%)	*P* value
Age (y)		57 ± 14	62 ± 12	<.001
Weight (kg)		72 ± 13	70 ± 13	.3
Male sex (n, %)		392 (55)	82 (60.7)	.2
ANCA (n, %)	MPO	274 (40.7)	52 (40)	.9
	PR3	400 (59.3)	78 (60)	
Diagnosis (n, %)	GPA	398 (55.8)	80 (59.3)	.5
	MPA-RLV	315 (44.2)	55 (40.7)	
BVAS score		18 ± 8	18 ± 8	.9
Randomisation period (n, %)	1995-1999	325 (45.6)	69 (51.1)	.2
	2000-2012	388 (54.4)	66 (48.9)	
Countries (n, %)	Central East	51 (7.2)	5 (3.7)	.07
	Northern east	339 (47.5)	65 (48.1)	
	Southern east	78 (10.9)	24 (17.8)	
	West	245 (34.4)	41 (30.4)	
RCTs (n, %)	CYCAZAREM	129 (18.09)	26 (19.26)	.88
	CYCLOPS	122 (17.11)	21 (15.56)	
	IMPROVE	143 (20.06)	24 (1778)	
	MEPEX	117 (16.41)	20 (14.81)	
	MYCYC	98 (13.74)	18 (13.33)	
	NORAM	75 (10.52)	19 (14.07)	
	RITUXVAS	29 (4.07)	7 (5.19)	
Creatinine (μmol/L)[a]		176 (97-389)	176 (95-352)	.5
eGFR(ml/min/1.73m^2)[a]		42.1 (16.2-89.3)	41.8 (16.3-85)	.4
Haemoglobin (g/dL)		10.1 ± 2	10.2 ± 2.2	.5
Platelets (10^9/L)		400 ± 172	385 ± 151	.4
Follow-up time (y)[a]		7.2 (2-13.1)	10.7 (6-16.4)	<.001

ANCA, anti-neutrophil cytoplasmic antibodies; BVAS, Birmingham Vasculitis Activity Score; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; MPA-RLV, microscopic polyangiitis including renal-limited vasculitis; MPO, myeloperoxidase; PR3, proteinase; RCT, randomised clinical trials.
Values for continuous variables are expressed as mean ± SD or median ([a]) (IQR), and values for categorical variables as percentages. The glomerular filtration rate was estimated using the chronic kidney disease-EPI equation.

incidence of malignancies was 10.8% at 5 years, 19% at 10 years, 24.3% at 15 years, and 38.2% at 20 years.

Most malignancies were diagnosed (70 patients, 51.9%) during the first 5 years of follow-up, another 37 patients were diagnosed with malignancy at 5 to 10 years of follow-up and 46 after 10 years of follow-up.

NMSC (30.1%), prostate malignancy (11.1%), and lung malignancy (9.8%) were the most frequently reported malignancies. Other types of malignancy included colorectal (7.8%), bladder (7.2%), breast (5.2%), skin melanoma (4.6%), leukaemia (3.9%), kidney (2.6%), ovary (2%), and non-Hodgkin lymphoma (2%).

A second malignancy was diagnosed in 22 patients (22/135), with NMSC (C44) being the most frequent. The second malignancies were identified after a median follow-up of 9.08 years (IQR: 3.13-15.91).

If we analysed in detail the number of cases of malignancy in each RCT, around 15% to 20% of patients have been diagnosed with a malignancy. We found that up to 20% of the patients included in the NORAM study had malignancy, while it was 19% in the RITUXVAS, 17% in the CYCAZAREM, and 15% of patients in CYCLOPS and MEPEX, respectively (Supplementary Fig S1). In the NORAM study, the cancer incidence rate was 1.98 cases per 100 person-years. For other RCTs, the rates were as follows: CYCAZAREM at 1.42 cases per 100 person-years, CYCLOPS at 1.56, IMPROVE at 1.58, MEPEX at 2.61, and RITUXVAS at 3.04 cases per 100 person-years.

Survival outcomes in patients with malignancies

Eighty patients (59.3%) diagnosed with malignancy died after a median duration of 1.77 years (IQR: 0.48-4.01) following their diagnosis. The leading cause of death among those patients was the malignancy itself (45%), followed by infections (13.8%) and cardiovascular disease (10%). Among those who developed malignancy and subsequently died, the distribution of malignancy types was as follows: 21/41 (51%) patients had NMSC (C44), 9/16(56%) had prostate malignancy (C61), 13/15 (87%) patients had lung malignancy (C33-C44), 5/6 (83%) had colorectal malignancy (C18-C21), and 6/11 (55%) a bladder malignancy (C67).

The number of deaths was significantly higher in patients with malignancies (59.3% vs 31.6%; $P < .001$). Kaplan–Meier survival curves further demonstrated reduced survival in patients with malignancies compared with those without (log-rank = 7.7; $P = .005$) (Fig 2). Median survival time for those patients with malignancy since randomisation to RCT was 12.98 years (95% CI: 10.65-15.31). Among patients with NMSC, the mortality rate also remained significantly higher than those without malignancy (48.78% vs. 46.28%; $P < .001$). However, Kaplan–Meier curves did not indicate a statistically significant increase in mortality risk in this subgroup (log-rank test = 0.104; $P = .075$).

Malignancy and types and duration of immunosuppression

Most patients received cyclophosphamide (795, 94%), of whom 126 (15.%) developed a malignancy. The latter were

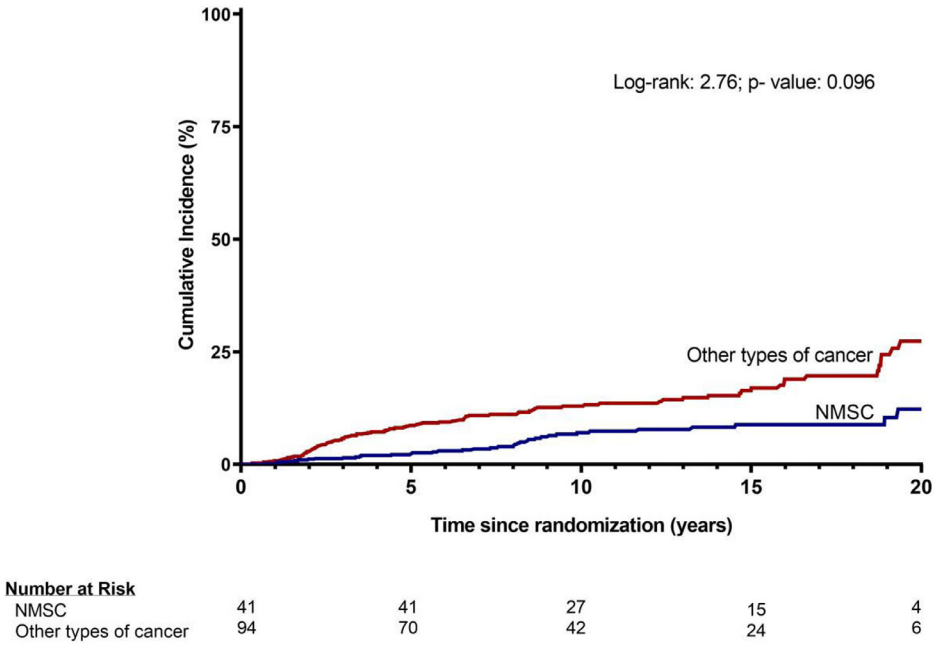

Figure 1. Cumulative incidence of malignancy at 5, 10, 15, and 20 years of follow-up.NMC Non Melanoma Skin Cancer

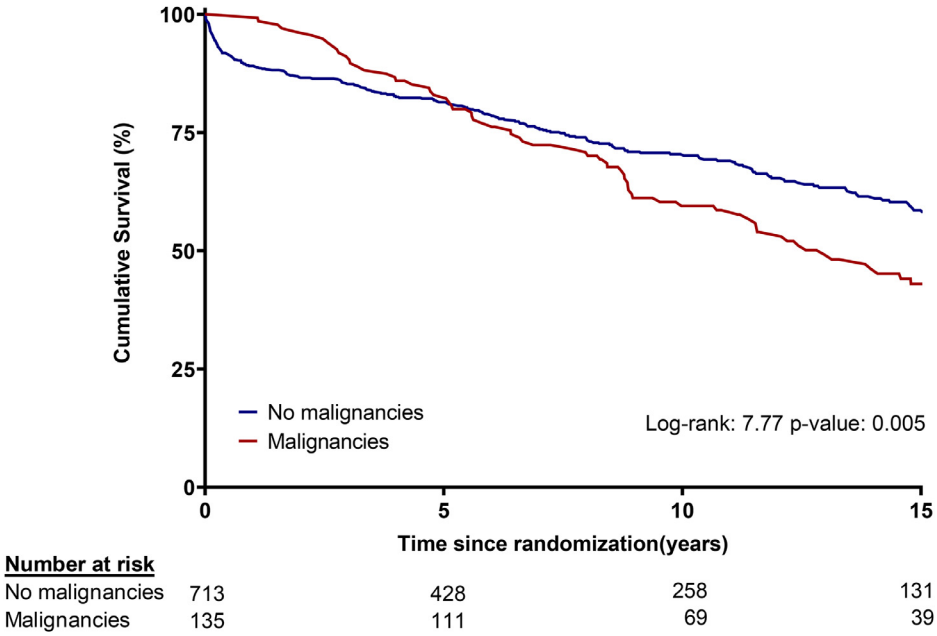

Figure 2. Kaplan–Meier curves comparing cumulative survival between patients with malignancy and those without malignancy.

treated with cyclophosphamide for a longer period than to those who did not develop a malignancy (8.8 months [IQR: 3-17] vs 6 months [IQR: 3-12], respectively) ($P = .04$) (Table 2).

In our cohort, 559 (65.9%) patients received azathioprine, of whom 103 (18.4%) developed a malignancy. Being treated with azathioprine and the duration of this treatment were associated with an increased risk of malignancies ($P = .006$ and $P < .001$, respectively).

SIR of malignancy in patients with AAV

The SIR for all malignancies was 1.4 (95% CI: 1.18-1.64). When NMSC was excluded, the SIR decreased to 1.17 (95% CI: 0.96-1.4). The SIR specifically for NMSC was 3.52 (95% CI: 2.6-4.7). SIRs for various malignancy types are detailed in Table 3.

Subgroup analysis

We compared the SIRs for malignancy across various subgroups, as summarised in Table 4. To evaluate the impact of renal function, patients were divided into 2 groups based on an eGFR threshold of 60 mL/min/1.73 m^2. For NMSC (C44), the SIR for those with an eGFR > 60 mL/min/1.73 m^2 was 4.4 (95% CI: 2.6-8.2), and that for those with an eGFR < 60 mL/min/1.73 m^2 was lower, 3.40 (95% CI: 2.26-4.91). Additionally, patients who developed malignancies had a significantly lower mean eGFR at 12 months (48.28 ± 22.5) than those who did not (56.58 ± 23.31; $P < .001$), further supporting an association between impaired kidney function and increased cancer risk in this population.

According to geographic areas in Europe, patients living in the Southern east region of Europe had an increased risk for all

Table 2
Immunosuppressive therapy

Immunosuppressive therapy	Entire cohort n = 848	No malignancies n = 713 (84.1%)	Malignancies n = 135 (15.9%)	*P*-value
Every treatment, n				
Methotrexate	95	77	18	.39
Cyclophosphamide	795	669	126	.83
Azathioprine	559	456	103	.006
Mycophenolate	237	197	40	.64
Rituximab	75	60	15	.31
Immunosuppressive duration (mo)				
Methotrexate[a]	24 (12-45)	24 (11.3-42)	24 (18-48)	.19
Cyclophosphamide[a]	6 (3-12)	6 (3-12)	8.8 (3-16.9)	.03
Azathioprine[a]	30 (12-49)	24 (12-48)	42 (17-65.1)	<.001
Mycophenolate[a]	36 (12-60)	38 (12-63)	21 (12-40.5)	.04
Rituximab[a]	24 (12-36)	24 (12-36)	24 (13-48)	.82

Values for continuous variables ([a]) are expressed as median (IQR).

Table 3
Types of malignancies of SIR

	Observed	Expected	SIR	95% CI
All sites	154	110.3	1.4	1.18-1.64
All sites without NMSC	107	91.1	1.17	0.96-1.4
Nonmelanoma skin malignancy (C44)	46	13.1	3.52	2.6-4.7
Prostate (C61)	17	18.5	0.9	0.5-1.5
Lung (C33-34)	15	13.4	1.1	0.6-1.9
Colorectum (C18-C21)	12	13.5	0.9	0.5-1.6
Bladder (C67)	11	5.5	1.99	0.99-3.6
Breast (C50)	8	10.3	0.8	0.3-1.5
Melanoma of skin (C43)	7	3.1	2.3	0.9-4.6
Leukaemia (C91-95)	6	2.4	2.5	0.9-5.4
Kidney (C64-65)	4	3.2	1.3	0.3-3.2
Ovary (C56)	3	1.4	2.1	0.4-6.1
Non-Hodgkin lymphoma (C82,86,C96)	3	3.2	0.9	0.2-2.7
Stomach (C16)	2	3.2	0.6	0.1-2.3
Liver (C22)	2	1.98	1.01	0.1-3.6
Lip, oral cavity (C00-06)	2	2.4	0.8	0.1-3
Larynx (C32)	2	1.03	1.95	0.2-7
Gallbladder (C23)	2	0.9	2.3	0.3-8.2
Corpus uteri (C54)	2	2.1	0.96	0.1-3.5
Thyroid (C73)	1	0.8	1.30	0-7.3
Pancreas (C25)	1	2.9	0.3	0-1.9
Multiple myeloma (C88- C90)	1	1.5	0.7	1-3.8
Malignant neoplasm of brain (C70-72)	1	1.5	0.7	0-3.7
Cervix uteri (C53)	1	0.6	1.7	0-9.3

NMSC, nonmelanoma skin cancer; SIR, standardised incidence ratios.

types of malignancy excluding NMSC (SIR: 1.66; 95% CI: 1.01-2.57) and for NMSC (SIR: 5.61; 95% CI: 2.05-12.21).

Patients recruited before the year 2000 had an increased risk for all types of malignancy (SIR: 1.75; 95% CI: 1.33-2.27), but not for the patients recruited afterwards (SIR: 0.85; 95% CI: 0.63-1.13).

Patients diagnosed with AAV at younger ages had a markedly higher risk of developing NMSC. Specifically, patients aged <40 years exhibited a 30-fold increased risk (SIR 30; 95% CI 6.03-87.65). In comparison, the risk was lower among those aged 40 to 65 years, with an SIR of 4.31 (95% CI: 2.55-6.81), and among those aged >65 years, with an SIR of 3.11 (95% CI: 2.01-4.59).

The risk of NMSC was higher among patients who had PR3-ANCA (SIR: 4.35; 95% CI: 2.9-6.21) than patients with MPO-ANCA (SIR: 1.55; 95% CI: 1.55-4.76). Although the increased risk of NMSC was observed in both males and females, it was notably higher in females (SIR: 4.76; 95% CI: 2.82-7.53).

Risk factors for malignancy

In the competing-risks survival regression analysis, azathioprine was significantly associated with an increased risk of malignancies (subhazard ratios [SHR]: 1.50; 95% CI: 1.01-2.23; $P = .043$), and the duration of azathioprine treatment in months (SHR: 1.01; 95% CI: 1.00-1.01; $P = .001$) was associated with increased risk for malignancy. Cyclophosphamide use for more than 6 months was also significantly linked to an elevated malignancy risk (SHR: 1.41; 95% CI: 1.00-1.99; $P = .047$). Additionally, age over 65 years was associated with an increased malignancy risk (SHR: 1.54; 95% CI: 1.095-2.16; $P = .013$). In the multivariate competing-risks survival regression, after adjusting for age, both cyclophosphamide and azathioprine remained independently significant predictors of malignancy risk (Table 5).

Independent risk factors for NMSC were azathioprine use (SHR: 4.43; 95% CI: 1.58-12.44; $P = .01$), the duration of

Table 4
SIR by subgroup analysis of malignancies and NMSC, respectively, according to age, sex, geographical region in Europe, RCTs, clinical diagnosis, type of ANCA, period of inclusion in the RCTs, kidney function at inclusion in RCTs, and duration of follow−ups, age <40 years is not it?

	All malignancies (including NMSC)				NMSC			
	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
Age								
<40 y	6	3.23	1.86	0.68-4.04	3	0.1	30	6.03-87.65
40-64 y	54	43.99	1.23	0.92-1.60	18	4.18	4.31	2.55-6.81
>64 y	47	43.88	1.07	0.79-1.42	25	8.04	3.11	2.01-4.59
	107	91.1			46	12.32		
Sex								
Female	40	32.67	1.22	0.87-1.67	18	3.78	4.76	2.82-7.53
Male	67	58.4	1.15	0.89-1.46	28	8.53	3.28	2.18-4.74
	107	91.07			46	12.31		
Region								
Central east	4	5.62	0.71	0.19-1.82	1	0.3	3.33	0.04-18.55
Northern east	49	42.45	1.15	0.85-1.53	26	5.74	4.53	2.96-6.64
Southern east	20	12.04	1.66	1.01-2.57	6	1.07	5.61	2.05-12.21
West	34	30.99	1.10	0.76-1.53	13	5.21	2.50	1.33-4.27
	107	91.1			46	12.32		
Trial								
CYCAZAREM	18	21.02	0.86	0.51-1.35	9	2.55	3.53	1.61-6.70
CYCLOPS	17	16.74	1.02	0.59-1.63	6	2.13	2.82	1.03-6.13
IMPROVE	18	20.66	0.87	0.52-1.38	8	3.28	2.44	1.05-4.81
MEPEX	18	11.51	1.56	0.93-2.47	7	1.79	3.91	1.57-8.06
MYCYC	12	8.78	1.37	0.71-2.39	8	1.12	7.14	3.08-14.08
NORAM	19	9.1	2.09	1.26-3.26	5	0.92	5.43	1.75-12.68
RITUXVAS	5	3.29	1.52	0.49-3.55	3	0.52	5.77	1.16-16.86
	107	91.1			46	12.31		
Diagnosis								
GPA	61	51.58	1.18	0.90-1.52	30	6.96	4.31	2.91-6.15
MPA/RLV	46	39.53	1.16	0.85-1.55	16	5.35	2.99	1.71-4.86
	107	91.11			46	12.31		
ANCA								
PR3	58	50.98	1.14	0.86-1.47	30	6.9	4.35	2.93-6.21
MPO	46	35.8	1.28	0.94-1.71	14	4.93	2.84	1.55-4.76
	104	86.78			44	11.83		
Period of inclusion								
1995-1999	57	32.5	1.75	1.33-2.27	20	5.42	3.69	2.25-5.70
2000-2012	50	58.48	0.85	0.63-1.13	26	6.89	3.77	2.46-5.53
	107	90.98			46	12.31		
eGFR								
>60 mL/min/1.73m^2	41	32.5	1.26	0.91-1.71	18	4.05	4.44	2.63-7.02
<60 mL/min/1.73m^2	66	58.48	1.13	0.87-1.44	28	8.24	3.40	2.26-4.91
	107	90.98			46	12.29		
Follow-up (y)								
<8 y	41	22.78	1.80	1.29-2.44	7	3.37	2.08	0.83-4.28
8-16 y	41	41.73	0.98	0.70-1.33	24	6.03	3.98	2.55-5.92
>16 y	25	26.59	0.94	0.61-1.39	15	2.91	5.15	2.88-8.50
	107							

ANCA, anti-neutrophil cytoplasmic antibodies; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; MPA-RLV, microscopic polyangiitis including renal-limited vasculitis; MPO, myeloperoxidase; NMSC, nonmelanoma skin cancer; PR3, proteinase; RCT, randomised clinical trial; SIR, standardised incidence ratios.

azathioprine treatment (SHR: 1.02; 95% CI: 1.01-1.02; P = .005), and age >65 years (SHR: 2.03; 95% CI: 1.10-3.72; P = .02) (Table 5).

DISCUSSION

Immunosuppressive treatment has improved outcomes for patients with AAV and has significantly changed the prognosis of the disease. A major issue in the daily practice now consists of managing comorbidities developing during follow-up, including infections, cardiovascular disease, and malignancies, the impaired quality of life, and the eventual side effects of the therapy. These disabling conditions increase the complexity of AAV management and its costs.

Previous studies have suggested that the frequency of malignancy is higher in patients with AAV than in the general population. Indeed, in a meta-analysis from 2015, the overall meta-analytical SIR for all types of malignancy was found to be 1.74 (95%CI: 1.37-2.21) [12].

In our cohort, NMSC was the most frequent type of malignancy (30.1%). Our results indicate a significantly elevated risk of 3.52 (95% CI: 2.6-4.7) for NMSC, which is in accordance with previous studies. Indeed, in the previous follow-up study of the EUVAS cohort, the SIR for NMSC was the only site-specific malignancy that was significantly increased (SIR: 2.78) [6]. Evidence consistently indicates that the risk of NMSC remains high. For instance, van Daalen et al [21] reported that NMSC was the most frequent malignancy in their cohort, with a 4.58-fold increased risk (95% CI: 2.96-6.76). Similarly, Faurschou et al

Table 5
Risk factors for malignancies

All types of malignancies						
	Univariate			Adjusted		
	SHR	95% CI	*P*-value	SHR	95% CI	*P*-value
Azathioprine	1.50	1.01-2.23	.04	1.54	1.03-2.295	.04
Azathioprine (mo)	1.007	1.003-1.01	.001	1.008	1.003-1.012	.001
Cyclophosphamide > 6 mo	1.41	1.004-1.99	.047	1.51	1.07-2.14	.02
Age > 65 y	1.54	1.096-2.16	.01			
NMSC						
	Univariate			Adjusted		
	SHR	95% CI	*P*-value	SHR	95% CI	*P*-value
Azathioprine	4.24	1.52-1.19	.006	4.43	1.58-12.44	.01
Azathioprine (mo)	1.01	1.01-1.02	<.001	1.02	1.01-1.02	.005
Age > 65 y	2.03	1.10-3.72	.02	2.14	1.17-3.93	.01

NMSC, nonmelanoma skin cancer; SHR, subhazard ratios.
In the adjusted model, azathioprine and cyclophosphamide were adjusted by age.

[5] reported an SIR of 4.7 (95% CI: 2.8-7.3) for NMSC and stratifying to the dose of cyclophosphamide; the SIR was 3.9 (95% CI: 1.4-8.4) for patients receiving less than 36 g, and 5.2 (95% CI: 2.1-11) for those receiving more than 36 g of cyclophosphamide (Supplementary Fig S4).

The SIR for all malignancies was 1.4 (95% CI: 1.18-1.64), mainly driven by NMSC, as excluding these, the SIR was 1.17 (95% CI: 0.96-1.4). Similar results were found in other cohorts, suggesting that with a reduction in cyclophosphamide dosing only, NMSC is increased. One exception is the South Sweden cohort [6]. In that Swedish population-based cohort, including 195 patients, Heijl et al. [4] reported an SIR of 1.8 (95% CI: 1.3-2.5) for all malignancies excluding squamous cell carcinoma (Supplementary Figs S2 and S3). However, even if the overall SIR was not elevated in our cohort, specific subgroups such as patients from Southern east Europe seemed to have an increased risk for all sites of malignancies, as did patients recruited before the year 2000.

Cyclophosphamide (in combination with glucocorticoids) has traditionally been the cornerstone of treatment for severe forms of AAV, and current guidelines continue to recommend its use. Most patients in our study received cyclophosphamide, which remains a mainstay in the management of severe AAV, as endorsed by the main therapeutic guidelines [22,23], and widely used in daily practice for severe forms of the disease. However, cyclophosphamide is associated with significant side effects, particularly at high doses or with prolonged use.

Our findings indicated a significant increase in the risk of NMSC among patients, potentially reflecting the lower cumulative doses of cyclophosphamide in contemporary treatment regimens. Notably, patients who developed malignancy during follow-up had a slightly longer median duration of cyclophosphamide treatment (8 vs 6 months). We observed that receiving cyclophosphamide for more than 6 months was associated with an increased malignancy risk (SHR: 1.51; 95% CI: 1.07-2.14; $P = .02$).

In earlier cohorts where cyclophosphamide was a primary and longer-lasting treatment, significantly increased SIRs were reported for malignancies such as bladder malignancies. In contrast, our cohort did not demonstrate a statistically significant increase in bladder malignancy risk. Nonetheless, the observed SIR was nearly twice the expected rate, and the CI bordered unity. Given the well-established association between cyclophosphamide exposure and bladder cancer, this signal warrants attention. The higher incidence of bladder carcinomas reported in previous cohorts likely reflects the substantially greater cumulative cyclophosphamide doses those patients received compared with our population. Prior studies have reported SIRs for bladder malignancy ranging from 3.6 to 4.8 [2,3,5], with risks as high as 31-fold above the general population among patients exposed to very high cumulative doses [24].

As previously mentioned, AAV has long been associated not only with malignancy but also with haematologic malignancies, particularly due to the use of high doses of cyclophosphamide, although this has not been definitively proven. In 2015, Shang et al [12] conducted a meta-analysis on this topic, reporting a pooled SIR for leukaemia of 4.89 (95% CI: 2.93-8.16) and a pooled SIR for lymphoma of 3.79 (95% CI: 1.87-7.69). In contrast, we did not find such an increased risk for haematological malignancies, consistent with some other previous reports [21,25,26]. Lower doses of cyclophosphamide and/or the combination with other agents such as rituximab might prevent the risk of developing such malignancies [27].

However, it is not solely cyclophosphamide that has been associated with an elevated risk of malignancy; azathioprine has also been implicated in an increased risk of skin malignancy [28]. In our study, patients who developed a malignancy received azathioprine more frequently (76.3% vs 64%, $P = .006$) and during a significantly longer time (42 months [IQR: 17-65.1] vs 24 months [IQR: 12-48]; $P < .001$). The use of azathioprine and the length of the treatment were independent risk factors for developing all types of malignancies, including NMSC [29,30].

Over the past 2 decades, the known substantial toxicity of cyclophosphamide instigated many efforts to develop cyclophosphamide-sparing regimens for AAV treatment. Newer biologic therapies have been shown to demonstrate equivalent efficacy as cyclophosphamide for remission, but the hope for reduction in adverse events has yet to be realised. van Daalen et al [21] demonstrated that rituximab treatment was not associated with an increased malignancy risk compared with the general population. Nevertheless, our results suggest that in the RITUXVAS study, the risk for NMSC was increased (SIR: 5.77; 95%CI: 1.16-16.86); however, they also received cyclophosphamide, but in a low cumulative dose [31].

As newer treatment alternatives, such as rituximab for both induction and maintenance, are increasingly preferred in clinical practice, exposure to cyclophosphamide and azathioprine is expected to decrease. Consequently, the malignancy risks associated with these agents observed in our cohort may not be fully representative of patients starting therapy today.

Another important consideration is that age was an independent significant risk factor for developing malignancy even when it was adjusted by the type of immunosuppressive drugs (azathioprine or cyclophosphamide). Therefore, we would like to emphasise the need to tailor individualised therapeutic regimens for frail populations due to potential side effects.

The main strengths of our study are well-characterised clinical presentation and treatment of patients and the long-term follow-up. We believe our study provides essential baseline information for the development and consideration of newer therapies that may have fewer side effects. Although it would have been ideal to calculate more precise cumulative doses of immunosuppressants for each patient, this was not feasible due to the multicentre nature of our study, the inclusion of patients from several years ago, and the extended follow-up period.

In conclusion, the findings of this study reinforce the results of our previous follow-up, showing an increased risk of NMSC in patients with AAV. Although NMSC does not metastasise, it remains a significant concern due to its potential for recurrence and, in some cases, severe outcomes. The development of de novo malignancies associated with immunosuppressive therapy is a major concern for patients with AAV. Although nearly all patients in our study received cyclophosphamide, only those treated for more than 6 months demonstrated an increased risk of solid tumours. This suggests that cyclophosphamide should be reserved for short-term use. Similarly, azathioprine should be prescribed with caution, as it has been identified as a risk factor for malignancy development.

Competing interests

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CRediT authorship contribution statement

Beatriz Sanchez Alamo: Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **Solange Gonzalez Chiappe:** Writing – original draft, Validation, Formal analysis. **Laura Moi:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ingeborg Bajema:** Writing – review & editing, Validation. **Mikkel Faurschou:** Writing – review & editing, Investigation, Conceptualization. **Oliver Flossmann:** Writing – review & editing, Methodology, Conceptualization. **Caroline Heijl:** Writing – review & editing, Methodology. **David Jayne:** Writing – review & editing, Supervision, Conceptualization. **Alfred Mahr:** Writing – review & editing, Methodology, Investigation. **Kerstin Westman:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

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Patient consent for publication

Informed consent was obtained from all patients involved in the study, from the original RCTS.

Ethics approval

Ethical approval obtained from the original RCTS resepctively. The long term follow-up was performed in accordance to the principles laid down in the 1964 Declaration of Helsinki and subsequent amendments, and ethical approval was obtained by local end national ethics committees in accordance with national legislation. 10year long-term followup Dnr LUM 2013/272 Data belonging to EUVAS (European Vasculitis Society).

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REFERENCES

[1] Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488–98. doi: 10.7326/0003-4819-116-6-488.
[2] Knight A, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. Int J Cancer 2002;100:82–5. doi: 10.1002/ijc.10444.
[3] Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. J Am Soc Nephrol JASN 1998;9:842–52. doi: 10.1681/ASN.V95842.
[4] Heijl C, Westman K, Höglund P, Mohammad AJ. Malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis: A population-based cohort study. J Rheumatol 2020;47:1229–37. doi: 10.3899/jrheum.181438.
[5] Faurschou M, Sorensen IJ, Mellemkjaer L, Loft AGR, Thomsen BS, Tvede N, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35:100–5.
[6] Heijl C, Harper L, Flossmann O, Stucker I, Scott DGI, Watts RA, et al. Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials. Ann Rheum Dis 2011;70:1415–21. doi: 10.1136/ard.2010.145250.
[7] De Groot K, Rasmussen N, Bacon PA, Tervaert JWC, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461–9. doi: 10.1002/art.21142.
[8] Jayne David, Rasmussen Niels, Andrassy Konrad, Bacon P, Tervaert JWC, Dadoniene J, et al. A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies. N Engl J Med 2003;349:36–44. doi: 10.1056/NEJMoa020286.
[9] Jayne DRW, Gaskin G, Rasmussen N, Abramowiczz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol JASN 2007;18:2180–8. doi: 10.1681/ASN.2007010090.
[10] de Groot K, Harper L, Jayne DRW, Suarez LFF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80. doi: 10.7326/0003-4819-150-10-200905190-00004.
[11] Heijl C, Mohammad AJ, Westman K, Höglund P. Long-term patient survival in a Swedish population-based cohort of patients with ANCA-associated vasculitis. RMD Open 2017;3:e000435. doi: 10.1136/rmdopen-2017-000435.
[12] Shang W, Ning Y, Xu X, Li M, Guo S, Han M, et al. Incidence of cancer in ANCA-associated vasculitis: a meta-analysis of observational studies. PloS One 2015;10:e0126016. doi: 10.1371/journal.pone.0126016.
[13] He M, Lo C-H, Wang K, Polychronidis G, Wang L, Zhong R, et al. Immune-mediated diseases associated with cancer risks. JAMA Oncol 2022;8:209–19. doi: 10.1001/jamaoncol.2021.5680.
[14] Elkoshi Z. Cancer and autoimmune diseases: a tale of two immunological opposites? Front Immunol 2022;13.
[15] Folci M, Ramponi G, Shiffer D, Zumbo A, Agosti M, Brunetta E. ANCA-Associated Vasculitides and Hematologic Malignancies: Lessons from the Past and Future Perspectives. J Immunol Res 2019;2019:1732175. doi: 10.1155/2019/1732175.
[16] Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101–7. doi: 10.1002/art.1780330807.
[17] Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187–92. doi: 10.1002/art.1780370206.
[18] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro III AF, Feld HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12. doi: 10.7326/0003-4819-150-9-200905050-00006.
[19] Sánchez Álamo B, Moi L, Bajema I, Faurschou M, Flossmann O, Hauser T, et al. Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis. Nephrol Dial Transplant 2023;38:1655–65. doi: 10.1093/ndt/gfac320.
[20] Cancer (IARC) TIA for R on. Global Cancer Observatory. https://gco.iarc.fr/ (accessed 9 October 2024)
[21] Daalen EE van, Rizzo R, Kronbichler A, Wolterbeek R, Bruijn JA, Jayne DR, et al. Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. Ann Rheum Dis 2017;76:1064–9. doi: 10.1136/annrheumdis-2016-209925.
[22] Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis 2024;83:30–47. doi: 10.1136/ard-2022-223764.
[23] Kidney Disease: Improving Global Outcomes (KDIGO) ANCA Vasculitis Work Group. KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis. Kidney Int 2024;105:S71–116. doi: 10.1016/j.kint.2023.10.008.
[24] Talar-Williams C, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 1996;124:477–84. doi: 10.7326/0003-4819-124-5-199603010-00003.
[25] Rahmattulla C, Berden AE, Wakker SC, REinders MEJ, Hagen EC, Wolterbeek R, et al. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis diagnosed between 1991 and 2013. Arthritis Rheumatol 2015;67:3270–8. doi: 10.1002/art.39317.
[26] Holle JU, Gross WL, Latza U, Nolle B, Ambrosch P, Heller M, et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum 2011;63:257–66. doi: 10.1002/art.27763.
[27] McAdoo SP, Medjeral-Thomas N, Gopaluni S, Tanna A, Mansfield N, Galliford J, et al. Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis. Nephrol Dial Transplant 2019;34:63–73. doi: 10.1093/ndt/gfx378.
[28] Jiyad Z, Olsen CM, Burke MT, Isbel NM, Green AC. Azathioprine and risk of skin cancer in organ transplant recipients: systematic review and meta-analysis. Am J Transplant 2016;16:3490–503. doi: 10.1111/ajt.13863.
[29] Maisonneuve P, Agodoa L, Gellert R, Buccianti G, Lowenfels AB, Wolfe RA, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999;354:93–9. doi: 10.1016/s0140-6736(99)06154-1.
[30] Cengiz K. Increased incidence of neoplasia in chronic renal failure (20-year experience). Int Urol Nephrol 2002;33:121–6. doi: 10.1023/a:1014489911153.
[31] Jones RB, Furuta S, Tervaert JWC, Hauser T, Luqmani R, Morgan MD, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis 2015;74:1178–82. doi: 10.1136/annrheumdis-2014-206404.