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Predictive factors of mortality in granulomatosis with polyangiitis: A single-center study

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ABSTRACT

Objectives: The aim of this study was to identify predictors of mortality in granulomatosis with polyangiitis (GPA) patients and to seek the ways of improving survival in GPA patients.

Patients and methods: Between January 2005 and June 2020, a total of 60 patients (26 males, 34 females; median age: 49 years; range, 19 to 75 years) who were diagnosed with GPA were retrospectively analyzed. Demographic, clinical, laboratory, and radiological findings of all patients were recorded. Survival rates were analyzed using the Kaplan-Meier plot.

Results: The median follow-up was 36 months, and 10 (16.7%) patients died during the study period. Univariate analysis showed that the prognostic values were attributed to high serum creatinine levels (>2.1 mg/dL; p=0.01), proteinuria (p=0.01), dialysis-requiring renal damage at the time of diagnosis (p=0.01) or at any time during follow-up (p=0.01), low lymphocyte levels (p=0.01), hypoalbuminemia (p=0.04), absence of upper respiratory tract involvement (p=0.01), presence of lung involvement with cavitary lesions (p=0.01), high Birmingham Vascular Activity Score (p=0.02), and history of serious infection (p=0.01). In the multivariate analysis, the presence of renal damage requiring dialysis at any time during follow-up (relative risk [95% confidence interval]: 21 [4.1-18.3]; p=0.01) was found to be an independent predictor of mortality. Immunosuppressive drugs exerted no effect on mortality, and the most common causes of death were infections (50%).

Conclusion: The presence of dialysis-requiring renal damage is the most important risk factor for mortality in GPA patients. These patients should be followed more closely and carefully to improve survival.

Keywords: Granulomatosis with polyangiitis, mortality, prognostic factors, survival analysis.

Granulomatosis with polyangiitis (GPA), which is formerly known as Wegener's granulomatosis, is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) of unknown etiology.[1,2] Mortality is 2.6 times higher in patients with GPA than in an age- and sex-matched general population.[3] In GPA patients, the 10-year survival rate is about 40% with renal involvement and 60 to 70% without renal involvement.[1] Survival has improved since the

introduction of cyclophosphamide (CYC)-based immunosuppressive regimens and, currently, the five-year survival is nearly 80%.[3,4]

The major risk for GPA patients is the adverse events associated with the treatment, rather than those associated with active vasculitis.[3] Myelosuppression, infection, cardiovascular disease (CVD), and malignancy, which are adverse events associated with GPA treatment, are the most common causes of mortality during

follow-up,[3-5] and most deaths occur within the first year after diagnosis.[6] Renal failure and advanced age are the other main factors which can best predict a poor prognosis in AAV.[6]

In the literature, there are not enough studies investigating the risk factors for mortality in GPA patients. In the present study, we aimed to identify predictors of mortality in GPA patients and to seek the ways of improving survival in GPA patients.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Baskent University Faculty of Medicine Department of Rheumatology between January 2005 and June 2020. A total of 60 patients (26 males, 34 females; median age: 49 years; range, 19 to 75 years) who were diagnosed with GPA and fulfilled the 1990 American College of Rheumatology (ACR) diagnostic criteria[7] were included in the study. Patients under 18 years of age and with a follow-up period of less than three months were excluded. A written informed consent was obtained from each patient. The study protocol was approved by the Başkent University Institutional Review Board (No. KA19/287). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data on demographic, clinical, laboratory and radiological findings were retrospectively retrieved from the medical records of the patients. Patients whose conditions were last evaluated six months before June 1st, 2020 were considered lost to follow-up. For each patient, the following data were obtained at the time of diagnosis: age, sex, ear, nose and throat involvement (defined as rhinorrhea, nasal crusting, epistaxis, oral or nasopharyngeal ulceration, persistent sinusitis, otitis media, chondritis, saddle nose deformity, mastoiditis, or hearing loss), pulmonary involvement (subglottic stenosis, hemoptysis, or abnormal thoracic imaging in the absence of concomitant infectious pneumopathy), glomerulonephritis (microscopic hematuria or red cell casts in the urinary sediment with either proteinuria (>0.5 g/day) or serum creatinine (>140 µmol/L), joint involvement (arthralgias or arthritis), cutaneous involvement (vascular purpura or nodules), ophthalmologic involvement

(conjunctivitis, episcleritis, or scleritis), neurologic involvement (mononeuritis multiplex, cranial neuropathy, seizures, or chronic meningitis), gastrointestinal involvement (pain, hematemesis, or bloody diarrhea), and cardiovascular system involvement.

In addition, the following laboratory parameters were documented: erythrocyte sedimentation rate, C-reactive protein, serum creatinine, hemoglobin, lymphocyte count, albuminemia, ANCA positivity as measured by enzyme-linked immunosorbent assay (ELISA), and presence of proteinuria and hematuria at the time of diagnosis. Pulmonary findings (presence of ground-glass opacity, cavity, nodule, and/or bronchiectasis) obtained by chest X-rays and thoracic computed tomography were also noted.

The time of occurrence of the first symptoms attributable to GPA was recorded, the number of involved organs or tissues was determined, and the Birmingham Vasculitis Activity Score (BVAS) was calculated at the time of diagnosis.

A classification tool called the Five-Factor Score (FFS) was used to determine the prognosis in AAV.[4] An FFS of >1 indicates severe disease, suggesting the need for more aggressive immunosuppressive therapy.[4]

Patient outcomes including treatment, response to treatment, relapses, occurrence of severe infectious complications or other adverse events, and death were evaluated. Complete remission was defined as the absence of any sign of disease activity, whereas partial remission was defined as the stabilization of disease activity. Infectious diseases requiring hospitalization or treatment with intravenous antibiotherapy were considered severe.

Clinical procedure

The CYC and corticosteroid were administered in the remission induction therapy. The CYC (500 mg) was administered intermittently (every 10 days during the first month, every two weeks during the next two months, and then every six to eight weeks depending on the disease activity) and intravenously. Prednisolone was administered intravenously at 500 mg/day for three to five days, depending on the disease activity. For the maintenance therapy, per oral

prednisolone was administered at 1 mg/kg/day. The prednisolone dose was tapered such that the 10 to 15 mg/day dose was achieved within three months. All patients received the same dose of prednisolone at the beginning of the treatment and, also, the patients were subjected to a uniform tapering regimen.

Rituximab (RTX) alone was not used in the remission induction therapy. After 2011 (upon receiving the approval from the Republic of Turkey, Ministry of Health), the patients with life-threatening and severe GPA who relapsed or who were refractory were administered with RTX twice with a two-week interval at a total dose of 2 g (repeated every six months). In our protocol, the methylprednisolone dose received by the patients before RTX, which was added to the treatment, was reduced to 32 mg/day. Following an average of two or three cycles of CYC, two cycles of RTX were applied. The patients with severe kidney damage and/or alveolar hemorrhages underwent five to seven cycles of plasmapheresis. For the maintenance therapy, azathioprine (AZA) (at a dose of 2 mg/kg/day during the first 12 months, 1.5 mg/kg/day at 12 to 18 months, and 1 mg/kg/day after 18 months), methotrexate (MTX; 15 to 20 mg/week), mycophenolate mofetil (2 g/day), or RTX were administered.

For the treatment of relapse, the dose of the currently administered corticosteroid in the maintenance therapy was increased, the frequency of intravenous CYC administration was increased, or RTX was administered. All patients who were administered with CYC and RTX received additional trimethoprim/sulfamethoxazole (800/160 mg) per oral three days a week for six months for *Pneumocystis jirovecii (P. jirovecii)* prophylaxis.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD), median (min-max), while categorical variables were expressed in number and percentage, where applicable. The chi-square test or Fisher's test was used to compare categorical variables. Distributions were analyzed for a comparison of continuous measurements between the groups, while the Student's t-test was used for variables with a parametric distribution and the Mann-Whitney U test for variables with a non-parametric distribution. Univariate and multiple logistic regression analyses (stepwise model) were used to identify correlations between the measurements within the groups as dependent variables (mortality as a dependent variable). Overall survival was analyzed using the Wald test, and the log-rank test was used to examine their relationship when different parameters were applied. The overall survival curve was plotted using the standard Kaplan-Meier methodology. A p value of <0.05 was considered statistically significant.

RESULTS

The median survival was 58 (range, 3 to 233) months. Diagnoses in 80% of the patients were confirmed with tissue biopsies.

Nearly all (92%) of the patients presented with symptoms such as fatigue, weight loss, and fever. Involvement was most frequently observed in the lungs (87%), kidneys (72%), and upper respiratory tract (72%). A total of 44% of the patients (n=22) had both renal and pulmonary involvement, while 30% (n=18) presented with severe renal insufficiency requiring hemodialysis. Baseline demographic, clinical, and laboratory data of the patients are shown in Table 1.

The rate of remission was 83% and the rate of refractory disease was 17%. Of the patients, 10% exhibited full remission and immunosuppressive therapy was discontinued in these patients. One or more relapses were observed in 51.6% of the patients in remission.

The median duration of treatment with corticosteroids was 36 (range, 0 to 120) months, 24 (range, 1 to 48) months with AZA, nine (range, 2 to 27) times with CYC, and two (range, 1 to 7) times with RTX. The doses for corticosteroids were tapered and discontinued in 31.7% of the patients.

The overall mortality rate in our study was 16.7%. In the order of decreasing frequency, the most common causes of death were infection (n=5), active vasculitis (n=3), cardiovascular event (n=1), and cerebrovascular (n=1) event.

Table 1. Baseline demographic, clinical, and laboratory data of patients

	n	%	Mean±SD	Median	Min-Max
Parameters					
Age (year)				49	19-75
Sex					
Female	34	56.7			
Follow-up duration (month)				36	2-180
Survival (month)				58	3-233
Laboratory data					
ESR (mm/h)				79	17-134
C-Reactive protein (mg/dL)				86.5	9-220
Creatinine (mg/dL)				1.3	0.5-13.8
Albumin level (gr/dL)			3.3±0.6		
Hemoglobin (gr/dL)			10.6±1.9		
Lymphocyte (/µL)				1,400	320-4,000
Proteinuria (gr/day)				1.5	0-9
PR3-ANCA positivity				39	65
MPO-ANCA positivity				18	30
BVAS score				21	6-33
FFS>1				41	68.3
Clinical data					
Constitutional symptoms	55	92			
Lung involvement	52	87			
1. Ground glass opacities	28	47			
2. Nodular lesions	34	57			
3. Alveolar hemorrhage	23	38			
4. Cavitary lesions	23	38			
5. Bronchiectasis	8	13			
Kidney involvement	43	72			
1. Proteinuria	41	68			
2. Hematuria	41	68			
3. Proteinuria and hematuria	37	62			
Upper respiratory tract involvement	42	70			
Ear involvement	18	30			
Ophthalmologic involvement	8	13			
Musculoskeletal system involvement	27	45			
Skin involvement	7	12			
Nervous system involvement	6	10			
Gastrointestinal tract involvement	5	8			
Cardiovascular system involvement	1	2			
Lung and kidney involvement	22	44			
Renal failure	18	30			

SD: Standard deviation; Min: Minimum; Max: Maximum; ESR: Erythrocyte sedimentation rate; PR3: Proteinase 3; ANCA: Antineutrophil cytoplasmic antibody; MPO: Myeloperoxidase; BVAS: Birmingham Vasculitis Activity Score; FFS: Five-Factor Score.

The univariate analysis showed that a prognostic value was attributed to high serum creatinine levels (p=0.01), proteinuria (p=0.01), dialysis-requiring renal damage at the time of diagnosis (p=0.01) and at any time during follow-up (p=0.01), cavitary lesion in the lung (p=0.01), low lymphocyte levels (p=0.01), hypoalbuminemia (p=0.04), absence of sinus involvement (p=0.01), high BVAS (p=0.02), and serious infection (p=0.01). Plasmapheresis

Table 2. Comparison of mortality and survival in GPA patients

	Mortality group (n=10)					Survival group (n=50)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	p
Age (year)				58	32-70				48	19-75	0.16
Sex											0.73
Female	5	50				29	58				
Clinic symptoms											
Constitutional symptom	10	100				45	90				0.58
Renal involvement	8	80				35	70				0.71
Hematuria	8	80				33	66				0.48
Proteinuria (gr/dL)				4	0-6				1	0-9	0.01
Dialysis, initially	8	80				10	20				0.01
Dialysis, after treatment	7	70				5	10				0.01
Upper respiratory tract											
Otitis	1	10				17	34				0.26
Sinusitis	3	30				39	78				0.01
Lung involvement	10	100				42	84				0.33
Ground glass opacities	7	70				21	42				0.17
Alveolar hemorrhage	6	60				17	34				0.16
Nodular lesions	6	60				28	56				1.00
Cavitary lesions	8	80				15	30				0.01
Bronchiectasis	1	10				7	14				1.00
Other involvements											
Skin	1	10				6	12				1.00
Musculoskeletal	4	40				23	46				1.00
Cardiovascular	1	10				0	0				0.17
Ophthalmologic	0	0				4	8				0.33
Gastrointestinal	1	10				4	8				1.00
Nervous system	2	20				4	8				0.26
Laboratory											
Hemoglobin (gr/dL)			10.3±1.9					10.6±2.0			0.58
Lymphocyte (/μL)				900	320-2,200				1400	600-4,000	0.01
Creatinine (mg/dL)				4.6	0.7-13.8				1.1	0.5-9.3	0.01
Albumin level (gr/dL)				3	2.1-4				3.5	2.3-4.6	0.04
ESR (mm/h)			87±15.3					73.6±28.3			0.16
CRP (mg/dL)				111	45-220				78.5	9-209	0.05
PR3-ANCA	7	70				32	64				1.00
MPO-ANCA	2	22.2				15	30				1.00
BVAS				27	17-30				21	6-33	0.02
FFS>1	9	90				32	64				0.15
Remission induction treatment											
CYC*	7	70				34	68				0.80
CYC and RTX*	2	20				16	32				0.70
Maintenance treatment											
RTX*	2	20				21	42				0.34
AZA*	3	30				34	68				0.05
Plasmapheresis*	6	60				10	20				0.01

GPA: Granulomatosis with polyangiitis; SD: Standard deviation; Min: Minimum; Max: Maximum; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PR3: Proteinase 3; ANCA: Antineutrophil cytoplasmic antibody; MPO: Myeloperoxidase; BVAS: Birmingham Vasculitis Activity Score; FFS: Five-Factor Score; CYC: Cyclophosphamide; RTX: Dituximab; AZA: Azathioprine.

treatment was applied more frequently in the mortality group than in the survivor group (p=0.01). Age was not found to be a risk factor for mortality (p=0.67). The comparison of mortality and survival in GPA patients is shown in Table 2. The results of the multivariate logistic regression analysis showed that the presence of dialysis-requiring renal damage at any time during follow-up was an independent predictor of mortality (Table 3).

The survival rates at one, three, five, and nine years were 94.7%, 86.6%, 83.8%, and 77.4%, respectively. The mean estimated survival time was 183.5±14.3 months (95% confidence interval [CI]: 155-211) (Figure 1).

Serious infections as side effects of treatment were observed in 30% of the patients. Of these infections, 44.4% were lower respiratory tract infections *(Staphylococcus aureus, Klebsiella,*

Table 3. Multivariable analysis of mortality predictors

Parameters	Multivariate analysis	
	p	OR (95% CI)
Lung cavitary lesion	0.98	1.17 (0.01-23.7)
Creatinine	0.61	0.71 (0.2-2.53)
Proteinuria	0.15	1.40 (0.9-2.1)
Lymphocyte	0.44	0.99 (0.99-1.1)
Albumin level	0.93	1.09 (0.16-7.7)
BVAS	0.37	1.10 (0.9-1.3)
Dialysis, initially	0.83	1.40 (0.1-30.5)
Dialysis, after treatment	0.01	21.0 (4.1-18.3)
Plasmapheresis	0.99	0.90 (0.1-11.7)

OR: Odds ratio; CI: Confidence interval; BVAS: Birmingham Vasculitis Activity Score; p<0.05 significant.

Figure 1. Kaplan-Meier curve of patients overall survival.

Candida, Gram-negative bacilli, P. jirovecii) and 38.9% were urinary tract infections. Hepatitis B reactivation was observed in two patients, and persistent catheter infection was observed in one patient.

DISCUSSION

In the current study, we investigated the predictors of mortality in GPA patients. Our study results showed that the presence of dialysis-requiring renal damage is the most important risk factor for mortality in GPA patients. Currently, the mortality rate in GPA remains high, despite available effective immunosuppressive treatments.[3,8,9] We believe that this study contributed to improve the survival rates of GPA patients by identifying risk factors of mortality in this patient population.

The mortality rate in Polish Vasculitis (POLVAS) registry was reported to be as low as 10%.[10] In our study, the mortality rate was also lower, compared to the reported rates (16.7% *vs.* 22 to 27%, respectively).[2,11,12] The lower mortality rate in this study can be attributed to the younger age of the patients and regular follow-up in a single center.

In terms of the survival rate, de Joode et al.[13] found that the survival rate at 12 and 60 months was 98% and 93%, respecti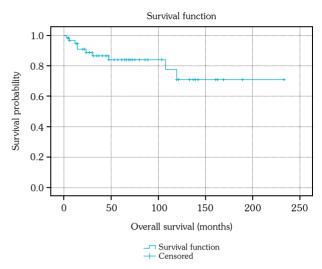vely. Our five-year survival rate was also high, similar to that reported in other studies (83.8% *vs.* 74 to 93%, respectively).[2,14] In addition, the median survival time in this study was 58 months, similar to a previous study (58 months).[11]

Numerous studies have shown that advanced age is an independent risk factor for mortality in GPA patients.[2,6,9,11,12,14] However, compared to the patients included in other studies, our patients were younger, and only 10 patients were over 65 years old, indicating that age was not a risk factor.

Furthermore, consistent with the findings of previous studies,[2,6,8,9,11,12,15] our results showed that high serum creatinine level was a risk factor for mortality. The cut-off value for creatinine was found to be >2.1 mg/dL. Also, the presence of renal involvement and renal failure requiring dialysis was reported as a risk factor for mortality.[6,11] Renal involvement is observed in 60 to 80% of the patients during the course of the disease.[3,11] Within five years, 20% of the patients with renal involvement develop end-stage renal failure.[3] The above findings are consistent with the current results indicating that the rate of renal involvement in our patient group was 72%, and 30% of the patients had renal involvement developed end-stage renal failure at the time of diagnosis.

In a study, the absence of upper respiratory tract involvement was reported as a risk factor for mortality,[2,9,11] consistent with our findings. Meanwhile, although low hemoglobin was

reported to be a risk factor in some studies, it was not found to be a risk factor in our study.[2,6,12]

In previous studies, low albumin and lymphocyte levels were also reported as risk factors for mortality, similar to our results.[6,11] Additionally, high disease activity at the time of diagnosis was shown to be a risk factor for mortality.[9,11] Also, high BVAS was found to be an independent risk factor for mortality, consistent with our findings.[12] On the other hand, although an increased FFS value was reported to be a risk factor for mortality in previous studies,[6,8,15] the increase in FFS was not significant in our study (p=0.15).

Cardiac involvement has been shown to be a risk factor for mortality.[9,11] However, we were unable to confirm whether cardiac involvement was, indeed, a risk factor for mortality given that only one of our patients died from cardiac involvement. In the European Vasculitis Study (EUVAS) study, the risk of CVD within the first five years after the diagnosis was found to be 14%.[3] In our series, the CVD rate was 10%.

Although Lega et al.[16] reported that skin involvement was a risk factor for mortality, this phenomenon was not observed in our study. Skin involvement was not frequently observed in our patient group. On the other hand, pulmonary-renal involvement was significantly more common in our patients, compared to the reported rates (63% vs. 14%, respectively),[11] suggesting that our patient cohort had more severe organ involvement. As for pulmonary involvement, the current rate was close to the rates reported in the literature (87% vs. 50 to 90%, respectively).[17] Several publications have reported on the effect of pulmonary involvement on mortality in GPA. Bligny et al.[2] found that the presence of pulmonary nodule or pulmonary consolidation was not a risk factor for mortality. Similarly, Reinhold-Keller et al.[14] found that the presence of infiltrative pulmonary involvement was not a risk factor for mortality, although the presence of pulmonary hemorrhage was found to be one.

In pulmonary involvement, the presence of granulomatous lesions does not influence the mortality rate, while the presence of alveolar hemorrhage is considered a poor prognostic factor.[14] Russell et al.[17] also reported that the presence of cavitary nodules in the lung was not a risk factor for mortality. In contrast, the presence of cavitary lesions in the lung was found to be a risk factor for mortality in our study.

The risk of infection requiring hospitalization is four-fold higher in AAV than in the general population.[3] The most common infectious agent in this disease is *Staphylococcus aureus*.[3] The risk of infection is increased by the use of high-dose CYC and glucocorticoids.[3] Unfortunately, the use of RTX does not reduce the risk of infection.[3] The presence of severe infections and bacterial infections have been reported as predictors of mortality.[6,11] Serious infection was observed in 30% of the patients in our study.

The most common cause of death within the first year was infection (48 to 50%).[2,3] The mortality rate due to vasculitis activity was 9.1 to 24%.[2,3,18] Flossmann et al.[12] reported that infection (48%) and active vasculitis (19%) were the main causes of deaths in the first year. In our patient group, 67% died in the first year due to infection. Beyond the first year, the causes of mortality were infections, active vasculitis, and cardiovascular and cerebrovascular causes. End-stage renal failure was previously reported in 45% of the non-survivors.[18] In our series, 70% of the non-survivors had end-stage renal disease.

In a study, the most common causes of death during long-term follow-up were CVD, infection, and malignancy.[13] Another study reported that the most common causes of death after the first year were CVD (26%), malignancy (22%), infections (20%), and active vasculitis (8%).[12]

It has been reported that mortality and morbidity increase in patients with renal failure and in need of dialysis.[18] Similarly, in our study, the presence of end-stage renal disease was found to be an independent risk factor for mortality in GPA patients. This finding indicates that adjusting the dose and frequency of immunosuppressive therapy is of vital importance in patients with renal failure.

Relapse is known to increase the mortality rate.[2] However, one study reported that relapse had no effect on mortality.[19] In our study, the effect of relapse on mortality was unable to be determined. Although the non-relapse patient group had a better survival than the relapse

patient group, this difference was not significant. Relapses may be associated with mortality due to the more intensive use of immunosuppressive therapy, to the increase in secondary infections, and to progressive organ damage. Therefore, we can speculate that the relationship between relapse and mortality would become more apparent in larger series.

In the literature, the rate of use of the combination treatment containing CYC and corticosteroid ranges from 74 to 85%,[10,11] which was lower than that in our study (98.3%). Recent studies have also shown that the combination of RTX, CYC, and glucocorticoid effectively induce remission in severe ANCA vasculitis.[20] Nevertheless, data regarding the effect of the combined use of RTX and CYC still remain insufficient. However, Cortazar et al.[21] showed that the combination therapy containing RTX and CYC was highly efficacious, allowing for the rapid tapering of high glucocorticoid doses. Moreover, Pepper et al.[22] suggested that rapid withdrawal of corticosteroids within two weeks was feasible with the RTX/CYC remission induction regimen. The CYC and RTX combination was used in 30% of our patient group. The total administered CYC dose in our study was lower than the doses reported in other works (4.5 g vs. 7.9 to 14 g, respectively).[10,23] This difference can be attributed to the reduced need for CYC as a result of the use of RTX/CYC.

The mean total RTX dose administered in our study was similar to the doses reported in the literature (4 g vs. 2 to 8 g).[10,23] As regards infections, Besada et al.[23] found that the rate of serious infections in patients treated with RTX was 26%. The RTX was discontinued in three of our patients due to infection (hepatitis B, n=2 and *P. jirovecii* pneumonia, n=1. The increased risk of infection in patients receiving RTX was associated with impaired kidney function and advanced age.[20] Serious hypogammaglobulinemia requiring <5% replacement due to RTX treatment has been also reported.[20] Hypogammaglobulinemia requiring replacement, however, was not detected in any patient in our study.

The total number of administrated CYC treatments was higher in the mortality group than the survival group (15 times vs. 8 times, respectively). This result was associated with the more active disease in the mortality group, rather than with the CYC-related side effects.

In the Rituximab versus Cyclophosphamide in ANCA-associated Vasculitis (RITUXVAS) study, CYC and RTX did not significantly differ in terms of mortality.[20] Similarly, in our study, no significant difference in mortality was observed between CYC and CYC/RTX. After 2011, due to the use of RTX, our mortality rate decreased from 37.5 to 9.0%, although this decline did not reach statistical significance.

In our study, none of the patients showed any adverse side effects such as severe infection, hypogammaglobulinemia, or leukopenia requiring discontinuation of the treatment.

Furthermore, the risk of malignancy related to long-term immunosuppression is a known fact.[3] In our patient group, non-Hodgkin lymphoma developed in one patient only.

The mortality rate in patients who received AZT for maintenance treatment was 13%.[13] In our study, the mortality rate in the group receiving AZA for maintenance therapy was 8.1%. A study compared a group receiving AZA for less than 12 months and another group receiving AZA for longer than 48 months, and no significant difference was found in terms of mortality between the groups.[13] In our study, the median duration for AZT treatment was 24 months. The duration of treatment with AZA was longer in the survival group than in the mortality group (24 vs. 12 months, respectively), although this difference was not significant. The patients who received AZA on maintenance therapy had a lower mortality rate (30% vs. 70%, respectively), compared to those who did not (p=0.03). Another study comparing two groups that separately received AZA and RTX as maintenance therapy, survival at 60 months was found to be higher in the group receiving RTX.[24] In our study, no significant difference was observed between the AZA and RTX groups in terms of survival. In the Wegener's Granulomatosis-Entretien (WEGENT) study, MTX and AZA used as maintenance therapy were compared and no significant difference was found between the two groups in terms of survival.[25] In our study, however, the number of patients treated with MTX was not sufficient for comparison.

Currently, there are many reasons for improved survival in GPA patients, compared to the past, mainly including earlier diagnosis, new treatment regimens, reduction of the corticosteroid dose used, closer patient follow-up, early detection of infections, reduction in the progression to end-stage renal failure, and trimethoprim/sulfamethoxazole prophylaxis.

The single-center, retrospective design with a small sample size is the main limitation to this study. Further large-scale, long-term prospective studies through a meticulous analysis of the using medical records may better identify the possible predictors of mortality in GPA patients.

The main strength of this study is that it has a homogeneous patient group (those only diagnosed with GPA) without vasculitis subgroups. In addition, the patients were followed regularly by a single physician in the long-term, compared to previous studies.

In conclusion, identifying prognostic factors at the time of diagnosis in GPA patients is important to improve survival. End-stage renal disease is the most important risk factor for mortality in GPA patients. These patients should be followed more closely and carefully. The CYC dose adjustment and avoidance of high-dose steroids may reduce mortality and morbidity in patients with renal insufficiency. Nonetheless, there is a need for further prospective and multi-center studies in larger series to identify the risk factors for mortality in GPA patients.

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