PROGNOSTIC FACTORS IN ACQUIRED APLASTIC ANEMIA

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Abstract: *The objective of the study was to examine the prognostic factors involved in the survival of patients with acquired aplastic anemia. Methods. We included in the study 80 patients diagnosed with aplastic anemia. We analyzed the prognostic factors related to the patient and disease. Results. Survival at 2 months, 5 years and 10 years was of 86.1%, 67.5% and 31.3%. By multivariate analysis, we obtained: severity of the disease, duration until the start of treatment, major bleeding and CsA were risk factors for death in 10 years.*

INTRODUCTION

Aplastic anemia is a bone marrow failure syndrome that is characterized by pancytopenia and varying degrees of morrow hypocelularity. The disease can be congenital or acquired. The acquired form can be idiopathic (most cases) or secondary.

In the physiopathogenetic mechanism of the disease, activated T cells (cytotoxic T) are involved which along with type 1 cytokines determine bone marrow stem cell and progenitors (1-3) destruction. The disease is fatal in the absence of treatment, but even after the administration of the right treatment it has significant morbidity and mortality, around 30-40% (4), especially in the first weeks of disease onset.

The treatment of choice in young patients with severe aplastic anemia (SAA) and very severe aplastic anemia (VSAA), with compatible donor is the allogeneic stem cell transplant; and in elderly patients, or ineligible for stem cell transplantation, it is the immunosuppressive treatment (IST) (5-7) combined: antithymocyte globulin ATG (either horse or rabbit) and cyclosporine A (CsA). The response rate in ATG is between 60 and 80%.(8,9) Recent studies show that horse antithymocyte globulin (hATG) has superior efficiency compared to the rabbit (rATG) as first-line therapy in severe aplastic anemia (10-12), but the horse ATG preparation is no longer available in many countries. There is (China) a study on the effectiveness of a pig ATG preparation, with much lower costs and that has proven to have effects similar to the two other preparations.(13) For patients with moderate (non-severe) aplastic anemia, CsA is used as treatment.(14,15)

Most studies investigating the survival time in aplastic anemia describe the influence of horse antithymocyte globulin compared to the rabbit one, sometimes in combination with granulocyte growth factors or assess survival after stem cell transplantation and only as secondary endpoints they analyze the influence of other prognostic factors.

PURPOSE

The objective of our study is to analyze the risk factors involved in the survival of patients with acquired aplastic anemia, focusing mainly on those related to patient (age, gender) and disease.

MATERIALS AND METHODS

This retrospective study included all patients diagnosed with acquired aplastic anemia in Hematology Clinic Cluj between 2000-2014. All patients were followed for at least 2 months, 80% of patients were followed for at least 5 years and 60% of patients were followed for at least 10 years. The diagnosis of aplastic anemia was set based on clinical criteria, marrow aspirate and bone-marrow biopsy. Although the range of recruitment of patients is high, all samples were processed in the same laboratory.

Aplastic anemia severity was evaluated after Camitta et al. criteria namely: severe aplastic anemia defined as: marrow cellularity <30% and two of the following three criteria: absolute number of reticulocytes < $20x10^6$/ dl, number of granulocytes <$0.5x\ 10^6$/ dl and number of platelets <$20x10^6$ / dl, very severe aplastic anemia defined as the number of granulocytes <$0,2x10^6$ / dl, otherwise the other conditions as in case of the severe form, medium severity aplastic anemia (non-severe) defined as bone marrow cellularity <50% and two of the following 3 conditions: number of granulocytes <$1.5x10^6$ / dl, number of platelets <$50x10^6$ / dl, hemoglobin <10g / dl. The form of aplastic anemia was framed as idiopathic or secondary. Osteomedullary biopsy pieces (BOM) were fixed in 10% formalin for 24 hours, decalcified in Ethylenediaminetetraacetic acid (EDTA) for 3 hours, embedded in paraffin and sectioned at 4 microns. They appreciated bone marrow cellularity.

Patients received one of the following regimes: 1) horse or rabbit ATG, cyclosporin A (CsA), methylprednisolone, with or without granulocyte-macrophage growth factor; 2) Cyclosporine; 3) Other treatments (a corticosteroid) or no treatment.

Complete response (CR) was defined as: hemoglobin level (Hb)> 12 g / dl, granulocytes> $1.5\ x10^6$ / dl, platelet count> $100x\ 10^6$/ dl. Partial response (PR) was defined as transfusion independence, granulocytes> $0,5x10^6$ / dl, platelet count> $20x10^6$ / dl, and the lack of response is defined as transfusion dependence or the fulfilment of severe aplastic anemia criteria. Relapse is defined as loss of response (dependence on transfusions after a period of at least 3 months of transfusion independence). If hematologic damage occurs after decreasing or stopping the cyclosporine dose and improves

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upon the reintroduction of cyclosporine, it is ranked as CsA dependent.

All patients signed an informed consent to participate in trials. This study was approved by the Ethics Committee of our university.

Statistical analysis

Factors involved in survival were evaluated in 2 months, 5 years and 10 years.

Statistical analysis was performed with Statistics.

Data were expressed as mean ± standard deviation for normally distributed and median variables (25^{th}-75^{th} percentiles) for non-normally distributed variables. To test the normal distribution, we used Kolmogorov-Smirnov test. Comparison between groups was performed by Student t test or Mann-Whitney test. The frequencies were compared with the chi-square test. Survival was analyzed by Cox regression method and Kaplan-Meyer method. Log-rank test was applied to calculate the significance of differences between survival curves. Cox regression was used for multivariate analysis of independent prognostic factors significant in univariate analysis. The cut-offs for the quantitative variables were analyzed with ROC curves method (receiver operating characteristic) by maximizing the Youden index. The level of significance chosen was $p < 0.05$.

RESULTS

We included in the study 80 patients diagnosed with acquired aplastic anemia. The mean age at diagnosis was 45 years old (26 to 58.7), with a slight predominance of females (47 cases, 58.75%). We divided the patients into two groups, the deceased and the survivors and we analyzed the clinical and biological characteristics of patients. We obtained statistically significant differences in terms of age at diagnosis (patients who died had a median age of 50 years old as compared to 34 in case of survivors) and severity of the disease (most very severe cases died). Clinical and biological characteristics of patients at diagnosis are presented in table no. 1.

Table no. 1. Clinical and biological characteristics, at diagnosis, of patients with acquired aplastic anemia and the comparison of deceased patients with survivors

Characteristics	Patients (n=80)	Deceased (n=55)	Survivors (n=25)	p
Age, year	45.14 (26-58.75)	50 (44.8-55.5)	34 (28.4-38.6)	**<0.001**
Women, n (%)	47 (58.75)	35 (74.4)	12 (26.6)	0.18
Idiopathic form, n (%)	67 (83.75)	45 (67.1)	22 (32.9)	0.31
Granulocytes $x10^3$/dl	817.56 (200-1100)	814 (582-1047)	824 (614-1034)	0.24
Lymphocytes $x10^3$/dl	1206 (700-1600)	1271 (1028-1514)	1064 (865-1262)	0.28
Hemoglobin g/dl	7.9 (5.9-9.4)	7.85(7.19-8.52)	8.02 (6.88-9.15)	0.79
Platelets $x10^3$/dl	40883 (7000-52.250)	41612 (24266-58958)	39280 (24130-54429)	0.87
Reticulocytes ‰	15.06 (3.25-20)	14.7 (10.3-19.1)	15.8 (8.4-23)	0.79
ESR mm/1h	66.33 (36.5-98.75)	70 (60-79)	58 (41-75)	0.19
ESR mm/2h	97.16 (72.5-131)	101 (93-110)	87 (91-101)	0.08
Very severe form n(%)	18 (22.5)	16 (88.8)	2 (11.1)	**0.036**
Bone marrow cellularity BOM %	18.06 (10-25)	18.4 (14.9-21.8)	16.9 (10.1-23.7)	0.69

ESR=erythrocyte sedimentation rate, BOM= osteomedullary biopsy

Following evolving patients, 31 (38.7%) were treated with ATG, 30 (37.5%) with CsA and other treatments in 19 (23.7%) patients. We noticed statistically significant differences between the deceased and the survivors in terms of obtaining PR, CR (patients who have not achieved CR or PR died in a much higher proportion), the duration until the start of treatment and CsA (patients who received treatment with CsA died in far greater proportion than those who had been treated with ATG). Clinical course and complications are presented in table no. 2.

Table no. 2. Clinical course and complications of patients in the study group

	Patients (n=80)	Deceased (n=55)	Survivors (n=25)	p
ATG n (%) CsA n (%)	31 (38.75) 30 (37.5)	19 (61.2) 26 (86.6)	12 (38.8) 4 (13.3)	0.24 **0.007**
The duration until the start of treatment	4.8 (1-3)	2.43 (1.16-3.70)	9.58 (3.63-15.5)	**0.006**
Major bleeding, n (%)	14 (17.5)	12 (85.7)	2 (14.3)	0.10
Infections (%)	36 (45)	27 (75)	9 (25)	0.18
PR, CR (%)	37 (46,2)	19 (51.35)	18 (48.64)	**0.001**
Clonal evolution, n (%)	9 (11,25)	5 (55.5)	4 (44.4)	0.46

ATG= antithymocyte globulin, CsA= cyclosporine A, CR= complete response, PR= partial response

The survival rate at 2 months, 5 years and 10 years was of 86.1%, 67.5%, 31.3%.

Early death (<2 months) occurred in 11 patients (13.75%). Univariate analysis shows that the severity of the disease (hazazrd ratio -HR 12.55, 95% confidence interval - CI 3.32-47.47, $p < 0.001$), the number of lymphocytes (HR 0.99, 95% CI 0.99-1.00, $p = 0.01$), major bleeding (HR 3.88, 95% CI 1.18-12.74, $p = 0.02$), infections (HR 10.85, 95% CI 1.38-84.83, $p = 0.02$) were significantly associated with mortality in two months. We separately analyzed the parameters included in the severity of the disease, so the number of granulocytes (HR 0.99, 95% CI 0.99-1.00, $p = 0.02$) and platelet count (HR 1.00, 95% CI 1.00-1.00, $p = 0.02$) were statistically significant, while bone marrow cellularity and the number of reticulocytes was not statistically significant between patients who died and survivors. Multivariate Cox regression revealed very severe form (HR 12.7, 95% CI 3.36-48.20, $p < 0.001$) and platelet count (HR 1.00, 95% CI 1.00-1.00, $p = 0.037$) as statistically significant factors for death in two months.

In 5 years, 26 patients died (32.5%) and 20% of patients were lost to study (persons who have been studied after 2010 and whom at the end date of the study were still alive). Univariate analysis showed that age (HR 1.03, 95% CI 1.01-1.05, $p = 0.005$), disease severity (HR 20.7, 95% CI 15.3-25.7, $p < 0.001$), the number of lymphocytes (HR 0.99, 95% CI 0.99 - 1.00, $p = 0.01$), hemoglobin (HR 0.83, 95% CI 0.70-0.99, $p = 0.04$), ESR at 1 hour (HR 1.01, 95% CI 1.00-1.01, $p = 0.04$), ESR at 2 hours (HR 1.01, 95% CI 1.00-1.02, $p = 0.02$), major bleeding (HR 3.38, 95% CI 1.47-7.78, $p = 0.004$), infections (HR 2.41, 95% CI 1.03-5.64, $p = 0.04$) obtaining a partial or complete response (HR 0.47, 95% CI 0.01-0.2, $p = 0.004$) were significantly associated with mortality at 5 years. Separately analyzing the parameters included in the severity of the disease, we obtained the number of granulocytes (HR 0.99, 95% CI 0.99-1.00, $p = 0.02$) as statistically significant. Multivariate Cox regression revealed bleeding (HR 2.69, 95% CI 1.02-7.08, $p = 0.045$), age (HR 1.03, 95% CI 1.01-1.06, $p = 0.001$), severity (HR 3.92, 95% CI 1.44-10.63, $p = 0.007$) as statistically significant factors.

Death in 10 years occurred in 55 patients (68.75%), 40% of patients were lost to study (persons who have been studied after 2005 and who, at the end date of the study, were still alive). Univariate analysis showed that age (HR 1.03, 95% CI 1.01-1.04, p <0.001), severity of disease (HR 3.03, 95% CI 1.68-5.48, p <0.001), the duration until the start of treatment (HR 0.92, 95% CI 0.86-0.99, p = 0.03), ATG (HR 0.52, 95% CI 0.29-0.92, p = 0.02), CsA (HR 2.39, 95% CI 1.36-4.18, p = 0.002), major bleeding (HR 2.34, 95% CI 1.21-4.53, p = 0.01) were statistically significantly associated with mortality in 10 years. Cox multivariate regression was performed to compare the relative contribution of risk factors associated with mortality in 10 years and reveals: very severe form (HR 2.23, 95% CI 1.10-4.40, p = 0.025), the duration until the start of treatment (HR 0.90, 95% CI 0.82-0.99, p = 0.038), CsA (HR 4.39, 95% CI 1.52-12.6, p-0.006) and major bleeding (HR 2.86, 95% CI 1.29-6.32, p = 0.009).

Table no. 3. Risk factors for death in patients with aplastic anemia

		Cox univariate regression		Cox multivariate regression	
		HR (95% CI)	p	HR (95% CI)	p
Early death (<2 months)	severity of disease	12.55 (3.32-47.47)	<0.001	12.7 (3.36-48.20)	<0.001
	granulocytes <355x10^3/dl	0.99 (0.99-1.00)	0.02	1.00 (1.00-1.00)	0.037
	platelet <9500x10^3/dl	1.00 (1.00-1.00)	0.02		
	major bleeding	3.88 (1.18-12.74)	0.02		
	infections	10.85 (1.38-84.83)	0.02		
	lymphocytes < 575x10^3/dl	0.99 (0.99-1.00)	0.01		
Death in 5 years	Age>40 years	1.03 (1.01-1.05)	0.005	1.03 (1.01-1.06)	0.001
	severity of disease	12.7 (9.3-25.7)	<0.001	3.92 (1.44-10.63)	0.007
	granulocytes <570x10^3/dl	0.99 (0.99-1.00)	0.02		
	lymphocytes <1350x10^3/dl	0.99 (0.99-1.00)	0.01		
	hemoglobin <6g/dl	0.83 (0.70-0.99)	0.04		
	major bleeding	3.38 (1.47-7.78)	0.004	2.69 (1.02-7.08)	0.045
	infections	2.41 (1.03-5.64)	0.04		
	ESR1h>60 mm	1.01 (1.00-1.01)	0.04		
	ESR2h>103 mm	1.01 (1.00-1.02)	0.02		
	PR, CR	0.47 (0.01-0.2)	0.004		
Death in 10 years	Age>40 years	1.03 (1.01-1.04)	0.001		
	severity of disease	3.03 (1.68-5.48)	<0.001	2.23 (1.10-4.40)	0.025
	major bleeding	2.34 (1.21-4.53)	0.01	2.86 (1.29-6.32)	0.009
	the duration until the start of treatment	0.92 (0.86-0.99)	0.03	0.90 (0.82-0.99)	0.03
	ATG	0.52 (0.29-0.92)	0.02		
	CsA	2.39 (1.36-4.18)	0.002	4.39 (1.52-12.6)	0.006

ESR= erythrocyte sedimentation rate, CR= complete response, PR= partial response, ATG= antithymocyte globulin, CsA= cyclosporine A

For quantitative parameters that significantly influence survival, we found a cut-off using ROC curves. For two months survival, in patients with granulocyte over 355x10^3 / dl survived significantly longer than those with low granulocyte (p <0.001), with lymphocytes over 575x10^3 / dl (p <0.001) and platelets over 9500x10^3/ dl (p <0.001). Analyzing survival at 5 years, patients aged under 40 years (p <0.001), with granulocytes over 570x10^3 / dl, with lymphocytes over 1350x10^3/ dl (p = 0.01), hemoglonina over 6g / dl (p = 0.02), ESR at 1 hour below 60 mm (p = 0.005) and ESR at 2 hours under 103 mm (p = 0.005) survived significantly longer. Analyzing survival in 10 years, patients aged under 40 years have survived significantly longer than patients over 40 years (p <0.001).

Figure no. 1. Kaplan-Meier survival curve in 2 months in patients with aplastic anemia: a) severe or moderate form, b) very severe form (p <0.001)

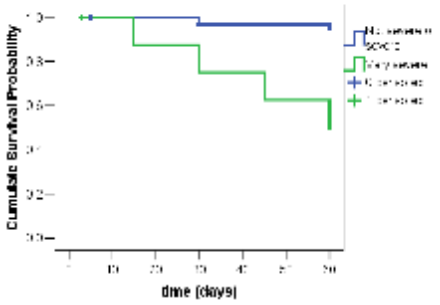


Figure no. 2. Kaplan-Meier survival curve in 2 months in patients with aplastic anemia: a) granulocytes >355x10^3 / dl, b) granulocytes < 355x10^3 / dl (p = 0.02)

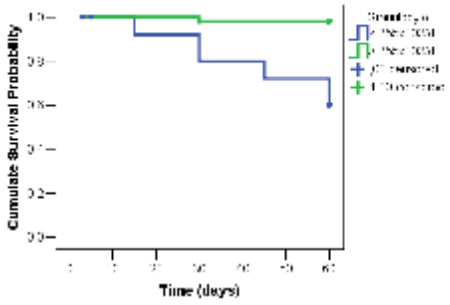


Figure no. 3. Kaplan-Meier survival curve in 2 months in patients with aplastic anemia: a) lymphocytes count <575x10^3 / dl, b) lymphocytes> 575x 10^3/ dl (p = 0.01)

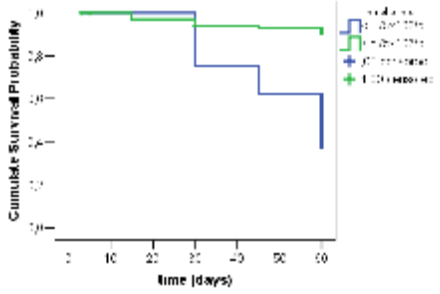


Figure no. 4. Kaplan-Meier survival curve in 2 months in patients with aplastic anemia: a) platelets >9500x 10^3/ dl, b) platelets< 9500x 10^3/ dl (p = 0.02)

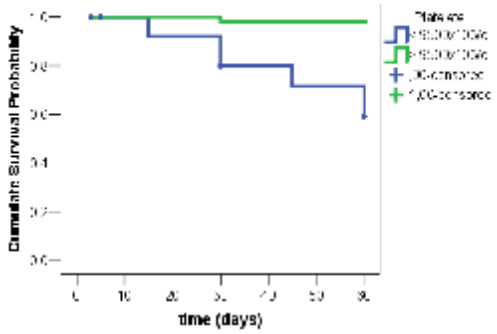
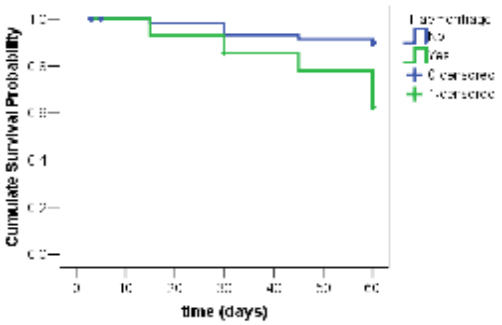
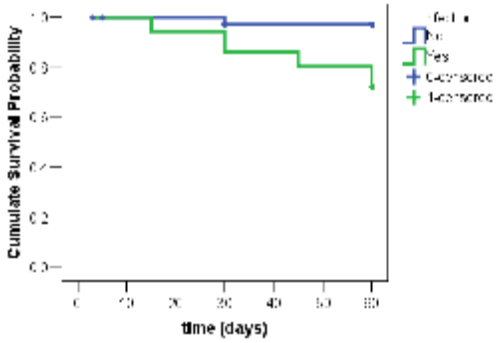


Figure no. 5. Kaplan-Meier survival curve in 2 months in patients with aplastic anemia, with or without major bleeding (p = 0.02)



We analyzed the factors that determine the duration until obtaining PR or CR. The median of time until obtaining CR or PR was 6 months. None of the factors studied influenced the duration statistically significant.

Figure no. 6. Kaplan-Meier survival curve in 2 months in patients with aplastic anemia, with or without infection (p = 0.02)



If we take into account only the obtaining of CR, the duration until obtaining CR was influenced by ATG (HR 2.42, 95% CI 0.98-6.04, p = 0.055). Comparing patients who achieved CR with those who have not achieved CR, the only statistically significant factors were the severity of the disease (p = 0.044) and ATG (p = 0.017).

DISCUSSIONS

In this study, we analyzed the influence of risk factors on survival in 2 months, 5 years and 10 years.

In our study, early mortality (<2 months) was 13.75%, comparable to other studies, which give a mortality rate between 10-33%.(5.7) Risk factors for early death are disease severity (granulocytes <355x10^3 / dl, platelets <9500x10^3 / dl), lymphocytes <575x10^3 / dl, major bleeding, infection. Among the factors studied, age, sex, type of treatment, duration until the start of treatment, BOM cellularity had no prognostic significance etc. In Wei et al. (13), and pre-existing infections and refractory thrombocytopenia appear as prognostic factors for early death, but it differs from our study as only patients with very severe aplastic anemia with a younger age at diagnosis, receiving ATG are included. In Tang et al. (16) study, prognostic factors for early death are: age, granulocytes, reticulocytes, platelets, the study includes 25 patients with very severe aplastic anemia, followed up for 1 year.

Mortality in 5 years, in the group of patients studied by us was 32.5%, and the risk factors were: age> 40 years, disease severity (granulocytes <570x /10^3 dl), lymphocytes <1350x10^3 / dL hemoglobin <6 g / dl, infections, major bleeding, ESR> 60 mm / h, ESR> 103 mm / 2h, failure to obtain a PR or CR. Compared to Bacigalupo et al. study (17), mortality observed by us is higher, but there are major differences between the studies, regarding age at diagnosis (median 16 years versus 45 years in our study), the treatment administered, etc. Risk factors found in the respective group were granulocytes and age at diagnosis. Obtaining a treatment response (PR or CR) is an important prognostic factor, found by Rosenfeld et al (18), along with age and number of granulocytes from diagnosis. We preferred to have 20% of study patients lost and to take more patients in the study, the 5-year survival study keeping its validity.

In our study, mortality in 10 years was 68.7%, with prognostic factors: age> 40 years, severity of illness, major bleeding, treatment type (ATG or CsA) and duration until the start of treatment. Frickhofen's study does not show higher survival depending on the severity of the disease (19), the only risk factors found being the type of treatment administered. Clonal evolution, age at diagnosis, relapse and the emergence of solid tumours are prognostic factors in survival according to Socie et al. study.(20) The best survival in 10 years was observed in children (21) of 80-90%.

Obtaining RC to treatment is influenced by disease severity and ATG. In Yoshida's study, they found as factors that influence treatment response: sex, granulocyte and shortest interval between diagnosis and treatment.(22)

Study limits: in the study of survival in 10 years, there is a bias due to loss of 40% of patients in the study, mortality at 10 years is probably actually higher than that found by us.

CONCLUSIONS

Interesting to note is that the severity of the disease is a risk factor for death in patients with aplastic anemia, regardless of the time to which we refer (both early death <2 months, and death in 5 years, 10 years), but at the same time, severity influences the achievement of CR. We have obtained in the survival study in 2 months and 5 years, prognostic values (cut-off) of granulocytes and platelets different from "classical" ones found in the definition of aplastic anemia severity, thus

granulocyte <$355x10^3$ / dl and platelets <$9500x10^3$ / dl mortality at 2 months and granulocytes <$570x10^3$ / dl for mortality at 5 years.

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