Concurrent treatment of aplastic anemia/paroxysmal nocturnal hemoglobinuria syndrome with immunosuppressive therapy and eculizumab: a UK experience

Paroxysmal nocturnal hemoglobinuria (PNH), an ultra-orphan disease with a prevalence of 15.9 per million in Europe, is a life threatening disorder characterized by hemolysis, bone marrow failure and thrombosis. Patients with PNH prior to eculizumab had a median survival of between 10 and 22 years.[1,2] Eculizumab (Soliris®, Alexion), a fully humanized immunoglobulin G (IgG) monoclonal antibody to C5, is currently the only licensed treatment for PNH.[3]

Aplastic anemia and PNH are intimately linked, with 40-60% of patients with aplastic anemia having a PNH clone, albeit often small.[4] Patients are at risk of developing clinical PNH on recovery from aplastic anemia, due to PNH clone expansion. Patients with aplastic anemia should be treated according to current guidelines, depending on disease severity and concomitant health problems.[5] Concurrent treatment of PNH and aplastic anemia is uncommon, with aplastic anemia treatment often predating PNH. There are very few publications as to the best course of treatment for these patients. Single case reports and small case series suggest this is safe, and report a positive outcome when patients are treated as per national guidelines whilst remaining on eculizumab, however there is likely a positive reporting bias.[6-9]

Table 1. Patient demographics and results for those treated for aplastic anemia/PNH.

Pt	Age at AA	Severity of AA	% PNH granulocytes	LDH IU/L	Eculizumab indication	1st line tx	Response	2nd line tx	Response	Alive	Previous tx for AA
1	21	SAA	89%	550*	T	ATG and CSA	CR			Alive	
2	29	SAA	88%	3133*	H	ATG and CSA	PR			Alive	
3	69	SAA	95%	4240*	H	ATG and CSA	PR			Dead	
4	50	SAA	84%	1825*	H	ATG and CSA	PR			Alive	
5	40	NSAA	79%	1314*	H	ATG and CSA ANDR added	PR CR			Alive	
6	52	NSAA	67%	2104*	H	ATG and CSA	NR	ATG and CSA	CR	Alive	
7	16	NSAA	45%	996*	H	ATG and CSA	NR	HSCT	CR	Alive	
8	46	NSAA	23%	553**	HSCT	ATG and CSA	NR	HSCT	CT	Alive	
9	35	SAA	90%	1323**	H	HSCT	CR			Alive	ATG and CSA 6 yrs prior
10	16	SAA	54%	403**	HSCT	HSCT	CR			Alive	
11	7	SAA	76%	3541*	H	HSCT	CR			Alive	
12	27	SAA	71%	546**	HSCT	CSA	NR	HSCT	Died	Dead	ATG and CSA 12 yrs prior
13	21	NSAA	98%	373**	HSCT	CSA	NR	HSCT	CR	Dead	
14	62	NSAA	99%	2044*	H	CSA	PR			Alive	CSA
15	32	NSAA	70%	728**	H	CSA	PR			Alive	
16	48	NSAA	68%	2789*	H	CSA	NR			Yes	
17	76	NSAA	50%	1299*	H	CSA	PR			Yes	
18	71	H-MDS	98%	241**	T	CSA	NR			Dead	
19	36	SAA	58%	667**	H	CSA	CR			Alive	ATG and CSA 7 yrs prior
20	60	SAA	73%	487**	H	CSA	PR			Alive	ATG and CSA 7 yrs prior
21	61	NSAA	35%	958**	H	CSA	PR			Alive	
22	39	NSAA	81%	912**	H	CSA	NR	ELT	Awaited	Alive	
23	21	NSAA	80%	3034*	H	CSA	PR			Dead	ANDR 2 yrs prior and continued
24	39	NSAA	96%	2142*	H	CSA and ANDR	CR			Alive	
25	38	SAA	97%	1800**	T	CSA	PR	HSCT	CR	Alive	ATG and CSA 22 yrs prior

Tx: treatment; AA: aplastic anaemia; SAA: Severe aplastic anaemia; NSAA: nonsevere AA; H-MDS: hypoplastic MDS; upper limit of normal lactate dehydrogenase (ULN LDH) *=430iu/l, **=240iu/l; indications for eculizumab: H: hemolytic PNH; T: thrombosis; HSCT: hematopoietic stem cell transplant. treatment: ANDR: androgen; ELT: eltrombopag; Pt: patient; PNH: paroxysmal nocturnal hemoglobinuria; ATG: antithymocyte globulin; CSA: cyclosporine; CR: complete recovery; PR: partial response; NR: no response.

The UK PNH National Service (Leeds and London) receive referrals from physicians in the UK for all patients with PNH positive screens, currently treating 695 patients, with 250 on eculizumab. A high proportion of these patients also have an element of bone marrow failure, although not all patients require concurrent treatment for aplastic anemia and PNH.

In this case series we assess treatment and outcome of UK patients established on eculizumab who required treatment for aplastic anemia, and patients who commenced eculizumab within a year of aplastic anemia treatment (and thus remained on concurrent immunosuppression). Patients previously treated for aplastic anemia who relapsed whilst on eculizumab requiring immunosuppressive therapy (IST) had their relapse treatment assessed. All patients in the PNH Service are entered onto a local database which was retrospectively interrogated. Age-matched controls treated for aplastic anemia but not requiring eculizumab were also identified for comparison of outcome (with similar treatments received). Hematological response was defined as per current guidelines.[5]

25 patients were treated with eculizumab and immunosuppressive therapy (IST) concurrently, with a median age of 39 years (range: 7-76). Median length of follow-up was 22 months (range: 2-96 months). The median granulocyte clone immediately prior to eculizumab was 79% (range: 23-99%), the patient with a 23% granulocyte clone was placed on eculizumab peritransplant.

Eleven patients had severe aplastic anemia, 13 had non-severe aplastic anemia and one patient had hypoplastic myelodysplastic syndrome (MDS; Table 1). Patients were treated as per national guidelines dependent on age, prior treatment and syndrome. All patients were treated with eculizumab in accordance with national recommendations during or within a year of receiving treatment for aplastic anaemia.

Sixty-two percent (5/8) of patients treated with antithymocyte globulin (ATG) and cyclosporine responded, with one patient responding rapidly to a second ATG. Fifty-seven percent (8/14) of patients treated with single agent cyclosporine responded. One patient achieved a complete response with cyclosporine and danazol. Twelve percent (3) of patients had a frontline allograft achieving complete remission, and a subsequent five patients underwent hematopoietic stem cell transplantation (HSCT) as salvage therapy (Table 1). Two of these patients died, one during the procedure, and one of graft-*versus*-host (GvHD) disease and infection one year after transplantation (Table 1). Patients undergoing HCST stopped eculizumab either at conditioning for HSCT or at engraftment post HCST.

Indications for commencing eculizumab were PNH related thrombosis (3), hemolytic PNH (18) and peritransplant (4). Median lactate dehydrogenase (LDH) prior to commencing eculizumab was three times the upper limit of normal (ULN) for the assay (range 1-9.9 x ULN), while those with LDH values commenced eculizumab peritransplant (Table 1).

Twenty percent (5/25) patients died; one patient who had not responded to treatment died of intracranial hemorrhage. Of the two patients achieving a partial response, one died four months post ATG and cyclosporine from presumed infection, and one died of unknown causes following a partial response to cyclosporine. One patient died during HSCT, and one who had achieved complete remission with HSCT died one year later of GvHD and infection

Age-matched controls: 11 had severe or very severe aplastic anemia, and 14 had non-severe, with a median age of 33 at diagnosis of aplasia (range: 8-75). The median length of follow-up was 84 months (range: 6-294 months). Fifty-two percent (13/25) in the control group received ATG and cyclosporine with a response rate of 76% (10/13), and 44% (11/25) received single agent cyclosporine with a response rate of 54%. One patient underwent upfront HSCT with complete remission (CR). A further three patients in the control group underwent HSCT, and all achieved CR.

Sixty percent (15/25) of the control patients had a detectable PNH clone, with median granulocyte cell of 2.2% (range: 0.1%-68%). No control patients required eculizumab. There was no significant difference in outcome between those treated with eculizumab and the age-matched controls by paired t-test of frontline treatment received: ATG and cyclosporine P=0.5; cyclosporine single agent P=0.64.

This is the largest case series of patients treated concurrently for PNH and aplastic anemia, with all patients treated as per aplastic anemia guidelines. There are small case series and single case reports published of patients successfully undergoing aplastic anemia treatment whilst on eculizumab.[6-9] Treatment outcomes in the aplastic anemia/PNH group and the control group were slightly higher than expected for those treated with ATG and cyclosporine or single agent cyclosporine, likely reflecting changes in supportive care for these patients over the last decade, and the small cohort of patients.[9] It is, however, very reassuring that there was no difference in outcome between the two groups, supporting the statement that aplastic anemia treatment decisions should not be influenced by the presence of PNH.

HSCT is curative for both conditions, with patients able to stop eculizumab. The number of patients in this cohort undergoing HSCT was small, thus conclusions cannot be drawn, however the published two-year overall survival rate following HSCT in aplastic anaemia/PNH patients on eculizumab is approximately 72%. Although this is lower than that of patients treated for aplastic anemia alone, it remains a viable treatment option.[10-12] HSCT for PNH alone is not advised in countries where eculizumab is available, due to high treatment-related mortality.[13]

As with all retrospective reviews a limitation of the study is data omission. Age-matched controls treated similarly to the study cohort were selected from a wider group of aplastic anemia patients.

Prospective data collection as part of a clinical trial or registry, whilst preferred, is challenging in this group of patients containing two rare overlapping hematological conditions, as demonstrated by the limited evidence and relatively small cohort.

In conclusion this is the largest case series reported of patients treated for concurrent symptomatic PNH and aplastic anaemia. Patient outcomes are similar irrespective of treatment requirements for PNH, and thus the presence of symptomatic PNH requiring treatment should not influence decisions relating to aplastic anaemia treatment. Prospective studies, although challenging, should be encouraged to provide further supportive evidence in this rare disease area. Physicians and patients should be reassured that treating both diseases concurrently is advised by this encouraging case series; aplastic anaemia guidelines should be adhered to, irrespective of the requirement to treat PNH, in order to provide optimal patient outcome.

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