Short-term efficacy and safety of antithymocyte globulin treatment in elderly patients with acquired aplastic anaemia

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Short-term efficacy and safety of antithymocyte globulin treatment in elderly patients with acquired aplastic anaemia

Guidelines for the diagnosis and management of adult aplastic anaemia patients were published recently on behalf of the British Society for Standards in Haematology (Killick *et al*, 2016). The combination of horse-derived anti-thymocyte globulin (ATG) and ciclosporin (CSA) is considered to be the standard first-line immunosuppressive therapy (IST). However, in elderly patients (aged ≥ 60 years) it is advised to weigh-up the risks and benefits of this intensive treatment for each individual patient as older age is associated with an increased risk of acute and delayed toxicity of ATG-based treatment and the overall survival might be worse due to inferior tolerability.

We agree that it is important to look for the right balance between toxicity and efficacy of an intensive and potential hazardous treatment, especially in vulnerable patient groups such as patients aged ≥ 60 years. Unfortunately, data regarding the safety and toxicity of ATG-based treatment schedules in this age group are scarce. Current recommendations are partly based on data from the European Society for Blood and Marrow Transplantation (EBMT) registry. Retrospective analysis of these data showed a similar response rate but an inferior overall survival in patients aged ≥ 60 years compared to younger patients (Tichelli *et al*, 1999). Within the first year after IST, 40 deaths were observed among the 127 elderly patients. The majority of these elderly patients received IST consisting of only CSA or received a reduced dose of ATG. Data on direct ATG-associated toxicity were lacking in this study (Tichelli *et al*, 1999). A single centre analysis from the National Institute of Health of 316 patients (including children) showed that age is inversely correlated with the probability of response at 6 months after IST with ATG and CSA (Scheinberg *et al*, 2009). In another retrospective single centre study, three out of seven elderly patients who were treated with standard dosed ATG died within a month after start of the treatment (Kao *et al*, 2008). In a British multicentre study, 14 elderly patients were treated with a reduced dose of ATG without CSA, which was associated with low toxicity. The response rate, however, was

Table I. Patient characteristics and outcomes.

N = 23		
Median age, years (range)	64	(60–79)
Median follow-up time, months (range)	12	(1–45)
Male	17	(74%)
Disease severity		
Non severe	7	(30%)
Severe	8	(35%)
Very severe	8	(35%)
Charlson comorbidity index		
0	15	(65%)
1	3	(13%)
≥2	5	(22%)
Survival, % (95% confidence interval)		
6 months	96	(88–100)
12 months	88	(73–100)
N = 17		
Response at 6 months		
Complete	1	(6%)
Partial	9	(53%)
None	7	(41%)

disappointing as only one patient achieved a partial haematological response after 6 months (Killick *et al*, 2006).

The national guidelines from the Dutch Society for Haematology (NVvH) for the diagnosis and treatment of aplastic anaemia in adult patients recommends first-line treatment with IST consisting of horse-derived ATG (ATGAM, Pfizer, New York, NY, USA) at 40 mg/kg/day for 4 days in combination with oral CSA in patients with acquired aplastic anaemia who are not eligible for first-line allogeneic stem cell transplantation (alloSCT). In order to gain more insight in

Table II. Comorbidities and adverse events.

Gender	Age (years)	Disease severity	Comorbidities	CCI	Adverse events during admission for ATGAM* (CTCAE-grade)	Late complications / Deaths
M	60	S	Hypertension, angina pectoris	0	Angina pectoris (1)	
M	60	VS	COPD, hypertension, atrial fibrillation	1	Prolonged QTc interval (1), acute kidney injury (1–2)	Secondary AML at 40 months, death at 45 months due to infection
M	62	NS	Hypertension	0	None	
M	62	VS	None	0	Acute kidney injury (1–2)	
M	62	NS	None	0	None	
M	63	VS	None	0	None	
M	64	NS	None	0	Chronic kidney injury (2)	
M	64	S	None	0	None	
M	64	VS	None	0	None	Death at 1 month due to haemorrhagic stroke
M	64	S	Hypertension, diabetes, chronic kidney disease	3	Hypertension (1–2)	
F	64	VS	None	0	None	Death at 10 months due to complications of second-line alloSCT
M	64	NS	Hypertension, diabetes	1	TRALI after platelet infusion	
M	64	S	History of treated thymoma	2	Hypertension (1–2), acute kidney injury (1–2)	
M	66	NS	COPD, Hypertension, elevated liver enzymes	2	Hypertension (1–2)	
M	66	S	Obstructive sleep apnoea syndrome	0	None	
F	67	VS	Possible pulmonary aspergillosis, medication- induced elevated liver enzymes	2	Subdural haematoma resulting in epileptic seizure (2), systemic infection	
M	68	NS	None	0	Hypertension (1–2), acute kidney injury (1–2)	
F	69	VS	None	0	Pulmonary embolism (3), atrial fibrillation (1), chronic kidney injury (2), systemic infections	
M	72	NS	COPD gold II, hypertension, CVA, aortic valve stenosis, aortic tube graft	3	Atrial fibrillation resulting in myocardial ischaemia (3), heart failure (3), acute kidney injury (1)	
M	72	S	History of cured tuberculosis	0	None	
F	75	VS	Hypertension, TIA	1	Acute kidney injury (1–2)	
F	77	S	None	0	None	
F	79	S	Hypertension	0	None	

ATGAM, horse-derived anti-thymocyte globulin; CTCAE, Common Terminology Criteria For Adverse Events; M, male; F, female; NS, non-severe; S, severe; VS, very severe; CCI, Charlson Co-morbidity Index; COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack; CVA, cerebrovascular incident; TRALI, transfusion related acute lung injury; AML, acute myeloid leukaemia.
*Excluding fever, rigor and reversible hypotension during ATGAM infusion.

the efficacy and safety of this treatment, a registry of adult patients with aplastic anaemia who received ATGAM as first-line treatment was started in 2012 in two university hospitals (Leiden University Medical Centre and the Amsterdam Medical Centre). In 2014, this registry formed the basis of a national NVvH registry, in which seven Dutch University Hospitals and two large non-academic hospitals collect data on all consecutive adult aplastic anaemia patients receiving IST with ATGAM and CSA as first-line treatment. Completeness of patient cohorts per hospital was checked using delivery data for ATGAM to the hospital pharmacies. In March 2016, 55 consecutive patients were registered, of which 23 were aged $\geq$ 60 years at start of the treatment. Here we report efficacy and toxicity of IST with standard dosed ATGAM and CSA in this subgroup.

The median age of the 23 patients at start of the treatment was 64 years and median follow-up time was 12 months (Table I). Seventeen patients were evaluable for response at 6 months after treatment; 1 patient had died and 5 patients had not reached the 6-month follow-up at the time of analysis. One patient had a complete haematological response at 6 months and 9 patients had a partial response, defined as transfusion independency and neutrophil count $>0{\cdot}5 \times 10^9$/l (Table I). Overall survival after 6 and 12 months was 96% and 88% respectively (Table I, Fig S1). Comorbidity before the start of IST was determined using the Charlson co-morbidity index (Charlson *et al*, 1987) and toxicity during the admission for ATGAM up to 1 month after treatment was graded using (National Institute of Cancer Common Terminology Criteria for Adverse Events criteria for all 23 patients (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Before start of IST, 15 patients had no significant comorbidity, whereas 8 patients had a co-morbidity index score $\geq$1 (Tables I and II). During admission for ATGAM infusion, atrial fibrillation occurred in two patients, of whom one had a history of aortic valve stenosis and developed myocardial ischaemia related to the atrial fibrillation. Other cardiac adverse events were angina pectoris (n = 1) and prolonged QTc interval (n = 1). During, or shortly after IST, 8 patients developed (partly) reversible kidney injury as a result of CSA toxicity (Table II). One patient had a subdural haematoma, which resulted in epileptic seizure. During follow-up, one patient died at 1 month due to a haemorrhagic stroke, 1 patient died at 10 months due to complications after second-line alloSCT and one patient died at 45 months due to infectious complications during treatment for secondary acute myeloid leukaemia (Table II).

Based on this unselected consecutive cohort of elderly patients with aplastic anaemia who received first-line treatment with standardized IST consisting of ATGAM and CSA, we conclude that in daily practice, this treatment leads to a 6-month response rate of 59% in patients $\geq$60 years, which is comparable to the response rates reported in previous studies with younger adults (Scheinberg *et al*, 2009, 2011). Although serious cardiac side effects were seen in 2 patients during and shortly after treatment with ATGAM, the overall survival at 6 months is 96% (Fig S1). In our cohort, no clear correlation can be seen between comorbidity before start of the treatment and the efficacy and/or toxicity of the treatment.

We conclude that age should not be an absolute contra-indication for treating elderly patients with acquired aplastic anaemia with ATGAM combined with CSA. Prolongation of the Dutch national registry and extended follow up of the registered patients will provide knowledge on toxicity and long-term efficacy of ATG-based IST in elderly patients.

Author contributions

J.M-L. Tjon analysed the data and wrote the paper. S.M.A. Sypkens Smit and L.C. de Wreede analysed the data. M.R. de Groot, T.J.F. Snijders, H.R.Koene, E. Meijer, M.H.G. Raaijmakers, N. Schaap, R.Raymakers and S.S. Zeerleder all contributed essential data for the analysis. C.J.M. Halkes wrote the paper and designed the study.

Conflict of interest

The authors have no conflicts of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig S1. Overall survival of aplastic anaemia patients ≥60 years treated with horse-derived anti-thymocyte globulin and ciclosporin. Open circles represent censoring due to closure of the dataset in March 2016 in order to perform the analysis described in this manuscript. IST, immunosuppressive therapy.

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