Clinical and morphological predictors of outcome in older aplastic anemia patients treated with eltrombopag

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SUPPLEMENTARY MATERIALS AND METHODS

Forty-nine patients with AA, either treatment naïve or refractory/relapsed after IST, were retrospectively evaluated. Patients had been followed at two tertiary hematologic Institutions in the UK between January 2012 to January 2018. Eltrombopag was approved individually for each patient (through the individual funding requests IFR) by the clinical commissioning groups. All patients gave informed consent in accordance with the Declaration of Helsinki.

AA patients were categorized into moderate, severe, and very severe categories as per Camitta and EBMT criteria[1]. Further evaluation included differential diagnosis of inherited versus acquired forms, and of idiopathic versus secondary AA including patients with some features suggestive of hypoplastic myelodysplastic syndrome (MDS).

Patients' clinical and hematologic parameters at diagnosis, at the time of eltrombopag indication, and after treatment were collected. PNH clones, and their dynamics after eltrombopag treatment, were also evaluated by high sensitivity FLAER technique on red blood cells (RBC), polymorphonuclear neutrophils (PMN), and monocytes, according to reported methods[2]. Telomere length (TL) was measured in PB mononuclear cells by multiplex qPCR.

Past hematologic history was retrospectively collected, including transfusion requirement and previous therapies, including ATG, CyA, androgens, alemtuzumab, and HSCT.

Eltrombopag dosing, discontinuation date, and reason for stopping were registered for each patient. Time from diagnosis to eltrombopag was also calculated. In all patients, eltrombopag was given at the maximum dose of 150 mg per day.

Response to treatment was evaluated according to EBMT criteria[3,4] and considered complete (CR) if PLT >100x10^9/L, Hb >100 g/L, ANCs > 1,5x10^9/L. Partial response was defined as transfusion independence, and minimal response as any grade of one or more lineage hematologic improvement. Relapse was defined as a drop of Hb, PLT or ANCs and/or re-appearance of transfusion dependency.

NIH response criteria were used to define tri-lineage hematological improvement by platelet count increase of 20x10^9/L above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks, hemoglobin increase by >15 g/L or a reduction in >4 units of RBC transfusion for 8 consecutive weeks, and absolute neutrophils increase of 100% or an ANC increase >0.5 x10^9/L. A robust response was defined as platelets >50 x10^9/L, Hb >100 g/L, and ANC >1 x10^9/L for longer than 8 weeks without transfusion support[5].

Time to first and best response, and treatment related adverse events were also collected, and the latter were graded according to CTCAE V4 scoring system[6].

Bone marrow (BM) trephine samples for cellularity, fibrosis (graded from MF0 to MF3 according WHO 2016[7], megakaryocyte features, and lymphoid infiltrate, were also evaluated before and after eltrombopag therapy. Cytogenetics was evaluated before and after eltrombopag treatment by both conventional metaphase karyotyping and FISH for chromosome 7 and chromosome 8.

For statistical analysis, demographic variables were reported using descriptive statistics. Means were compared using the Student's t-test. The Chi-squared or Fisher's exact tests were used for the comparison of categorical variables, where appropriate. The overall survival (OS) was calculated as the time that elapsed between the start of eltrombopag and the last follow up or death. Survival curves were estimated by using the Kaplan-Meier method and the outcomes in groups were compared using the log-rank test.

SUPPLEMENTARY RESULTS

Safety

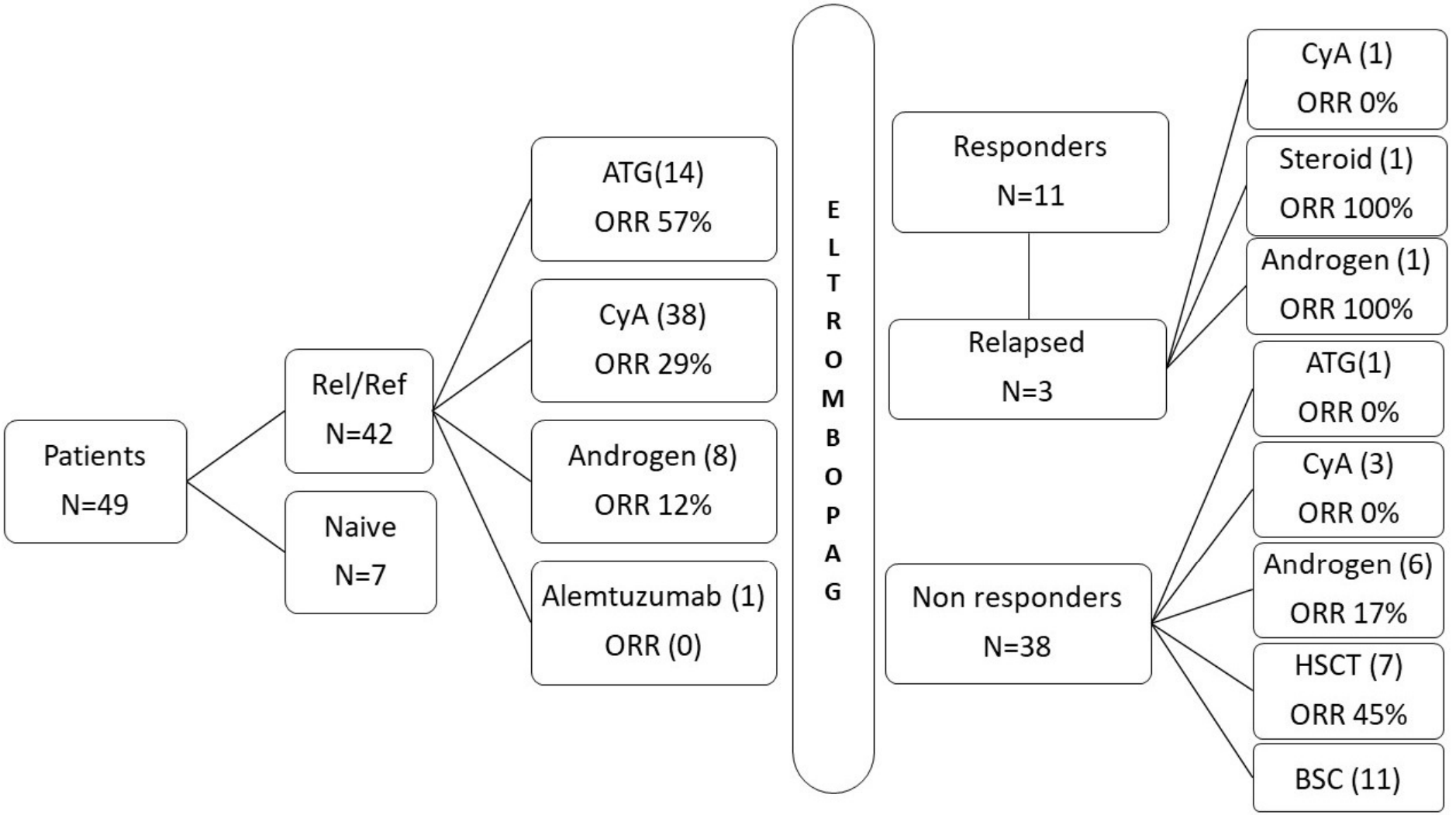
Any grade adverse effects were observed in 29% of patients, mostly grade I/II (8/14, 57%). Gastrointestinal disturbances were the most common, with nausea in 2 patients (grade I and II), diarrhea in 2 (grade III in one case, grade II in the other), and liver enzyme elevation (no greater than grade II) in 3 cases. One patient developed a rash (grade II), and another muscle cramps (grade I) that resolved spontaneously during treatment course. One patient developed pneumonia (grade III), and another one sepsis (grade III); both required hospitalization for intravenous antibiotics and ventilation support. Finally, BM fibrosis significantly increased in two patients, from MF0 to MF3 and from MF0 to MF2, respectively. The first patient had failed eltrombopag and discontinued the drug, the second achieved a longstanding CR and discontinued the drug with resolution of fibrosis (the patient maintained hematologic CR). Of these two cases, only the first displayed some dysplastic megakaryocytic features at baseline (although <10%).

Reasons for stopping

Eleven patients (9 responding and 2 unresponsive) are still on treatment, whereas 38 patients discontinued eltrombopag after a median of 4 months (1-32). Reasons for stopping were lack of response (22), death (11 cases), loss of response (2), evolution to MDS (1 case evolved to refractory cytopenia with multilineage dysplasia), treatment intolerance (1), and longstanding CR with increased reticulin fibrosis(1).

Supplementary References

1. Marsh JC, Ball SE, Cavenagh J, et al. British Committee for Standards in Haematology. Guidelines for the diagnosis and management of aplastic anaemia. Br J Haematol. 2009;147(1):43-70.
2. Sachdeva MU, Varma N, Chandra D, Bose P, Malhotra P, Varma S. Multiparameter FLAER-based flow cytometry for screening of paroxysmal nocturnal hemoglobinuria enhances detection rates in patients with aplastic anemia. Ann Hematol. 2015;94(5):721-8
3. Marsh JC, Bacigalupo A, Schrezenmeier H,et al; European Blood and Marrow Transplant Group Severe Aplastic Anaemia Working Party. Prospective study of rabbit antithymocyte globulin and cyclosporine for aplastic anemia from the EBMT Severe Aplastic Anaemia Working Party. Blood. 2012;119(23):5391-6.
4. Marsh J, Schrezenmeier H, Marin P et al. Prospective randomized multicenter study comparing cyclosporin alone versus the combination of antithymocyte globulin and cyclosporin for treatment of patients with nonsevere aplastic anemia: a report from the European Blood and Marrow Transplant (EBMT) Severe Aplastic Anaemia Working Party. Blood. 1999;93(7):2191-5.
5. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia. N Engl J Med. 2017;376(16):1540-1550.
6. Common Terminology Criteria for Adverse Events (CTCAE) v4.0
7. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-405.


Patients
N=49
Rel/Ref
N=42
Naive
N=7
ATG(14)
ORR 57%
CyA (38)
ORR 29%
Androgen (8)
ORR 12%
Alemtuzumab (1)
ORR (0)
ELTROMBOPAG
Responders
N=11
Relapsed
N=3
Non responders
N=38
CyA (1)
ORR 0%
Steroid (1)
ORR 100%
Androgen (1)
ORR 100%
ATG(1)
ORR 0%
CyA (3)
ORR 0%
Androgen (6)
ORR 17%
HSCT (7)
ORR 45%
BSC (11)