ELSEVIER

Blood 142 (2023) 5638–5639

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

508.BONE MARROW FAILURE: ACQUIRED

No Benefits from Glucocorticoid Maintenance Therapy in Patients with PNH

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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, complement-mediated hemolytic anemia resulting from a somatic phosphatidylinositol glycan class A (*PIGA*) mutation which bugs the biosynthesis of glycosylphosphatidylinositol (GPI). The lack of GPI-anchored proteins, especially CD55 and CD59 molecules, prompts blood cells to be prone to complement attack and lysis. Targeted on the terminal complement inhibitor has been recommended as a first-line treatment, such as eculizumab (C5 inhibitors), which not only controls hemolytic anemia, reduces thrombosis and blood transfusion, but also improves the staging status of chronic kidney disease in PNH patients. Complement inhibitors are not yet widely administrated by Chinese PNH patients, so glucocorticoids are still mostly used for the first-line treatment. However, the efficacy of glucocorticoid maintenance therapy in PNH is uncertain.

Methods

We conducted a prospective self-controlled comparison of 40 PNH patients with high disease activity (HDA), collecting anemia, hemolysis, thrombosis and renal function indicators at baseline and 1st, 3rd and 6th month after treatment in the Chinese Eastern Collaboration Group of Anemia (CECGA). All enrolled patients were administrated with prednisone 1.0 mg/kg/d at first and then adjusted the dosage according to the situation. The clinical trial registration number is ChiCTR2100050945.

Results

A total of 40 patients with PNH were enrolled in this study, 21 (52.5%, 21/40) were male, 19 (47.5%, 19/40) were female and the median age was 33.5 years (range 18-69 years). 29 of 40 (72.5%) presented classical PNH and 11 patients (27.5%) were diagnosed as PNH associated with bone marrow disease (BMD)-10 were aplastic anemia and 1 was myelodysplastic syndrome. Four cases detected single-site thrombosis and one had multi-site thrombosis. The most common locations were portal vein thrombus (2/6, 33.33%) and lower extremity intermuscular thrombus (2/6, 33.33%), others included mesentery vein, hepatic vein, splenic vein and intracranial microthrombus. The laboratory indexes at baseline were presented in Table 1.

Compared to the baseline (Table 2), at 1 st, 3 rd, and 6 th month after treatment, both hemoglobin and red blood cell (RBC) have improved, but hemoglobin and RBC didn't keep rising, and showed no difference when comparing 3 rd month with 1 st month and 6 th month with 3 rd month. 19 patients (19/40, 47.5%) required blood transfusion before treatment, and 11 patients (11/40, 27.5%) needed transfusion at 1 st month (P=0.021). Then 13 patients (13/40, 32.5%) at 3 rd month, 15 patients (15/40, 37.5%) at 6 th month were transfusion dependent (P=0.109; P=0.388). After 6-month treatment, 3 cases of severe anemia (Hb $<$ 30 g/L) at baseline were still severe anemia (3/7, 42.86%), and 4 cases (4/7, 57.14%) were upgraded to moderate anemia (60 g/L $\leq$ Hb $\leq$ 90 g/L). Among the original moderate anemia, 20 (20/31, 64.52%) cases were still moderate anemia, 6 (6/31, 19.35%) cases decreased to severe anemia and 5 (5/31, 16.13%) cases were improved to mild anemia (Hb $>$ 90 g/L). 1 (1/2, 50%) patient of mild anemia originally maintained mid anemia and one (1/2, 50%) patient decreased to moderate anemia.

The levels of LDH, indirect bilirubin (IBIL) and reticulocyte (Ret) were not changed significantly at 1 st, 3 rd, 6 th month after treatment. At 1 st, 3 rd, 6 th month, only 1, 2 and 2 patients achieved hemolytic control (LDH $<$ 1.5 ULN). The d-dimer and glomerular filtration rate (GFR) also were indicated no difference. At 1 st, 3 rd, 6 th month, 3 (3/11, 27.27%), 4 (4/11, 36.36%), 6

Table 1. Clinical characteristics of PNH patients at baseline

Characteristics	Values
Median age (range) (years)	33.5 (18-69)
Gender (male / female)	21/19
Classification	
Classical PNH	29 (72.5%)
Subclinical PNH	0
PNH associated with BMD	11* (27.5)
PNH clones (%)	(84.92±18.38)
≥50% (n)	38 (95%)
10%-50% (n)	2 (5%)
Thrombosis (n)	6 (15%)
LDH （×ULN)	
< 1.5	0
1.5~3.0	4
≥3.0	36
LDH （U/L)	(1496.05±745.62)
IBIL （μ mol/L)	(22.63±13.68)
Hb （g/L)	(70.38±16.03)
Ret （%)	(7.33±4.2)
APC （×109/L)	(152.18±96.92)
ANC （×109/L)	(3.21±2.43)
D-dimer	(1.39±2.18)
GFR (ml/min/1.73m²)	(115.71±42.17)

*10 of 11 PNH associated with bone marrow diseases were diagnosed as aplastic anemia and 1 of 11 was myelodysplastic syndrome.

Table 2. Changes of indexes after prednisone for PNH

Index	Baseline	1st month	3rd month	6th month	*P* value
Hemoglobin level (g/L)	70.38±16.03	79.73±17.54	76.28±19.62	77.50±20.32	*P1*<0.001
					P2=0.045
					P3=0.028
					P4=0.151
					P5=0.565
RBC (x10¹²/L)	2.37±0.62	2.73±0.65	2.69±0.69	2.72±0.69	*P1*<0.001
					P2=0.001
					P3<0.001
					P4=0.559
					P5=0.686
LDH (xU/L)	1496.05±745.62	1397.2±783.46	1401.78±720.10	1437.6±690.67	*P1*=0.148
					P2=0.624
					P3=0.845
IBIL (μ mol/L)	22.63±13.68	21.4±9.63	22.45±14.03	24.88±16.06	*P1*=0.729
					P2=0.937
					P3=0.424
Ret (%)	7.33±4.2	6.76±4.11	7.11±4.36	7.47±4.83	*P1*=0.098
					P2=0.673
					P3=0.777
D-dimer (mg/L)	1.39±2.18	0.82±1.48	0.80±0.98	0.51±0.45	*P1*=0.171
					P2=0.231
					P3=0.056
GFR (ml/min/1.73m²)	115.71±42.17	119.04±31.51	124.14±37.27	114.29±31.30	*P1*=0.196
					P2=0.142
					P3=0.749

P1, *P2*, *P3*: Null hypothesis is that there is no difference in indexes at 1st, 3rd, 6th month compared with indexes before treatment.

P4: Null hypothesis is that there is no difference in indexes at 3rd month compared with 1st month.

P5: Null hypothesis is that there is no difference in indexes at 6th month compared with 3rd month.

Abbreviation: PNH, paroxysmal nocturnal hemoglobinuria; BMD, bone marrow disease; LDH, lactate dehydrogenase; IBIL, indirect bilirubin; Hb, hemoglobin; Ret, reticulocyte; APC, absolute platelet count; ANC, absolute neutrophil count; GFR, glomerular filtration rate.

Figure 1

(6/11, 54.54%) patients were back to normal range, 1 (1/11, 9.09%), 2 (2/11, 18.18%), 4 (4/11, 36.36%) patient was newly elevated (D-dimer > 0.55 mg/L) separately. At baseline 2 patients' renal function was severely reduced (GFR<60ml/min/1.73m ^{2}), and at 1 st, 3 rd, 6 th month, 1, 1, 2 patients had declined respectively.

Discussions and Conclusions

The use of prednisone in PNH patients with HDA may initially improve anemia, but the improvement in anemia may also be due to self-remission after paroxysmal episodes of PNH itself, or transfusion. The maintenance therapy with prednisone cannot control hemolysis, improve thrombosis and renal function damage. Long-term glucocorticoid maintenance therapy for PNH is not recommended.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-189210