Acta Biomedica Scientia

e - ISSN - 2348 - 2168
Print ISSN - 2348 - 215X

www.mcmed.us/journal/abs

Research Article

EFFECTIVENESS OF CYCLOPHOSPHAMIDE PULSE THERAPY IN TREATING STEROID-REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA: A PROSPECTIVE STUDY

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ABSTRACT

The management of steroid-refractory autoimmune hemolytic anemia (AIHA) poses significant challenges due to the absence of evidence-based guidelines. This study evaluated the efficacy of cyclophosphamide pulse therapy in treating severe refractory warm AIHA in a cohort of 40 patients. Hemoglobin levels, reticulocyte counts, and direct anti-globulin levels were assessed before and after cyclophosphamide treatment. Among the 28 patients who received cyclophosphamide therapy, 83% achieved partial response after 4 cycles, with only 3% showing no response. After 6 months, 47% demonstrated complete response, while 54% showed partial response. Following pulse cyclophosphamide therapy over four months, significant elevations in hemoglobin levels were observed compared to baseline, and reticulocyte levels decreased notably from the second month onwards. These findings suggest that pulse cyclophosphamide therapy yields favorable responses in patients with severe refractory warm AIHA.

Keywords:- Autoimmune Hemolytic Anemia, Cyclophosphamide Pulse Therapy, Steroid Refractory, Treatment Response, Hemoglobin Levels.

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Home Page: **www.mcmed.us/journal/abs**		**Quick Response code**
Received:02.06.2018	**Revised**:12.06.2018	**Accepted**:28.06.2018

INTRODUCTION

Almost no cases of autoimmunity hemolytic anemia (AIHA) have been reported. According to a population-based study, there is an incidence of 0.8/10000, but a prevalence of 17/1000 [1]. AIHA caused by primary (idiopathic) causes is less common. In secondary cases of AIHA, it was necessary to diagnose and treat the underlying disease(s) [2]. Lab tests were the main means of diagnosing AIHA, and they had improved significantly. AIHA was characterized by a low haptoglobin level, increased lactate dehydrogenase (LDH) levels, and broad-spectrum antibodies against immunoglobulins and complement. It was possible to miss some of the typical laboratory findings of AIHA, especially in secondary cases [3]. There were several factors that can be used to diagnose secondary AIHA, including the onset, recent infections, blood transfusions, vaccinations, and signs of immune disease (arthritis). Particularly important was excluding drug-induced hemolytic anemia, since drug discontinuation was the best treatment option. History, clinical findings, and antibody type determine whether additional investigations were necessary. Among the additional work-ups relevant to treatment decisions were computed tomography of the abdomen, immunoglobulin determination, lupus anticoagulant testing if warm antibodies were present, and bone marrow examination [4].

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The majority of cases improve with glucocorticoids, but relapses were common. Second-line treatment involves splenectomy in patients with refractory conditions or those who do not respond to glucocorticoids [5].

A variety of immunomodulating agents were administered as salvage treatments, including intravenous immunoglobulin, danazol [6] as well as cyclophosphamide, azathioprine, cyclosporine, and vincristine at low doses [5]. Rituximab is another second-line treatment option. In general, 375 mg/m2 are administered on days 1, 8, 15, and 22. For patients who are not eligible for or who refuse splenectomy, rituximab offers the best short-term benefit/risk ratio. A small number of patients were selected, the patient population was heterogeneous, and there was a lack of long-term safety and efficacy data. In patients with CR after rituximab, splenectomy can be avoided or delayed [7]. Both azathioprine and cyclophosphamide suppress the immune system, resulting in a decrease in autoantibodies. If steroid therapy fails to produce satisfactory results, steroid maintenance doses above 20 mg/day or steroid dose tapering could be considered. As a monotherapy or as a combination with steroids, cyclophosphamide (100 mg/day) or azathioprine may be administered. As a result of myelosuppressive properties, regular monitoring of peripheral blood cell counts is recommended, with dosages modified as necessary. Rituximab trials suggest that azathioprine and cyclophosphamide were common second-line treatments before rituximab, but since then, immunosuppressants have rarely been used due to their ineffectiveness and side effects [4]. Patients undergoing chronic high-dose steroid therapy become refractory to multiple therapies. AIHA patients who were resistant to standard treatments were studied with high-dose cyclophosphamide [8]. It has been reported that pulse therapy with cyclophosphamide has been effective for treating nephritis caused by systemic lupus erythematosus [9]. Pulse cyclophosphamide inhibits both T and B lymphocytes in autoimmune disorders, which reduces production of autoantibodies [10]. In allogeneic bone marrow transplantation, cyclophosphamide had strong immunosuppressive effects on the transplanted cells [11]. A cyclophosphamide-sensitive lymphocyte is resistant to its cytotoxic effects [12] since it contains aldehyde dehydrogenase, a resistant enzyme. In patients with severe aplastic anemia, high-dose cyclophosphamide induces durable treatment-free remissions [13]. Other autoimmune conditions can also be treated with this approach [14], and alloantibodies can be eliminated [15]. Those suffering from severe refractory AIHA who did not respond to steroids were treated with pulse cyclophosphamide (injection of 1g/month) for four consecutive months.

METHODOLOGY

As part of this prospective study, pulse cyclophosphamide (one gram/month) was administered on an intravenous basis to individuals suffering from severe refractory warm AIHA who had not responded to other treatments, such as steroids, azathioprine, intravenous immunoglobulin, and oral cyclophosphamide. The prednisone dose could not be tapered down to less than 10 mg/day in those patients. For suspected cases of secondary AIHA, the diagnosis of warm AIHA was based on symptoms, physical findings, and a complete blood picture, which included reticulocyte count, DAT positivity, unconjugated hyperbilirubinemia, elevated LDH, ANF, and anti-dotactical DNA. Prior to taking verbal consent, patients were informed about the steps and aim of the study and invited to participate. Laboratory assessments were conducted at least monthly, which included complete blood counts, DAT levels, bilirubin levels, as well as AST and ALT levels. Hb [12] was defined as a complete response (CR), Hb [10g/dL or a 2g/dL increase in Hb, and no response (NR) as not meeting either CR or PR criteria.

Table 1: Patient demographics before and after cyclophosphamide treatment.

Age (years) and Patients sex	Types of AIHAa	Therapy prior to pulse cyclophosphamide	HB (g/dL)	RC %	DAT	HB (g/dL)	RC %	DAT	Type of response	HB (g/dL)
21/Male	Primary	Steroids+ azathioprine	6	34	+	10.9	8	_	112	PR
31/Female	Primary	Steroids+ azathioprine	8	24	+	11.3	7	_	13.3	PR
41/Female	Secondary (SLE)	Steroids+ azathioprine Intravenous immunoglobulin + oral cyclophosphamide	10	13	+	12.2	5	_	13.7	PR
51/Female	Primary	Steroids+azathioprine+oral cyclophosphamide	4.5	15	+	11.7	7	_	PR	14

31/Male	Primary Steroids+azathioprine	7.3	13	+	10.7	7	+	PR	11.8
32/Male	Primary Steroids+oral cyclophosphamide	6.3	24	+	11.2	8		PR	12.5
24/Female	Primary Steroids + azathioprine + Intravenous	5.7	19	+	10.4	6	+	PR	13.3
	immunoglobulin + oral cyclophosphamide								
36/Male	Primary Steroids+ azathioprine	7.8	15	+	10	5	+	PR	11.5
23/Female	Secondary (SLE) Steroids+ azathioprine + oral cyclophosphamide	5.5	8	+	11.2	5		PR	13.3
47/Male	Primary Steroids + azathioprine	5.6	9	+	9.9	6	+	PR	10.2
53/Male	Primary Steroids + azathioprine	8.3	8	+	10.3	5	_	NR	12.2
44/Female	Secondary (SLE) Steroids+ azathioprine + oral cyclophosphamide	7.4	8	+	11.6	7	_	PR	13.6
45/Male	Primary Steroids + azathioprine + oral cyclophosphamide	9.3	13	+	10.4	8	_	NR	14.3
28/Female	Secondary (SLE) Steroids + azathioprine + oral cyclophosphamide	6.7	9	+	10.3	7	_	PR	13
36/Male	Primary Steroids + azathioprine	7.2	13	+	10	7	+	PR	12.1
35/Male	Primary Steroids + azathioprine	9.3	9	+	10	7	+	NR	13.9
34/Male	Primary Steroids + azathioprine	5.5	8	+	8.4	7	+	PR	10

Table 2: Hemoglobin levels before and after cyclophosphamide treatment at 1, 2, 3 and 4 months.

Hemoglobin level (g/dL)	*P* value
Prior to cyclophosphamide therapy (6.6 ± 2.6) vs. After 1 month	**
2 months later	***
3 months later	***
4 months later	***
One month later (8.1 ± 2.2) vs.	
Two months later	**
3 months later	***
4 months later	***
Two months later (9.1 ± 0.9) vs.	
Three months later	**
Four months later	***
Three months later (9.8 ± 0.9) vs.	
After 4 months (10.6 ± 0.10)	**

STATISTICS

Using the SPSS data analysis program, statistical analysis was performed on the data obtained. Statistical significance was defined as a value of P / 0.05.

RESULTS

This study included 20 males and 14 females. Among them, 21 to 53 years of age were represented (35.52 times 10); 26 had primary warm AIHA, and four (all females) had secondary warm AIHA. In the last year, patients who received packed RBCs had hemoglobin levels (g/dL) and reticulocyte counts (%) that were 6.6 ± 2.6 and 14.23 ± 8.29 before cyclophosphamide treatment. During four consecutive months of pulse cyclophosphamide therapy (1 g/month), hemoglobin (g/dL), DAT levels, and reticulocyte counts were measured. Following the fourth cyclophosphamide cycle (83%) of patients achieved PR, while 26 achieved NR. Seven patients (42%) had hemoglobin levels of at least 10 g/dL without blood transfusion, 16 (48 %) took less than 10 mg/day of prednisone without blood transfusion, and 4 (12.7%) had values between 8 and 8.4 g/dL. Six months after stopping cyclophosphamide, there was CR, following less than 10 mg/day prednisone and transfusion

independence (Table1). Following cyclophosphamide treatment for (1, 2nd, 3rd and 4th months), hemoglobin levels significantly increased, whereas reticulocytes (%) decreased significantly. After every cyclophosphamide cycle, hemoglobin levels gradually increased to reach their maximum levels by the fourth cycle (Table2). The number of reticulocytes (%) decreased significantly after every cycle of cyclophosphamide when it reached its lowest point. There were no abnormalities in WBC count, platelet count, or renal chemistry during this experiment.

DISCUSSION

Patients with severe AIHA that is resistant to steroids, treatment is complicated, particularly when the patient rejects the maximum steroid dose, ± azathioprine ± intravenous immunoglobulin ± cyclophosphamide. In addition, patients prefer to avoid surgery (splenectomy), blood transfusions are not readily available, even washed RBCs, and restrictions imposed by the health funding authorities created additional difficulties. Our study demonstrated good results with no detectable hazards associated with pulse cyclophosphamide therapy. AIHA generally begins acutely, but it is considered chronic. There is only a low chance of long-term remission or cure with primary AIHA. With the use of medical interventions that have the least possible short- and long-term side effects, the main goal is to maintain the patient's clinical comfort and prevent "hemolytic crises" [4]. The management of AIHA is still primarily experience-based, which is surprising and regrettable. In addition to a few prospective phase 2 trials, no randomized studies are available. Refractoriness (PR) and complete remission (CR) are not defined in any formal way [4]. The management of autoimmune hepatitis when corticosteroid therapy fails or splenectomy is not an option is unclear [5]. These patients are treated with low-dose cytotoxic therapies [16], danazol, and intravenous immunoglobulins in a combination [17]. Many patients require these treatments only partially, and many need to take glucocorticoids [18]. Treatment progress has been slow [19]. The treatment is being examined by several investigators, but there are no guidelines in place yet. Second-line treatment for AIHA patients whose glucocorticoids fail is splenectomy [16]. In secondary AIHA, splenectomy has a lower success rate and more complications [21]. It is unknown whether rituximab is effective or safe for AIHA, and it must be repeated every 1–3 years, increasing infection risks, such as progressive multifocal leukoencephalopathy [4]. WAIHA patients' second line treatments are primarily determined by the physician's experience, the patient's age and comorbidities, the availability and cost of drugs, and their preferences. In selecting any drug, safety should be the main factor, as none of these drugs have a high cure rate, and treatment may cause more harm than the illness itself. Hematologists discuss the case with the patient and then make an individual decision [4]. Two earlier articles [22, 23] support the effectiveness of cyclophosphamide. No specific patient information was provided in those studies

Further research into this approach was needed to treat refractory AIHA. This study obtained nearly similar results as [8] with a low dose without using mesna. Our patients did not experience transient alopecia, nausea, vomiting, or neutropenia associated with high-dose cyclophosphamide. It is recommended that the two regimens be compared with more patients.

CONCLUSION

For patients with severe refractory AIHA, relatively small doses of pulsed cyclophosphamide induce remission, and provides a reasonable alternative to spleenotomy and toxicity, as well as rituximab at a higher cost. However, a large number of patients would have to be enrolled to test this option

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Cite this article:
Dr. Sateesh Chandra Jasti. (2018). Effectiveness Of Cyclophosphamide Pulse Therapy In Treating Steroid-Refractory Autoimmune Hemolytic Anemia: A Prospective Study. ***ActaBiomedicaScientia***, 5(2), 234-238.