PROTOCOLS OF CONDUCT

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GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) AT HOSPITAL UNIVERSITÁRIO WALTER CANTÍDIO

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ABSTRACT

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare and poorly understood clonal disease in our region. It is caused by somatic mutations in the PIGA gene on the X chromosome. Such mutations result in the absence of GPI production, which is an anchoring structure for proteins like CD55 and CD59 that protect red blood cells from lysis mediated by the complement system. PNH presents a diverse clinical course that includes intravascular hemolysis, thrombosis, and cytopenias. Following the advent of the humanized monoclonal antibody Eculizumab, which inhibits the C5 portion of the complement system, thereby preventing the destruction of red blood cells by the membrane attack complex, there has been a significant change in the treatment of PNH and in the lives of its patients. This study aims to present the guidelines for the diagnosis and management of patients with PNH followed at a reference public hospital in Ceará, Brazil.

Keywords: Hemoglobinuria, Paroxysmal. Public Health. Brazil.

INTRODUCTION

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare, acquired clonal hematological disorder that is potentially fatal and arises from a somatic mutation in the PIGA gene, which is located on the X chromosome[1]. This disease is mediated by the complement system, characterized by uncontrolled activation of its terminais pathway, leading to intravascular hemolysis, hemolytic anemia, and a pro-thrombotic state.

Intravascular hemolysis is the primary contributor to morbidity and mortality associated with PNH. Due to its rarity, the true prevalence and incidence of PNH are not well established. It is estimated that the global prevalence is approximately 15.9 individuals per 1 million people, with an annual incidence of about 5 to 6 individuals per 1 million people[2]. Research suggests that PNH occurs more frequently in Southeast and East Asia. It can arise at any age, from children as young as 2 years to adults aged 80 years and older. Most patients are initially diagnosed in their 30s, and there is no sex predominance.

PNH presents with a diverse range of clinical manifestations. Patients may exhibit symptoms associated with the disease's characteristic triad: hemolysis, bone marrow failure, and thrombotic events, or they may present with other clinical manifestations such as fatigue, abdominal pain, esophageal spasms, pulmonary hypertension, and renal failure[1,3]. The leading cause of mortality in PNH is due to thrombotic events, accounting for approximately 67% of deaths.

WHEN TO INVESTIGATE

Certain patients in clinical medical practice should be investigated with heightened attention for a potential diagnosis of PNH[4]:

- Patients with unexplained cytopenias, aplastic anemia, hypoplastic myelodysplastic syndromes, and/or young patients;
- Patients with unprovoked thromboses and/or thromboses in atypical sites, or who continue to experience new venous thromboses despite adequate anticoagulation; patients affected by Budd-Chiari syndrome;
- Patients presenting with hemoglobinuria;

Patients with positive hemolysis tests and negative direct Coombs test.

DIAGNOSIS

Currently, the diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) is made through flow cytometry, which allows for the identification of the PNH clone in hematological cells. Following this step, it is essential to conduct a detailed assessment of the patient's clinical presentation, along with the analysis of laboratory tests. Based on this evaluation, it is possible to determine whether there is an indication to initiate treatment.

Laboratory Work-up:

Confirmatory Diagnostic Test: Conduct flow cytometry to detect the PNH clone in a peripheral blood sample[5].

Follow-up Tests:

- Screening and Monitoring Protocol for Paroxysmal Nocturnal Hemoglobinuria (PNH) in Patients with Aplastic Anemia (AA)[6]

  - Initial Screening: All patients diagnosed with Aplastic Anemia (AA) are required to undergo screening for the presence of a PNH clone at the time of diagnosis. This assessment must be performed using peripheral blood flow cytometry.

  - Monitoring Protocol for Negative Results: In cases of a negative initial screening, follow-up testing should be conducted at six-month intervals for a duration of two years. If results remain persistently negative throughout this two-year period, the monitoring frequency may be reduced to annual testing.

  - Management and Monitoring Protocol for Positive Results: A positive screening result necessitates an immediate evaluation to determine the clinical indication for PNH-specific therapy. Concurrently, monitoring

via flow cytometry must be intensified to three-month intervals for a period of two years. A reduction in this testing frequency is permissible only if the PNH clone size demonstrates consistent stability over time.

• Screening and Monitoring Protocol for Paroxysmal Nocturnal Hemoglobinuria (PNH) in Patients with classic PNH:

Initial Evaluation[7]:

- Medical history and physical examination;
- Determine the size of the PNH clone by flow cytometry;
- Complete blood count, reticulocytes count;
- LDH, total and fractionated bilirubins, haptoglobin, urinalysis;
- Direct Coombs test;
- PT, aPTT, D-dimer;
- Abdominal venous doppler ultrasound;
- Transthoracic echocardiogram;
- Measurement of folic acid and vitamin B12;
- Urea, creatinine;
- Iron profile tests: serum iron, ferritin, and transferrin saturation.

TREATMENT

In 2007, the first medication for the treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH) was approved, marking a significant shift in the natural history of the disease. Eculizumab is a monoclonal antibody that specifically acts by binding to the C5 component of the complement system. This binding inhibits complement activation, thereby preventing the attack and lysis of erythrocytes[8]. The medication received regulatory approval in Brazil in 2015 and was subsequently incorporated into the public health system (SUS) for use in 2018. Its dosing regimen for PNH in adult patients (≥18 years) consists of an initial phase followed by a maintenance phase[9]:

TABLE 1. Criteria for Treatment of PNH

Treatment Indication Criteria as Defined by the 2019 Clinical Protocols and Therapeutic Guidelines (PCDT) from Brazil's Public Health System (SUS)
A patient eligible for treatment with Eculizumab must have PNH in its hemolytic presentation and demonstrate high disease activity defined as lactate dehydrogenase (LDH) ≥ 1.5 times the upper limit and a clone size > 10%, in addition to at least one of the following criteria:
- History of thromboembolic event requiring therapeutic anticoagulation (confirmed by imaging studies), after excluding other common causes of acquired thrombophilia, such as antiphospholipid antibody syndrome (APS) and neoplasia;
- Chronic anemia demonstrated by more than one measurement of hemoglobin ≤ 7 mg/dL or by more than one measurement of hemoglobin ≤ 10 mg/dL with concomitant symptoms of anemia, in which other causes besides PNH have been excluded;
- Pulmonary arterial hypertension, evidenced by echocardiogram with mean pulmonary artery pressure (mPAP) > 35 mmHg, in which other causes besides PNH have been excluded;
- History of renal failure, demonstrated by a glomerular filtration rate (GFR) ≤ 60 mL/min/1.73 m^2, in which other causes besides PNH have been excluded; or
Pregnancy, evidenced by serum hCG > 6 mUI/mL, with a previous history of gestational complications.

Initial Phase: 600 mg administered by intravenous infusion over 25 to 45 minutes, once a week for the first 4 weeks.

Maintenance Phase: 900 mg administered by intravenous infusion over 25 to 45 minutes in the fifth week, followed by 900 mg administered by intravenous infusion over 25 to 45 minutes every 14 ± 2 days.

Not every patient with a PNH clone identified by flow cytometry is indicated to start treatment with Eculizumab. It is necessary to meet the criteria outlined in Table 1[10]:

SPECIAL CARE DURING TREATMENT:

Monitoring of patients receiving Eculizumab – laboratory tests[7]:

- Complete blood count, reticulocytes, LDH, and biochemistry: monthly for the first 3 months; thereafter, every 3 months;
- Renal function: every 3 months;
- Iron profile: every 6 months;
- Reevaluation of transfusion history: every 6 months;
- Measurement of vitamin B12 and folic acid: annually;
- Flow cytometry for monitoring the PNH clone: every 6 months for the first 2 years, then annually if on Eculizumab treatment and the disease is stable.

Vaccination:

- Vaccination for Neisseria meningitidis (A, C, W, Y, and B):

  Patients can be vaccinated two weeks before starting Eculizumab. If it is their first exposure to the vaccines, administer 2 doses of each (ACWY and B) with an interval of eight weeks. The booster for each vaccine should be given every 3 years. Vaccines can enhance the activity of the complement system, which may result in acute hemolysis; therefore, treatment with Eculizumab can be initiated before vaccination. If the decision is made to start with a complement inhibitor first, antimicrobial prophylaxis should be implemented[11].

Antimicrobial Prophylaxis:

Due to their nature, patients with PNH may have an increased risk of infections, making antimicrobial prophylaxis an important consideration. If the patient has not been vaccinated at least 2 weeks prior to starting treatment with Eculizumab, prophylactic antibiotics should be initiated and maintained for at least 2 weeks after the second dose of the vaccines. Continuous prophylaxis should be considered for those patients who experience recurrent bacterial infections or are using immunosuppressive medications[11,12].

Prophylaxis Options:

1. Amoxicillin 875 mg every 12 hours;
2. Oral Penicillin V 250 mg every 12 hours;
3. Ciprofloxacin 500 mg daily.

Anticoagulation:

PNH is associated with complement activation and the production of free hemoglobin, which may contribute to thrombus formation. Patients with PNH have a high risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), with a significantly higher incidence compared to the general population. Anticoagulants such as warfarin or direct oral anticoagulants (DOACs) can be used, depending on the patient's characteristics and the presence of comorbidities (pay attention to the presence of thrombocytopenia). In special situations, unfractionated heparin or low molecular weight heparins may be utilized[7,11–13].

- Primary Prophylaxis: Indicated in the presence of a PNH clone greater than 50% or in patients with high disease activity; it should be discontinued when the patient shows normalization of LDH levels.

- Secondary Prophylaxis: Evaluate the maintenance of anticoagulation on an individualized basis.

Pregnancy

Before the advent of Eculizumab during pregnancy, the mortality rate among pregnant women with PNH was quite high, ranging from 8% to 20%. Women with PNH who become pregnant are at increased risk of complications such as thrombosis and premature births. Today, there are many years of experience with the use of Eculizumab in pregnancy, demonstrating a good safety profile for both

mothers and infants. Patients should be monitored in collaboration with the obstetric service, and the use of low molecular weight heparin should be considered throughout the entire pregnancy and into the postpartum period[11,14].

EVALUATION OF RESPONSE TO ECULIZUMAB

When treatment with the monoclonal antibody that inhibits the C5 component of the complement system is initiated, the following outcomes are sought[8,15]:

- A reduction in serum LDH levels;
- A reduction in thrombotic events;
- A reduction in mortality;
- An improvement in overall symptoms and anemia—transfusion independence.

To assess patient response to Eculizumab treatment, we utilize the classification proposed in the 2021 study by the Severe Aplastic Anemia Working Party (SAAWP) of the European Group for Blood and Marrow Transplantation (EBMT)[16]. This classification features a specific division into four groups and will be assessed after 12 months of regular medication use:

Group A: Complete Response (complete response, major response) - patients with transfusion independence and no anemia;

Group B: Good Response - patients with transfusion independence with mild anemia (10–12 g/dL);

Group C: Partial Response - patients with persistent anemia (8–10 g/dL) requiring occasional transfusions (≤ 2 units of red blood cell concentrates in 6 months);

Group D: Minor Response (minor, no response) - persistent anemia requiring ongoing red blood cell transfusions.

The categorization of responses is of utmost importance for better understanding the efficacy of treatment and thus effectively evaluating patients who may benefit from new treatments for PNH that are becoming available in the country, such as, proximal complement inhibitors (pegcetacoplan, danicopan, iptacopan)[16].

Evaluation of Causes of Residual Anemia in Eculizumab Treatment and Its Management:

Residual anemia in patients treated with Eculizumab may occur in up to approximately 78% of these patients (16). This anemia can have multiple causes, necessitating careful and comprehensive evaluation. Identifying and appropriately treating the underlying causes is crucial to optimizing treatment response and improving patients' quality of life[17,18].

Presence of Intravascular Hemolysis: There may be pharmacokinetic or pharmacodynamic breakthrough hemolysis.

Corrective Measures: Consider reducing the interval between doses (to 10–12 days) or increasing the dose of Eculizumab (to 1,200 mg); the underlying cause responsible for the new increase in intravascular hemolysis should be addressed.

Presence of Extravascular Hemolysis: Extravascular hemolysis mediated by C3 may be occurring.

Corrective Measures: Consider the use of proximal complement inhibitors.

Bone Marrow Disorders: There may be bone marrow failure or clonal evolution of myeloid neoplasia.

Corrective Measures: Conduct a bone marrow evaluation and treat according to the findings.

Assess for Nutritional Deficiencies: Deficiencies in iron, vitamin B12, or folic acid may be present.

Corrective Measures: Perform laboratory tests to evaluate levels of iron, vitamin B12, and folic acid, and provide nutritional supplementation as needed.

FINAL CONSIDERATIONS AND UNMET NEEDS

Paroxysmal Nocturnal Hemoglobinuria (PNH) is an extremely rare disease, and it is essential that knowledge about the management of this condition is widely disseminated among healthcare professionals. Despite advancements in understanding the disease, significant challenges remain, particularly regarding early diagnosis and accessibility to effective treatments, such as complement inhibitors[11].

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