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Hydroxyurea as A Therapeutic Approach in Transfusion-dependent Thalassemia

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Abstract

Major thalassemia, or transfusion-dependent thalassemia (TDT), is a severe form of hemoglobin disorder that requires a lifetime regular blood transfusion. Longterm transfusion leads to iron overload that damaging vital organs and increasing morbidity and mortality. Therefore, alternative therapies are needed to reduce transfusion frequency and its complications. Hydroxyurea (HU) is currently being studied for its potential benefit in TDT. Hydroxyurea is an antimetabolite and antineoplastic agent for sickle cell disease. Hydroxyurea induces the production of fetal hemoglobin (HbF) by stimulating γ-globin expression and inhibiting ribonucleotide reductase, which is essential in DNA synthesis, thereby suppressing ineffective erythropoiesis. This pharmacological effect may increase total hemoglobin levels and reduce transfusion requirements in TDT. Hydroxyurea also improves erythropoiesis, decreases ferritin levels, and enhances red blood cell morphology. Meta-analyses indicate that approximately 25–60% of patients experience at least 50% reduction in transfusion needs, with mild and reversible adverse events. While it is not recognized as standard therapy, current studies support the efficacy and safety of hydroxyurea as an adjunctive therapy for TDT, particularly in resource-limited settings in developing countries. Further studies are needed to confirm its long-term safety profile and to identify the patient populations most likely to benefit from this therapy.

Keywords: hydroxyurea, thalassemia dependent-transfusion, iron overload

Abstrak

Thalassemia mayor, atau thalassemia yang bergantung pada transfusi (TDT), adalah bentuk gangguan hemoglobin yang parah yang membutuhkan transfusi darah secara teratur seumur hidup. Transfusi jangka panjang menyebabkan kelebihan zat besi yang merusak organ vital dan meningkatkan morbiditas serta mortalitas. Oleh karena itu, terapi alternatif diperlukan untuk mengurangi frekuensi transfusi dan komplikasinya. Hidroksiurea (HU) saat ini sedang dipelajari potensi manfaatnya pada TDT. Hidroksiurea adalah antimetabolit dan agen antineoplastik untuk penyakit sel sabit. Hidroksiurea menginduksi produksi hemoglobin janin (HbF) dengan merangsang ekspresi γ-globin dan menghambat ribonukleotida reduktase yang penting dalam sintesis DNA, sehingga menekan eritropoiesis yang tidak efektif. Efek farmakologis ini dapat meningkatkan kadar hemoglobin total dan mengurangi kebutuhan transfusi pada TDT. Hidroksiurea juga meningkatkan eritropoiesis, menurunkan kadar feritin, dan meningkatkan morfologi sel darah merah. Meta-analisis menunjukkan bahwa sekitar 25–60% pasien mengalami setidaknya pengurangan kebutuhan transfusi sebesar 50%, dengan efek samping ringan dan reversibel. Meskipun belum diakui sebagai terapi standar, studi saat ini mendukung kemanjuran dan keamanan hidroksiurea sebagai terapi tambahan untuk TDT, khususnya di lingkungan dengan keterbatasan sumber daya di negara berkembang. Studi lebih lanjut diperlukan untuk mengkonfirmasi profil keamanan jangka panjangnya dan untuk mengidentifikasi populasi pasien yang paling mungkin mendapat manfaat dari terapi ini.

***Kata kunci**: hidroksiurea, transfusi dependen talasemia, kelebihan zat besi*

I. INTRODUCTION

Beta-thalassemia is a prevalent inherited hematologic disorder characterized by impaired hemoglobin synthesis and is classified as hemoglobinopathy. Defective hemoglobin syntesis resulting from mutation in globin genes encoding adult hemoglobin (HbA) production leads to hemoglobinopathy. Genetic mutation affecting β-globin gene lead to β-hemoglobinopathy which subsequently reduce β-globin chain production, as observed in sickle cell disease and thalassemia-β.[1] The prevalence of thalassemia gene mutation is estimated to be 1-5% globally. Although mutation may affect any globin gene, α- dan β-thalassemia are the most clinically important types.[2]

A high prevalent of thalassemia gene has been reported in Indonesia, where epidemiological studies estimate the β-thalassemia gene frequency to be 3-10%. On a global scale, an estimated 300.000-500.000 newborns present with severe hemoglobin abnormalities anually, leading to 50.000-100.000 death, with nearly 80% of cases occurred in developing contries.[3]

Thalassemia International Federation classified thalassemia into two grups based on disease severity: (1) non-transfusion-dependent β-thalassemia (NTDT) and (2) transfusion-dependent β-thalassemia (TDT). TDT is the more severe phenotype that requires lifelong regular transfusion at interval of 2-5 weeks to survive.[4]

Until recently, allogenic hematopoietic stem cell transplantation (HSCT) was the only promising therapy for β-thalassemia. However, its clinical application remains limited due to donor availability and cost consideration.[5] Moreover, gene therapy and genome editing have emerged as promising therapeutic approach, demonstrating encouraging result in preclinical studies. however, none of those treatments are considered as standard patient care. Consequently, supportive care, primarily lifelong blood transfusion, remains the mainstay for most patients. Although essential for survival, chronic transfusion leads to iron overload, resulting in progressive organ damage and increased mortality. Therefore, alternative strategies are needed to reduce blood transfusion frequency and decrease iron accumulation, such as the use of hydroxyurea.[6]

Despite extensive global investigation, its application in thalassemia remains limited. According to International Thalassemia Federation treatment of Non-Transfusion Dependent Thalassemia should begin at dose of 10 mg/kg/day that followed by stepwise dose escalation every 8 weeks 3-5 mg/kg/day to a maximum tolerable dose, generally not exceeding 20 mg/kg/day. Neverthelles, FDA approval currently applies to its use in sickle cell disease only.[7]

II. TRANSFUSION-DEPENDENT THALASSEMIA

The term thalassemia refers to a group of hematological disorder marked with decrease or absent synthesis of one or more normal globin chains. Based on affected globin chain, thalassemia is classified into α-, β-, γ-, δ-, δβ- and εγδβ-thalassemia.[8] β-thalassemia results from more than 200 mutations in HBB globin gene which encoding the β-globin subunit of HbA. These mutations lead to reduced or absent β-globin synthesis, promoting intracellular hemichrome presipitation, ineffective hematopoiesis, chronic hemolysis, and severe anemia.[9]

Patients with TDT depend on lifelong transfusion to survive, and without adequate transfusion support, complications arise and survival declines. TDT includes β-thalassemia major, severe HbE/β-thalassemia, transfusion dependent Hb H disease, Hb H hydrops fetalis, and Hb Bart's

hydrops fetalis. While NTDT includes β-thalassemia intermedia, HbE/β- thalassemia, and Hb H disease. [10]

Mutations in HBB gene underlie β-thalassemia, producing either a complete absence or partial reduction of β-globin synthesis. Reduced β-globin synthesis impairs hemoglobin formation and normal blood red cell development, causing ineffective erythropoiesis and anemia. Over 200 mutations have been identified in β-thalassemia, and this condition is classified into thalassemia major, intermedia, and minor according to clinical severity.[11]

The primary pathological mechanism in β-thalassemia involves decreased or absent β-globin chain synthesis, resulting in excess α-globin chains that accumulate and form intracellular inclusion body in erythroid precursor. These inclusion bodies attached to skeleton membrane cause oxidative injury within bone marrow and lead to ineffective erythropoiesis. Hemolysis is a secondary process and is less pronounced in thalassemia major than in intermedia. In response to anemia, erythropoietin production increased, promoting extensive erythroid hyperplasia in both medullary and extramedullary tissues. This process contributes to skull deformity, cortical bone thinning, pathological fractures, extramedullary hematopoietic masses, and splenomegaly.[10]

In patient with TDT, excess iron intake may exceed the binding capacity of transferrin, leading to elevation of non-transferrin-bound iron (NTBI) species. NTBI accumulates in tissue such as liver, heart, and endocrine organ, promoting organ damage. Serial measurements have shown that ferritin serum liver above 2500 ng/mL is associated with increased cardiac risk and mortality, whereas level below 1000 ng/mL are linked to better survival outcomes. In addition, liver iron levels exceeding 7 mg/g are also associated with liver disease.[12]

Lifelong treatment is necessary for patients with TDT to prevent and manage clinical consequencies of the disease, with adherence playing a critical role in outcomes. At present, management includes regular transfusion, iron chelation, splenectomy, and stem cell.[4]

III. THERAPI

A. Blood transfusion and iron chelation

Regular transfusions are administered at interval 2-4 weeks to achieve hemoglobin target of 9-10,5 g/dL (may be different with other centers). This regimen promotes growth, normal physical activities, and ensure effective suppression of bone marrow activity. For patient with cardiac involvement or other comorbidities, a higher pretransfusion hemoglobin target of 11-12 g/dL is recommended.[10]

A whole unit blood of 420 mL contains approximately 200 mg of iron, equivalent to about 0,47 mg/mL. For packed red cell (PRC) preparations, iron levels depend on hematocrit that may be estimated as 1.16 mg/mL per unit hematocrite fraction.[13] Chronic transfusion recipients should be closely monitored for iron overload through serial ferritin measurement and MRI of liver and cardiac iron. Initiation of iron chelation therapy is advised after 10 units of PCR transfusion or when ferritin serum reaches 1000 ng/mL. Available chelating agents include subcutaneous deferoxamine (DFO), and oral agent deferiprone (DFP) and deferasirox (DFX), which may be used either as monotherapy or in combination. The choice of chelating agent is individualized based on clincial factors, iron burden, and local practice guideline. Favorable treatment outcomes depend on adherence, monitoring, and appropriate management of adverse events with deferoxamine remaining a key option in patient with cardiac dysfunction.[12]

B. *Hematopiestic stem-cell transplantation* (HSCT)

HSCT offers a potentially curative therapeutic opportunity for patients with β-thalassemia. Nearly 90% of patients receiving HSCT at experienced European medical centers have 2-year disease-free survival rates above 80%.[5] Disease-free survival rates have been reported to exceed 90% in low-risk patients undergoing HSCT with matched donors.[12] HSCT has been shown to improve quality of life in children with severe disease compared with lifelong therapy, iron chelation, and complication management. However, HSCT remain associated with mortality risk of up to 12% within 2 years post-transplantation. The risk is influenced by factors such as intensity of the pre-transplant myeloablative conditioning regimen, graft-versus-host disease, and graft failure.[5,14]

C. Splenectomy

Clinical rationale for splenectomy in thalassemia, especially in patient with significant disease burden is to reduce the extramedullary hematopoiesis, increase hemoglobin levels, and decrease transfusion requirements, thereby limiting iron overload.[15] It may be beneficial in patients with inadequate response to iron chelation, particularly when excessive iron accumulation in organs such as liver, heart, and edocrine tissue becomes clinically significant. This procedure may also relieve symptoms of massive splenomegaly, including abdominal discomfort and reduce the risk of splenic rupture. Moreover, it helps correct hypersplenism-induced thrombocytopenia and leukopenia, thereby reducing the risk of bleeding and infection and improving overall quality of life.[16]

IV. HYDROXYUREA

Hydroxyurea (hydroxycarbamide) is a specific S-phase antimetabolite that reversibly inhibits ribonucleoside reducatse enzyme (ribonucleoside diphosphate reducatse, rNDP). This action disrupts de novo DNA synthesis and repair, leading to cell cycle arrest and cytotoxic effect. Its effects are lagely confined to DNA metabolism while RNA synthesis remain unaffected.[17]

In addition to its cytotoxic effects, hydroxyurea promotes γ-globin synthesis in erythroid cells. γ-globin is the predominant type of β-like globin expressed throughout fetal life which gradually suppressed after birth until minimum level in first year of life. In hemoglobinopathies with impaired β-globin production, induction of γ-globin is advantageous as it binds with α-globin to form HbF.[18]

Following oral administration, hydroxyurea is efficiently absorbed in gastrointestinal tract and distributed systemically. Maximum plasma levels are achieved within 1-4 hours after ingection. The drug has transient effects due to rapid elimination from bloodstream and is cleared primarily through renal excretion after hepatic metabolism.[19]

A. Role of Hydroksyurea in TDT Management

As an antimetabolite with cytotoxic and antineoplastic properties, hydroxyurea is widely used in the management of myeloproliferative disorder. Its ability to induce HbF makes it as a key therapeutic agent in sickle cell disease. By increasing HbF level, hydroxyurea may elevate total hemoglobin and reduce transfusion needs. However, its effectiveness may diminish with prolonged use. Chemically, hydroxyurea is a synthetic compound belonging to aminoketone group.[20,21]

The exact mechanism of HbF induction by hyroxyurea is not yet fully understood. The predominant hypothesis suggests a cytotoxic effect that suppresses erythropoiesis and promotes HbF synthesis. Other proposed mechanisms include release of nitric oxide and guanylyl cyclase and cyclic guanosine

monophosphate-dependet protein kinase pathway gene. Hydroxyurea has been reported to increase γ-mRNA expression by 2 to 9 folds, contributing to improve α/non-α globin chain balance and more effective erythropoiesis. Although upregulation of γ-mRNA fold in vitro collerate well with HbF fold elevation in vivo, clinical studies indicate that higher HbF levels do not always result in increased total hemoglobin levels, due to an increasing of biosynthetic α/β ratio without changing in α/γ ratio.[17]

Several studies have evaluated the efficacy of hydroxyurea in patients with TDT that showed favorable outcomes. A placebo-controlled RCT by Yasera et al. (2022) assessed oral hydroxyurea at dose of 10-20 mg/kg/day for TDT, comparing blood volume, HbF percentage, and erythropoietic stress between two groups. The study reported that hydroxyurea signifiicantly increased HbF levels and reduced blood transfusion needs. [22] In addition, Ansari et al. conducted study to 152 patients and found that therapeutic effect of hydroxyurea became evident after two months of continuous treatment.[23] Other studies have also reported increases in hemoglobin levels and reduction in serum ferritin following hydroxyurea therapy. Furthermore, Italia et al. demonstrated 74% positive response rate in patients with thalassemia intermedia, woth approximately one-third of patients requiring only half of their previous transfusion volume after treatment.[24, 25]

A significant reduction in transfusion requirements among patients with thalassemia treated with hydroxyurea was reported by Hussain et al. (2022). Among 87 patients, 66 demonstrated decreased transfusion needs following therapy, while 21 showed no response. Patients categorized as having “good” or “very good” response exhibited significantly higher HbF levels compared to non-reponder ($p<0.0001$).[26]

A meta-analysis by Algiraigi et al. (2017) recommended hydroxyurea to treat TDT in both adult and children, considering the following: (a) the serious consequences of chronic blood transfusion; (b) the growing evidences of long-term safety of hydroxyurea; (c) its relatively rapid clinical response (within months); and (d) availability and affordability of hydroxyurea (especially for developing countries).[27]

B. Safety of hydroxyurea

Hydroxyurea is generally well-tolerated with adverse effects are typically mild to moderate and transient. The observed adverse events include 39.2% of dermatologic manifestation (alopecia, hyperpigmentation, rash, and nail changes), 23.2% neurological symptoms (headache, vertigo, drowsiness, and seizure), 17.5% of gastrointestinal disturbance (nausea, vomiting, abdominal pain, anorexia, and constipation), and 10.7% of hematological effects (neutropenia and decreased hemoglobin levels).[28]

Huang et al. (2025) investigated the safety of hydroxyurea in β-thalassemia focusing on bone marrow suppression and systemic adverse events, including hematologic, neurologic, dermatologic, and gastrointestinal manifestation. Myelosuppression was commonly observed but reversible; patients may recover after dose adjustment or discontinuation of treatment. Leukopenia was the most prevalent hematologic complication, followed by neutropenia.[29] This reversibility is linked to reactivation of ribonucleotide reductase after hydroxyurea withdrawal. In vivo, the effects of hydroxyurea are predictable and transient, reflecting its rapid absorbtion, metabolism, and excretion. [19]

A safety study involving 299 patients with sickle cell anemia reported that hematological adverse events were the most common finding, including neutropenia and reduction in reticulocyte and platelet count.

These effects are likely related to its inhibitory property on DNA synthesis and cell proliferation, which impacts hematopoietic, stimulate gastrointestinal epithelial cells, induce oxidative stress and inflammation leading to adverse reactions. Although hydroxyurea is initiated as dose of 10 mg/kg/day and increased by 5 mg/kg/day every 4-6 week based on response or tolerability, no significant dose-related adverse event was observed.[29]

V. CONCLUSION

Hydroxyura is a potential adjunctive therapy in management of TDT to reduce transfusion needs and iron overload. Its ability to induce fetal hemoglobin contributes to increased total hemoglobin level. While some studies have demonstrated significant reduction in transfusion and iron chelation needs, others reported limited or no benefit. Consequently, current evidence remains inconclusive regarding its routine use in TDT. Hydroxyurea is well tolerated with reversible and mild to moderate adverse events.

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