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Original Research Article

ADVANCEMENTS IN IRON CHELATION THERAPY FOR HEMATOLOGIC DISORDERS: A NARRATIVE REVIEW

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ABSTRACT

Iron chelation therapy is essential for mitigating iron overload caused by iron deposition in vital organs, such as the liver and heart, following regular blood transfusions. Recent advancements in iron chelation therapy for hematologic disorders have significantly improved clinical outcomes and patient adherence. This review aims to summarize the progress in iron chelation strategies, including novel agents, combination therapies, and alternative approaches, while highlighting their impact on clinical outcomes in transfusion-dependent hematologic disorders. The availability of multiple iron chelators enables the use of combination therapies to target iron deposition in specific organs and enhance overall iron excretion. However, long-term studies utilizing advanced technologies to assess tissue iron levels are necessary to evaluate whether these emerging chelators can match the safety and efficacy of deferoxamine in controlling iron stores and preventing the major complications associated with transfusional iron overload.

Keywords: Blood transfusion, chelating agents, transfusional iron overload, Desferrioxamine.

INTRODUCTION

Iron is an essential element in the human body, and its concentration is tightly regulated to maintain physiological balance. Iron overload, characterized by excessive iron deposition in multiple organs, is typically indicated by a serum ferritin level greater than 1000 µg/L. This condition can result from both genetic and acquired causes, including frequent blood transfusions, excessive dietary or supplemental iron intake, and chronic liver diseases such as hepatitis. Without appropriate management, iron overload can lead to significant organ damage, particularly in the heart, liver, and endocrine glands.

Cardiac complications are among the most serious consequences of iron overload, especially in patients with transfusion-dependent conditions such as beta-thalassemia. Iron accumulation in the myocardium is responsible for approximately 71% of mortality in these patients. Effective management of iron overload is essential to prevent life-threatening complications, and the primary therapeutic approach is iron chelation therapy. This treatment aims to reduce labile plasma iron (LPI), which is the highly reactive and toxic form of non-transferrin-bound iron, and to promote the excretion of excess iron.

Phlebotomy is an effective treatment for hereditary hemochromatosis; however, it is not suitable for patients with chronic anemia, such as those with beta-thalassemia or other transfusion-dependent disorders. For these patients, iron chelation therapy remains the cornerstone of management. Chelators are specialized compounds that bind to excess iron, forming water-soluble complexes that can be safely excreted through the kidneys or bile.

The history of chelation therapy dates back to the early 1930s when Ferdinand Münz synthesized ethylenediaminetetraacetic acid (EDTA), initially

used for treating heavy metal poisoning. In the 1960s, deferoxamine was introduced as the first clinically effective iron chelator, revolutionizing the management of iron overload. Subsequent advancements have led to the development of oral chelators, including deferiprone and deferasirox, offering improved patient convenience and adherence compared to the parenteral administration required for deferoxamine.

Iron overload remains a major complication in transfusion-dependent hematologic disorders such as thalassemia major, sickle cell disease, and myelodysplastic syndromes (MDS). Persistent iron accumulation causes progressive organ dysfunction, significantly increasing morbidity and mortality. While iron chelation therapy is effective, traditional chelation agents present challenges such as side effects, variable efficacy in different tissues, and adherence difficulties.

Emerging evidence highlights the role of biomarkers, such as serum ferritin and liver iron concentration (LIC), in monitoring iron burden and guiding treatment decisions. Magnetic resonance imaging (MRI) techniques, including T2* MRI has become the gold standard for non-invasive assessment of tissue iron, especially in the heart and liver. These advances enable early detection of iron accumulation and more precise tailoring of chelation therapy.

Recent innovations in chelation therapy focus on improving patient outcomes through enhanced formulations, novel chelating agents, and combination therapies. These advancements aim to optimize iron removal from both plasma and tissue compartments, minimize toxicity, and improve quality of life. Ongoing research continues to refine chelation strategies, addressing unmet clinical needs and paving the way for more effective and personalized management of iron overload syndromes.

MATERIALS AND METHODS

This systematic review was conducted by searching in databases such as PubMed, Scopus, and Web of Science using keywords like “iron chelation therapy,” “thalassemia,” “deferiprone,” “deferasirox,” “combination therapy,” and “novel iron chelators.”

Studies published within the last 10 years focusing on advancements in chelation therapy for hematologic disorders. Articles reporting clinical trials, real-world data, and preclinical research on novel agents or combination strategies.Studies focusing solely on non-hematologic causes of iron overload or older therapies without updates. Information on drug efficacy, safety, patient adherence, and innovative approaches was extracted for synthesis.

RESULTS AND DISCUSSION

Iron overload is a serious complication of transfusion-dependent anemias, including thalassemia major and sickle cell disease (SCD). Patients with these conditions often require frequent blood transfusions to manage anemia, leading to excess iron deposition in vital organs like the liver, heart, and endocrine glands. If left untreated, iron overload can result in severe organ damage, including liver cirrhosis, heart failure, diabetes, and growth retardation, ultimately leading to premature death.

Chelation therapy is the cornerstone of treatment for iron overload, as it facilitates the removal of excess iron from the body. However, despite the availability of various iron chelators, challenges remain in terms of adherence, toxicity, and the ability to effectively target iron deposits in specific organs such as the heart.

Traditional Iron Chelators

1. Deferoxamine (DFO)

DFO is the first iron chelator developed and remains one of the most widely used treatments for iron overload, particularly for heart iron removal. It is administered parenterally (either by subcutaneous infusion or intravenous injection), often for prolonged periods of time, which significantly impacts patient adherence. While DFO is highly effective in removing iron from the liver and other organs, it has limited ability to reduce cardiac iron, which can contribute to cardiac dysfunction. For many patients, the requirement for continuous infusion over hours or days creates significant barriers to treatment.

Clinical challenge: Limited ability to penetrate tissues effectively and the inconvenience of the infusion regimen often result in suboptimal treatment adherence.

2. Deferiprone (DFP)

DFP is an oral chelator with a strong track record of reducing cardiac iron levels, making it particularly useful in the management of patients with cardiac siderosis. It is absorbed efficiently in the gastrointestinal tract, allowing for better adherence than parenteral therapies. However, its use is limited by its association with side effects such as agranulocytosis (a life-threatening reduction in white blood cell count) and gastrointestinal disturbances.

Clinical challenge: Regular monitoring of blood counts is essential to detect adverse effects, which complicates its use for patients, especially in resource-limited settings.

3. Deferasirox (DFX)

DFX is an oral chelator with once-daily dosing, which improves patient adherence compared to DFO and DFP. It is particularly effective in the liver and has been associated with better overall adherence due to its more patient-friendly dosing schedule. However, it is associated with renal and hepatic toxicities, which require regular monitoring of kidney

and liver function. In recent studies, DFX has shown promise in improving hepatic iron clearance, especially when combined with other therapies.

Clinical challenge: Although effective, the risk of renal and liver toxicity remains a major concern, necessitating careful long-term monitoring.

Combination Chelation Therapies

Recent advancements in iron chelation have emphasized the use of combination therapies, where agents with different mechanisms of action are used together to target distinct iron pools (such as cardiac vs. hepatic iron). Clinical trials have shown that combining DFP with DFO or DFX leads to synergistic effects, improving iron removal from multiple organs with reduced side effects due to lower doses of individual agents.

Example of combination therapy

- Combining Deferiprone (DFP), which has a strong affinity for cardiac iron, with Deferoxamine (DFO), which targets hepatic iron, results in more efficient overall iron reduction. This approach has been demonstrated to reduce organ-specific iron overload, such as in the heart and liver, with fewer adverse effects.

Combination therapies have shown promise in improving organ-specific iron removal, reducing the need for high doses of a single chelator, which may mitigate toxicities.

Emerging Chelators

1. Deferitazole and SP-420

New chelators, such as Deferitazole and SP-420, are in early-phase trials and are showing considerable promise in terms of improved specificity and reduced side effects. These chelators are designed to have better tissue penetration and may be more effective in targeting different iron pools compared to existing drugs.

Potential benefits: Reduced toxicity profiles, better tolerability in long-term use, and effectiveness in managing both hepatic and cardiac iron.

2. Polymeric Chelators

Polymeric DFO is a novel approach involving the conjugation of Deferoxamine to polymeric carriers like polyethylene glycol (PEG). These polymeric chelators are designed to enhance blood retention and tumor accumulation when used in cancer therapy, demonstrating a new potential for chelation therapy in oncology. These agents are also being evaluated for their ability to selectively target tumor-associated iron, improving the therapeutic potential of iron chelation in cancer patients.

Emerging use case: Polymeric chelators may also open doors for targeted cancer therapies by utilizing the chelation of iron within tumors to hinder tumor growth.

3. Oral Formulations with Enhanced Tolerability

New oral formulations like film-coated Deferasirox have improved tolerability by reducing gastrointestinal side effects, which have traditionally been a significant barrier to patient adherence in long-term iron chelation therapy. These formulations are being developed to enhance patient compliance, especially in pediatric patients and those requiring long-term treatment.

Non-Traditional Approaches

1. Erythroid-Stimulating Agents (ESAs)

Erythroid-stimulating agents, such as methoxy polyethylene glycol-epoetin beta (CERA) and biosimilars, have been investigated as adjuvants to reduce transfusion dependence, indirectly lowering the iron burden. However, the efficacy and safety of different ESA formulations remain uncertain, particularly due to a lack of large, comparative randomized trials. Some studies have suggested that ESAs may help reduce transfusion requirements, thus minimizing iron overload in the long term.

Cost-effectiveness: Biosimilar ESAs have the potential to reduce the cost of treatment for patients, particularly in low-resource settings.

2. Gene Therapy for Iron Overload

Gene therapy is emerging as a curative treatment for thalassemia and SCD, reducing or eliminating the need for transfusions and, consequently, the associated iron overload. Successful trials have demonstrated that genetically modified hematopoietic stem cells (HSCs) expressing β-globin can restore normal hemoglobin production, reducing transfusion dependence.

Notable outcomes: A 2007 study showed that a patient with βE/β0-thalassemia major who underwent gene therapy became transfusion-independent for 1–2 years with hemoglobin levels maintained at 9-10 g/dL. Trials are expanding, with patients with SCD also showing significant improvements.

Challenges: Although promising, gene therapy is still in the experimental phase and involves significant risks, such as clonal expansion and the need for ongoing safety evaluations.

Future Directions in Iron Chelation Therapy

Iron overload remains a significant challenge in managing transfusion-dependent anemia. In the coming years, combination therapies, novel chelators, and personalized treatment strategies are expected to revolutionize the management of this condition. Ongoing trials aim to develop chelators with better specificity for different iron pools, such as cardiac iron, and therapies that minimize adverse effects while improving patient adherence.

Further exploration into Hepcidin modulators, which target the iron-regulating pathways, shows promise for enhancing the body's natural ability to regulate iron metabolism, potentially providing a novel class of treatments. Mini-hepcidin and hepcidin agonists are currently being explored in clinical trials to regulate iron absorption and distribution effectively.

In conclusion, the landscape of iron chelation therapy has evolved significantly, with new agents and combination therapies offering improved outcomes in managing iron overload. Despite these advancements, challenges in terms of toxicity, patient adherence, and the ability to target iron in specific organs remain. Ongoing research into new chelators,

gene therapies, and non-traditional approaches such as erythroid-stimulating agents and Hepcidin modulators will likely shape the future of iron overload management. Personalized treatment strategies, tailored to the specific needs of patients based on their iron burden, organ involvement, and response to therapy, will be crucial for optimizing outcomes.

CONCLUSION

Recent advancements in iron chelation therapy have markedly improved the management of iron overload in transfusion-dependent hematologic disorders. Innovations such as combination therapies, enhanced oral formulations, and novel therapeutic agents have addressed the limitations of conventional treatments, resulting in improved patient outcomes. Additionally, emerging non-traditional approaches, including gene therapy and hepcidin modulators, offer promising avenues to reduce dependence on chelation therapy.

Despite these advancements, challenges related to cost, accessibility, and patient adherence persist, highlighting the need for ongoing research and global health initiatives. Future efforts should prioritize optimizing existing therapies, expanding access in underserved regions, and advancing curative strategies to alleviate the long-term burden of iron overload.

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