Chapter 5

IRON OVERLOAD SYNDROMES AND CHELATING LIGANDS

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Introduction

Iron is an essential element for cellular metabolism with a major role in redox cycling. Since it functions both as an electron donor and an acceptor, iron also serves as a co-factor in the active site of several key enzymes via critical biochemical pathways including ATP generation, oxygen transport, cell cycling, and DNA Synthesis (Özbolat, Yegani & Tuli, 2018).It is estimated that more than a quarter of human population are affected by the abnormalities of iron metabolism such as iron-deficiency anemia and iron overload (Barton & Edwards, 2000). Iron deficiency also leads to the deficiency of neurotransmitters such as dopamine and serotonin in the brain, thereby inducing several mental diseases such as schizophrenia, Parkinson's disease, and depression (Nishida, 2009). Iron overload syndromes are classified as genetic (hereditary hemochromatosis) or secondary syndromes (anemias and thalassemia) (Sadeek & El-Razek, 2010).

Iron overload occurs when excess iron accumulates in the body. When iron is present in excess, iron-mediated oxidative stress can lead to the damage of proteins, lipids, and nucleic acids and can be cytotoxic. Due to its ability to undergo cyclic oxidation and reduction, iron generates reactive oxygen species (ROS) (Potuckova, Hruskova & Bures, 2014; Etheram, Bavarsad & Mokhtari, 2014; Kontoghiorge & Komtoghiorghes,2016). In the presence of molecular oxygen, the ''loosely-bound'' iron is able to undergo redox cycling between its two most stable oxidation states, namely iron (II) and iron (III), thereby generating oxygen-derived free radicals such as hydroxyl radicals. Hydroxyl radicals are highly reactive and capable of interacting with most types of biological molecules including sugars, lipids, proteins and nucleic acids, resulting in peroxidative tissue damage and life-threatening complications such as cirrhosis, hepatocellular cancer, diabetes and heart diseases (Özbolat & Tuli, 2018).

Iron chelation therapy involves the use of ligating drugs that avidly bind iron for the treatment of iron overload (Sadeek & El-Razek, 2010). Currently,

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the first-line iron chelator for iron overload in thalassemia patients in many countries worldwide (Mettananda, 2018).

However, although DFX is well-tolerated with a high safety profile,it leads to several adverse effects including gastrointestinal disturbances, increased liver enzymes, maculopapular skin rash, and elevation of serum creatinine levels (Ejaz, Baloch &Arif, 2015). Moreover, it also leads to several side effects,with most common ones including diarrhea, abdominal pain, nausea, vomiting, changes in renal and liver function, auditory and ocular alterations, skin rash, headache, and dizziness (Şenol et al., 2016).

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