Clinical Applications of Deferiprone and the Maltol–Iron Complex

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The historical insights and background of the discovery, development and clinical use of deferiprone (L1) and the maltol–iron complex, which were discovered over 40 years ago, highlight the difficulties, complexities and efforts in general orphan drug development programs originating from academic centers. Deferiprone is widely used for the removal of excess iron in the treatment of iron overload diseases, but also in many other diseases associated with iron toxicity, as well as the modulation of iron metabolism pathways. The maltol–iron complex is a recently approved drug used for increasing iron intake in the treatment of iron deficiency anemia, a condition affecting one-third to one-quarter of the world's population.

deferiprone iron anemia

1. Diseases of Iron Metabolism Imbalance and Their Treatment

Iron imbalance is associated with serious clinical conditions affecting many categories of patients [1][2][3][4]. In particular, iron deficiency anemia (IDA) affects about one-third to one-quarter of the world's population, with the symptoms including increased child and maternal mortality, pregnancy complications, cardiac complications, fatigue, reduced physical and mental performance and paleness [5][6][7][8]. In many of these cases, the symptoms of iron deficiency are cured using iron supplements, which are widely available in different formulations [9][10][11][12]. In general, however, most of the iron formulations suffer from low specificity, which causes reduced iron absorption and also toxicity in the gastrointestinal tract due to the presence of excess non-absorbed iron [13][14][15]. In many clinical cases such as cancer, kidney disease and other categories of patients, intravenous iron formulations are used, which can also be effective in treating IDA, but toxic side effects have also been reported [16][17][18][19][20][21][22][23]. As in many diseases, a risk/benefit assessment is required for the selection of the appropriate iron formulation and route of administration in each IDA patient case. Additional factors may also be observed in the selection of the iron formulation, such as demographic reasons and costs [24][25].

There are many other diseases related to iron metabolism imbalances in addition to IDA, including the hemoglobinopathies and idiopathic hemochromatosis, which are the most common genetic diseases affecting humans [26][27][28][29][30][31][32]. The hemoglobinopathies include thalassemia and sickle cell disease, which are mainly found in developing countries. It is estimated that about 100,000 children are born annually with thalassemia, mainly in Southeast Asia, the Middle East and Mediterranean countries, and about the same number are born with sickle cell anemia [26][27][28]. For example, thalassemia is endemic in Cyprus, where 1 in 6 persons is

an asymptomatic thalassemia heterozygote carrier and about 1 in 1000 is a thalassemia major or thalassemia intermediate patient. The prevention and treatment programs for thalassemia and especially chelation therapy impose a great financial burden to the health budget of many developing countries [26][33][34].

The major form of treatment of thalassemia major is regular red blood cell transfusions every 1–4 weeks and daily chelation therapy [28][34]. Multiple transfusions cause increased iron deposition and damage to the heart, liver, spleen and other organs unless iron chelation therapy is introduced early in life [28][34]. Iron overload in thalassemia has the highest rate of morbidity and mortality of metal-related intoxication in humans [34]. Iron chelation therapy in thalassemia and other transfusional iron loading conditions is carried out worldwide using the generic drugs deferoxamine (DF), deferiprone (L1) and deferasirox (DFRA) [35][36][37][38][39][40]. The combination of chelating drugs, and especially the L1/DF combination, is also widely used in many countries [34][35][36][37][38][39][40].

There are many other diseases related to iron and other metal imbalance and toxicity conditions, where iron-chelating drugs and iron chelator complexes could be used as originally suggested in 2003 [41]. Many of these diseases affect millions of patients, including cancer, Alzheimer's and Parkinson's diseases, Freidreich's disease, AIDS, infectious diseases and aluminum and other metal intoxication conditions [41]. The priority in the selection of diseases for testing the efficacy and toxicity of chelating drugs is based on a risk/benefit assessment in comparison to other available therapeutics in each disease [38]. The repurposing of chelating drugs in non-iron-loaded diseases was facilitated following new scientific evidence and also safety findings, especially related to the number of non-iron-loaded patients and conditions used for clinical trials, which progressively has increased in the last few years [42].

2. The Use of Deferiprone in Transfusional Iron Overload and Other Diseases

Thousands of patients suffering from iron overload and also other illnesses, as well as normal volunteers, have been treated in the last 40 years with L1, which is regarded as one of the safest drugs in the world per dose, e.g., 50–100 mg/kg received on a daily basis. In this context, the major category of patients receiving L1 is β-thalassemia major patients, followed by many other categories of iron-loaded patients, including β-thalassemia intermedia, HbE β-thalassemia, HbS β-thalassemia, sickle cell anemia, myelodysplastic syndrome, aplastic anemia, Fanconi's anemia, Blackfan–Diamond anemia, pyruvate kinase deficiency, idiopathic hemochromatosis, iron overload in hemodialysis, and juvenile hemochromatosis [34][36][37][43][44][45][46][47][48][49][50][51].

Similarly, many other categories of patients with normal iron stores have also been receiving L1, mostly in short- but also in long-term clinical trials. The repurposing of L1 for diseases other than iron overload was organized based on similar dose protocols to those of iron overload and took place originally in the in the UK but also other countries within a few years of initiating the clinical trials with transfusional iron-loaded thalassemia and myelodysplasia patients [52][53][54][55]. The clinical use of L1 in several other categories of patients with normal iron stores has increased with time and involved many other different dose protocols, durations of administration and numbers of patients in each category. The decision to use L1 in these conditions was in most cases related to the

absence of other effective therapies. Some of the categories of diseases reported to have received L1 include renal dialysis, aluminum overload, Friedreich's ataxia, Parkinson's and Alzheimer's diseases, neurodegeneration with brain iron accumulation, pantothenate kinase 2-associated neurodegeneration (PKAN), rheumatoid arthritis, aceruloplasminemia, glomerulonephritis and diabetic nephropathy, malaria and HIV [56][57][58][59][60][61][62][63][64][65][66][67].

In general, no serious toxicity was reported for clinical trials of up to 9 months duration and with a maximum dose of 100 mg/kg/day in patients with normal iron stores. Most importantly, significant clinical improvements have been reported in most of these categories of patients [56][57][58][59][60][61][62][63][64][65][66][67]. Positive outcomes have also been reported, where L1 was used in adjuvant and combination therapies, which was similar to iron-loaded cases [65][68].

However, it is unfortunate that in many of the recent clinical trials involving mainly neurodegenerative disease patients, no rationale for the selection of the L1 dose protocol nor of iron metabolism balance studies was given [59][60][61]. For example, in many such studies, L1 was used in single or repeated doses of 15 mg/kg/day with disappointing results [59][60][61]. It should be noted that previous dose escalation and iron metabolism balance studies have shown that the use of such low doses of L1 in iron-loaded and non-iron-loaded conditions was mostly ineffective in increasing iron excretion or the improvement of other hematological parameters [52][53][68][69]. The selection of posology is critical for evaluating the risk/benefit assessment of L1 and all other drugs. Furthermore, the rationale for the dose protocol selection for the use of L1 and all other drugs in any disease should be accompanied by pharmacological and therapeutic evidence such as the estimation of the pharmacokinetic, metabolic and other parameters and the critical drug concentration for optimal therapeutic activity, as previously shown for the use of L1 in thalassemia patients [52][53][70][71].

It can be suggested in general that the positive results in terms of safety and the diverse categories of iron-loaded and other patients treated in clinical trials with L1 have increased the prospects of the wider use of the drug in many other diseases, including diseases related to free radical pathology and also in cancer [72][73][74].

3. The Use of Maltol–Metal Complexes in Diseases Other Than Iron Deficiency Anemia

The identification of the possible applications of maltol and the maltol–iron complex in medicine was proposed following their physicochemical characterization, protein and cellular interactions and in vivo and other studies [75]. Within this context, many investigations have been carried out on the possibility of the clinical use of metal complexes of maltol other than iron, such as zinc complexes as supplements for zinc deficiency, maltol–gallium complexes for the treatment of cancer, maltol complexes with diagnostic metals such as indium for use in clinical diagnosis and maltol complexes with theranostic metals such as (68-Ga) gallate [16][75].

The maltol–gallium complex (gallium maltolate or maltol gallate) has attracted a lot of interest because it has reached the stage of clinical trials and veterinary use, mainly for its anticancer and antimicrobial activities [76][77][78]

[79][80][81][82][83]. The basic mode of action in relation to the anticancer and antimicrobial targeting of the maltol–gallium complex is the disruption of iron metabolism pathways by mimicking iron. In particular, the antimicrobial activity of the maltol–gallium complex is thought to cause the partial deprivation of iron, which is essential for the rapid growth of pathogenic microbes [80][81][82][83][84][85][86]. Similarly, the anticancer activity of the maltol–gallium complex is thought to be based on the delivery of gallium to transferrin, causing a reduction in iron uptake by the cancer cells and a reduction in their growth through the slow turnover of the iron-dependent enzyme ribonucleotide reductase, resulting in the inhibition of DNA synthesis [87][88][89][90]. This mechanism of cancer cell inhibition mainly affects cancer types such as breast, prostate and bladder cancers and leukemias, which involve an abundance of transferrin receptors and the upregulated production of ribonucleotide reductase [87][88][89][90][91][92]. A further mechanism of DNA inhibition by the maltol–gallium complex is thought to involve the transfer and incorporation or binding of gallium to nucleotide substrates and subsequently reduced DNA synthesis [87].

Another major area of application to medicine in relation to iron and other metal complexes of maltol is their use in the theranostic and diagnostic fields, which are rapidly expanding, involving many diseases [87][93][94][95][96]. The maltol complexes involving different metal ions have variable physicochemical and biochemical properties, which appear to affect the bodily distribution of the metal ions and radiotracers, similar to other metal chelator complexes [87][93][94][95][96][97][98][99]. Targeted chelator metal complexes have been identified for the diagnostic and theranostic application of radiotracer metals in cancer, inflammation and other diseases [87][97][98][99]. In clinical studies in hepatocellular carcinoma patients, for example, cancer cells have been found to be highly gallium-avid in (67)Ga diagnostic scans. In this context, treatment with an oral maltol–gallium complex caused significant improvements of cancer indices and necrosis of the tumor [77].

The increased number of applications of maltol–metal complexes in medicine and veterinary medicine, as well as the pharmacological and toxicological information obtained from relevant studies, has increased the prospect of their wider use in many other fields of diagnostic and theranostic medicine [100][101][102][103]

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