Effects of micronised microencapsulated ferric pyrophosphate supplementation in patients with advanced cancer and iron deficiency: a single-centre cohort pilot study

Alessandro Pappalardo[1,2], Walter Currenti[3], Rossella Ponzio[4], Giulio Mellini[2], Daniela Nicolosi[4], Lucia Longhitano[4], Daniele Tibullo[3], Sergio Castorina[1,5], Giuseppe Palumbo[5]

[1]Polyclinic "G.B. Morgagni" Mediterranean Foundation, Catania; [2]"SAMOT Catania" Onlus, Catania; [3]Department of Biomedical and Biotechnological Sciences, University of Catania, Catania; [4]"ARNAS Garibaldi" Hospital, Catania; [5]Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Section of Haematology, University Hospital "Policlinico-Vittorio Emanuele", University of Catania, Catania, Italy

Background. Iron deficiency is the most common nutritional deficiency in advanced cancer patients and causes anaemia. Iron deficiency anaemia treatment (i.e. intravenous or oral iron administration) has been demonstrated to be effective but is often associated with adverse reactions. Micronised microencapsulated ferric pyrophosphate (MMFP) is a recently developed formulation characterised by a higher intestinal bioavailability due to the small particle size distribution at nanometer level. The aim of this study was to evaluate the efficacy of an oral administration of 30 mg of MMFP associated with 80 mg of ascorbic acid in advanced cancer patients with hyposideraemia.

Materials and methods. This was an observational prospective cohort study (10 months) conducted on 42 adult patients with advanced cancer and serum iron levels lower than 60 μg/dL. All patients received one capsule/day for 30 days of a supplement containing 30 mg of MMFP and 80 mg of ascorbic acid. At enrolment (T0) and at 30 days (T1) patients were subjected to blood sampling for evaluation of serum iron, ferritinaemia and blood count. In addition, any undesirable effects reported by patients were evaluated.

Results. MMFP treatment increased sideraemia from 36.1±8.37 μg/dL to 73.22±28.60 μg/dL, haemoglobin from 10.43±1.09 g/dL to 11.52±1.90 g/dL, and ferritinaemia from 42.10±16.90 ng/mL to 123.33±55.79 ng/mL. No adverse effects were noted from the use of MMFP supplementation.

Discussion. The supplementation of 30 mg/d of MMFP in combination with 80 mg/d of ascorbic acid in advanced cancer patients with hyposideraemia led to a significant increase in sideraemia and ferritinaemia. Moreover, in some of the patients whose serum iron level did not increase, an increase in haemoglobin was observed.

Keywords: micronised microencapsulated ferric pyrophosphate, hyposideraemia, cancer, iron deficiency anaemia, iron.

Introduction

Iron deficiency is the most common nutritional deficiency in advanced cancer patients[1,2]. This deficiency is frequently associated to the presence of anaemia ("sideropenic anaemia"), which is present in 67% of cancer patients[1-3]. Many factors may be responsible for the onset of hyposideraemia in cancer patients, such as an increased need secondary to increased erythropoiesis, intestinal absorption reduction (i.e. dietary deficiency, impaired absorption), the increase in losses secondary to acute or chronic bleeding, and increased exfoliation of gastrointestinal epithelial cells. Furthermore, the vast majority of anaemic cancer patients present some degree of anaemia of chronic disease (ACD) due to cancer.

Data from the European Cancer Anaemia Survey (ECAS) study show that only 40% of patients suffering from sideropenic anaemia are treated with *ad hoc* medical care, and among these patients, 18% are treated with erythropoietin (Epo), 15% with blood transfusions, and 7% exclusively with iron supplementation[3].

The gold standard of iron therapy consists in the intravenous administration of iron preparations[4], even though it may be associated with adverse reactions (i.e. allergy, thrombophlebitis). Furthermore, compared to oral treatment, parenteral intravenous therapy may be uncomfortable and put the patient at higher risk, and can also increase patient management costs. Therefore, oral iron (ferrous sulphate) supplementation may represent

an alternative to intravenous therapy, although it is frequently associated to gastroenteric adverse effects (i.e. nausea, vomiting, constipation)[5-7]. Furthermore, since it is a non-haeme iron, response time is generally slow due to its well-known modest bioavailability, which could be further reduced by inflammation[5].

Micronised microencapsulated ferric pyrophosphate (MMFP) is a recently developed formulation characterised by a higher intestinal bioavailability due to the small particle size distribution at nanometer level[8]. Like other oral iron formulations, MMFP contains ascorbic acid, since this modulates iron metabolism by stimulating ferritin synthesis, inhibiting lysosomal ferritin degradation, and decreasing cellular iron efflux. Furthermore, ascorbate cycling across the plasma membrane is responsible for ascorbate-stimulated iron uptake from low-molecular-weight iron-citrate complexes, which are prominent in the plasma of individuals with iron-overload disorders[9].

As MMFP is a relatively new pharmacological product, and since there are no data regarding its efficacy or the incidence of adverse effects, the aim of the present study was to evaluate whether daily administration of low-dose MMFP (30 mg) (Sideremil®, Enfarma, Misterbianco, CT, Italy) was efficacious in correcting iron deficiency (ID) in patients with advanced cancer.

Patients and methods

Study design and patients

This observational prospective cohort study took place over a period of ten months (September 2017-June 2018). A total of 42 patients with advanced cancer were enrolled. There were 22 men and 20 postmenopausal women with mean age: 66±12 years. Cancer sites were: lung (n=9), breast (n=7), colorectal (n=7), liver n=5), head and neck (n=5), pancreas (n=4), gallbladder (n=3), other (1 skin melanoma, 1 liposarcoma). At enrollment (T0), all patients presented hyposideraemia, hypoferritinaemia and anaemia. Patients with a clear recent history of bleeding were excluded from the study. Participation in the study protocol was strictly voluntary, without remuneration. The study design, as well as the collection, analysis and interpretation of the results, comply with the provisions of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, available through the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network (*http://www.equatornetwork.org/*). The study design was approved by an independent Ethics Committee (*Comitato Etico Catania 2, Azienda Ospedaliera "Garibaldi"*, Approvation n. 671, September 12, 2017). All patients received one capsule/day for 30 days of a supplement containing 30 mg of MMFP and 80 mg of ascorbic acid. At T0 and at 30 days (T1) blood samples were taken to evaluate serum iron, ferritinaemia and blood count. Patients were asked to report the onset of new symptoms or worsening of their overall clinical conditions (including gastrointestinal disorders, such as diarrhea, constipation, nausea, vomiting, abdominal pain, and black stool colour). Furthermore, clinical data regarding specific therapy toxicity were recorded during the follow up by the same physician co-ordinating the study. Standard laboratory procedures were used for blood sampling and measurements.

Sample size and statistical analysis

The primary efficacy end point of the study was to test the null hypothesis that the administration of an oral preparation of 30 mg of MMFP associated with 80 mg of ascorbic acid in advanced cancer patients maintains stable levels of serum iron, against an alternative hypothesis that there is an increase in serum iron during the evaluation period. Assuming an average sideraemia value of 50±20 mg/dL, an increase in values of at least 5 mg/dL, a test power of 90%, a probability of 0.05 for the type I error, a loss of 10% of patients during the study and taking a single-tail test, a sample size of 41 patients was obtained.

Quantitative variables were expressed as frequencies and percentages or through measurement of central tendency parameters (mean and median) and dispersion (standard deviation and range), and analysis of changes in post-baseline visits (comparison between the various analysis over times) by Student's *t*-test for paired data.

Results

All patients presented hyposideraemia and hypoferritinaemia at T0. During the period of treatment with iron pyrophosphate, patient adherence was high and there were no adverse effects associated with MMFP administration. MMFP treatment was associated with a significant increase in all the haematochemical values tested (T1 *vs* T0) (Figure 1). In detail, sideraemia increased from 36.1±8.37 μg/dL to 73.22±28.60 μg/dL and ferritinaemia increased from 42.10±16.90 ng/mL to 123.33±55.79 ng/mL. Overall, an increase in haemoglobin (Hb) ranging from ≥1 g/dL and <2 g/dL was observed in 15 patients (36%), an increase in Hb ≥2 g/dL was observed in 10 patients (24%), while 14 patients (33%) reached an Hb level of 12 g/dL.

Discussion

Oral supplementation with iron salts may be an effective strategy to increase Hb levels in ID anaemia[10]. However, its efficacy in replenishing iron stores may be reduced by its low bioavailability, potential adverse

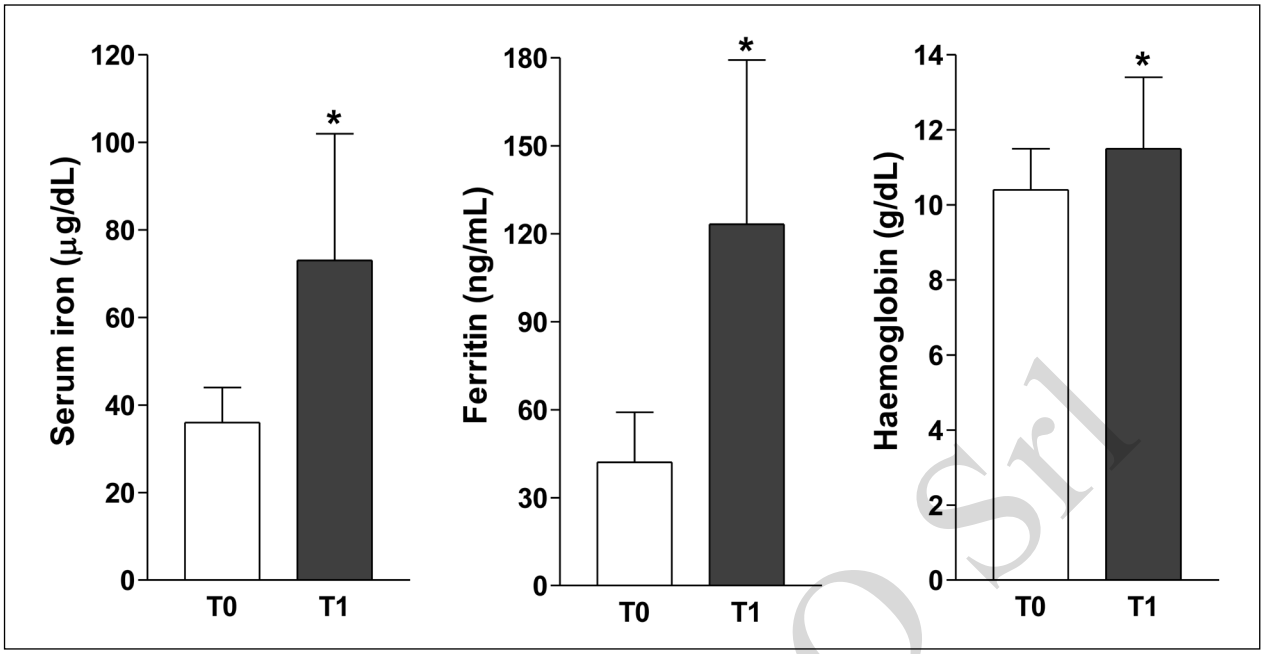

Figure 1 - Haematologic parameters (sideraemia, ferritinaemia and haemoglobin) at baseline (T0) and at 30 days after micronised microencapsulated ferric pyrophosphate supplementation (T1). p<0.001.

gastrointestinal events, non-compliance[11-13], as well as inflammation associated with increased hepcidin levels, which lead to impaired absorption of iron from the gastrointestinal tract and retention of iron in the reticuloendothelial system[14].

MMFP is soluble in water and its bioavailability is superior to that of non-micronised iron pyrophosphate, which has a larger particle size, and to that of non-encapsulated iron pyrophosphate[15]. Another possible mechanism to explain the higher bioavailability of MMFP is the M cells preferential binding of particulates up to 10 μm in diameter and their transport to immunocompetent cells in underlying mucosal lymphoid tissue[16]. However, this latter mechanism has only been demonstrated in mice and thus needs to be confirmed in human studies.

Currently, the available evidence concerning the bioavailability and efficacy of MMFP in humans is limited[17] and the lack of studies in cancer patients does not allow any comparison with our data to be made.

The limitations of the present study are the observational uncontrolled experimental design. However, to the best of our knowledge, no studies in cancer patients are currently available concerning the efficacy of MMFP as exclusive therapy. Furthermore, no randomised controlled trials (RCT) are available comparing MMFP to other oral iron or intravenous (i.v.) iron to demonstrate its superiority in this population. In our study, we evaluated sideraemia and ferritin as biomarkers since they represent a direct expression of body iron content. Given this, our data showed that MMFP was able to increase sideraemia (+98%), ferritin (+293%), and Hb (+14%). Our data are consistent with a previous report showing that orally administered microencapsulated iron pyrophosphate was able to increase both sideraemia and ferritin levels, even though the increase was lower compared to that observed in our study[17].

The level of Hb was selected as a secondary target because, especially in advanced cancer patients, it depends on other variables, such as levels of red blood cell precursors in bone marrow, erythropoietin levels, nutritional status (i.e. amino acid availability for the globin synthesis) that could bias our results. However, Hb levels were taken into due account in the present study since it can reduce circulating iron, thus indirectly regulating both sideraemia and ferritin levels.

Conclusion

Treatment with MMFP (30 mg/d) in combination with ascorbic acid (80 mg/d) results in a significant increase in sideraemia and ferritin in advanced cancer patients with hyposideraemia, without any significant adverse effects. The reason of such efficacy is likely due to its favourable bioavailability, even though further comparative studies with other iron forms (i.e. oral iron salt or i.v. iron) are needed.

Authorship contributions

All Authors contributed equally to the study.

The Authors declare no conflicts of interest.

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Correspondence: Walter Currenti
Department of Biomedical and Biotechnological Sciences
University of Catania
Via Santa Sofia 89
95125 Catania, Italy
e-mail: currentiw@gmail.com