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IRON CITRATE (SYNTHESIT) SUPPLEMENTATION DURING PANCREAS CANCER SHOWED SURPRISING RESULTS – CASE STUDY

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Abstract

Iron is a crucial mineral for our organism and its deficiency can cause serious health problems such as anaemia, fatigue, and impaired physical fitness. It has been shown that anaemia or iron deficiency is very common in patients with cancer. These patients benefit from iron supplementation either in intravenous or oral form. Our patient is a 67-year-old Russian woman with pancreatic cancer diagnosed in 2019. She fought off lymphocytic leukaemia in 2015. She refused treatment for her pancreatic cancer. The specific type of pancreatic cancer was not specified as the patient chose not to undergo targeted testing. Between March 2020 and February 2023, she took the dietary supplement Synthesit for three cycles (1 cycle lasted about a month).

After taking the dietary supplement, a total percentage of neutrophils became in the reference range. Subjectively, the patient started to feel better after taking Synthesit and her quality of life and well-being has improved as well. It might be supposed that the dietary supplement could have some effect on her well-being and various blood parameters such as white cells count.

Even though the dietary supplement is not supposed to be used for treatment of diseases, it can change some blood parameters and improve the immune system.

This short case study presents the patient with pancreatic cancer who started to take the dietary supplement Synthesit which contains iron in the form of citrate salt in a dosage of 800 µg per capsule, 1 capsule per day. The dietary supplement was administered over three treatment cycles (1 cycle took about a month) from March 2020 to February 2023. It describes a difference in blood test results before taking Synthesit and after the administration of Synthesit.

Keywords: pancreatic cancer, iron supplementation, iron citrate

INTRODUCTION

Iron (Fe) is a vital mineral for various physiological processes in our organism including oxygen metabolism and uptake, electron transport in mitochondria, and energy metabolism. Additionally, iron plays a critical role in maintaining proper muscle function and haematopoiesis, making it indispensable for overall physical functioning and well-being (1,2).

However, the balance of iron homeostasis is crucial, as the presence of free bivalent iron can lead to the generation of free oxygen radicals, causing tissue damage. Therefore, precise control of iron levels is necessary to minimize the concentration of free iron (1).

In the context of cancer, iron regulation and homeostasis may be compromised (3). This can result in an inadequate iron supply for erythroblasts leading to weakness, fatigue, impaired physical fitness, well-being, and anaemia (2). Notably, deficient iron levels are prevalent in patients with pancreatic cancer (63%), underscoring the significance of addressing iron imbalances in this population. This study has indicated that iron supplementation can offer benefits to individuals with cancer (4).

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Pancreatic cancer has one of the lowest combined five-year survival rates among various cancers, with only 5 to 10 percent of patients still alive five years after the diagnosis (5).

If pancreatic cancer has spread, patients may observe new symptoms. It commonly metastasizes to the liver and it can also extend to the lymph nodes, abdomen, lungs, and occasionally the bones. The symptoms of advanced pancreatic cancer include weight loss, abdominal discomfort, a general feeling of being unwell, jaundice, ascites, lack of appetite (6).

Pancreatic cancer's poor prognosis profoundly impacts patients' quality of life, leading to substantial deterioration, including mental changes, cognitive decline, and coping with the disease. Comorbid depression is common and overall health-related quality of life is notably low (7).

In this case study, it is presented that the patient diagnosed with pancreatic cancer started taking the dietary supplement Synthesit containing iron citrate (800 µg per capsule), 1 capsule per day, for a total of 3 months over 3 years. A comparison of blood test results before and after the administration of Synthesit is examined to explore any potential impacts of the dietary supplement.

Case description

This case study presents a unique clinical scenario involving a 67-year-old woman from Russia diagnosed with pancreatic cancer in 2019. The patient declined to undergo any testing for a specific type of pancreatic cancer. The patient's medical history includes a dental intervention for tooth extraction in 2015. After the tooth extraction, a complication of infection emerged. Subsequent laboratory analyses revealed the presence of chronic B-lymphocytic leukaemia (B-CLL), specifically categorised as stage B according to the Binet staging system, with CD20+ positivity. To address the B-CLL diagnosis, the patient underwent a six-month chemotherapy regimen consisting of 6 treatment cycles. She completed her chemotherapy regimen after half a year, in May 2016. Eventually, a remission from leukaemia was achieved in May 2016. In an effort to support her immune system after chemotherapy, she incorporated the use of thymus extract intravenously in June 2016 (after a month of the 6th cycle of chemotherapy). The treatment involved administering thymus extract intramuscularly at a dose of 20 mg/day for 10 days, followed by a break of 10 days. This procedure was repeated thrice and continued until July 2016. Following a monthly interruption, the regimen was repeated once more as a 10-day administration period. After an extended interval, the patient resumed the administration of thymus extract in the spring and autumn of 2017.

However, this therapeutic approach of chemotherapy was not without challenges, as the patient experienced complications, including pneumonia episodes after the first and the sixth treatment cycles. Furthermore, nephropathy manifested during chemotherapy, leading to a decline in renal function to 35% of its efficiency. The patient also endured various severe adverse effects of chemotherapy such as joint pain, a cataract, gastropathy, elevated hepatic enzyme levels, and oral candidiasis.

In December 2019, a haematologic examination revealed elevated levels of gamma-immunoglobulins (IgG), surpassing 17% of the overall immunoglobulin levels (Table 1). This finding raised a suspicion of an underlying a pancreatic pathology, which was later confirmed to be pancreatic cancer, possibly related to her prior history of leukaemia.

The specific type of pancreatic cancer was not specified as the patient chose not to undergo targeted testing. Despite the diagnosis, the patient made an informed decision to decline conventional anticancer treatments and instead chose to alter her lifestyle significantly. She also didn't undergo pancreatic cancer surgery.

Opting for a shift from urban to rural living, the patient embraced a lifestyle characterised by regular physical exercise and adherence to a healthful dietary regimen.

Additionally, the patient initiated the consumption of a dietary supplement Synthesit, enriched with iron citrate at a dose of 800 µg/capsule, 1 capsule per day. The dietary

supplement was administered over three treatment cycles (1 cycle took about a month) from March 2020 to February 2023, during which her blood parameters exhibited notable improvements (Figure 1).

RESULTS

After the administration of three treatment cycles of the dietary supplement Synthesit, a comparative evaluation of blood analyses conducted in July 2021 and March 2023 demonstrated that the total percentage of neutrophils had improved and now fell within the reference range. Notably, the values observed three years prior to Synthesit intake were lower than the reference range for neutrophils.

Conversely, the analysis conducted in July 2021 indicated that the thrombocyte count was within the reference range, whereas in March 2023, thrombocytopenia and lymphocytosis persisted (Table 2).

In conjunction with the objective findings, the patient also reported experiencing a notable improvement in her overall well-being and quality of life following the administration of Synthesit. Subjectively, she expressed enhanced satisfaction with her health status, an essential aspect during cancer treatment.

These results suggest a potential beneficial impact of Synthesit on specific haematological parameters, particularly neutrophils and thrombocytes. However, the continued presence of thrombocytopenia and lymphocytosis indicates that additional evaluation and monitoring are required to comprehensively assess the supplement's long-term effects on haematological profiles.

It is imperative to acknowledge that while subjective improvements in the patient's well-being are noteworthy, further investigations encompassing a larger cohort and controlled clinical studies are warranted to establish a robust correlation between Synthesit supplementation and haematological parameters in the context of cancer treatment.

Table 1 Analyses of blood plasma proteins done in December 2019 and March 2023. Parameters that were out of the reference range are highlighted. Values marked as dash mean no data available.

December 2019				March 2023	
Fraction	**%**	**Reference range %**	**g/l**	**g/l**	**Reference range**
Albumin	62.9	60.3 – 72.8	44.0	41.4	37.5 – 50.1
Alpha1-globulins	2.2	1.0 – 2.6	1.5	3.0	1.9 – 4.6
Alpha2-globulins	8.6	7.2 – 11.8	6.0	6.1	4.8 – 10.5
Beta1-globulins	6.0	5.6 – 9.1	4.2	-	-
Beta2-globulins	3.3	2.2 – 5.7	2.3	-	-
Beta-globulins	-	-	-	6.8	4.8 – 11.0
Gamma-globulins	**17.0>**	6.2 – 15.4	11.9	11.7	6.2 – 15.1
Albumin/Globulin ratio	1.70	1.2 – 2.0	-	1.5	1.2 – 2.0
Monoclonal IgG kappa	0.9	-	0.6	-	-
Total protein	69.9	62 – 81	-	67	62 – 81

Table 2 Blood analyses before taking Synthesit in February 2020, during taking in July 2021, and after taking it in March 2023. Parameters that were out of the reference range are highlighted. Values marked as dash mean no data available.

Parameter	Before taking Synthesit **02/2020**	During taking Synthesit **7/2021**	After taking Synthesit **03/2023**	**Reference range**	**Unit of measurement**
Haematocrit	40.9	-	42.7	35.0 – 47.0	%
Haemoglobin	14.0	14.8	14.5	11.7 – 16.0	g/dl
Erythrocytes	4.58	4.90	4.72	3.80 – 5.30	$*10^6/\mu l$
Thrombocytes	**116**	260	**123**	150 – 400	$*10^3/\mu l$
Leukocytes	7.07	**4.20**	6.80	4.50 – 11	$*10^3/\mu l$
Neutrophils (total), %	**40.30**	66	48.40	48.0 – 78.0	%
Lymphocytes, %	**50.5**	-	**44.1**	19.0 – 37.0	%
Monocytes, %	7.5	-	5.6	3.0 – 11.0	%
Eosinophils, %	1.4	3	1.6	1.0 – 5.0	%
Basophils, %	0.3	-	0.3	<1.0	%
Neutrophils abs.	2.85	-	3.29	1.56 – 6.13	$*10^3/\mu l$
Lymphocytes abs.	3.57	-	3.00	1.18 – 3.74	$*10^3/\mu l$
Monocytes abs.	0.53	**1**	0.38	0.20 – 0.95	$*10^3/\mu l$
Eosinophils abs.	0.10	-	0.11	0.00 – 0.70	$*10^3/\mu l$
Basophils abs.	0.02	-	0.02	0.00 – 0.20	$*10^3/\mu l$
Erythrocyte Sedimentation Rate (ESR)	12	4	7	<30	mm/h

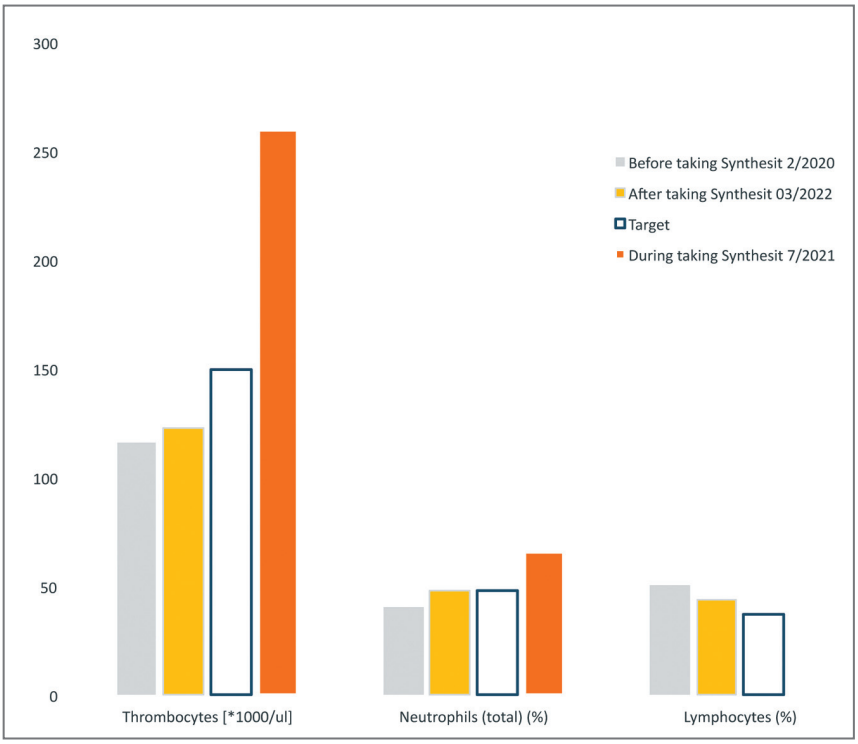

Fig. 1 Comparison of various haematological parameters

DISCUSSION

Pancreatic cancer is a highly aggressive and deadly malignancy with limited treatment options. However, there have been promising advancements in understanding the molecular mechanisms of pancreatic cancer and identifying potential therapeutic approaches (8). Here are some possibilities for pancreatic cancer treatment:

Surgery

Surgery offers a potential cure for pancreatic cancer, but only 20% of patients reach a questionable "cure". Conventional surgery involves pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy for extensive tumour growth. 5-year survival rates are less than 5% (8,9).

Pancreatic cancer chemotherapeutics

Pancreatic cancer recurrence rates are high, making chemotherapy an inevitable choice for patients after surgery. However, the overall prognosis of patients undergoing adjuvant chemo-treatments remains dismal due to low vasculature and the buildup of immunosuppressive microenvironment around the pancreas (9). Gemcitabine, the first FDA-approved agent for treating pancreatic cancer patients, is used in chemotherapy and has modest overall survival rates. Its clinical beneficial response appears more positive than other drugs. Although, it faces challenges due to the establishment and development of cancer microenvironment in progressive cancerous lesions, which reduces or blocks persistent drug penetration (10).

5-Fluorouracil (5-FU) is another important anti-cancer drug, promoting the incorporation of fluoridine triphosphate into RNAs, of fluorodeoxyuridine triphosphate into DNAs and

suppressing thymidalate synthase, resulting in severe genomic damages for eliminating cancer cells. It is often used in combination with other anticancer drugs gemcitabine, cisplatin, doxorubicin, or others (11).

Folfirinox is a relatively effective but aggressive combination treatment for pancreatic cancer patients, composed of four anticancer drugs: 5-FU, irinotecan, oxaliplatin, and leucovorin (12).

Immunotherapy

Pancreatic cancer lesions form a solid fibrotic and cancerous microenvironment, preventing drug penetration, and suppressing immune reactions. This microenvironment is caused by immunosuppressive cytokines which stimulate further expansion of immunosuppressive lymphocytes to antagonize anticancer responses (8). Immunotherapy is promising but more complex than we anticipate. Ipilimumab is an antibody-based treatment (13). The drug is shown to improve the overall survival of pancreatic cancer patients. Nivolumab and pembrolizumab are used clinically for melanoma treatment and still under clinical trials for treating pancreatic cancer. Therapeutics targeting immunosuppressive cells to reach the pancreatic tumour microenvironment may enhance the efficacy of immune-based therapies (8).

Other approaches for pancreatic cancer therapy

Pancreatic tumour-associated microenvironment cells promote epithelial-mesenchymal transition and remodelling surrounding tissues. Hyaluronan, a major element in cancer extracellular matrix, binds to cell surface receptors to maintain tumour cell survival and activate downstream signalling pathways related to tumour proliferation, migration, and invasion. Clinical trials have investigated a pegylated hyaluronidase (PEGPH20) that can break down hyaluronan. However, overall survival rates have not improved and hyaluronan derived drugs are more toxic (14).

Mutant *K-ras* gene is a potential drug target, but inhibitors against this oncoprotein have not been successful due to its complexity. Small molecules that can covalently bind to the mutant *K-ras* offer hope for treating oncogenic *K-ras* cancers. Several candidates are currently in clinical trials for solid tumours like pancreatic, colon and lung cancers (15). Sotorasib is the first one approved by FDA for treating *K-ras* lung cancer patients (8). Introducing wild type *p-53* protein (*wt-p53*) into cancer cells has increased the cytotoxicity of gemcitabine for eliminating pancreatic tumours (16).

Cyclopamine, an inhibitor of formation of cancer stroma, has been explored for treating pancreatic cancer (8). The Janus kinase and activator of transcription (JAK/STAT) signalling pathway is believed to induce inflammation in host tissues and tumour lesions. Inhibitors of these pathways such as napabucasin were shown to be very promising in treating pancreatic cancer. Early clinical trials targeting JAK/STAT signalling pathway showed no obvious toxicity, indicating the ongoing development of drugs inhibiting this pathway (17).

Dietary supplementation during pancreatic cancer

Weight loss before cancer diagnosis often indicates malnutrition, as side effects and metabolic changes contribute to this issue. One in three cancer patients are malnourished, with pancreatic cancer having the highest prevalence (18). For example, low selenium levels have been shown in pancreatic cancer patients (19). Moreover, selenium supplementation is quite rare in those patients (18).

The risk of pancreatic cancer was inversely associated with total vitamin E intake. A high level of vitamin E might be a protective factor for populations at risk for pancreatic cancer (20).

Other common options are methionine and folate as nutritional supplementation. Methionine and folate are precursors for the methyldonor of S-adenosylmethionine, which showed anti-tumoural effects in liver cancer (21). Rather, when it comes to supplementing

with folate and methionine for pancreatic cancer, current research only finds a few correlations between these nutrients' dietary intake and a decreased risk of the disease's onset; however, no investigation is currently being done to examine these nutrients' impact on the treatment of these cancer patients or when combined with gemcitabine (22).

Curcumin has been shown to have anti-neoplastic properties by inhibiting pathways involved in proliferation and inflammation, which can support the development of colorectal cancer. Studies have shown that curcumin can decrease cancer incidence, colonic inflammation, and adenoma/adenocarcinoma appearance in colorectal cancer mice. Preclinical studies have also shown that curcumin can reduce tumour volume and chemoresistance when combined with common chemotherapy drugs. Curcumin's potential in treating pancreatic ductal adenocarcinoma (PDAC) is still under investigation, but it has shown promising effects in both cases (23).

Many pancreatic cancer patients present with cachexia at diagnosis. L-carnitine supplementation showed an improved quality of life and an increase in lean body mass (24). Presently, cutting-edge dietary approaches to alleviate cachexia involve the use of natural substances like silibinin, supplementing with 3-polyunsaturated fatty acids, and implementing a ketogenic diet. Increased ketone bodies have anticachectic and anticancer properties. It has been demonstrated that silibinin inhibits pancreatic cancer cell proliferation, induces metabolic alterations, and lessens myofiber degradation. It has been demonstrated that consumption of 3-polyunsaturated fatty acids greatly reduces resting energy expenditure and controls metabolic dysfunction (25).

It has been shown that oral high-fat supplementation improved nutritional risk index by increasing oral caloric and meal intake in postoperative pancreatic cancer patients. Serum metabolites associated with pancreatic cancer were altered in benefit of the surgical patients receiving high fat oral supplementation compared with the control group. Oral high fat supplementation may have positive effects on the health status of postoperative pancreaticobiliary cancer patients (26).

The cancer-associated fibroblasts (CAFs) in pancreatic ductal adenocarcinoma (PDAC) are well known to play a dominant role in distant metastasis. Patients with PDAC tend to develop distant metastases with a greater number of CAFs. The number of CAFs is increased by radiotherapy if patients do not have adequate levels of vitamin D in the plasma. Therefore, vitamin D supplementation would be effective in inhibiting metastasis by inactivating CAFs (27).

Ferric citrate and its usage

Ferric citrate (FC) as a medicine has been approved as an oral iron replacement product for patients with iron-deficiency anaemia (28).

It is intriguing to note that, even in the case where there is no apparent iron deficiency, the dietary supplement appears to potentially assist the patient in maintaining normal haemoglobin levels (Table 2). However, the extent of its efficacy in this situation remains uncertain.

Additionally, the patient experienced decreased kidney efficiency in 2019. In cases of chronic kidney disease (CKD), ferric citrate has been shown to be an effective source of enteral iron (29). A randomized, placebo-controlled trial in CKD patients demonstrated that ferric citrate significantly improved iron status (30). Considering the patient’s nephropathy as an adverse effect of chemotherapy, the dietary supplement containing iron citrate might assist in maintaining normal iron levels.

Furthermore, the study revealed that ferric citrate significantly reduced the concentration of fibroblast growth factor 23 (FGF23) (30). FGF23 is involved in phosphate regulation and can mitigate hyperphosphatemia in CKD patients. However, elevated FGF23 levels are associated with CKD progression (31). Given that both dietary phosphate absorption (32) and iron deficiency (33) potently stimulate FGF23 production, ferric citrate treatment targets both factors to lower circulating FGF23 levels (29).

In a more recent study, ferric citrate administration in mice resulted in reduced serum phosphate concentrations and increased serum iron levels. This effect, along with the potential improvement in iron status, led to decreased circulating FGF23 levels. Notably, ferric citrate also demonstrated anti-inflammatory properties, improved kidney function, reduced albuminuria, and decreased kidney inflammation and fibrosis. These results suggest potential renoprotective effects of ferric citrate (29).

Based on this study, it is reasonable to consider that the dietary supplement containing ferric citrate may have some protective effects on kidneys, particularly when administered in larger doses. However, further scientific investigations and clinical trials are necessary to validate these observations and establish the safety and efficacy of ferric citrate supplementation for renal protection in human subjects.

From 2016 to 2017, the patient took extract of thymus which can enhance the immune system of cancer patients. The patient started to take Synthesit after four years, in 2020. It can be supposed that thymus extract didn't have any effect on immune system at time when the patient took Synthesit.

CONCLUSION

This case study serves as an intriguing example of chronic B-lymphocytic leukaemia and pancreatic cancer in a patient who opted for a non-conventional treatment approach. The outcomes observed during the course of this study warrant further investigation into the potential synergetic effects of lifestyle modifications and dietary supplements in the management of such complex medical conditions. Nevertheless, this case underscores the importance of personalised and integrative approaches to healthcare and individualized therapeutic decisions.

It is important to highlight that the dietary supplement Synthesit is not classified as a medicine and is not intended to diagnose, treat, cure, or prevent any diseases, including chronic-B-lymphocytic leukaemia and pancreatic cancer. As a dietary supplement, its purpose is to complement a balanced diet and support general well-being.

Patient consent

The participant has voluntarily provided informed consent to participate in the case study.

Conflicts of interest

The author is an employee of Research Centre Synthestech, Sochi, Russia.

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