بسم الله الرحمن الرحيم

Drug treatment of anemia (Part 1)

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INTRODUCTION

Red blood cells (RBCs) have the principal function of carrying oxygen to tissues.

Their oxygen-carrying power depends on their hemoglobin content. The most important site of formation of red blood cells in adults is the **bone marrow**, whereas the spleen acts as their graveyard.

Red cell loss in healthy adults is precisely balanced by production of new cells.

Anemia is a condition in which the body does not have enough healthy red blood cells.

Clinical Presentation of Anemia

Pallor – Fatigue – Dizziness – Dyspnea.

These symptoms will lead to cardiovascular adaptation in the form of tachycardia , increased cardiac output and vasodilatation which may worsen the situation in patients with cardiovascular disease.

Types of Anemia

Classification depends on RBC size, hemoglobin content and microscopic examination of blood smear.

Two famous types of anemia:

1- Hypochromic, microcytic anemia (small red cells with low hemoglobin; caused by iron deficiency).

2- Macrocytic anemia (large red cells, few in number; caused by vitamin B12 or folic acid deficiency).

Other types: Aplastic anemia, anemia of chronic diseases, Congenital forms of anemia, hemolytic anemia and autoimmune causes.

Treatment of Megaloblastic anemia

1-Vitamin B_{12} deficiency anemia

Metabolism of vitamin B_{12}:

- Vitamin B_{12} is present in all animal foods.
- Vitamin B_{12} binds with the intrinsic factor which secreted from gastric parietal cells and the complex is absorbed in the terminal ileum.
- Once in the circulation, it binds to transcobolamin II and then stored in the liver.
- Stored forms of Vit B 12 in the liver can supply the body for more than 3 years after absorption is stopped
- The active forms of vit B 12 are ***methylcobalamin*** & ***deoxy-adenosylcobalamin***.
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Causes of vitamin B12 deficiency anemia:

1-The main cause of deficiency is failure of secretion of the intrinsic factor by the gastric mucosa as in cases of pernicious anemia where there is atrophic gastritis with achlorhydria and failure of secretion of intrinsic factor.

2- After intestinal resection.

3- Insufficient intake of Vit B 12 in Diet (e.g. strict vegetarian diet).

Manifestations of vitamin B12 deficiency anemia:

1-Megaloblastic anemia

2- Neuronal demyelmation and cell death in spinal column and cerebral cortex (which needs treatment within **6 months** to avoid irreversible neurological defects).

The neurological manifestations are aggravated if treated by folic acid **instead of vitamin B12,** so the diagnosis must be accurate by determination of the levels of folic acid and B12 in the plasma.

Treatment of vitamin B_{12} deficiency anemia:

1-Cyanocobalamin or ***hydroxocobalamin***

- These are stable formulations and changed to the active forms (methylcobalamin & deoxyadenosylcobalamin).
- In patients with pernicious anemia, parenteral therapy is used because oral therapy is ineffective as the cause is usually defect in site of absorption.
- Cyanocobalamin and hydroxocobalamin are used I.M. or deep S.C. but never I.V.

2- Combination of **oral vitamin B_{12}** and **intrinsic factor** can be used in patients with pernicious anemia who refuse the injection but the formation of intraluminal **antibodies to human intrinsic factor** may interfere with the absorption of vitamin B_{12}.

Oral and sublingual preparations containing Vitamin B12 are available.

Hydroxocobalamin is preferred as it is highly bound to proteins and so it remains longer in the circulation with sustained effect.

Dose and duration of treatment:

- 100 µg / day for 1 week I.M.
- then 100 µg / week for 1 month (but for 6 months if there is neurological defects)
- then 100 µg /month for life.

➢ Now vitamin B_{12} is available as spray and gel for intranasal use as a maintenance therapy in cases of pernicious anemia.

2- folic acid deficiency anemia

Metabolism of folic acid:

- Folic acid is found in most fruits, vegetables, liver and yeast.

- It is inactive and reduced by dihydrofolate reductase to dihydrofolic acid then to tetrahydrofolate which is a cofactor that enters in synthesis of **DNA and RNA**.

- Folinic acid (leucovorin) is converted directly to tetrahydrofolate.

- Folic acid is absorbed in upper small intestine then it is reduced and methylated to methyl tetrahydrofolate.

Causes of folic acid deficiency anemia:

1. Inadequate intake.
2. Increase in requirements as in pregnancy, hyperthyroidism and chronic dialysis.
3. Inhibition of absorption as in malabsorption syndrome, the use of some drugs as phenytoin, phenobarbital and oral contraceptive.
4. Inhibition of dihydrofolate reductase enzyme by methotrexate, trimethoprim and pyrimethamine.

Manifestations of folic acid deficiency anemia:

Deficiency of folic acid leads to megaloblastic anemia without neurological manifestations.

Treatment of folic acid deficiency anemia:

It is treated by oral folic acid as oral therapy is well absorbed even in presence of malabsorption.

It is used for 4-6 weeks which is a sufficient time for correction of anemia and replenish body stores.

I.M. injection is used in severe ill patients followed by oral maintenance therapy.

Treatment should be continued until correction of the cause of deficiency, otherwise treatment should be continued for life.

In case of severe deficiency of vitamin C, oral folic acid is ineffective.

Folinic acid is used only in cases of obstruction of folate activation as by the use of methotrexate or trimethoprim.

Hematopoietic growth factors

These are hormone-like glycoprotein that regulate the division and maturation of the progeny blood cells in bone marrow.

1- Erythropoietin:

It is produced by the kidney in response to hypoxemia and regulates the formation of RBCs.

It is prepared by recombinant DNA technology and used S.C. or I.V. for: ***Anemia of chronic renal failure*** (due to decrease in erythropoietin release and excess loss of RBCs during dialysis).

Anemia of AIDS, cancer, rheumatoid arthritis and anemia occurs in premature infants.

2- Myeloid growth factors:

It is produced by fibroblasts, endothelial cells, macrophages and T lymphocytes in response to systemic infection, it regulates the formation of WBCs and include:

A. Filgrastim is a synthetic Granulocyte-colony stimulating factor (G-CSF), it affects neutrophils.
B. Sargramostim is a synthetic Granulocyte /macrophage-colony stimulating factor (GM-CSF), it affects neutrophils, monocytes and eosinophils.

Myeloid growth factors are given S.C. or I.V. for:

1- Patient suffering from **aplastic anemia.**
2- After **bone marrow transplantation**.
3- To prevent and treat bone marrow depression of **cancer chemotherapy** .

3- Megakaryocyte growth factors:

They regulate the formation of platelets and include:

1-Interleukin 11, it produced by fibroblasts and stromal cells in the bone marrow.

2-Thrombopoietin , it produced by hepatocytes.

They are given parenterally in treatment of thrombocytopenia.

thank you