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The Impact of Ribonucleotide Reductase Enzyme and Zinc on Leukemia

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Annotation: Leukemia is a cancer that affects blood cells and their component tissues, such as the bone marrow and lymphatic system. It results from mutations in blood-forming stem cells, leading to abnormal cell growth and proliferation, which hinders normal blood formation. Types of blood cancer (acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL)

Symptoms: anemia, bleeding, recurrent infections, enlarged liver and spleen. Diagnosis: blood tests, bone marrow biopsy, genetic testing, and imaging. Treatment is of two types: chemotherapy (the primary treatment for AML, but its effectiveness decreases in older patients) or stem cell transplantation (used to improve outcomes, especially in younger patients).

Ribonucleotide reductase: Scientific name: Ribonucleotide reductase EC 1.17.4.1 is an essential enzyme and a speed regulator in DNA synthesis, converting ribonucleotides (rNDPs) to deoxyribonucleotides (dNDPs), the building blocks of DNA. It is the enzyme The only known enzyme in cells that converts rNDP to dNDP, and is therefore essential for DNA replication and cell division. Its chemical structure is a complex enzyme consisting of two main protein subunits (RRM1 + RRM2), containing an iron-oxygen center essential for its enzymatic activity. It requires a tyrosine radical to carry out deoxygenation reactions. Its biological effect is the conversion of rNDP to

dNDP, which is necessary for DNA synthesis and thus supports cell division, participates in DNA repair, and maintains the balance of nucleotide pools. Any enzyme defect leads to an imbalance in dNTPs → genetic mutations or DNA damage. Its relationship to leukemia: In leukemias (especially AML - Acute Myeloid Leukemia), cancer cells have an excessive need for dNTPs, so: enzyme activity increases significantly; RRM2 levels are particularly high in leukemia cells. The enzyme is considered An important target for cancer therapy.

Zinc is an essential mineral with the chemical symbol Zn and atomic number 30. It is an important trace element in the human body and participates in many biochemical and enzymatic processes. It is found in all cells of the body and is concentrated in muscles, bones, skin, and liver. The body cannot store zinc in large quantities, so it must be obtained regularly from the diet. Patients with acute leukemia may suffer from zinc imbalance due to: Tumor lysis syndrome: zinc is released from dying cancer cells. Chemotherapy also affects the kidneys and electrolyte balance. Kidney dysfunction resulting from the disease. The study aims to understand the relationship between ribulose-5-phosphate isomerase activity and the effect of certain minerals, such as zinc, on the metabolic status of leukemia patients, to understand the biochemical mechanisms that contribute to the progression of the disease and its complications.

Keywords: Ribonucleotide reductase, Leukemia, Zinc.

1. Introduction

Leukemia is defined as a cancer of the blood cells and tissues that produce blood cells, such as the bone marrow and lymphatic system. Mutations in hematopoietic stem cells or progenitor cells may be the primary cause of the disease. The main clinical symptoms of the disease are the presence of abnormal blood cells and bone marrow, uncontrolled proliferation, and abnormal growth of hematopoietic tissue, which inhibits the growth of normal hematopoietic tissue and produces further clinical symptoms[1].

The term leukemia is derived from the Greek words "leukos" and "heima," which refer to an increase in white blood cells (WBCs) in the body, making the blood appear pale. This is due to the anemia that afflicts patients due to the invasion of abnormal white blood cells into tissues and

blood, resulting in a decrease in the number of red blood cells and an increase in the number of white blood cells[2]. Leukemia, which was once considered a single type, was first recognized around the fourth century. By the end of the nineteenth century, leukemia had been classified into four subtypes: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myeloid leukemia (CML). Chronic lymphocytic leukemia (CLL). It is known that leukemia consists of a diverse group of hematopoietic tumors (myeloid and lymphoma)[3] that are complex and unique. Each subtype can also be distinguished by morphological differences, cytogenetic abnormalities, immunophenotype, and clinical symptoms, which affects prognosis and the choice of optimal treatment [4].

Types of Leukemia

Leukemia is classified into four main types:

1. Acute myeloid leukemia (AML): Most common in adults, characterized by the rapid proliferation of immature cells[5].
2. Acute lymphoblastic leukemia (ALL): Common in children, affecting lymphocytes[6].
3. Chronic myeloid leukemia (CML): Slow-growing and affecting myeloid cells[7].
4. Chronic lymphocytic leukemia (CLL): Most common in older adults, progressive[8].

Symptoms and Diagnosis

- ✓ Symptoms: Anemia, bleeding, recurrent infections, enlarged liver and spleen[9].
- ✓ Diagnosis: Blood tests, bone marrow biopsy, genetic testing, and imaging[10].

Treatment

- ✓ Chemotherapy: The mainstay of treatment for AML, but its effectiveness decreases in older patients[11].
- ✓ Stem cell transplantation: Used to improve outcomes, especially in younger patients[12].

Risk factors include: (advancing age (especially over 65 years), male gender, exposure to radiation or chemicals such as benzene, heredity and genetic mutations, smoking)[13].

Ribonucleotide Reductase

Scientific name: Ribonucleotide Reductase (EC 1.17.4.1) is an essential enzyme and a speed regulator in DNA synthesis, converting ribonucleotides (rNDPs) to deoxyribonucleotides (dNDPs), the building blocks of DNA. It is the only known enzyme in cells that converts rNDPs to dNDPs, and is therefore essential for DNA replication and cell division.

RNRs are produced within cells and expressed in the nucleus (cytoplasm) as the cell needs to divide[14].

The enzyme consists of two main subunits: the large subunit (RRM1) and the small subunit (RRM2) or (RRM2B). RNR production is regulated according to the cell cycle, with its expression increasing during the S phase (replication phase).

Chemical structure: A complex enzyme consisting of two main protein subunits (RRM1 + RRM2), containing an iron-oxygen center essential for its enzymatic activity. It requires a tyrosine radical to carry out deoxygenation reactions[15].

Its biological effect: It converts rNDP to dNDP, which is essential for DNA synthesis, thus supporting cell division, participating in DNA repair, and maintaining nucleotide pool balance. Any defect in the enzyme leads to an imbalance in dNTPs, leading to genetic mutations or DNA damage[16].

Its relationship to leukemia: In leukemia (particularly AML – Acute Myeloid Leukemia), cancer cells have an excessive need for dNTPs. Therefore, enzyme activity increases significantly.

RRM2 levels are particularly high in leukemia cells. The enzyme is an important target for cancer therapy[16].

Recent studies have confirmed that overexpression of the RRM2 gene is associated with resistance to chemotherapy, a weakened immune response, and decreased survival rates in leukemia patients. Enzyme inhibitors, such as hydroxyurea, a direct enzyme inhibitor, and triapine, an RRM2 inhibitor, are used to reduce dNTP levels and prevent cancer cell proliferation[17]

Zinc

Zinc is an essential mineral with the chemical symbol Zn and atomic number 30. It is an important trace element in the human body and participates in many biochemical and enzymatic processes[18]. It is found in all cells of the body and is concentrated in muscles, bones, skin, and liver. The body cannot store zinc in large quantities, so it must be obtained regularly from food, as zinc is not produced within the body; it must be obtained from the diet or nutritional supplements[19]. Zinc is absorbed primarily in the small intestine (the upper part of the jejunum) and transported to the liver, from where it can be used to transport other tissues. Zinc-rich foods (red meat, liver, nuts, whole grains, seafood, especially oysters) have biological effects. Zinc is essential for: (a) Immunity: It enhances the immune system's response. Its deficiency leads to weakened immunity and increased susceptibility to infection. (b) Growth and development: It is essential for healthy growth in children and adolescents. Its deficiency causes delayed growth. (c) Antioxidant: It protects cells from free radicals and inhibits DNA damage[20]. Its relationship to leukemia: (a) Potential protective role: Zinc has antioxidant properties that may protect cells from genetic mutations that lead to cancer. It plays a role in regulating the activity of T and B cells, which helps fight cancer cells. (b) In leukemia: Studies have shown that zinc levels may be low in leukemia patients, which may contribute to impaired enzyme activity, a weakened immune system, and irregular cell proliferation[21].

2. Materials and Methods:

2-1 Determination of Ribonucleotide Reductase in Blood Serum

Basic Principle:

This kit is an enzyme-linked immunosorbent assay (ELISA). The test plate is pre-coated with antibodies to human RRM1. RRM1 protein present in the sample is added and binds to the antibodies immobilized on the holes. Biotin-labeled antibody to human RRM1 is then added, binding to RRM1 in the sample. Streptavidin-HRP is then added, binding to the biotin-labeled antibody. After incubation, the plate is washed to remove unbound streptavidin-HRP. Substrate solution is then added, and color develops directly proportional to the amount of human RRM1 protein in the sample. The reaction is stopped by adding acidic stop solution, and the absorbance is measured at a wavelength of 450 nm (10)[22].

Assay Procedure:

1. Prepare all reagents, standard solution, and samples according to the instructions. Bring all reagents to room temperature before use. The assay is performed at room temperature.

2. Determine the number of strips required for the assay. Insert the strips into the trays for use. Unused strips should be stored at 2-8°C.

3. Add 50 µL of standard solution. Note: Do not add the biotinylated antibody to the standard well, as the standard solution already contains the biotin-labeled antibody.

4. Add 40 µL of sample, then add 10 µL of anti-HRM1 antibody, followed by 50 µL of streptavidin-HRP to the samples. Mix well. Cover the plate with a sealant. Incubate for 60 minutes at 37°C. 5. Remove the sealant and wash the plate 5 times with the wash solution. Soak the holes in 300 µL of wash solution for 30 seconds to 1 minute per wash. For automatic

washing, draw or pour each hole and wash 5 times with the wash solution. Drain the plate on paper towels or other absorbent material.

6. Add 50 µL of matrix solution A to each hole, then add 50 µL of matrix solution B to each hole. Incubate the covered plate with the new sealant for 10 minutes at 37°C in the dark.

7. Add 50 µL of stop solution to each hole; the blue color will immediately turn yellow.

8. Determine the optical density (OD value) of each hole immediately using a microplate reader set to 450 nm within 10 minutes after adding the stop solution.

2-2 Estimation of Zinc Concentration in Blood Serum

Basic Principle:

Zinc reacts with the chromogen in the reagent, forming a colored complex with a color intensity proportional to the zinc concentration in the sample.

Reagents Used:

Reagent A: 0.37 M borate buffer, pH 8.2, 1.25 mM saliciladoxime, surfactant, and preservatives.

Reagent B: 0.4 mM nitro-paps, preservatives.

Standard: 200 µg/dl (30.6 µmol/l) zinc ion; stabilizers and preservatives.

Preparation of Reagents

2 ml of Reagent B was added to the Reagent A vial, stored at 2-8°C.

Procedure

Pipette:	BLANK	SAMPLE	STANDARD
Reagent	1000 µl	1000 µl	1000 µl
Water	15 µl		
Sample		15 µl	
Standard			15 µl

Mix at room temperature and read the absorbance at 578 nm after 5 minutes. The color remains stable for 30 minutes.

Calculation

Zinc concentration is calculated as follows:

$$\text{Zn µl/dl} = [A_{sample} / A_{standard}] \times 200$$

$$\text{Zn µmol/dl} = [A_{sample} / A_{standard}] \times 30.6$$

2-3 Measurement of ribonucleotide reductase concentration in leukemia patients and the control group

3. Results and discussions

Measurement of ribonucleotide reductase concentration in leukemia patients and the control group

The results shown in Figure 1-1 show that the mean ± standard deviation of ribulose-5-phosphate isomerase in the control group was 368.4 ± 48.3 ng/L, while the mean ± standard deviation in the leukemia group was 259.9 ± 40.8 ng/L. A p-value of <0.001 indicates a statistically significant difference between the mean concentration of ribulose-5-phosphate isomerase in leukemia patients compared to healthy controls. That is, the level of ribulose-5-phosphate isomerase is significantly lower in leukemia patients compared to their healthy peers.

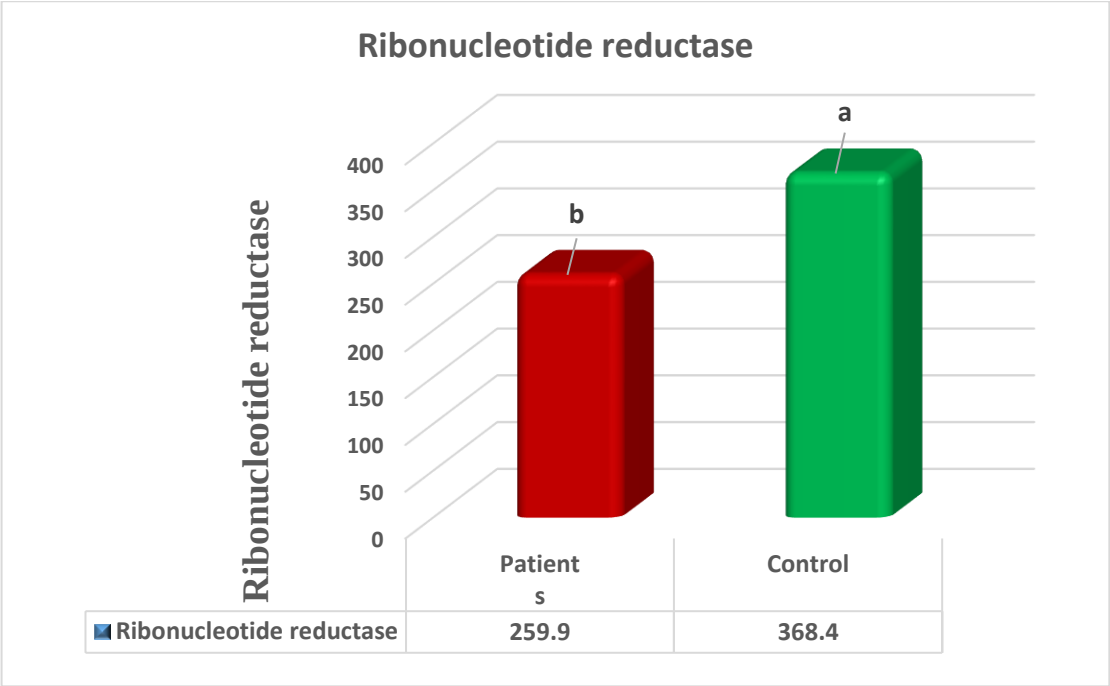

Figure (1-1): Mean ± standard deviation of Ribonucleotide Reductase enzyme in leukemia patients and the control group

It converts ribonucleotides to deoxyribonucleotides, which is essential for DNA replication and repair. It plays a central role in cancer cells, where demand for dNTPs is high. The balance between activity and dNTP quantity is important for maintaining genetic stability, and deficiency can cause genetic abnormalities or programmed cell death[23]. indicated that in MDS, RRM1 levels are predictive of a better response to 5-azacitidine, indicating the prognostic value of ribonucleotide reductase. Research (Chatzidavid et al., 2023) in myelodysplastic syndrome (MDS) patients showed that higher levels of RRM1—the large subunit of the enzyme ribonucleotide reductase—are associated with improved response to treatment with 5-azacitidine. This suggests that RRM1 could be a prognostic/predictive biomarker used to estimate treatment effectiveness and identify patients most likely to benefit. A study[24]. also indicated that the use of the ribonucleotide reductase (RNR) inhibitor Didox resulted in AML cell death in cell lines and serologically resilient models. Didox did not harm healthy stem cells. As a ribonucleotide reductase inhibitor, Didox has proven effective in killing acute myeloid leukemia (AML) cells in both laboratory experiments and models, with good serological levels (meaning the dose is relatively effective and safe). Most importantly, it did not harm normal blood stem cells. A study[25] showed that ribonucleotide reductase inhibitors such as hydroxyurea and gemcitabine improve the effectiveness of ara-C by inhibiting SAMHD1, a dNTP transporter and a factor in drug resistance. A study confirmed that dNTP interference and enhancement of dNTP balance via ribonucleotide reductase hyperactivation stimulates AML differentiation as a potential marker and therapeutic approach. Stimulating differentiation means pushing these immature cells to transform into mature cells (such as neutrophils), which is one of the goals of treatment. In acute myeloid leukemia (AML) cells, studies have shown that ribonucleotide reductase hyperactivation Ribonucleotide reductase leads to an imbalance in dNTPs, which in turn stimulates immature cancer cells to enter the normal differentiation pathway[25].This suggests that targeting the balance of dNTPs within the cell could be a therapeutic approach, by reprogramming cells rather than simply killing them, representing an advance in targeted therapy with less toxicity[26].

A 2017 study[27] using computational analyses (pan-cancer) showed an association between RRM2 and survival rates and genetic markers in AML, suggesting a role in the immune environment, promoting resistance to chemotherapy: by providing dNTPs to repair DNA damage

caused by drugs such as cytosine arabinoside (Ara-C). Interaction with common genetic mutations in AML: such as FLT3-ITD or NPM1 mutations, which may explain the variation in response between patients.

Zinc level in leukemia patients and control group

Figure (1-2) shows the mean ± standard deviation of zinc in the control group (154.0 ± 21.4 mg/dl), while the mean ± standard deviation of zinc in the leukemia group was (149.8 ± 12.2 mg/dl). A p value of > 0.05 indicates no statistical significance, meaning there is no significant difference between the mean zinc concentration in patients compared to healthy controls.

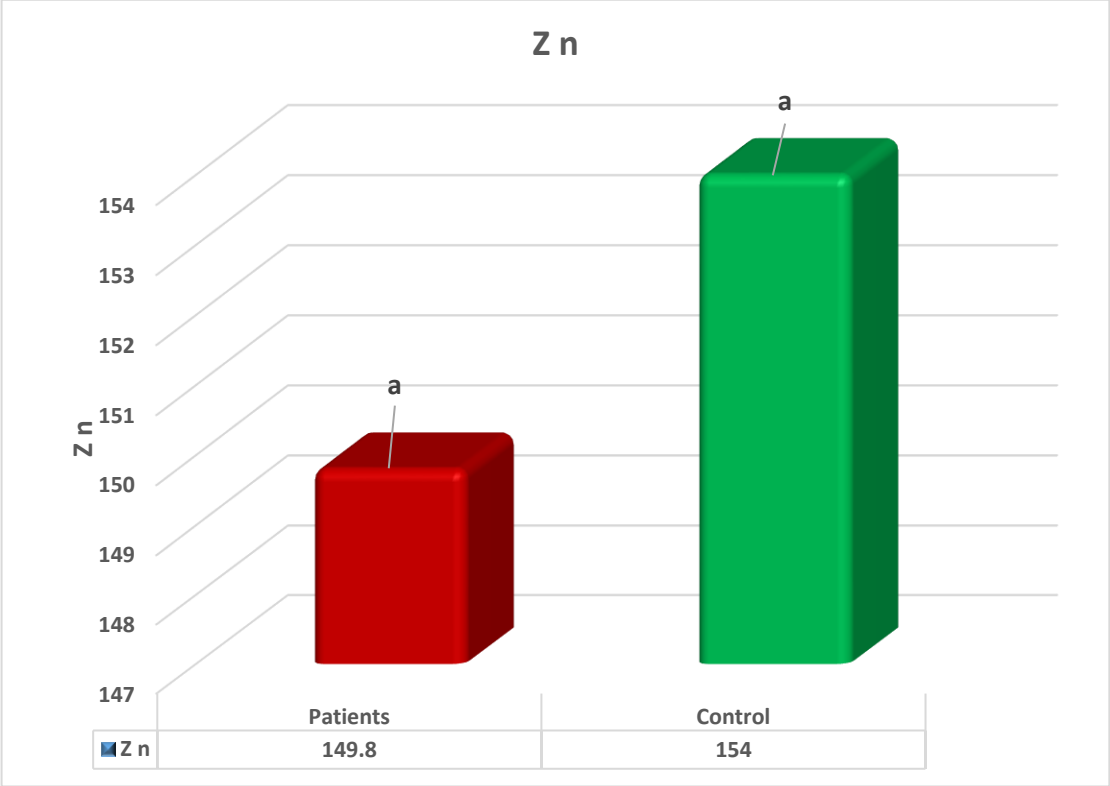

Figure (1-2): Mean ± standard deviation of zinc (Zn) level in leukemia patients and the control group

Interpretation of the results: Although there was no significant difference, the trend toward decreased zinc in patients deserves discussion in light of the scientific literature. (A slight decrease in zinc (~3%) may be of biological importance in cancer, given zinc's critical role in cellular functions. Previous studies have shown that mild to moderate zinc deficiency (even if within the "normal" range) may affect antitumor immune function, genome stability, and response to chemotherapies)[28]. The role of zinc in immunity and cancer (zinc and antitumor immunity (T cells & NK cells), T cell development. Zinc is essential for the maturation of T cells in the thymus via activation of the Notch signaling pathway. Zinc deficiency leads to decreased production of healthy T cells (CD4+/CD8+) [29], impaired T cell receptor diversity, and the function of killer T cells (CD8+ T cells). Zinc regulates the secretion of interferon-gamma. (IFN-γ) and perforin are essential for killing cancer cells. A study[30] found that zinc deficiency reduces the effectiveness of T cells against leukemia cells by 40%, natural killer cells (NK cells), zinc stimulates the production of granzyme B in NK cells. In zinc deficiency, the ability of NK cells to recognize cancer cells decreases (MHC class I downregulation). Role and immune function: Zinc is essential for the development and activity of T cells and natural killer cells (NK cells)[31]. Zinc deficiency is associated with a weak immune response against tumors. A second role for zinc is inhibiting inflammation, as zinc regulates the NF-κB and STAT3 pathways that cause chronic inflammation associated with cancer development. Zinc is involved in genome stability, and zinc is a component of zinc fingers in DNA repair proteins.

Conclusions:

1. The significant decrease in RPI levels indicates a metabolic disorder in cancer cells, which could be a potential therapeutic target.
2. Zinc may have an indirect role in leukemia development via its effects on immunity and genome stability, warranting further research.

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