Editorial

Anemia: Old Disease, New Solutions!

Anemia how old? Lo! It was one gift from the Pandora's box. As true as the devil, it is there since the genesis of life as a symbiotic friend of nature. As a part of female physiology it opened its saga from iron deficiency and evolved with us since time immemorial with its many forms and features.

Anemia is the patriarch of blood disorders, affecting about one third of the global population. Basically, the main types of anemia are due to excessive blood loss, increased red blood cell (RBC) destruction (hemolysis), or impaired RBC production (ineffective erythropoiesis). It leads to decrease in the total amount of RBCs and/or hemoglobin in the blood. This in turn causes a decline in tissue oxygenation.

Etiology ranges from deficiency states (iron, vitamin B12, and folic acid), genetic mutations in the formation of abnormal hemoglobin (thalassemias, sickle cell anemia, unstable hemoglobins), RBC defects, enzyme defects, marrow failure states, and immunologic destruction of RBCs.

Erythropoietin

In the past, the treatment of anemia was mainly centered on frequent blood transfusions in order to replenish RBCs. In the 1950s and 1960s, it was confirmed that, erythropoietin, a hormone secreted from the kidneys, was responsible for regulating red cell production. Twenty years later, a synthetic form of erythropoietin (epoetin alfa, Epo) was developed that could be mass-produced and administered subcutaneously. Today, Epo, produced by recombinant deoxyribonucleic acid (DNA) technology, has revolutionized anemia treatment by abating the need of recurrent blood transfusions, especially in anemias due to chronic inflammatory states.

Bone marrow transplant/hematopoietic stem cell transplantation is a method of treating some specific anemias. Stem cell therapy focuses on transplanting cells of erythropoietic series, or erythrocyte precursors, thereby increasing the pool of cells responsible for hematopoies in the patient's body. It involves the intravenous infusion of autologous or allogeneic stem cells to reestablish hematopoietic function, when there is lack of response to conventional treatments. Some of the anemias where stem cell therapy is now becoming an evidence-based standard treatment are sickle cell anemias, thalassemias, aplastic anemias, Fanconi anemia, sideroblastic anemias, pure red cell aplasias, and paroxysmal nocturnal hemoglobinuria. In the case of hereditary anemias, stem cell therapy also has many benefits for the patient, but treatment effects decrease with time and successive courses of stem cell treatment are necessary. Immunosuppressive therapy has been the cornerstone in the treatment of aplastic anemia. Anti-thymocyte globulin, anti-lymphocyte globulin, and Cyclosporin A are the drugs from this group. Approximately one third of patients with aplastic anemia do not respond to immunosuppression. The thrombopoietin-receptor agonist eltrombopag is approved for use in patients with severe aplastic anemia who fail to respond adequately to immunosuppressive therapy.

Gene Therapy

Mario R. Capecchi, Sir Martin J. Evans, and Oliver Smithies were awarded the Nobel Prize in 2007 for medicine. Their work was on gene targeting, which emphasized the modification of embryonic stem cell by homologous recombination (HR) with engineered template DNA to alter virtually any gene. This work revolutionized the study of in vivo consequences of selected gene alteration. Hoban and Bauer described the various nucleases and their potential applications for treatment of blood disorders. Especially, mutational screening using the clustered regularly inter- spaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9) nuclease can identify new gene regulatory elements, and therapeutic gene targets.

Two scientists, Canver and Orkin, suggested that, it may be possible to correct β-globin gene mutations directly by HR to restore the synthesis of normal adult hemoglobin ($\alpha 2\beta 2$). It is possible to disrupt some of the several genetic control elements that regulate the switch from γ- to β-globin. Consequently, gene

therapy can switch on the reactivation of the fetal hemoglobin (α2β2) eliminating the pathophysiology and symptoms of β-hemoglobinopathies. Gene therapy of thalassemia and sickle cell disease has proved to be an elusive goal. Uptake of lentiviral-type vectors that can transduce nondividing cells may solve this problem.

Monoclonal Antibodies

Monoclonal antibodies (MoAbs) are cells derived by cell division from a single ancestral cell. They target various proteins that influence cell-activating receptors or other proteins present on the surface of cells.

The MoAbs have been used to treat idiopathic and secondary autoimmune hemolytic anemias (AIHAs), with encouraging results. Rituximab which targets CD20 on B cells is now used to treat AIHA. The mechanism proposed is cell-associated immunoglobulin G immune complexes, generated by the binding of rituximab to CD20 on B cells, which serve as decoys that attract FcγR-expressing effector cells and downregulate effector cell pathogenic action, thus reducing inflammation and tissue destruction in AIHA. Another humanized MoAb, eculizumab, directed against the complement component C5, is used in the treatment of paroxysmal nocturnal hemoglobinuria (PNH). The mechanism of action is by blocking the complement cascade downstream of C5, abrogating the complement- dependent intravascular hemolysis of PNH patients.

Treatment of anemia has come a long way from conventional blood transfusions to molecular level. Researchers are toiling to alter the pathologic codes at a quantum level. As clinicians, our approach should be multimodal from prevention to cure.

The old disease will continue to haunt with its multifold manifestations and our efforts to hunt it will go on.

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