field of hematology are mainly focused on hemostasis disorders. His studies on platelet adhesion and aggregation have been referred to in numerous foreign researches. He has conducted studies on some hereditary or acquired coagulation disorders, leukemias, some anemias, and plasma cell dyscrasias. He is one of the four Turkish hematologists that Wintrobe included in the book "Hematology, The Flowering of a Science: A Story of Inspiration and Effort". He has shown the recognition and diagnostic methods of many hemostasis disorders in our country with his Turkish publications. Prof. Dr. Inceman's followers became Prof. Dr. Y. Tangun, Prof. Dr. Y. Pekcelen, Prof. Dr. T. Atamer and Prof. Dr D. Sargin. He retired in 1986. He succumbed to colon cancer in 1994. He was a good listener, a serious and kind gentleman. He paid attention to details, closely followed contemporary information.

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07

SICKLE CELL DISEASE UPDATE: NEW TREATMENTS

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Sickle-cell disease is the most common genetic blood disorder, causing blockage of the circulation and resulting painful vaso-occlusive episodes, acute chest syndrome, stroke, chronic anemia, and multiorgan failure, with increased mortality. Three novel medications have been approved in the past five years: L-glutamine in 2017, and voxelotor and crizanlizumab in 2019. L-glutamine treatment was linked to a reduction in the rate of RBC transfusions as well as a decrease in hospitalizations, pain crises, and the period between the first and second crises. By raising adenosine triphosphate and lowering 2,3-diphosphoglycerate, a glycolytic red blood cell intermediate, mitapivat, an oral pyruvate kinase activator, also has therapeutic potential. Crizanlizumab, a P-selectin inhibitor, reduces the grade of inflammation by lowering the adhesion between the endothelium and leukocytes, sickled red blood cells, platelets, and endothelial cells. Crizanlizumab is associated with a decrease in the requirement for opiate use as well as a decrease in the number of pain crises and the time until the first crisis. Adverse effects include infusion reactions, headache, nausea, and insurance difficulty. Voxelotor increases hemoglobin levels and affinity for oxygen, preventing HbS polymerization, and lowering hemolysis indicators in the process and was associated with lower hemolysis indicators and higher hemoglobin. Insurance denial and adverse effects like headache, rash, and diarrhea were obstacles to using Voxelotor. None of these therapies, however, are curative. There are efficient cell-based treatments including red blood cell exchange, and hematopoietic stem cell transplantation is the only treatment that can cure the disease. Gene editing has shown promise in the treatment of β-thalassemias and sickle cell disease.

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08

PNH TREATMENT: TREATMENTS OF TODAY AND TOMORROW

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired blood disorder characterized by chronic destruction of red blood cells (hemolytic anemia) and blood clots (thrombosis).[1] PNH can occur at any age, although it is most often diagnosed in young adulthood. the only cure for paroxysmal nocturnal hemoglobinuria (PNH) is an allogeneic hematopoietic stem cell transplantation.[2] Stem cell transplantation is associated with high mortality and it is reserved for severe cases of PNH with aplastic anemia or transformation to leukemia, both of which are life-threatening complications. Other treatment strategies include complement mediators that inhibit components of the complement system. Several monoclonal antibodies (ie, eculizumab, ravulizumab, crovalimab) that target the C5 complement component have been approved for treatment of PNH by the US Food and Drug Administration (FDA).[3,4] A monoclonal antibody that inhibits C3, pegcetacoplan, has also been approved for treatment of PNH. Pegcetacoplan is a C3 inhibitor that is administered subcutaneously, twice weekly, and is capable of blocking both intravascular and extravascular hemolysis.[5] Iptacopan, an oral inhibitor of factor B (a component of the alternative complement pathway) was approved by the FDA in 2023. It is indicated as monotherapy for PNH.[6] Danicopan, a selective inhibitor of complement factor D, was approved by the FDA in 2024 for patients who experience clinically significant extravascular hemolysis, as an add-on to C5 inhibitor therapy (eg, eculizumab, ravulizumab).[7] Additional treatment strategies are focused on managing the symptoms and complications of PNH. Depending on the anemia symptoms they experience, patients with PNH may receive supportive treatments, such as blood transfusion, iron replacement therapy, growth factors, and erythropoeitin. Steroids may also be used only for short-term use in symptomatic extravascular hemolysis. [8,9] Treatment with anticoagulants, including heparin and coumarin derivatives, may reduce the risk of thrombosis.[1] Supplementation with folate, iron, and vitamin B12 can be used to support increased erythropoiesis in the bone marrow.

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09

NOVEL TARGETS AND THERAPIES IN MULTIPLE MYELOMA

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Multiple Myeloma (MM) is the second most frequent cancer and constitutes 10 % of hematological malignancies. Median age at onset is older than 65 years old.Despite significant improvement has been gained for management of the

diasease in the last decades cure has not been achieved. Clinicial use of monoclonal antibodies targeting cluster of differentiation (CD) 38 or signaling lymphocye activation molecular family 7 (SLAMF7) combined with immunomodulatory drugs and preoteosome inhibitors lead to prolonged progression free survival in a group of relapsed refractory MM (RR MM) patients. High risk disease forms such as extramedullary involvement, advanced stage or poor cytogenetic features still suffer decreased survival. Novel immunotherapies targeting B cell maturation antigen (BCMA), G protein- coupled receptor family C group 5 member D (GPRC5D), Fc receptor homolog 5 (FcRH5), CD138, CD 48, CD 56 and CD74 as well as cellular therapies such as chimeric antigen receptor (CAR) T / CAR NK cells therapies has been emerging. Daratumumab, elotuzumab and isotuxumab are approved monoclonal antibodies that have been in clinical use since 2015. Thereafter Belantamab mafodotin,AMG 224 and MEDI 2228 are the examples of antibody- drug conjugates with the approval of Belantamab after 4 lines of therapy in relapsed refractory MM. Teclistamab and elranatamab are the approved bispesific antibodies targeting BCMA on MM cells and CD3 on T lymphocytes. They both showed overall response rate exceeding 60 % in RRMM. Cytokin release syndrome was observed in two thirds of patients but were mostly low grade. Bispesifics showed objective responses on patients with prior antiBCMA targeted and CAR-T directed therapies. Two CAR T cell therapies has been approved in MM up to date. Idecabtagene vicleucel (ide-cel) and ciltacabtagene autocel (cilta-cel) are anti BCMA autologous CAR T cell products that have FDA approvals in RRMM. Both agents improved progression free survival compared to standard regimens. Allogeneic anti BCMA CAR T cells can also be an option in a near future based on earlier phase trials. Along with approved novel agents investigational studies for earlier lines of therapy and newer agents are emerging.Minimal residual disease (MRD) negativity is an emerging term for depth of response giving the possibility of cure and novel agents promise better MRD negativity as well as disease control.

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10

NOVEL MAINTENANCE THERAPIES IN ACUTE MYELOID LEUKEMIA: PROLONGING REMISSION AND IMPROVING OUTCOMES

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Maintenance therapy, defined as the administration of less intensive treatment following initial intensive induction and consolidation chemotherapy, has shown promise in enhancing long-term outcomes for AML patients. Allogeneic stem cell transplantation (HSCT) improves disease-free survival (DFS) in patients with AML who are suitable for transplantation. However, not all patients are suitable for transplantation. From past to present, maintenance treatment for AML has evolved from chemotherapy to immune modulatory and targeted therapies. In the early studies, low-intensity chemotherapy was used in different combinations in maintenance treatment of AML, but it could not be shown to increase overall survival. In general, novel maintenance therapy includes HMAs, the combination of HMAs with other agents, and targeted therapies. HOVON97 trial showed that azacitidine maintenance after CR/CRi after intensive chemotherapy is feasible and significantly improves DFS. The most important trial regarding HMA care is the QUAZAR AML-001 trial. CC-486 (oral azacitidine) resulted in an improvement in OS compared with placebo at approximately 12 months of follow-up. In AML 342 trial, azacitidine/venetoclax maintenance therapy was tolerable and improved RFS in AML patients not eligible to HSCT. The SORAML study demonstrated improved EFS in the sorafenib arm in adult patients with AML regardless of FLT3 status (3-year EFS: 40% vs 22%), but there was no difference in OS. The phase III ADMIRAL trial led to the approval of gilteritinib as monotherapy in adult patients with relapsed or refractory FLT3-ITD/tyrosine kinase domain-mutated AML In a long-term follow-up (37 months) of the trial, continued gilteritinib therapy preserved the superior OS. In the QuANTUM First trial, the addition of quizartinib to intensive chemotherapy followed by maintenance in patients with FLT3-ITD AML improved RFS and OS. In the phase I study, ivosidenib (n=60) or enasidenib (n=91) was added to intensive chemotherapy and continued as a maintenance agent until relapse, toxicity, or HSCT. Twelve-month OS was 75% in both groups. A phase I study of posttransplantation enasidenib (scheduled for 1 year) in 19 patients with IDH2 mutations) showed 2-year PFS and OS to be 69% and 74%, respectively. In conclusion, maintenance treatment with HMAs with or without venetoclax is recommended for intermediate and adverse-risk AML patients. Corresponding inhibitor therapies can be used in patients with targetable mutations such as FLT3 and IDH.

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11

ADVANCES IN THALASSEMIA MANAGEMENT AND CHELATION THERAPY

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Autosomal recessive thalassemias are a heterogeneous group of diseases characterized by hypochromic microcytic anemia, which develops as a result of defective synthesis of one or more of the hemoglobin (Hb) chains. It occurs when the Hb chain or chains are produced in small numbers or not at all. In other words, while the production of beta chains is insufficient, the production of alpha chains causes alpha thalassemia. Approximately 3 babies in every 1000 births in the world are affected by severe beta chain disorders, and approximately 350,000 new babies with the disease are born each year. Even under modern treatment conditions, severe clinical complications may develop in the clinical follow-up of patients. In recent years, the introduction of oral chelators and the ability to determine organ iron load with non-