HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Speech Summaries

01

Z-EMATOLOGY IN TURKEY

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In alignment with this vision, we are excited to introduce a new initiative: Z-Ematology. This concept is designed to bridge the gap between Generation Z and the evolving field of hematology. The new generation brings fresh perspectives and skills, especially in areas such as artificial intelligence, big data, telemedicine, and digital health technologies. Z-Ematology reflects our belief that adapting to these trends is essential for the future of hematology, and we are committed to integrating innovation into every aspect of the profession.

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02

OPTIMIZATION OF IMID-BASED THERAPIES

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The word optimization, meaning "to achieve the best possible," is a branch of science called the science of the best. It has also created a field within the health care system, which is a complex system, called "medical optimization". Medical optimization is defined as "a person-centered approach to the safe and effective use of medicines to ensure that people achieve the best possible outcomes from treatment. In this context, what can be said on the basis of the treatment of myeloma and the use of IMIDs? Multiple myeloma is a disease of advanced age. Although there are classical findings such as anemia, bone disease, loss of renal function, hypercalcemia, a significant proportion of patients suffer from sleep disorders, anxiety and depression, pain, malnutrition, which are not less common than classical signs and symptoms and lead to serious deterioration in the patient's quality of life. Due to the advanced age of most patients, polypharmacy, defined as the use of 4 or more drugs, can reach 80% in multiple myeloma patients, while inappropriate drug complications can reach 50%. Treatment compliance was 68% and treatment discontinuation rate was 36%. In this case, it is clear that multiple myeloma treatment optimization cannot be achieved by considering multiple myeloma treatment only as applying the appropriate drug combination.In order to ensure the optimization of IMID-based therapies, it is necessary to take a broad perspective. This perspective should include the correct selection of the patient to be treated with IMID, the development and implementation of IMID forms that will increase patient compliance, the use of techniques to predict the development of resistance, side effect management during treatment, preventing the increase in disease burden with appropriate maneuvers by following the disease burden after treatment, and drug-free follow-up. It is recommended to avoid thalidomide in the presence of peripheral neuropathy, to prefer other agents instead of lenalidomide in the presence of renal function loss, and to avoid pomalidomide in patients with COPD. Nex-20, a once-monthly subcutaneous formulation of lenalidomide, is expected to be an important breakthrough in improving patient compliance. Prediction of which patients will develop resistance will be very useful in order to have the best treatment outcomes.Calculation of miRNA risk scores, measurement of lenalidomide metabolite levels in urine, measurement of cereblon levels in blood, or immunohistochemical detection of cereblon levels are some of the methods currently being tried to predict disease resistance. Patients who develop anemia should be treated with erythropoietin, skin reactions should be treated with steroids and antihistamines, diarrhea should be treated with loperamide and colestyramine, and in general, the drug should be discontinued and the same dose or a lower dose should be insisted upon. An important part of treatment is maintenance therapy with lenalidomide. Drug discontinuation is the best possible treatment outcome. In the IFM-2009, GEM2014MAIN and MASTER trials, patients receiving lenalidomide for a fixed duration stopped the drug with MRD monitoring and had prolonged PFS.

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03

ATYPICAL HEMOLYTIC UREMIC SYNDROME DIAGNOSIS AND TREATMENT

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Atypical hemolytic uremic syndrome (aHUS), more commonly known as complement-related HUS is a kind of thrombotic microangiopathy (TMA) characterized by inherited pathogenic variants in complement genes or acquired autoantibodies against complement factors, predominantly involving kidney [1]. Activation of the alternative complement pathway (AP), which occurs due to dysfunction in complement regulatory proteins or, less commonly, activation of mutations in the complement proteins themselves, constitutes the pathogenesis of aHUS and enables endothelial damage [2]. It may also present as secondary aHUS triggered by COVID-19, Shiga toxin-producing Escherichia coli, or other identifiable conditions [1]. As a triad for the diagnosis of aHUS; thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and acute kidney injury are used, however, there is no universally accepted diagnostic criterion and it is considered inadequate because it is established without even histological findings in the kidney [1]. Complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP, CD46), thrombomodulin, complement factor B (CFB), and complement 3(C3) mutations are the mutations that play a dominant role in the pathogenesis of aHUS [2,3]. In 30% to 40% of patients who respond to complement inhibition, these mutations are not detectable or have genetic variants of unknown significance [2]. In a patient presenting with TMA findings, thrombotic thrombocytopenic purpura (TTP) must be excluded by showing that ADAMTS13 activity is above 10%. Short-acting C5 blockade (eculizumab) should be initiated without delay in those with ADMTS13 levels above 10% and those with severe oliguric acute renal failure [1]. Stool sampling should be done in individuals with diarrhea to detect Shiga toxin and/or microorganisms that produce Shiga toxin. Ravulizumab is a long-acting C5 inhibitor that is considered safe and effective in both treatment-naive adult and pediatric patients and in pediatric patients who have previously received complement inhibition [4]. Ravulizumab's half-life is four times longer than eculizumab (~51.8 days vs. ~11 days) and offers a reduced dosing frequency of up to 4-8 weeks instead of every 2-3 weeks [5]. All patients receiving complement inhibitors should be included in the vaccination program for Neisseria meningitis, Streptococcus pneumonia, and Haemophilus influenza type b, and early signs of infection should be carefully monitored and necessary parenteral antibiotic therapy should be started without delay. Although plasma exchange (PEX) treatment can provide partial benefit, especially in those with CFH, C3, and thrombomodulin gene variants, it has now been replaced by complement inhibitors where available. PEX treatment response is insufficient in CFI variants and does not provide additional benefits to complement inhibitors in MCP (CD46) deficiency [6]. Kidney transplantation treatment is associated with a high risk of recurrence, especially in patients with CFH mutations. However, the post-transplant relapse rate decreased with eculizumab treatment[7]. Iptacopan is an orally available, highly potent proximal complement inhibitor that specifically binds to CFB, the primary driver of the disease, thereby inhibiting AP [8]. Other treatments are being investigated, including alternative pathway-blocking agents and lectin pathway inhibitors.

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04

INNOVATIONS IN AL AMYLOIDOSIS MANAGEMENT

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Introduction: Immunoglobulin light chain (AL) amyloidosis is the most common type of systemic amyloidosis. AL amyloidosis is considered a plasma cell disorder caused by generally small and slowly proliferating clone of plasma cells in bone marrow that produces nonfunctional immunoglobulins. **Diagnosis:** Considering diagnosis of systemic amyloidosis is to evaluate for the presence of monoclonal paraprotein with electrophoresis and immunofixation of both serum and urine, serum kappa and lambda free light chain (FLC) levels, 24-hour urine protein. If testing confirms presence of a monoclonal immunoglobulin or abnormal FLC ratio, then tissue biopsy necessary for diagnosis should be performed. If amyloid is detected in the biopsy, the type of amyloid must be determined for a complete diagnosis. **Staging:** The most frequently used staging system is the Mayo 2012 model, which assigns a score of 1 for troponin T (≥0.025 μg/L), N-terminal probrain natriuretic peptide (NT-pro BNP; ≥1800ng/L) or BNP ≥400 ng/L, and a difference in serum FLCs (dFLC ≥180 mg/Land is believed to be superior at identifying very high risk individuals (1). An alternative model with high prediction performance is the European 2015 modification of the Mayo 2004 model assigning a score of 1 for troponin T (≥0.035 μg/L), NT-proBNP (≥ 332ng/L) and for stage 3 patients uses the absence or presence of ≥1800 ng/L criteria for IIIA, IIIB designation, respectively (2). Induction Therapy for Newly Diagnosed AL Amyloidosis: Many clinical studies investigated the role of bortezomib-based regimens, which were eventually accepted as the standart of care, the most commonly used regimen is combination of CyBorD. With the completion of the phase III Andromeda trial, the treatment paradigm has started to the addition of daratumumab together with CyBorD in the upfront setting. For patients who are eligible for autologous stem cell transplantation (ASCT), recommended beginning with induction therapy with daratumumab-CyBorD for two to four cycles and then evaluate the response. In patients who achieve a hematological very good partial response (VGPR) or better, forego ASCT and associated treatment-related morbidity and mortality in favor of completion of daratumumab-CyborD induction, followed by daratumumab maintenance for a total of 2 years. **Autologous Stem Cell Transplantation:**

Lack of consensus on optimal use of ASCT in patients with AL amyloidosis. A randomized phase II study involving 91 patients comparing high-dose intravenous melphalan (HDM) followed by ASCT with a course of oral melphalan 10 mg/m^2 given once daily and dexamethasone 40 mg given once daily for the first 4 days of a 28 day cycle for up to 18 cycles. At a median follow-up of 3 years, median overal survival (OS) in the HDM arm was significantly worse than those taking high dose melphalan and dexamethasone (22.2 versus 56 months). Clinical studies using modern induction regimens and strict selection criteria emphasize an improved outlook on early survival outcomes in transplantation. . The HOVON104 study evaluated ASCT after four cycles of bortezomib-based induction in 50 patients reported an estimated 3-year OS in the 86% and 72% cardiac response rate in evaluable patients at 2 years.

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05

CAR-T CELL THERAPY IN LYMPHOMAS: EXPANSİON OF INDICATIONS AND NEW APPROACHES

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CAR-T (chimeric antigen receptor T-cell) therapy represents a revolutionary advance in treating hematologic cancers, offering promising outcomes for lymphoma patients, especially those with relapsed or refractory disease. Initially approved for diffuse large B-cell lymphoma (DLBCL), CAR-T therapy is expanding to address a broader range of lymphomas, including other B-cell and T-cell subtypes. As CAR-T technology evolves, researchers are exploring innovative delivery strategies and engineering methods to enhance efficacy and address the unique challenges of treating different lymphoma types. CAR-T cell therapy works by genetically modifying a patient's T cells to express a receptor targeting specific cancer cell antigens. In B-cell lymphomas, CD19 has proven an effective target, with CAR-T therapies such as axicabtagene ciloleucel and tisagenlecleucel demonstrating remarkable responses. Recent studies reveal high remission rates in DLBCL, mantle cell lymphoma, and follicular lymphoma when using CD19-targeted CAR-T therapy, even in patients who have exhausted other treatment options. The success of these therapies has catalyzed research into additional lymphoma subtypes and new antigen targets, allowing CAR-T cell therapy to benefit an expanding patient population (Denlinger et al., 2022). One notable development is the investigation of CAR-T cell therapy in T-cell lymphomas. T-cell lymphomas pose unique challenges due to their antigen overlap with healthy T cells, leading to risks like T-cell fratricide, where CAR-T cells inadvertently destroy each other. To address this, researchers are designing CAR-T cells targeting less common antigens, such as CD30, which is often overexpressed in Hodgkin lymphoma and some T-cell lymphomas, but not in normal T cells. CD30-directed CAR-T therapies have shown early success in clinical trials, offering hope for relapsed Hodgkin lymphoma patients who lack other viable options (Brudno et al., 2024, Ramos et al., 2020). Localized CAR-T cell therapy is another emerging strategy, particularly for lymphomas affecting the central nervous system (CNS). CNS lymphomas present an additional barrier because CAR-T cells administered intravenously may struggle to cross the blood-brain barrier (BBB) and reach tumor cells. Direct intrathecal CAR-T administration, which bypasses the BBB, has shown promising early results for CNS lymphoma, providing high CAR-T cell concentrations directly within the CNS and improving patient outcomes. This approach may reduce systemic side effects like cytokine release syndrome (CRS) and neurotoxicity, although localized neurotoxicity remains a concern (Sagnella et al., 2022). Engineering advancements are also helping address antigen escape, where cancer cells evade CAR-T cells by losing the targeted antigen. Dual-target CAR-T cells can recognize multiple antigens, reducing the risk of relapse due to antigen loss. For example, dual CD19/CD22 CAR-T therapies are being studied for their ability to sustain long-term remission by targeting two markers common to B-cell lymphomas, thus enhancing durability and reducing escape mutations. Also combining CAR-T with immune checkpoint inhibitors improve CAR-T cell efficacy. (Roddie et al., 2023). In summary, CAR-T cell therapy has transformed the lymphoma treatment landscape, extending beyond DLBCL to address Hodgkin lymphoma, follicular lymphoma, and other challenging subtypes. As new approaches evolve—such as local delivery for CNS lymphoma, dual-target CAR-T constructs, and novel T-cell lymphoma strategies—CAR-T therapy's role continues to expand, offering new hope to patients with previously untreatable lymphomas. Continued innovation will be crucial for refining CAR-T technology, overcoming barriers, and realizing its full potential across diverse lymphoma types.

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06

PROFESSOR DOCTOR SEREF INCEMAN'S BIOGRAPHY AND LEGACY

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Dr Inceman was born in Istanbul in 1919. He completed his primary education at Galatasaray High School (1940). He graduated from Istanbul University Faculty of Medicine (1940-1946). After graduation, he started his residency at the Internal Medicine Clinic (Capa) of the same faculty. He completed his military service in Erzincan (1949-1950). He worked in the clinic of Professor Jean Bernard, who conducted studies on leukemia and immunohematology at the University of Paris (1950-1951). in 1951, he stayed with Professor Swen Moeschlin at the Internal Medicine Clinic of the University of Zurich, Switzerland for a month. He was promoted to Associate Professor in 1956 and to Professor in 1966. Between 1963 and 1986, he directed the Hematology Department and served as its chairman. He was one of the founding members of THD in 1967 and was its first president. His research interest in the

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-

invasive methods have played a very important role in improving the prognosis of patients with thalassemia. Today, the only and definitive treatment option for cases with beta thalassemia major is hematopoietic stem cell transplantation. After myeloablative conditioning treatment, allogeneic stem cell transplantation from an HLA-compatible sibling donor is considered the treatment of choice. However, for patients who do not have a suitable donor, the risk of mortality and morbidity, especially in transplants from unrelated or haploidentical donors, creates anxiety. Therefore, in recent years, alternative gene therapy strategies have been studied that aim to correct the defective β-globin gene by transferring a normal β-globin gene or replacing the defective gene with homologous recombination. RNA-based treatment approaches, known as RNA Therapies, are also being investigated in the treatment of thalassemia. These treatments target the genetic mutations that cause thalassemia and aim to correct faulty RNA production. In addition to regular blood transfusions applied to improve the quality of life of patients, Iron Chelators are among the new drugs and treatment approaches in thalassemia patients. Iron binders used as part of thalassemia treatment help to remove iron accumulated in the body due to continuous blood transfusions. The most commonly used iron binders today include deferoxamine, deferasirox, and deferiprone. These drugs help prevent iron accumulation from causing damage to organs. New drugs used other than chelators Hydroxyurea: Although hydroxyurea is usually used to treat sickle cell anemia, it is also being investigated in the treatment of thalassemia. This drug can relieve anemia symptoms by increasing hemoglobin production. In some thalassemia patients, hydroxyurea treatment can reduce the frequency of blood transfusions. Luspatercept: Luspatercept is a biologic drug that reduces the need for blood transfusions by increasing the production of red blood cells. This drug can improve the quality of life of patients by regulating the production of blood cells. Ferroportin Modulators: Ferroportin is a protein that plays an important role in iron transport in the body. New treatment strategies aim to reduce iron imbalance and excessive iron accumulation by modulating ferroportin. This treatment is among the future treatment options for controlling iron overload in thalassemia patients. Epoetin Alfa and Epoetin Beta: Epoetin alfa and epoetin beta are analogs of the hormone erythropoietin (EPO). These drugs may improve anemia management and reduce the frequency of blood transfusions in some thalassemia patients. Conclusion: Future treatment options include alternative treatment approaches such as genetic therapies, biologics, and bone marrow transplantation. Clinical studies are constantly being conducted on new treatment methods, which aim to further improve patients' response to treatment. These new drugs and treatment options used in the treatment of thalassemia aim to improve patients' quality of life and manage the symptoms of the disease. However, each patient's response to treatment may vary, so the treatment plan should be individualized for each patient. More research is needed on the effectiveness and safety of new treatment approaches.

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12

PRECISION MEDICINE IN CLL: TREATMENT BASED ON MOLECULAR PROFILES

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Chronic Lymphocytic Leukemia (CLL) is a genetically and clinically heterogeneous disease, characterized by a wide range of genetic mutations and chromosomal abnormalities that contribute to its variable clinical course and response to treatment. This heterogeneity makes CLL a complex disease to manage, with genetic factors playing a crucial role in prognosis and treatment decisions. Approximately 80% of patients with CLL have at least one of the chromosomal abnormalities: del(13q), del(11q), del(17p), or trisomy 12. The most commonly used genetic tests are FISH (Fluorescence In Situ Hybridization) and next-generation sequencing (NGS). Conventional cytogenetics is not preferred in CLL due to its lower sensitivity for detecting smaller chromosomal abnormalities and subtle genetic mutations. FISH is highly effective at detecting specific chromosomal abnormalities, such as del(13q), del(11q), del(17p), or trisomy 12, while NGS provides a detailed analysis of molecular mutations, including those in genes like TP53, NOTCH1 and SF3B1. The immunoglobulin heavy chain variable region (IGHV) mutation status plays a critical role in prognosis. IGHV mutation status is typically assessed using Sanger sequencing or NGS. The prognostic significance of the chromosomal abnormalities and mutations described above in CLL is well-established(Gaidano& Rossi, 2017; Hallek et al.,2021). Multiple studies have shown that del(17p), TP53 mutations, and/or unmutated IGHV status are associated with poor prognosis in CLL. In addition to poor survival outcomes, these factors also carry a high risk of poor response to initial chemoimmunotherapy and earlier relapse after achieving remission(Eichhorst et al.,2021; Mato et al.,2022; Tausch et al.,2020). Currently, treatment guidelines for CLL include prognostic evaluations and treatment planning based on these three mutation statuses(Eichhorst et al.,2021; Eichhorst et al.,2024; Hampel & Parikh,2022) NOTCH1 mutations have been identified as potential biomarkers of resistance to anti-CD20 monoclonal antibodies, such as rituximab and ofatumumab, in CLL, with further clinical validation needed to confirm their role and assess the efficacy of obinutuzumab in overcoming this resistance(Estenfelder et al., 2016). While other mutations, such as NOTCH1, are being investigated, they are not yet ready for widespread use in clinical practice or treatment decision-making. In CLL, the use of measurable (previously referred to as ''minimal'') residual disease (MRD) is still largely limited to clinical trials. MRD is commonly used as a marker of treatment efficacy. Flow cytometry, PCR, and NGS are the primary methods employed to detect MRD. The threshold for MRD detection remains a subject of debate. The current international consensus defines "undetectable" MRD as U-MRD4, though some studies report data at MRD5 or lower levels. Currently, MRD is associated with disease prognosis and is utilized to adjust the duration of treatment. However, it is still unclear whether therapeutic decisions based on

MRD will consistently provide clinical benefits or be sufficient to challenge established treatment strategies for CLL(Fisher et al.,2023; Wierda et al.,2021; Yang et al,2021). Complex karyotype (CK) in CLL is defined by at least three numerical or structural abnormalities in two or more metaphases within the same clone. CK is linked to advanced disease, unmutated IGHV, TP53 mutations, adverse FISH abnormalities, and telomere dysfunction. Even within the CK subgroup, heterogeneity exists in the number and type of aberrations. While CK is a significant prognostic marker, its predictive value and role in treatment remain uncertain. (Chatzikonstantinou et al., 2021). Advances in understanding epigenetics in CLL, including DNA methylation and microRNAs, may lead to targeted therapies(Zhang et al., 2024). In conclusion, CLL's genetic and epigenetic landscape is complex, with numerous chromosomal abnormalities and molecular mutations playing a critical role in disease progression, prognosis, and treatment outcomes. Ongoing studies into genetic biomarkers and MRD monitoring continue to refine our understanding of the disease, thereby providing the foundation for more individualized and potentially more effective treatment approaches in the future.

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NEW GENERATION BTK INHIBITORS AND RESISTANCE IN CLL TREATMENT

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Chronic lymphocytic leukemia (CLL) is an indolent lymphoproliferative malignancy characterized by monoclonal B lymphocytosis. BCR signaling plays a critical role in B cell development and survival. Bruton Tyrosine Kinase inhibitors (BTKi) disrupt the BCR signaling pathway by inactivation of BTK, leading to inhibition of proliferation and survival of CLL cells. There are two classes of BTK inhibitors, covalent and non-covalent. İbrutinif is the first approved covalent BTKi (cBTKi) of its class. The second-generation cBTKi (acalabrutinib and zanubrutinib) were designed to increase selectivity against BTK and reduce off-target toxicity. Continuous therapy with BTKi contributes to the acquisition of secondary resistance leading to clinical relapse. Pirtobrutinib, a noncovalent BTKi (ncBTKi), represents a novel class of BTKi developed to improve effectiveness and overcome acquired resistance to cBTKi. Mutations in BTK, particularly in the c481s region, and mutations in the PLCG2 region are considered the predominant mechanism of BTKi resistance in patients with CLL. Pirtobrutinib, retains kinase inhibition even in the presence of a BTK C481 mutation and demonstrates high specificity for BTK, with minimal off-target effects. The toxicity profiles of BTKis are closely linked to their kinase-binding patterns, including both on-target inhibition of BTK and variable off-target inhibition of other kinases, such as interleukin-2-inducible T-cell kinase (ITK), tyrosine kinase expressed in hepatocellular carcinoma (TEC), and epidermal growth factor receptor (EGFR) family kinases. AEs such as cardiac arrhythmias, bleeding, diarrhea, arthralgia, hypertension and infection are the primary reasons for ibrutinib discontinuation. Optimal management of AEs is crucial to achieving good outcomes and maintaining quality of life.

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THE HYPOXIA INDUCIBLE FACTOR (HIF) PATHWAY IN AML: THERAPEUTIC TARGETING

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The increase in levels of the hormone erythropoietin, which leads to increased production of red blood cells in response to hypoxia, was a physiological response known in the early 20th century. However, the mechanism of the cellular reaction to hypoxia was unknown. William G. Kaelin Jr., Peter J. Ratcliffe, and Gregg L. Semenza received the 2019 Nobel Prize in Physiology and Medicine for their contributions to this field. HIFs have been identified as transcription factors that function in response to hypoxia. When oxygen levels are low, the HIF protein complex is protected from degradation and accumulates in the nucleus, where it connects with the aryl hydrocarbon receptor nuclear translocator (ARNT/HIF1-β) and binds to specific DNA sequences (HREs) in hypoxia-regulated genes. At normal oxygen levels, HIF-1α is rapidly degraded by the proteasome. Oxygen regulates the degradation process by adding hydroxyl groups (OH) to HIF-1α. The VHL protein can then recognize HIF and form a complex that leads to its degradation in an oxygen-dependent manner (1,2). It is known that there are 3 types of HIF: HIF-1, HIF-2, and HIF-3. Hypoxia activates all three HIFs, with HIF-3 acting as a regulator by suppressing the gene expression of HIF-1 and HIF-2. All three HIFs consist of two subunits, α and β. The β subunit is consistently expressed in the nucleus, independent of oxygen levels, whereas the α subunit exhibits differential responses to hypoxia and normoxia, serving as the primary site for HIF-1 in tumorigenesis. To date, three isoforms of the HIF α-subunit have been identified; these are HIF-1α, -2α, and -3α. In particular, HIF-1α is the most extensively studied isoform and is generally expressed in human cells. HIF-2α is expressed only in specific tissues and cell types, such as the lung, kidney, and liver. HIF-3α is mainly expressed in heart, kidney, and lung epithelial cells. Two genes, ARNT1 and ARNT2, encode HIF-1β subunits. HIF1A, EPAS1, and HIF3A encode the HIF1/2/3α proteins, respectively. HIF-1a has been detected in high amounts in many types of cancer and is known to regulate the expression of over 100 genes.It has an effect on gene categories related to angiogenesis, energy metabolism, invasion and metastasis, proliferation and apoptosis-related proteins, immune evasion, and drug resistance, which are important steps in tumor homeostasis (3).This makes the HIF pathway a targetable focus in cancer treatment. Studies have shown that there is an increase in HIF-1α and HIF-2α expression in

AML and that suppression of HIF-1α induces apoptosis (4-5). It has also been shown that hypoxic environment and HIF pathway play an important role in the long-term survival of leukemic stem cells in the bone marrow. However, there are also studies showing that HIF-1α deficiency causes AML to progress more rapidly (6).Therefore, these findings indicate that the role of HIF-1α should be considered carefully in practical applications depending on specific conditions. Pre- and post-clinical studies targeting the HIF pathway are ongoing. The HIF pathway appears promising as a new therapeutic target.

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TARGETED THERAPIES IN AML: CURRENT AND FUTURE TRENDS

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Acute Myeloid Leukemia (AML) encompasses several subtypes defined by distinct cytogenetic and molecular characteristics, which complicates treatment and necessitates therapies that can target multiple pathways. Despite advancements, there remains a significant need for molecular treatments that can achieve long-term remissions and potentially cure this heterogeneous disease. In the past 5 to 6 years, the FDA has approved several targeted therapies for both newly diagnosed and relapsed/refractory AML. These novel therapeutics, along with others currently being investigated, have shown promising activity against AML and have improved outcomes for many patients. This presentation will explore various molecular mechanisms that contribute to the pathogenesis of AML and review current research into how these mechanisms are being targeted in treatment strategiesA **Approved Drugs:** Since the 1970s, the classical therapy for AML has consisted of cytarabine combined with an anthracycline (daunorubicin or idarubicin), famously known as the "7 + 3" regimen. The small-molecule FDA-approved drugs for AML over the last decade include IDH inhibitors (olutasidenib, ivosidenib, enasidenib), FLT3 inhibitors (gilteritinib, midostaurin), BCL-2 inhibitor (venetoclax), hypomethylating agents (azacitidine, decitabine), and CPX-351 (liposomal cytarabine and daunorubicin). **Non-Approved Drugs:** Several FLT3 inhibitors, such as sorafenib and quizartinib, have undergone clinical trials for acute myeloid leukemia (AML). However, the FDA did not approve these drugs due to various concerns regarding the trial data. Recent reports from 2021 highlighted an oxoindoline-based selective FLT3 inhibitor as a potential candidate for treating FLT3-ITD-positive AML, a condition associated with a poor prognosis. Additionally, a first-in-class hydrazide-based HDAC inhibitor was reported in 2022, and a promising CDK9 inhibitor for AML treatment was identified in 2021. Rearrangements of the KMT2A (MLL1) gene occur in up to 10% of acute leukemias. Moreover, the TP53 tumor suppressor gene is often inactivated in cancers due to loss-of-function mutations or missense mutations in the DNA-binding domain, occurring in nearly 50% of cases. Targeting mutant p53 to restore its function could provide a promising avenue for new therapeutics. APR-246 is a compound designed to reactivate mutant p53. **Conclusions:** While this presentation does not cover all targeted agents, many promising options are available. A continuous and dedicated focus on understanding the fundamentals of molecular genetics and epigenetics, along with ongoing monitoring of clonal evolution before and after treatment with these targeted therapies, could lead to innovative changes in treatment strategies. This may ultimately provide the most beneficial outcomes for patients of all ages.

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HEMOPHILIA: ADVANCES IN TREATMENTS

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Introduction: Hemophilia is an X-linked recessive disorder. It is divided into two different subtypes; hemophilia A (HA) and B (HB), which result from the deficiency or complete absence of clotting factors VIII (FVIII) and IX (FIX) respectively. Current management of HA and HB includes prophylactic factor replacement[1]. Neutralising antibodies, as inhibitors, can develop against the infused factor and that can complicate the management of hemophilia patients. If inhibitors develop, immune tolerance induction can potentially promote tolerance to exogenous FVIII or FIX, and bypassing agents (BPAs) such as recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrates (aPCC) can be used to circumvent factor use. Inhibitor development impacts negatively upon quality of life and treatment compliance, highlighting the need for improved therapies. Several novel pharmacological therapies developed for hemophilia aim to rebalance the clotting cascade. These therapies utilise a range of different mechanisms, namely: the extension of the circulating half-life of standard recombinant factors; the mimicking of factor VIII cofactor activity; rebalancing of coagulation through targeting of natural anticoagulants such as antithrombin and tissue factor pathway inhibitor; and inducing the production of endogenous factors with gene therapy. **Discussion:** Extended half−life products involves fusing FVIII or FIX to a protein with a long half-life. Albumin and the constant region (Fc) of IgG have long plasma half-lives as they bind to the neonatal Fc receptor, which is critical for the endogenous recycling of both IgG and albumin. Another method is PEGylation, where one or more PEG chains are covalently linked to rFVIII or rFIX. PEG chains interfere with the recombinant factors binding to their clearance receptors, thereby prolonging circulating half-life. Emicizumab, a recombinant humanised bispecific IgG antibody, mimics the cofactor function of the missing FVIII in HA. It simultaneously binds activated FIX (FIXa) and factor X (FX), bringing them into spatial proximity to promote FIXa-catalysed FX activation, thereby restoring haemostasis. Fitusiran, a novel therapy applicable to both HA and HB, consists of the amino acid,

N-Acetyl- galactosamine, the ligand of the hepatic asialo-glycoprotein receptors, conjugated to a synthetic siRNA. It targets and degrades a region of the SERPINC1 gene mRNA, preventing antithrombin production and enhancing thrombin generation. Antithrombin is a potent anticoagulant which inactivates FIXa, activated factor X (FXa) and activated factor II (FIIa/thrombin). Therefore, fitusiran can correct the coagulation imbalance and prevent the bleeding phenotype. Concizumab is an IgG4 monoclonal antibody targeting tissue factor pathway inhibitor (TFPI). It presents an alternative therapy for HA and HB patients, both with and without inhibitors. TFPI is a coagulation inhibitor. It limits coagulation during the initiation of the coagulation cascade through inhibition of the tissue factor-activated factor VII (TF-FVIIa) complex and through FXa inhibition. Gene therapy presents a novel and effective treatment modality for hemophilia, potentially bypassing complications of other therapies. Gene therapy regimens consist of single infusions of a viral vector, which result in transduction of a gene coding for the deficient factor into patient hepatocytes. Current gene therapy regimens for hemophilia predominantly utilise adeno-associated virus (AAV) vectors to deliver the required gene. **Conclusion:** Current factor replacement poses numerous issues, resulting in poor adherence and reduced QoL. Inhibitor development presents a key limitation to factor replacement. EHL products, emicizumab, fitusiran, and concizumab (summarised in appear effective in patients with and without inhibitors, and their longer half-lives enable less frequent injections.

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OPTIMIZATION OF FIXED DURATION TREATMENT OPTIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA: CURRENT DATA AND FUTURE DIRECTIONS

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Introduction of Bruton tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 (Bcl-2) antagonists changed the historical approach to chronic lymphocytic leukemia (CLL). Fixed-duration, targeted combination of these novel agents have replaced chemoimmunotherapy and have become preferred treatment options. Benefit of treating asymptomatic early stage disease is yet to be shown and indications for treatment are still mostly guided by International Working Group for CLL (iwCLL) 2018 recommendations. However; risk stratification has also come to question as genetic studies such as 17p/TP53 mutations, IGHV mutation status showed better risk analysis following chemoimmunoterapy (CIT) era. BTKi and Bcl-2 inhibitors also led to investigations on duration of treatment (fixed duration versus continuous) and best combination that provides most overall survival (OS) and progression-free survival (PFS) benefit. Since most CLL patients are elderly, comorbidities limit treatment options and these comorbidities correlate with shorter OS. Prior studies have shown that young and fit patients benefited from first line CIT such as fludarabine, cyclophosphamide, rituximab (FCR) and FCR provided long term remissions in previously untreated patients. Advent of BTKi and venetoclax offered a better treatment option for older population with high Cumulative Illness Rating Scale (CIRS) with fewer side effects although negative impact of comorbidities persisted.[3] In recent years, trials such as CLL14 have included patients with CIRS>6 and low creatinine clearence and showed the FD obinituzumab plus venetoclax combination was superior and provided longer PFS compared with to obinituzumab plus chlorambucil (median, 76.2 vs 36.4 months; hazard ratio [HR], 0.40; 95% confidence interval [CI], 0.31-0.52; $P < .0001$). Treatment with FD ibrutinib plus venetoclax in older patients also provided better responses. PFS was significantly longer for ibrutinib-venetoclax compared to chlorambucil-obinutuzumab (hazard ratio, 0.216; 95% confidence interval [CI], 0.131 to 0.357; P<0.001). PFS remained higher including patients 65 years of age or older or with a CIRS >6.These studies have provided basis for the approval of FD ibrutinib plus venetoclax combinations and showed clear benefit compared with historical CIT. FD treatments versus continuous ibrutinib became the focus of recent trials as well as determination of optimal duration for any treatment. Although continuous ibrutinib is the treatment of choice, trials have shown increased PFS and OS with FD treatments. With ibrutinib and venetoclax combination 36 −month overall survival (OS) was >95% regardless of high-risk features. Following recent trials, minimal residual disease (MRD) status as well as its incorporation into treatment duration emerged as a marker to guide CLL treatment. Subgroup analysis of trials have reported better PFS in patients with MRD negativity. Recently MRD guided treatment was shown to be effective and re-initiation of treatment with ibrutinib plus venetoclax was able to achive MRD negativity following discontinuation of treatment. Trials with ibrutinib and next generation BTKi and venetoclax are expected to incorporate MRD to further expand its role as an independent risk factor for long term survival. MRD tailored treatments in clinical practice may allow for discontinuation of treatment and also predict relapse. Appropriate method to determine MRD status requires further data from trials.

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OPTIMISATION OF THERAPEUTIC APPROACHES FOR HIGH-RISK ALL SUBTYPES

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There are actually several subtypes of acute lymphoblastic leukemia (ALL), some of which are especially difficult to manage. The high risk ALL subtypes included in this overview are neonatal ALL, KMT2A rearrangement, Philadelphia chromosome-positive (Ph+), Philadelphia-like (Ph-like), and Early T-cell precursor (ETP). Ph+ ALL: Tyrosine kinase inhibitors

(TKIs), such as imatinib, dasatinib, and nilotinib, constitute a part of the the main treatment for Ph+ ALL, which is characterized by the BCR-ABL1 fusion gene. Chemotherapy and/or steroids are frequently utilized in combination with TKIs. ABL001 provides a new method of ABL inhibition, although ponatinib works well against T315I mutations. Ph-like ALL: This type of ALL frequently contains CRLF2 rearrangements and ABL-class fusions, but it lacks the BCR-ABL1 fusion yet shares a comparable gene expression profile.(Jain & Abraham, 2020) For CRLF2-rearranged cases, JAK inhibitors like as ruxolitinib show promise, although conventional TKIs might work well for ABL-class fusions. KMT2A Rearranged ALL: KMT2A rearrangements are frequent in infant ALL and have an undesirable prognosis. (Richard-Carpentier vd., 2021)By targeting protein interactions and epigenetic changes, DOT1L and menin inhibitors,(Candoni & Coppola, 2024) such as SNDX-5613, are becoming potential therapeutic options. ETP ALL: A rare and aggressive type of T-cell ALL, ETP ALL can be identified by certain genetic changes and immunophenotypic markers.(Onishi vd., 2023) JAK inhibitors and Venetoclax, a BCL-2 inhibitor, are being studied as potential therapies for the dysregulated IL-7 and BCL-2 receptor pathways. Infant ALL: Challenges with infant ALL include an underdeveloped immune system and high frequency of KMT2A rearrangements. To improve those results, epigenetic modifiers and improved immunotherapeutic strategies, such as CAR T-cell therapy, are being researched. To sum it up, understanding the particular characteristics each high-risk ALL subtype is critical to designing personalised treatments. To overcome the difficulties presented by drug resistance and immune system infancy, ongoing research and clinical trials are important.

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IMMUNOTHERAPY IN ALL: MONOCLONAL ANTIBODIES AND BEYOND

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In acute lymphoblastic leukemia (ALL) patients, overall survival is around 90% in childhood, whereas 5-year overall survival (OS) is less than 45% in adults. For eligible patients, allo-HCT remains the standard treatment, while immunotherapies are drawing attention in studies aimed at developing alternative treatment regimens. The most popular immunotherapies include bispecific antibodies (BsAbs), antibody-drug conjugates, CAR T-cell, and CAR NK cell therapies, which aim to target cancer cells using the patient's immune system. Blinatumomab is a bispecific T-cell-engaging (BiTE) antibody. It is designed to include binding regions that target two different antigens simultaneously. By binding to CD19 on B-ALL cells and CD3 on T cells, it activates T cells, leading to the polyclonal expansion of cytotoxic T cells, T cell activation, and the release of cytokines and cytotoxic granules, which cause the lysis of CD19+ lymphoblasts. Initially approved by the FDA in 2014 for the treatment of Ph(-) relapsed/refractory B-ALL, it has since received FDA approval for consolidation therapy in patients with MRD-positive disease as well as for MRD-independent consolidation therapy. Hematologic side effects are similar to those of standard chemotherapy, while non-hematologic side effects include cytokine release syndrome and neurological events, which are relatively manageable due to prophylactic measures and its short half-life. In the Alcantara study, it was shown that sustainable responses were achieved in patients with Ph(+) R/R ALL, despite the low number of patients enrolled in the study. Inotuzumab is an antibody-drug conjugate that consists of calicheamicin, a DNA-binding cytotoxic antibiotic, covalently linked to an anti-CD22 IgG4 mAb. In 2017, it received FDA approval after monotherapy with inotuzumab showed superiority over standard chemotherapy for relapsed/refractory CD22(+) B-ALL. The most common grade ≥3 side effects are hematologic and liver-related, including 11% VOD, which is mostly seen after sequential allo-HSCT. It is recommended for patients without known liver disease. To reduce VOD risk, it is advised to administer only up to two cycles of inotuzumab before SCT and avoid double alkylators in conditioning regimens. Inotuzumab monotherapy has shown high CR and MRD negativity rates when combined with low-intensity chemotherapy in elderly patients in first-line treatment, but it is still not approved by the FDA and EMA. Cell-based therapy, despite side effects limiting CAR T-cell, has shown remarkable efficacy in r/r B-ALL with CD19-targeted therapy, such as tisagenlecleucel (tisa-cel) for patients ≤25 years and brexucabtagene autoleucel for adults. Side effects include cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS), and B-cell aplasia. For relapsed/refractory T-cell leukemia, CD5-CART, CD7-CART, and NS7CAR studies are ongoing. Although experimental, CAR-NK therapies using NK cells, which are isolated from peripheral blood and do not pose a GVHD risk, hold promise with fewer side effects, reduced relapse, and prolonged survival. Studies on immune checkpoint inhibitors in combination with other immunotherapies may be significant for B-ALL, while combinations of BCL-2 and BCL-XL inhibitors with chemotherapy may be important for T-ALL, which currently lacks antibody therapy. While challenges persist in treating T-ALL and Ph-like ALL, immunotherapy and cellular therapies continue to be significant for B-ALL treatment, with ongoing research into the optimal combinations and integration stages into therapy.

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CAR-T CELL THERAPY IN ACUTE LEUKEMIAS

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Acute leukemias, particularly acute lymphoblastic leukemia (ALL) and, to a lesser extent, acute myeloid leukemia (AML), remain among the most challenging hematologic

malignancies due to high mortality rates and limited treatment options. In this context, Chimeric Antigen Receptor T (CAR-T) cell therapy has emerged as a promising approach for patients with refractory or relapsed disease. CAR-T cells are generated by genetically engineering the patient's T cells to express synthetic receptors targeting specific tumor-associated antigens. In ALL, CD19-targeted CAR-T cell therapies have demonstrated complete remission (CR) rates of 70–90%. For AML, ongoing research is exploring alternative targets. Clinical Studies and Outcomes ELIANA Trial The ELIANA trial, the largest global multicenter study of CD19-targeted CAR-T therapy, focused on pediatric and young adult ALL patients Tisagenlecleucel was infused into 75 ALL patients and evaluated for efficacy. The overall remission rate at 3 months was 81%, and all patients who responded to treatment were found to be negative for minimal residual disease by flow cytometry. Event-free survival and overall survival rates were 73% and 90% at 6 months and 50% and 76% at 12 months, respectively. Median duration of remission was not achieved. Tisagenlecleucel persisted in the blood for up to 20 months. Grade 3 or 4 adverse events thought to be related to tisagenlecleucel occurred in 73% of patients. Cytokine release syndrome occurred in 77% of patients, 48% of whom received tocilizumab. Neurological events occurred in 40% of patients and were managed with supportive care, and no brain edema was reported. ZUMA-3 Trial The ZUMA-3 an international, multicentre, single-arm, open-label study evaluating the efficacy and safety of the autologous anti-CD19 CAR-T-cell therapy KTE-X19 in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia. KTE-X19 was administered to 55 (77%) patients. At a median follow-up of 16.4 months (13.8-19.6), 39 patients (71%; 95% CI 57-82, p<0.0001) had CR or CRi and 31 (56%) achieved CR. Median duration of remission was 12.8 months (95% CI 8.7 - not estimable), median relapse-free survival was 11.6 months (2.7-15.5) and median overall survival was 18.2 months (15.9 - not estimable). Among responders, median overall survival was not reached and 38 (97%) patients had MRD negativity. Ten (18%) patients received allo-SCT consolidation after KTE-X19 infusion. The most common adverse events of grade 3 or higher were anemia (27 [49%] patients) and pyrexia (20 [36%] patients). 14 (25%) patients had grade 3 or higher infections. Two grade 5 KTE-X19-related events occurred (cerebral herniation and septic shock). Grade 3 or higher cytokine release syndrome occurred in 13 (24%) patients, and grade 3 or higher neurologic events occurred in 14 (25%) patients. AML Target Studies AML poses unique challenges due to its heterogeneous cell populations. Early-phase studies of CD33-targeted CAR-T cells have shown promising tumor burden reductions in specific patient cohorts. However, these studies are still in the clinical validation phase. Future Perspectives Next-generation CAR-T cell designs aim to enhance target specificity and minimize adverse effects, improving the therapy's safety and efficacy profile. Allogeneic CAR-T platforms and universal CAR-T cell technologies are also under development, potentially increasing accessibility for a broader range of patients. In conclusion, CAR-T cell therapy represents a transformative step in personalized treatment strategies for acute leukemias. Continued advancements in clinical trials and translational research will further unlock the potential of this innovative approach in hematology.

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PRECISION MEDICINE IN MULTIPLE MYELOM

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Precision medicine, an approach tailored to individual patient characteristics and disease profiles, has become increasingly important in the treatment of multiple myeloma (MM). Conventional MM treatment often yields variable results because the biological and clinical course of MM is heterogeneous. One of the main strategies in precision medicine for MM is genetic profiling. Certain genetic mutations such as t(4;14), t (14;16) and del(17p) are associated with a higher risk of aggressive disease. In addition, copy number alterations involving the long arm of chromosome 1 (1q) predict worse survival. In addition to cytogenetics, differential gene expression profile (GEP) signatures are independent prognostic factors for both PFS and OS, thus providing an additional method to identify high risk. By identifying these markers early, clinicians can classify patients into risk categories and tailor treatment accordingly. High-risk patients may receive more intensive treatments, while standard-risk patients may benefit from less aggressive regimens that preserve quality of life. Targeted therapies are another critical component of precision medicine in MM. Unlike conventional chemotherapy, which affects both cancerous and healthy cells, targeted therapies are designed to act specifically on the molecular pathways that drive MM cell growth. Drugs such as proteasome inhibitors, immunomodulatory agents and monoclonal antibodies are designed to attack key mechanisms in MM cells. For example, proteasome inhibitors disrupt protein excretion pathways in cancer cells, leading to cell death, while monoclonal antibodies can mark MM cells for immune destruction. These therapies offer more effective and tolerable treatment options when matched to patients whose disease characteristics are compatible with the drug's mechanism. CAR-T cell therapy and bispecific antibodies are promising options for relapsed/refractory MM and offer significant disease reduction for patients with limited options. Precision medicine also plays a role in monitoring minimal residual disease (MRD), which refers to the small number of cancer cells that can remain after treatment and potentially cause relapse. Multiparameter flow cytometry (MFC) and next-generation sequencing (NGS) are the most common and standardised methods. Whole body MRI and PET/CT provide better assessment for extramedullary disease. Patients with MRD-negative status generally have better long-term outcomes, so precision medicine approaches can tailor treatment to MRD status, aiming for complete eradication of disease in patients with evidence of remaining cancer cells. Finally, clinical trials are essential to develop precision medicine in MM. Studies focused on biomarker-driven therapies and novel agents give

patients access to cutting-edge treatments that may be more effective for specific disease profiles. As genomic data and biomarker research progress, trials are increasingly focused on matching patients with therapies based on individual molecular characteristics, increasing the likelihood of a favourable outcome. AI is supporting precision medicine in MM by improving diagnostic accuracy, risk stratification and treatment matching, potentially transforming personalised oncology care. Overall, precision medicine in MM, supported by AI insights, aims to optimise treatment efficacy, promote longer-lasting remission and improve quality of life by tailoring therapies to each patient's unique disease profile.

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SUPPORTIVE CARE AND QUALITY OF LIFE IN MDS: ESSENTIAL MANAGEMENT STRATEGIES

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Supportive care is critical for patients with Myelodysplastic Syndromes (MDS), aiming to enhance quality of life (QoL) amidst this chronic, hematologic disorder. MDS management focuses on alleviating symptoms of ineffective hematopoiesis and preventing complications like infections and cardiovascular disease. Managing Anemia and Transfusion Dependence: Anemia is prevalent in MDS, often requiring blood transfusions. However, frequent transfusions can lead to iron overload, risking damage to organs like the heart and liver. Iron chelation therapy mitigates this risk by reducing iron buildup, crucial for transfusion-dependent patients. Erythropoiesis-stimulating agents (ESAs) are effective in lower-risk MDS patients, reducing transfusion needs, while the recent COMMANDS Trial highlights luspatercept as an alternative to epoetin alfa, showing promising results in managing anemia and improving QoL. Addressing Thrombocytopenia and Bleeding Risks: Patients with MDS frequently experience thrombocytopenia, which increases bleeding risk. Thrombopoietin receptor agonists, like eltrombopag and romiplostim, aid platelet production, though long-term safety and efficacy require further research. For severe cases, prophylactic platelet transfusions are essential, with tailored transfusion thresholds improving patient outcomes. In addition, antifibrinolytic agents, such as tranexamic acid, are used adjunctively to manage bleeding. Infection Prophylaxis: Due to compromised immunity, MDS patients face high infection risks. Antimicrobial prophylaxis and vaccinations against common pathogens are critical. Prophylactic measures are especially relevant for patients with neutropenia, where antibiotics, antifungals, and antivirals provide protection. Vaccinations further support infection prevention, although immune responses in MDS patients may require adjustments. Nutritional and Metabolic Support: Malnutrition is common in MDS and correlates with poor prognosis. Regular nutritional assessments help address deficiencies, and supplements, particularly of B vitamins and folate, are beneficial in sustaining hematopoiesis. Recent findings suggest vitamin C's potential in supporting hematologic function through DNA demethylation, though optimal dosages are still under study. Cardiovascular and metabolic complications are also common, emphasizing lifestyle modifications and careful management of comorbidities like hypertension and diabetes. Psychological and Palliative Care: Chronic symptoms and disease progression often lead to depression and anxiety among MDS patients. Psychosocial support, including therapy and support groups, can significantly enhance emotional resilience. For those in advanced stages, palliative care, emphasizing dignity and comfort, is essential. Pain management and non-pharmacological approaches for symptoms like fatigue help improve end-of-life quality. Role of Technology and Geriatric Assessments: Telemedicine offers a means for remote monitoring, enhancing access to care for elderly or immobile patients. Geriatric assessments guide treatment decisions, balancing efficacy and tolerance, especially in older patients who may face higher treatment-related risks. In conclusion, MDS supportive care integrates various strategies, from anemia management to infection control, tailored for physical, emotional, and psychosocial well-being. Multidisciplinary approaches and emerging tools like telemedicine continue to improve outcomes, underscoring supportive care's pivotal role in MDS management.

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HARMONIZATION OF TREATMENT APPROACHES: DRAWING INSPIRATION FROM PEDIATRIC TREATMENTS IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA THERAPY

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Age, genetic characteristics, comorbidities, and minimal residual disease determine prognosis in patients with Acute Lymphoblastic Leukemia (ALL). Advanced age, the presence of adverse genetic markers and reduced treatment intensity typically lead to poorer outcomes, with disease-free survival and remission rates decreasing with age. In adult patients, disease remission rates are around 35%. In recent years, there has been a growing focus on applying treatment protocols developed for pediatric age groups to adult ALL patients. In pediatric ALL protocols, the main factor that enhances treatment success is the dose intensity. These protocols involve higher doses and more frequent dosing intervals of L-asparaginase, vincristine, methotrexate and steroids compared to adult ALL protocols. In recent years, it has been shown that treatment regimens applied to young adult/adolescent ALL patients have an independent impact on outcomes. Various retrospective studies have shown that complete response rates in the 15-20 age group were similar between adult and

pediatric protocols, but disease-free survival was significantly higher with pediatric protocols. There is no consensus about age range for the young adult/adolescent group. In some protocols, these protocols can be applied up to the age of 35 to 50 years. Rather than age, the intensity of chemotherapy can be determined according to patients' comorbidities and performance status. Current guidelines recommend pediatric-based chemotherapy protocols for young adult/adolescent patients with no comorbidities. These protocols include CALGB 10403, DFCI Protocol 00-01 and PETHEMA ALL-96. According to the prospective study results using the CALGB 10403 protocol, for ALL patients aged 17-39 years, the median event-free survival (EFS) was 78.1 months (historical control: 30 months); the 3-year EFS was 59%; and the median overall survival (OS) was not reached. The estimated 3-year OS was 73%, with a low treatment-related mortality rate of 3%. In a study by the Dana-Farber Cancer Institute (DFCI) group in adult ALL patients aged 18-50 using pediatric-based chemotherapy protocols, 85% of patients achieved complete remission (CR) after one month of intensive induction therapy. With a median follow-up of 4.5 years, the 4-year disease-free survival (DFS) for patients who achieved CR was 69%, and the 4-year OS was 67%. In the PETHEMA group's data for ALL patients aged 15-30 treated with a pediatric-based chemotherapy protocol, the CR rate was 98%. The 6-year EFS and OS were 61% and 69%, respectively. Other protocols recommended for ALL patients under 65 include the dose-adjusted CALGB 8811 Larson, MRC UKALLXII/ECOG 2993, GRAALL-2005, dose-adjusted HyperCVAD, USC/MSKCC ALL regimen based on the CCG-1882 regimen and the Linker 4-drug regimen. Studies using these protocols, CR rates were reported between 85% and 95%. Median survival was 36 months, with 3-year OS ranging from 50% to 70%, and 5-year OS ranging from 30% to 40%. Chemotherapy-related mortality is reported at approximately 5%. In conclusion, pediatric-based chemotherapy protocols offer higher CR rates compared to low-intensity treatments. Despite the lack of a significant increase in treatment-related mortality, the advantage of prolonged OS means that pediatric-based chemotherapy should be applied to all eligible adult ALL patients, whenever appropriate.

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ONGOING CLINICAL TRIALS IN MULTIPLE MYELOMA

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a) BCMA-Targeted Therapies: I. CAR-T Cell Therapies: 1- KarMMa-3 Trial: This is a multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of ide-cel versus standard regimens in subjects with R/R multiple myeloma. Ide-cel therapy significantly prolonged progression-free survival and improved response as compared with standard regimens. 2- CARTITUDE-4 Trial: The purpose of this study is to compare the efficacy of ciltacabtagene autoleucel (cilta-cel) with standard therapy, either PVd or DPd. A single cilta-cel infusion resulted in a lower risk of disease progression or death than standard care in lenalidomide-refractory patients. II. Bispesific Antibodies: 1- MajesTEC-1 Trial: The purpose of this study is to evaluate the efficacy of teclistamab at the recommended Phase 2 dose. Teclistamab resulted in a high rate of deep and durable response in patients with triple-class–exposed relapsed or refractory multiple myeloma. 2- MagnetisMM-3 Trial: The purpose of the study is to evaluate whether single-agent Elranatamab can provide clinical benefit in participants with R/R multiple myeloma. Elranatamab induced deep and durable responses with a manageable safety profile. III. Drug-Antibody Conjugates: 1- DREAMM-7 Trial: This is a Phase 3, randomized, open-label study designed to evaluate safety and efficacy of belantamab mafodotin in combination with bortezomib/dexamethasone (Arm A) versus daratumumab in combination with bortezomib/dexamethasone (Arm B). BVd therapy conferred a significant benefit with respect to progression-free survival among patients who had R/R multiple myeloma after at least one line of therapy. b) Selinexor Combinations: 1- Updated Results Of Boston Trial By Prior Therapies: Stratified subgroup data from longer follow-up in the BOSTON trial confirm the PFS benefit of SVd over Vd in patients. 2- STOMP Trial: This study will independently assess the efficacy and safety of 11 combination therapies in 12 arms, in dose-escalation/-evaluation and expansion phases, for the treatment of patients with R/R multiple myeloma and newly diagnosed multiple myeloma. X–containing regimens are potent and achieve durable responses with numerically higher overall response and clinical benefit rates, as well as median progression free survival c) Venetoclax Combinations: 1- CANOVA Trial: A study designed tocompare progression-free survival (PFS) in participants with t (11;14)-positive MM treated with venetoclax in combination with dexamethasone versus pomalidomide in combination with dexamethasone. Patients with $BCL2^{high}$ or gain(1q) had numerically improved clinical efficacy with VenDex versus PomDex. d) CELMoDs (Cereblon E3 Ligase Modulation Drugs): 1- CC-92480-MM-001 Trial: This is an open-label, multi-center, international, Phase 1/2 study to assess the safety, PK and efficacy of mezigdomide monotherapy and in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma (RRMM). The all-oral combination of mezigdomide plus dexamethasone showed promising efficacy in patients with heavily pretreated multiple myeloma, with treatment-related adverse events consisting mainly of myelotoxic effects. 2- CC-220-MM-001 Trial: This is a multicenter, multi-country, open-label, Phase 1b/2a dose-escalation study. Iberdomide plus dexamethasone was generally safe and showed meaningful clinical activity in heavily pretreated patients with multiple myeloma, including in disease that was refractory to immunomodulatory drugs.

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MONOCLONAL ANTIBODIES

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Obinutuzumab, an anti CD-20 monoclonal antibody, can be used in combination with venetoclax, ibrutinib or acalabrutinib in CLL patients with newly diagnosed or relaps patient's treatment indications. Another anti CD-20 monoclonal antibody, rituximab, has been used in combination with bendamustine, FC in del 17p/tp53 negative, ig H mutated patients in previous years. In addition, rituximab is currently used in combination with venetoclax. Chimeric antigen receptor T cells The CD19-directed chimeric antigen receptor (CAR)-T cell therapy lisocabtagene maraleucel (liso-cel) is an option for fit patients with relapsed or refractory CLL/SLL after two or more lines of systemic therapy, including a BTK inhibitor and a BCL2 inhibitor (venetoclax). This population has few therapeutic alternatives, and low-quality evidence suggests that liso-cel may produce sustained remissions in a subset. However, treatment is associated with substantial toxicity, and the manufacturing process is complex and expensive. As such, the decision to proceed with CAR-T cell therapy is individualized and highly dependent on an estimation of complication risk and the needs and wishes of the patient. CAR-T cells are genetically modified ex vivo, expanded in a production facility, and then infused back into the patient as therapy. Prior to reinfusion, patients receive a lymphodepleting chemotherapy preparative/conditioning regimen (ie, fludarabine plus cyclophosphamide). Trials have allowed for additional "bridging" therapy for disease control during the manufacturing process. Hematopoietic cell transplantation (HCT) Patients with CLL are generally older adults with a median age greater than 70 years, and due to the relatively benign course of the disease in the majority of patients, only selected patients are candidates for intensive treatments such as HCT. The determination of transplant eligibility should be made based on a risk-benefit assessment and the needs and wishes of the patient. HCT may also be appropriate for young patients with relapsed or refractory CLL already exposed to a BTK inhibitor and venetoclax. İnvestıgatıonal Therapies Most commonly, there is no better therapy to offer a patient than enrollment in a well-designed, scientifically valid, peer-reviewed clinical trial especially in relapsed/refractory patients. Additional information and instructions for referring a patient to an appropriate research center can be obtained from the United States National Institutes of Health. Many agents are under active investigation. These include novel agents (eg, additional noncovalent Bruton tyrosine kinase [BTK] inhibitors, BTK degraders), combinations of agents already used in CLL, and agents approved for other diseases. We await the results of these studies before incorporating medications not approved for CLL. Specifically, lenalidomide should not be used for patients with CLL outside of a clinical trial. While initial studies reported moderate activity for lenalidomide, some studies have been terminated due to toxicity concerns and excess deaths. We also do not use the anti-CD52 monoclonal antibody alemtuzumab for patients with CLL. While partial responses may be seen in approximately one-third of patients, use is limited by toxicities that include infusion-related side effects, myelosuppression, and infections

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ANTI-CD38 MONOCLONAL ANTIBODIES: TRANSFORMING MULTIPLE MYELOMA TREATMENT

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Introduction: Multiple myeloma (MM) is a neoplasm defined by the clonal proliferation of malignant plasma cells (PC) within the bone marrow (BM). Multiple myeloma (MM) originates from the asymptomatic proliferation of pre-malignant plasma cells, categorized as monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM). Patients with MGUS exhibit low serum M-protein levels (< 3 g/dL) and monoclonal plasma cells in bone marrow (< 10%), while patients with SMM demonstrate elevated serum M-protein levels (≥ 3 g/dL) and/or plasma cells in the bone marrow (≥ 10%). Conversely, the diagnosis of multiple myeloma necessitates the identification of end-organ damage correlated with the presence of serum M-spike and/or monoclonal plasma cells in the bone marrow. **CD38 structure and functions:** This protein is a type II transmembrane glycoprotein encoded on chromosome 4 (4p15.32) and comprises three domains: a 21-amino acid intracellular domain (N-terminus), an alpha-helix transmembrane domain, and a 256-amino acid extracellular domain (C-terminus). This extracellular domain exhibits multifunctional enzymatic activity. CD38, originally characterized as an ADP-ribosyl cyclase, catalyzes the cyclization of nicotinamide adenine dinucleotide (NAD) to cyclic ADP-ribose (cADPR). **CD38 expression in multiple myeloma:** It is essential to emphasize the role of CD38 in multiple myeloma, one of the most thoroughly researched CD38-related conditions. Numerous studies have demonstrated significant and elevated CD38 expression on malignant plasma cells in bone marrow samples of multiple myeloma patients. CD38, a glycoprotein, interacts with CD31, which is co-expressed on multiple myeloma cells, and plays a role in several cellular processes. These encompass T cell activation and proliferation, B cell differentiation, and the chemotaxis of neutrophils and monocytes. Furthermore, as an ectoenzyme, CD38 regulates intracellular NAD + levels, which are essential for sustaining low glycolytic activity that facilitates cell proliferation and survival (Morandi et al., 2018). Under varying pH settings, CD38 facilitates the transformation of NAD + into adenosine (ADO), a mediator of calcium signaling that enhances tumor survival and immune evasion. Alongside CD38, several ectoenzymes including CD39, CD73, and CD203a contribute to the extracellular synthesis of adenosine (ADO), with their concentrations indicating disease progression. Furthermore, CD38 functions as a metabolic sensor

through its interaction with osteoclasts (OCs) during adult skeletal remodeling. Osteoclasts, essential for bone remodeling, are influenced by CD38 inhibition, which not only impedes bone resorption but also reinstates T-cell functionality, thus preventing the advancement of bone disease. **Treatment with anti-CD38 monoclonal antibodies:** The increase of CD38 on cancer cells and its role in cancer progression has prompted researchers to create various monoclonal antibodies (mAbs) that target CD38. Commercially available CD38 monoclonal antibodies for multiple myeloma treatment include daratumumab. Additional novel drugs are currently in clinical trials, including MOR202 (Felzartamab) (completely human), TAK079 (Mezagitamab) (fully human), FTL004 (humanized Ig1), SAR442085 (totally human engineered), and TNB-738 (entirely human). Their anticancer efficacy relies on Fc-dependent immunological effector mechanisms and immunomodulatory actions that eradicate CD38 regulatory T cells, hence reinstating T-cell and NK-cell-mediated antitumor immune responses.

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EXPANSION OF INDICATIONS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT): CURRENT STATUS AND FUTURE DIRECTIONS

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Hematopoietic Stem Cell Transplantation (HSCT) is examined under 3 headings. 1. Autologous bone marrow transplantation 2. Syngeneic bone marrow transplantation 3. Allogeneic bone marrow transplantation (myeloablative, non-myeloablative) a. Sibling b. Unrelated c. Haploidentical Bone marrow, peripheral stem cell and cord blood are used as stem cell sources. Autologous stem cell transplantation It is based on the principle of being able to apply much higher doses of chemotherapy to patients and overcoming the bone marrow damage that will occur in the meantime by means of stem cells obtained from the patient himself. Therefore, the sensitivity of the tumor to chemotherapy and the dose-response relationship are of great importance in the success of the treatment. Autologous stem cell transplantation (ASCT) is an important treatment option in the treatment of hematological malignancies such as multiple myeloma and lymphoma. While it finds a place in the first-line treatment of multiple myeloma, it is a very important treatment approach in chemosensitive relapse disease in diffuse large B-cell lymphomas. The place of ASCT in acute leukemias is controversial and other No significant superiority has been shown to treatment options. ASCT has also been used in some solid organ tumors other than M. myeloma and lymphomas. With the introduction of high-dose chemotherapy in the nineties, it has been shown that survival rates of 30% can be achieved even in patients with negative prognostic factors in germ cell tumors. It has been determined that autologous stem cell transplantation increases survival in childhood cancers such as medulloblastoma, soft tissue sarcoma, osteosarcoma, Ewing sarcoma, and retinoblastoma. Allogeneic stem cell transplantation HSCT is a treatment modality with a potential curative effect in many malignant and benign diseases. The use of a reduced-intensity conditioning regimen has also enabled transplantation in elderly patients. Developments in transplantation technology, advances in preventive and supportive treatments have led to positive developments in early and late-term outcomes of transplantation. Donors can be categorized as HLA-compatible sibling or other family donors and unrelated donors. A well-matched unrelated donor requires a 10/10 or 8/8 match in high-resolution class 1 (HLA-A,B,C) and class 2 (HLA-DRB1, -DQB1) antigen assessment. If there is at least 1 incompatibility at the antigen or allele level in HLA A,B,C or DR, an incompatible unrelated donor is mentioned. A haplo-idetic donor is defined as at least 1 haplotype among family members being genetically identical to the patient. Its most important advantage is that it is easier and faster to find a donor for many patients. The fact that graft versus host disease (GvHD) events are more common and the relative chance of relapse is a significant disadvantage. It can be successfully applied especially in malignant diseases such as acute myeloid and lymphoblastic leukemias, relapsed refractory lymphomas, relapsed refractory multiple myeloma and also in thalassemia, sickle cell anemia, immune deficiencies and autoimmune diseases.

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MANAGEMENT OF INHIBITORS IN HEMOPHILIA

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Introduction: The improved understanding of Acute Myeloid Leukemia (AML) pathobiology has led to significant advances in treatment options. AML is a highly heterogeneous disease, with clinical, morphological, cytogenetic, and molecular variability, which is crucial for developing targeted therapies within different subgroups. The "7+3" regimen (7 days of cytarabine and 3 days of daunorubicin) remains the standard, but its long-term efficacy is limited, with remission rates below 40% in younger, fit patients. In contrast, for older patients or those unsuitable for intensive chemotherapy, median survival is approximately 9 months, and 5-year survival rates are under 10%. Treatment strategies are typically tailored, with intensive chemotherapy preferred for younger/fit patients, and low-intensity therapies for older/unfit patients. This section reviews emerging targeted treatment options. **Antibody-Drug Conjugates (ADCs):** Gemtuzumab ozogamicin (GO), a CD33-targeted ADC combined with high-dose cytarabine, has increased survival rates from 50% to 75-80%. IMGN779, a novel anti-CD33 ADC, is highly effective against AML cells, including those with adverse molecular abnormalities, and its sensitivity is correlated with CD33

expression levels. AVE9633, another anti-CD33-maytansin conjugate, has shown promising results in Phase I trials with relapsed/refractory AML patients. Targeting CD123 with ADCs and exploring NK cell therapies offer hope for AML with measurable residual disease (MRD) or high-risk forms. **Bispecific T-Cell Engagers (BiTEs):** Bispecific T-cell engagers (BiTEs), such as AMG330 and AMG673, redirect T-cells or NK cells to AML cells, yielding a 20-30% response rate, though they are associated with significant side effects like cytokine release syndrome. These therapies may benefit MRD-positive AML patients in remission. T-cell immunotherapies, including flotetuzumab (FLZ), enhance T-cell activation and MHC-independent killing of AML cells, showing promise in overcoming chemotherapy resistance. **Checkpoint Inhibitors:** Immune checkpoint inhibitors targeting PD-1/PD-L1 are being explored in AML and Myelodysplastic Syndromes (MDS). Preclinical studies suggest potential benefits, but challenges remain in identifying biomarkers and optimizing combination therapies. Magrolimab, an anti-CD47 monoclonal antibody, has shown a 71% response rate and 45% complete remission (CR) when combined with azacitidine in TP53-mutant AML. **CAR-T Cell Therapies:** The success of CAR-T cell therapies in hematologic cancers has sparked interest in applying this approach to AML. Preclinical studies show that CAR-T cells targeting AML surface proteins, such as CD33 and CD123, can effectively eliminate AML cells. However, off-target toxicity due to antigen expression on healthy stem cells remains a concern. **NK Cell-Based Therapies:** Natural killer (NK) cells are being explored as an alternative to allogeneic cell therapies. NK cells can recognize and kill AML cells without causing graft-versus-host disease or cytokine release syndrome, offering a potentially safer treatment approach. **Conclusion:** In conclusion, with accumulating data, new treatment standards are being developed for AML, particularly for younger and older patients, including induction, consolidation, hematopoietic stem cell transplantation (HSCT), and maintenance therapy.

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ADVANCES IN THE ASSESSMENT OF MINIMAL RESIDUAL DISEASE (MRD) IN ALL

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General Information: A “positive” or “negative” MRD test result indicates whether measurable disease is detected above certain thresholds that may vary by test and laboratory. It is important to recognize that a negative MRD result does not necessarily indicate eradication of disease, but rather represents disease below the test threshold in the tested sample, and patients may still experience relapse. **MRD Methods:** ELN identifies multiparametric flow cytometry (MFC) and quantitative polymerase chain reaction (qPCR) among useful methods suitable for detecting MRD. Recently, innovative techniques such as digital PCR (dPCR), next-generation sequencing (NGS), and next-generation flow cytometry (NGF) have also been applied in the detection of MRD. **MRD in ALL:** In the study by Yilmaz et al., it was seen that earlier MRD negativity in Ph(-) B-ALL was associated with higher survival. The best results were obtained with Flow Cytometry MRD negativity after the 1st cycle (i.e. CR time). The 3-year relapse rate in early MRD negativity was still approximately 25%. Short NJ et al investigated the effect of CMR in Ph (+) B ALL. In 85 Ph+ ALL patients who were treated with Hyper-CVAD plus TKI and did not undergo HSCT in CR1, the median OS was 127 months in the group achieving CMR; OS was 38 months in those without CMR (P=0.009). CMR at 3 months was seen as the only prognostic factor for OS. In the study by Sasaki K et al. evaluating the effect of TKI selection on achieving 3-month CMR; 84 Ph+ ALL patients were treated with Hyper-CVAD plus TKI and CMR was achieved at 3 months. 5-year OS was found to be 84% with ponatinib. 5-year OS was found to be 60-65% with other TKIs. Ponatinib treatment was the only prognostic factor for PFS or OS. Ghobadi A et al found no benefit from allogeneic SCT in patients with Ph+ ALL who achieved CMR. Short NJ et al. compared the correlation and prognostic impact of NGS MRD and MFC MRD in Ph(-) ALL. NGS MRD (-) 5-year OS: 90%; NGS MRD (+) 5-year OS: 61%; MFC MRD (-) NGS MRD (+) 5-year OS: 62% were seen. 46% of the MFC MRD (-) group was NGS MRD (+). Blinatumomab for MRD in B-Cell ALL showed MRD negativity rate = 78% after 1 cycle in BLAST Study. Pulsipher MA et al viewed pretransplantation NGS MRD status as prognostic in pediatric ALL. Prospective follow-up for posttransplantation MRD was superior with NGS. Liang EC et al assessed NGS MRD up to 1 year after SCT for 139 patients after allogeneic SCT. Muffly L et al evaluated the correlation of NGS MRD with Peripheral Blood and Bone Marrow. Strong correlation (r=0.87; P<0.0001) was seen between PB and BM NGS MRD. MRD was detected in PB in 100% of those who relapsed after SCT and in 85% of those who relapsed after CAR T. Pulsipher MA et al. study, MRD assessment after CAR T Cell for ALL was considered prognostic. NGS-detectable MRD after tisagenlecleucel was independently predictive of EFS and OS in multivariate analysis. Short NJ et al evaluated the effect of NGS MRD for IG/TR in Ph+ ALL. The study enrolled adults with Ph+ ALL receiving first-line therapy. Disagreements between MRD assessment by PCR and MRD assessment by NGS are relatively common. RT-PCR for BCR::ABL1 is not prognostic in patients who achieve NGS MRD negativity. Ph+ ALL patients who achieve NGS MRD negativity have good outcomes regardless of PCR response. Flow cytometry in T-ALL has been validated in T ALL, including ETP. Good agreement between bone marrow and peripheral blood. NGS has not been validated in T ALL because the cells have not yet undergone a TCR rearrangement. **MRD Follow-up Periods:** In first-line ALL, MRD from bone marrow should be measured after the end of induction, during early consolidation (after approximately 3 months of therapy), and then approximately every 3 months for at least 3 years (5 years for patients with Ph-positive ALL in first remission who do not undergo HSCT). In patients undergoing HSCT, MRD should be assessed immediately before HSCT; serial MRD measurements should be performed after HSCT (approximately every 3 months).”

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CHANGING IMAGE OF TKIS: ORIGINAL, BIOSIMILAR AND GENERIC OPTIONS

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BCR-ABL is a 210 kDa protein that is required for the proliferation of CML-specific myeloid cells and has sustained kinase activity. Kinase activity provides uncontrolled signal transduction related to cell proliferation, apoptosis and adhesion. Although there are many tyrosine kinase enzymes, imatinib is especially effective on ABL, c-kit and PDGF-R-dependent tyrosine kinases. The advantage of TKI is that it inhibits more than one receptor and therefore the possibility of signaling is increased. Another advantage is that these compounds offer ease of use to patients since they are used orally. In general, TKIs are well tolerated in clinical practice compared to the toxicity of cytostatic drugs. Side effects are usually mild (grade 2 and lower) and occur early in treatment. Due to the emergence of imatinib resistance and intolerance, second generation TKIs were developed (Dasatinib, Nilotinib and Bosutinib). In nonclinical models, they are 30 to 300 times more potent than Imatinib and can inhibit most imatinib-resistant BCR-ABL mutations. Patients with the T315I mutation respond only to treatment with the third-generation TKI Ponatinib. The crystal form of a drug's active ingredient may cause differences in solubility, stability, density, melting point, processability. The original imatinib is produced in b-crystalline form, generics are mostly in crystalline form and have been observed to be less stable at room temperature than the b-form. Several in vitro and in vivo studies comparing the pharmacological properties of the reference molecule and generics have proven that both forms are equivalent. The high financial burden of these treatments can be a serious problem for both patients and patients. With the emergence of generic imatinib, the reimbursement policies of many countries have changed and generic drugs have become an alternative treatment option for CML patients. In addition to their possible positive effects, there are concerns about these drugs, including bioequivalence, efficiency, effectiveness, safety, tolerability, adherence, permanence and healthcare costs, due to the use of generic imatinib in healthcare systems. In many countries other than the USA and in Turkey, CML patients can access more than one generic imatinib, and this competitive environment generally results in significant cost reductions. In general, the efficacy and safety profiles of generic and original imatinib were found to be similar in almost all studies. In light of these results, it is possible to say that generic drugs have a generally manageable toxicity profile and are not inferior to the original molecule in terms of effectiveness. Two pharmaceutical equivalent or pharmaceutical alternative drugs containing the same active ingredient in the same molar dose are considered bioequivalent if their bioavailability (rate and degree of absorption) is within predetermined acceptance limits. Generic pharmaceutical products are placed on the market if they are therapeutically equivalent to the reference product containing the same active substance in the same molar dose. Considering the data in the literature, both in vitro and in vivo studies have shown that generic drugs are comparable to the original imatinib in terms of bioequivalence and bioavailability. In most studies, generic drugs have shown similar results in terms of efficacy and safety, both in newly diagnosed patients and after switching from the original.

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OPTIMIZATION OF TKI SELECTION IN CML: BALANCING EFFICACY, SAFETY, AND PATIENT PREFERENCES

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The long-term results from key studies such as ENESTnd, DASISION, and BFORE have helped guide first-line treatment decisions in chronic myeloid leukemia (CML). These studies compare the efficacy of different TKIs, including imatinib, dasatinib, and nilotinib, showing the potential benefits of second-generation TKIs in achieving deeper and faster molecular responses. Early molecular response (EMR) is a crucial prognostic factor, as patients who achieve EMR are more likely to have better long-term outcomes. Risk scores such as Sokal, EUTOS, and ELTS play a role in determining the appropriate first-line TKI, with higher-risk patients potentially benefiting from second-generation TKIs due to their more aggressive nature. Second-generation TKIs, including nilotinib, dasatinib, and bosutinib, offer enhanced potency over imatinib but come with distinct safety profiles. Nilotinib has demonstrated superior efficacy in terms of molecular response, but it is associated with cardiovascular risks, including QT prolongation. Dasatinib, while effective in achieving rapid molecular responses, can lead to pulmonary complications like pleural effusion. Bosutinib, which is less commonly used, has a more favorable gastrointestinal side effect profile but may have less activity in some resistant CML cases. Management of cardiovascular, pulmonary, and metabolic side effects is crucial in selecting the appropriate TKI for each patient, particularly for those at higher risk of cardiovascular or pulmonary issues. TKI resistance, primarily due to BCR-ABL1 kinase domain mutations, presents a challenge in CML treatment. Mutations such as T315I are particularly problematic as they confer resistance to most TKIs. Ponatinib, a third-line treatment, is highly effective against T315I and other mutations, but it carries significant cardiovascular risks, necessitating careful monitoring. Asciminib, a newer drug that targets BCR-ABL1 through allosteric inhibition, offers a promising alternative for patients with resistance to other TKIs, as it bypasses common mutations like T315I and is associated with a different side-effect profile. Off-target inhibition of kinases by TKIs is a significant contributor to their side-effect profiles. For instance, nilotinib has been linked to glucose metabolism disturbances, leading to hyperglycemia, whereas dasatinib may cause pulmonary hypertension due to PDGFR inhibition.

Understanding these molecular mechanisms helps in managing side effects and improving patient outcomes. Monitoring for these adverse effects and adjusting treatment accordingly is essential to minimize long-term toxicity while maintaining treatment efficacy. The concept of TFR, where patients discontinue TKI therapy after achieving sustained molecular remission, is gaining ground. Studies such as EURO-SKI, ENESTfreedom, and DASFREE have demonstrated that certain patients can safely stop treatment without relapse, provided they remain MRD-negative. Selecting the right candidates for TFR is critical, and patients must be closely monitored for minimal residual disease (MRD). Even after discontinuation, immunological changes and potential relapse mechanisms must be carefully tracked. In special populations such as pregnant women, pediatric patients, and the elderly, TKI therapy requires careful consideration. TKIs are contraindicated in pregnancy due to potential teratogenic effects, and fertility preservation options should be discussed with male patients. In pediatric CML patients, concerns about growth and development arise, and TKI dosing must be adjusted for optimal treatment without affecting growth. Elderly patients or those with comorbidities may require lower doses and closer monitoring to minimize toxicity while ensuring adequate therapeutic effects. This summary highlights key aspects of TKI therapy in CML, including treatment selection, resistance mechanisms, side effects, treatment discontinuation strategies, and considerations for special populations. Each of these factors plays a significant role in optimizing treatment and improving patient outcomes.

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THE EVOLVING ROLE OF PROTEASOME INHIBITORS IN CANCER TREATMENT

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Recent developments in tumor immunology have led to a shift from chemotherapy to targeted therapy, focusing on blocking the pathways that drive cancer. An important aspect of this approach is the personalization of treatment, as the same cancer can present different immunopathologies in different individuals. Genetic mutations or variations in gene expression serve as determinants for identifying molecules that should be targeted in treatment. This has given rise to the concept of personalized therapy. One of the key therapeutic pathways is the proteasome system. This system is essentially a circular enzyme system that helps eliminate substances that may pose a threat to the cell. Its primary role is to process and degrade intracellular antigens and present them to CD8 T lymphocytes, in conjunction with the Major Histocompatibility Complex (MHC I) and Class II genes. The proteasome system carries out this function with the help of the endoplasmic reticulum (ER) and autophagy. Proteins that are continuously produced in the body are corrected within the ER if they misfold, in order to prevent potential antigenic properties. If the amount of misfolded proteins in the ER increases, it overwhelms the ER's capacity, resulting in a condition known as ER stress. In this case, the misfolded proteins are sent to the proteasome system for degradation, or alternatively, the autophagic pathway is activated through the enzyme Beclin to eliminate these faulty proteins. These mechanisms are essential for maintaining cellular integrity and survival. This survival strategy applies not only to healthy cells but also to cancer cells. In fact, proteasome inhibition is increasingly being used in the treatment of various cancers, including Multiple Myeloma. When the proteasome system is inhibited, cancer cells are unable to eliminate toxic or misfolded substances, leading them toward apoptosis. Proteasome inhibition can occur at different levels within the body and is not limited to the nucleus. Different proteasomes are responsible for degrading different substances. Thus, rather than aiming to completely eliminate the proteasome system, future cancer treatments are focusing on the selective inhibition of specific proteasomes. Research is ongoing in this direction, with the goal of developing more targeted and effective therapies for cancer.

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IMPROVING TREATMENT OPTIONS IN POLYCYTHEMIA VERA: FROM INTERFERON TO NEW AGENTS

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Polycythemia Vera (PV) is a chronic myeloproliferative neoplasm characterized by the overproduction of red blood cells, often accompanied by increased white blood cells and platelets. The disease is primarily driven by mutations in the Janus kinase 2 (JAK2) gene, specifically the JAK2 V617F mutation, which is present in approximately 95% of patients. The clinical presentation of PV includes a range of symptoms that significantly impact the quality of life (QoL) of affected individuals. Common symptoms include fatigue, pruritus, headaches, and visual disturbances, which are often attributed to the hyper viscosity of the blood resulting from increased red blood cell mass. The diagnosis of PV is based on the World Health Organization (WHO) criteria, which include elevated hemoglobin or hematocrit levels, the presence of the JAK2 mutation, and evidence of bone marrow hypercellularity. Diagnostic challenges may arise due to overlapping features with other myeloproliferative neoplasms, necessitating comprehensive blood evaluations and sometimes bone marrow biopsies. The disease is associated with a significant risk of thrombotic events, including stroke and myocardial infarction, which can occur in up to 26% of patients. Furthermore, the risk of transformation to more severe forms of hematological malignancies, such as acute myeloid leukemia (AML) or myelofibrosis, is notable, with studies indicating a

transformation rate of approximately 10% over a 20-year period. Management of PV focuses on reducing the risk of thrombotic complications and alleviating symptoms. Phlebotomy is often the first-line treatment to reduce hematocrit levels, particularly in patients with high thrombotic risk. In cases where phlebotomy is insufficient or not tolerated, cytoreductive therapies, such as hydroxyurea, are commonly employed. However, approximately 25% of patients may experience inadequate responses or unacceptable side effects from hydroxyurea, necessitating alternative treatments. Ruxolitinib, a JAK2 inhibitor, has emerged as a promising option for patients who do not respond adequately to conventional therapies, demonstrating efficacy in reducing splenomegaly and symptom burden. In conclusion, PV is a complex hematological disorder with significant clinical implications. Early diagnosis and appropriate management are crucial to mitigate the risks associated with the disease. Ongoing research into novel therapeutic agents and treatment strategies continues to enhance our understanding and management of this condition, ultimately aiming to improve patient outcomes and QoL.

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TREATMENT OF MYELOFIBROSIS: PRESENT AND FUTURE

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Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterised by stem cell-derived clonal myeloproliferation often, but not always, accompanied by JAK2, CALR or MPL mutations. It is associated with bone marrow reticulin/collagen fibrosis, abnormal inflammatory cytokine expression, anaemia, hepatosplenomegaly, extramedullary haematopoiesis (EMH), constitutional symptoms, cachexia, risk of leukaemic transformation and shortened survival. Somatic mutations in MPN are classified as 'driver' and 'other' mutations. Driver mutations are JAK2, CALR and MPL, other mutations are ASXL1, SRSF2, U2AF1, IDH1/2, SF3B1, TET-2, DNMTA3A. SRSF2, ASXL1, and U2AF1-Q157 mutations indicate poor prognosis in PMF. RAS/CBL mutations predict resistance to ruxolitinib treatment. Type 1/like CALR mutation is associated with better survival. The hallmark of MF is the disruption of the JAK/STAT signalling pathway. **TREATMENT** In the treatment approach, allogeneic stem cell transplantation (ASCT) should first be positioned as a priority option. Then, treatment should be planned according to risk stratification for the control of anaemia and improvement of splenomegaly and related symptoms. The recommended treatment strategy is what we call risk-adaptive treatment, which is treatment according to risk groups and symptoms/symptoms. The general approach is observation in low-risk asymptomatic patients, treatment selection according to symptoms (constitutional findings, splenomegaly, anaemia) in the medium and low risk group, stem cell transplant-based treatment in the high risk group. If additional risk factors are present in the intermediate risk group, ASCT should be considered as an alternative and a patient-based approach should be taken as basis. In the absence of symptomatic splenomegaly, non-JAK inhibitor drugs may be preferred as first-line treatment for anaemia. Androgens, prednisone (can be used in addition to androgen therapy or alone), danazol, thymodomide, lenalidomide, erythropoiesis-stimulating agents (ESAs) can be used. Although luspatercept is approved for the treatment of anaemia associated with beta thalassaemia and low/intermediate risk MDS, it has been largely ineffective in MF patients. Response rates to each of these drugs range between 15-25%. In the 2nd step, JAK inhibitors, especially momelotinib and pacritinib, can be considered. These drugs exhibit erythropoietic activity as well as favourable effects on splenomegaly and systemic symptoms. Among the available JAKi, Momelotinib shows activity against all three major complications in MF, including anaemia, splenomegaly and constitutional symptoms. Ruxolitinib (RUX) is the first oral JAK1-2 inhibitor. It received FDA approval in 2011. Long-term data from the COMFORT-I/II studies showed a 30 per cent mortality reduction in intermediate-2/high-risk patients compared to the control group. COMFORT-I and II analyses found that a reduction in spleen size with ruxolitinib treatment correlated with longer survival. Fedratinib (FEDR) received FDA approval in 2019. In the JAKARTA study, FEDR was reported to significantly prolong patients' prognosis compared with placebo. Fedratinib is a treatment option for the treatment of symptoms and splenomegaly or for patients who are resistant or intolerant to ruxolitinib. It includes a warning regarding the potential risk of serious encephalopathy, including Wernicke's encephalopathy. Pacritinib is a selective JAK 2 inhibitor. It received FDA approval in 2022 in moderate-to-high patients. Momelotinib received FDA approval in 2023. JAK1, JAK2 and ACVR1 inhibitor; targets symptoms, splenomegaly and anaemia. The new therapies, complementary or independent with JAK inhibitors, aim to improve patients' responses and quality of life, going beyond current treatment limitations with a focus on improving anaemia, thrombocytopenia and fibrosis, with an impact on overall survival. One future combination appears to be Pelabresib + Ruxolitinib. In the MANIFEST II study, the $_{SVR35}$ response at week 24 was significantly higher in patients assigned to pelabresib+ruxolitinib compared to ruxolitinib alone (66% vs. 35%). At Week 24, at least one degree of improvement in bone marrow fibrosis was seen in 24.2% of patients who received ruxolitinib alone and 38.5% of patients who received pelabresib+ruxolitinib.In conclusion, PELA+RUX shows the potential to improve the four key features of MF with a significant reduction in splenomegaly, improvement in symptom score, improvement in anaemia and reduction in bone marrow (BM) fibrosis at Week 24.

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CAR-T CELL THERAPY IN CLL

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The treatment paradigm for chronic lymphocytic leukemia (CLL) has shifted dramatically with the FDA approval of lisocabtagene maraleucel (liso-cel) in March 2024. This marks a historic moment as it introduces the first CAR T-cell therapy for CLL, providing renewed hope to patients who have exhausted conventional treatment options. CAR T-cell therapy represents a remarkable advancement in personalized medicine and immunotherapy. By engineering a patient's own T-cells to target and destroy cancer cells, this innovative approach has demonstrated significant potential. Among CLL patients who undergo this therapy, approximately 25% achieve sustained remission lasting six years or longer, raising the possibility of a curative outcome in select cases. Achieving this milestone, however, has been fraught with challenges. Response rates to CAR T-cell therapy in CLL have traditionally been lower than those seen in other hematologic malignancies. Despite these hurdles, recent clinical trials have produced encouraging results, with overall response rates exceeding 75% in some studies, particularly when the therapy is combined with agents such as ibrutinib. A key distinction of CAR T-cell therapy lies in its one-time treatment model, in stark contrast to the ongoing management required by traditional therapies. While adverse effects, including cytokine release syndrome and neurotoxicity, remain significant concerns, these risks are increasingly well-managed with modern protocols. The transformative potential of this therapy outweighs these challenges for many patients. Looking to the future, ongoing research aims to enhance the efficacy and accessibility of CAR T-cell therapy. Scientists are focused on understanding why some patients respond more favorably than others and are exploring strategies to overcome resistance. The approval of liso-cel signals not just the addition of a new therapy, but a paradigm shift in the treatment of CLL. This pivotal advancement extends beyond a new treatment option. It signifies hope for patients who previously had limited choices, offering the possibility of durable remission and, in some cases, even a cure. With liso-cel, the fight against CLL enters a new era, one defined by innovation, resilience, and optimism.

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