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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PRECISION MEDICINE IN CLL: TREATMENT BASED ON MOLECULAR PROFILES

Esra Terzi Demirsoy

Kocaeli University Faculty of Medicine, Department of Hematology

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

Aysun Gönderen

Kütahya Health Sciences University

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

Büşra Tuğçe Akman

Şırnak State Hospital

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