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.

https://doi.org/10.1016/j.htct.2024.11.091

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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.

https://doi.org/10.1016/j.htct.2024.11.092

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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.

https://doi.org/10.1016/j.htct.2024.11.093

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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