Abstract 019

INNOVATIVE TREATMENTS FOR MYELOFIBROSIS

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Myelofibrosis (MF) is a Philadelphia chromosome-negative chronic myeloproliferative neoplasm characterized by fibrosis in the bone marrow, cytopenias and extramedullary hematopoiesis (1). In the 2022 International Consensus Classification (ICC) and the 5th edition of the World Health Organization (WHO) classification, myelofibrosis is subclassified as prefibrotic and overt primary myelofibrosis (2). The 2022 WHO or ICC criteria should be used for PMF diagnosis. The disease is a clonal stem cell disorder, with the most common genetic mutations are JAK2 V617F (60%), MPL (13.6%) and calreticulin (CALR) (22-35%). Approximately 90% of PMF patients have these mutations, while triple-negative cases have non-driver mutations. Chromosomal abnormalities may also be observed in PMF (1, 3-5). After diagnosis, prognostic risk scoring is performed for the treatment and management of patients. Symptoms are assessed using the myeloproliferative neoplasm symptom assessment form. IPSS, DIPSS, DIPSS Plus, MIPSS70, MIPSS70+v2, and GIPSS are the scoring systems used in PMF. Patients are divided into low/high risk groups, the reatment planning is based on this and patient's symptoms (6-7). The only curative and survival-enhancing treatment method in PMF is allogeneic hematopoietic stem cell transplantation (ASCT), which has high mortality and morbidity rates. In high-risk PMF patients, the treatment decision is primarily shaped by whether the patient is a candidate for ASCT. Treatments other than ASCT are currently aimed more at palliative care, controlling symptoms, and reducing spleen size (2). In patients with low-risk PMF who are asymptomatic, they may be observed only or included in a clinical trial. In symptomatic patients, hydroxyurea, ruxolitinib, or interferon may be used, or enter a clinical trial (2). In PMF, treatment decisions related to symptoms are made by considering anemia, splenomegaly, and constitutional symptoms. Especially in patients with prominent anemia, androgens, prednisolone, lenalidomide, thalidomide, and pomalidomide may be preferred if the patient does not have splenomegaly. New studies are investigating the efficacy of combining ruxolitinib with immunomodulatory agents. The efficacy of erythropoiesis-stimulating agents is limited, and studies show that luspatercept has a low effect in PMF patients. Momelotinib and pacritinib are also other treatment options for these patients and they have positive effects on increasing erythropoietic activity, splenomegaly and constitutional symptoms (2,3,8,9). In patients with anemia, splenomegaly, and constitutional symptoms, momelotinib should be the first choice. If splenomegaly is present alone, hydroxyurea, interferon, or ruxolitinib may be preferred. In patients resistant to ruxolitinib, fedratinib or momelotinib is preferred, while pacritinib is recommended in thrombocytopenic cases (2,10-13). There are studies on many agents planned for use alone or in combination with ruxolitinib in PMF patients. Studies exist on pelabresib, navitoclax, parsaclisib, pegylated interferon alpha, selinexor and luspatarcept in combination with ruxolitinib, and ongoing studies exist on the use of navtemadlin, bomedemstat, RUV120, and imetelstat as single agents in PMF treatment. The preliminary analysis report of these studies at the 2022 American Society of Hematology annual meeting. There is also a preclinical study on monoclonal antibody therapy (INCA 033989) specifically targeting mutant CALR, which has been shown to be effective in thrombocytosis (2).

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Abstract 020

CURRENT TREATMENT APPROACHES IN ELDERLY PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with a median age at diagnosis of 68 years. Estimated 5-year survival differs significantly by age and is <10% for patients older than 60 years (1). Older patients represent highly heterogeneous group and require careful evaluation of comorbidities and frailty. When selecting a treatment plan for older patients, physicians must carefully weigh the risk of adverse events and the potential impact on quality of life (QOL) against possible survival benefits. They are generally unsuitable for curative treatment options such as intensive chemotherapy and hematopoietic stem cell transplantation. Consequently, treatment strategies aimed at improving outcomes and patient compliance continue to evolve. Lower intensity regimens include hypomethylating agents (HMA), such as azacitidine or decitabine, or low-dose cytarabine (LDAC). The introduction of azacitidine in 2012 and decitabine in 2015 significantly transformed the treatment landscape for these patients (2-4). However, HMA monotherapy has been associated with remission rates of 30% or less and survival of under one year (2, 5). As HMA therapy is considered the standard backbone for AML patients unfit for intensive chemotherapy, the majority of phase III trials have been designed to evaluate novel agents in combination with HMA versus HMA alone. In 2018, azacitidine and venetoclax combination was approved for patients with newly diagnosed AML aged ≥75 years old or ineligible for intensive chemotherapy (6). The VIALE-A trial demonstrated improved overall survival (OS) with venetoclax-azacitidine versus plasebo-azacitidine (14.7 and 9.6 months, respectively). Moreover, with long term follow-up, patients achieving CR/CRi with measurable residual disease (MRD) negativity had a longer median OS (34.2 months) compared to those without MRD response (18.7 months) (7). Profound cytopenias accompanied by concurrent infections, bone marrow evaluations during treatment cycles to evaluate cellularity, treatment delays, and prolonged hospitalizations are frequently observed. Nevertheless, due to its manageable side effect profile and a protocol allowing dose and schedule modifications,

venetoclax-azacitidine has become a first-line treatment for elderly AML patients worldwide who are unfit for intensive therapy. Similarly, the VIALE-C trial, which randomized patients to LDAC/venetoclax versus LDAC/placebo, demonstrated improved CR/Cri (48% vs 13%) and OS (8.4 vs 4.1 months) in the venetoclax arm.(8) The combination of HMAs with other agents, together with the establishment of genetic risk profiles and identification existing mutations, underscores the importance of individualized therapy. Among promising agents, Ivosidenib monotherapy or its combination with HMA has shown superiority in OS, CR/Cri, and EFS for IDH- 1mutated de novo AML (AGILE trail) (9). Patients with TP53 alterations, however, continue to experience significantly worse survival outcomes (10). The CD47 monoclonal antibody magrolimab has demonstrated clinical efficacy when combined with azacitidine or with azacitidine/venetoclax (11).Several multiple novel agents and combinations are under investigation, including fromtline FLT3i, oral HMAs, and triplets combining HMA, venetoclax and targeted agents (12). Considering that none of these regimens are curative, it remains a matter of debate whether dynamically assessing patient frailty and using non-intensive therapies can provide a bridge to allogenic stem cell transplantation.

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Abstract 021

HEPATIC VENO-OCCLUSIVE DISEASE

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Hepatic veno-occlusive disease, also called sinusoidal obstruction syndrome (VOD/SOS), is a severe complication which usually occurs due to conditioning regimens used for hematopoietic stem cell transplantation (HSCT). It is characterized by hepatomegaly, hyperbilirubinemia, ascites and right upper quadrant pain and usually develops within the first 20-30 days after transplant. It is accepted to be a result of endothelium and hepatocyte damage caused by chemotherapy and radiotherapy of the conditioning regimen. Current studies suggest that the primary site of toxic injury is the hepatocyte, subsequently followed by damage to the central veins in zone 3 of the hepatic acinus and sinusoidal endothelial cells. Early changes include fibrin deposition, venous occlusion, progressive venous micro-thrombosis and sinusoidal occlusion. These changes lead to severe clinical problems including portal hypertension, hepatorenal syndrome and hepatocellular necrosis, which may ultimately result in multiorgan dysfunction (MOD) and death. Previously, the Baltimore and Seattle criteria were used for VOD/SOS diagnosis; however, the limitations of these criteria for VOD/SOS diagnosis (especially in anicteric children and those who have symptom onset after 21 days), led to establishment of the EBMT (European Society for Blood and Marrow Transplantation) 2017 VOD/SOS criteria which evaluates pediatric and adult patients separately. The EBMT 2017 criteria is comprised of laboratory and clinical findings such as transfusion-resistant thrombocytopenia, unexplained weight gain, hepatomegaly, ascites and elevation in bilirubin levels. Despite the advantages brought by this criteria, it is still difficult to diagnose VOD/SOS. Several approaches to prevent its development of VOD/SOS were put forth, including individualized dosing of chemotherapy, reduction of the intensity of the conditioning regimens, close monitoring of the levels of busulfan and cyclophosphamide and also reducing their use. Prostaglandin E1 and tissue-plasminogen activator with or without concurrent heparin have been explored in VOD/SOS treatment; however, these approaches have shown little success, as is the case with supportive treatments. Defibrotide (DF) emerged as the most promising medication for both prophylaxis and treatment in patients with VOD/SOS. DF is a single-stranded polydeoxyribonucleotide with anti-inflammatory, anti-ischemic, anti-thrombotic, and thrombolytic properties in addition to its protective effects on endothelial cells. DF is approved for adult and pediatric patients with VOD/SOS with renal or pulmonary dysfunction after HSCT in the United States, and for severe VOD/SOS post-HSCT in patients aged >1 month in the European Union. In addition, several studies have examined DF prophylaxis can reduce the incidence of VOD/SOS in high-risk patients. Although the literature is unanimous for the use of DF in patients diagnosed with VOD/SOS, its use as a prophylactic agent has not been approved; even though many studies have reported reduced VOD/SOS incidence and severity with DF prophylaxis.

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Abstract 022

TREATMENT OF RELAPSED/REFRACTORY DLBCL

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Fifteen percent of DLBCL patients are refractory to the first line of therapy, while 25% experience relapse after response. The management of these patients is planned according to the patient's suitability for high-dose chemotherapy and whether the disease is refractory/early relapse (BSH guideline, 2025). While HSCT provides long-term survival in patients who are suitable for treatment and are chemosensitive (CORAL study), long-term survival compared to HSCT has been achieved in non-chemosensitive patients with CAR-T therapies ZUMA-7 and TRANSFORM studies. CAR-T therapies are approved as first-line treatment for patients with refractory/early relapse. However, some r/r DLBCL patients are not suitable for HSCT and CAR-T treatments due to age and comorbidities, and some are resistant to these treatments or relapse after these treatments. Tafasitamab – Lenalidomide combination is approved for patients with relapsed DLBCL, NOS who are not eligible for HSCT or CAR-T therapies (L-MIND study). The efficacy of Glofitamab – GemOx has also been proven in patients with relapsed DLBCL, NOS who are not suitable for HSCT or CAR-T therapy in the STARGLO study. Loncastuximab is a single-agent ADC used in r/r DLBCL. Due to its cumulative toxicity, long-term use is not suitable, and a one year treatment was planned in the LOTIS-