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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