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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