approaches such as gene therapy and hematopoietic stem cell transplantation, which may ultimately reduce or eliminate the lifelong requirement for transfusion and chelation.

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Abstract 028

RELAPS/REFRACTORY MANTLE CELL LYMPHOMA TREATMENT

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Mantle cell lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL) characterized by the overexpression of cyclin D1 due to the chromosomal translocation t(11;14)(q13;q32). Despite advances in therapeutic approaches, MCL remains a significant clinical challenge, particularly in relapsed and refractory (R/R) cases. Relapse occurs when the disease reappears after an initial response to therapy, while refractory MCL refers to cases where the disease fails to respond adequately to standard treatment regimens. Both conditions are associated with poor prognosis and limited treatment options, reflecting the need for novel therapeutic strategies. Relapsed MCL is characterized by clonal evolution and the emergence of more aggressive phenotypes, including resistance to previously administered therapies. Refractory cases, on the other hand, exhibit intrinsic or acquired resistance mechanisms, such as mutations in the B-cell receptor (BCR) signaling pathway, TP53 abnormalities, and alterations in DNA damage response genes. Recent therapeutic advances have improved outcomes for R/R MCL patients. Targeted therapies, including Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib, acalabrutinib, and zanubrutinib, have demonstrated significant efficacy by disrupting BCR signaling. Ibrutinib, the first BTK inhibitor approved for R/R MCL, has shown durable responses in clinical trials, although resistance to BTK inhibitors is a growing concern. Lenalidomide, an immunomodulatory agent, and venetoclax, a BCL-2 inhibitor, have also shown promise in heavily pretreated patients. Furthermore, chimeric antigen receptor (CAR) T-cell therapy targeting CD19, such as brexucabtagene autoleucel, represents a groundbreaking approach for patients with chemorefractory disease. While these therapies offer hope, their application is often limited by adverse events, accessibility, and high costs. Biological heterogeneity within MCL further complicates the management of R/R cases. The proliferation index (Ki-67), TP53 mutation status, and the presence of blastoid or pleomorphic variants are critical prognostic factors influencing treatment decisions. Additionally, the integration of next-generation sequencing (NGS) and molecular profiling enables the identification of actionable mutations and pathways, paving the way for personalized medicine. Despite these advancements, challenges remain in optimizing the sequencing of therapies, managing toxicities, and overcoming resistance. Clinical trials continue to explore novel agents, including bispecific antibodies, proteasome inhibitors, and checkpoint inhibitors, as well as combination strategies to enhance efficacy and minimize resistance. Moreover, the role of minimal residual disease (MRD) monitoring in guiding treatment remains an area of active investigation. In conclusion, relapsed and refractory MCL represents a complex clinical entity with significant unmet needs. While recent therapeutic innovations have improved outcomes, the heterogeneity of the disease necessitates a personalized approach to treatment. Future research should focus on elucidating resistance mechanisms, refining therapeutic strategies, and improving access to novel treatments to enhance the prognosis for this challenging patient population.

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Abstract 029

SUMMARY: OPTIMIZATION OF TREATMENT IN PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (PH+ ALL)

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Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) is a high-risk subtype of ALL, historically associated with poor outcomes. The introduction of tyrosine kinase inhibitors (TKIs) has dramatically changed its therapeutic landscape. Current optimization strategies focus on integrating TKIs with chemotherapy, immunotherapy, and, in selected cases, allogeneic stem cell transplantation (allo-HSCT), while tailoring treatment according to minimal residual disease (MRD) status and patient characteristics. Induction therapy now commonly consists of a TKI combined with corticosteroids and/or reduced-intensity chemotherapy, aiming to achieve remission with lower toxicity compared to traditional intensive regimens. Commonly used TKIs include imatinib, dasatinib, and ponatinib, with the latter being preferred in cases with the T315I mutation due to its broader activity. Consolidation therapy is designed to eradicate residual disease. Achieving MRD negativity is the primary goal, as it strongly predicts long-term survival. Strategies include continued TKI administration combined with short chemotherapy blocks or novel agents such as blinatumomab, a CD19-targeted bispecific T-cell engager. Allo-HSCT remains an important option for younger, fit patients, especially those with persistent MRD or high relapse risk. However, accumulating evidence suggests that deep and durable remissions may be achievable without transplantation when combining TKIs with immunotherapies. Maintenance therapy typically involves prolonged TKI treatment, often for at least two to three years, with ongoing MRD monitoring to guide adjustments. In the relapsed or refractory setting, therapeutic options expand to include next-generation TKIs such as ponatinib, immunotherapies including blinatumomab and the CD22-targeted antibody-drug conjugate inotuzumab ozogamicin, and chimeric antigen receptor T-cell (CAR-T) therapies targeting CD19, which have shown promising results in heavily pretreated patients. The core principles of treatment optimization in Ph+ ALL include: 1. MRD-directed decision-

making, as MRD negativity is the strongest predictor of favorable outcomes. 2. Reducing treatment-related toxicity, particularly in elderly or frail patients, by minimizing intensive chemotherapy and incorporating TKIs with immunotherapy. 3. Individualizing the role of allo-HSCT, reserving it primarily for patients with persistent MRD, high-risk features, or early relapse. 4. Integrating novel agents such as blinatumomab, inotuzumab, and CAR-T therapies earlier in the treatment course to improve long-term survival and potentially reduce the need for transplantation. In summary, modern management of Ph+ ALL emphasizes TKI-based regimens, MRD-guided therapeutic decisions, and the incorporation of targeted immunotherapies. While allo-HSCT remains relevant for selected patients, emerging evidence suggests that long-term remission may increasingly be achievable without transplantation, especially when potent TKIs and immunotherapies are combined. This evolving paradigm reflects a shift toward personalized, less toxic, and more effective treatment strategies for Ph+ ALL.

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Abstract 030

CRS AND ICANS MANAGEMENT

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CRS (Cytokine Release Syndrome) CRS is an exaggerated systemic inflammatory response triggered by treatments such as Bispecific Antibodies (BsAb), which activate T cells and cause the release of inflammatory cytokines. CRS symptoms range from mild flu-like symptoms to severe multiorgan failure. Symptoms: Fever, hypotension, hypoxia, tachycardia, organ dysfunction. Physical Examination - Temperature, blood pressure, pulse oximetry or arterial blood gas (or mixed venous blood gas/O2 saturation), skin, heart, and lung examination Laboratory Tests - Complete blood count with differential diagnosis; Coagulation (PT/PTT, fibrinogen, fibrin D-dimer); Chemistry (serum electrolytes, kidney and liver function, uric acid, lactate, LDH; C-reactive protein and ferritin (inflammation); Microbiological tests, especially in neutropenic patients (blood and urine cultures); cardiac markers are clinically indicated. Do not await laboratory results. Laboratory findings: Cytopenias, elevated creatinine, elevated liver enzymes, irregular coagulation parameters, elevated C-Reactive Protein • Management of CRS (see Management Section below) does not require laboratory testing and should not be delayed pending laboratory results. **Management by grade:** • Grade 1: Support only (antipyretic, fluid support, close monitoring). • Grade 2: Low-dose oxygen, IV fluids, low-dose vasopressors if necessary. Tocilizumab may be initiated. • Grade ≥3: High-dose oxygen, intensive care support, vasopressor requirement. **Medical Treatment:** • First choice: Tocilizumab (anti-IL-6 monoclonal antibody) • If no response: Corticosteroids (e.g., dexamethasone, methylprednisolone) are added. • Other support: Antibiotic prophylaxis/treatment, electrolyte balance, close monitoring of organ functions. **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):** Neurological toxicity caused by the inflammatory effects of cytokines released after BsAb treatment results in disruption of the blood-brain barrier and accumulation of inflammatory cytokines in the central nervous system. ICANS is a diagnosis of exclusion after other possibilities have been excluded. Neurological toxicity develops after immune activation. Flu-like symptoms: Fever (≥38.0°C/<100.4°F) (unattributable to another cause); nausea; fatigue; headache; rash; diarrhea, arthralgia, myalgia Hypotension Systemic inflammatory response syndrome (circulatory collapse; vascular leakage; peripheral and/or pulmonary edema; renal failure; cardiac dysfunction; multiorgan failure) Respiratory symptoms: cough; tachypnea; hypoxia, ARDS Rash and Urticaria (allergic reaction) Low-grade CRS is common and high-grade is rare **Diagnosis:** • ICANS should be suspected if there are new or worsening neurological symptoms following recent immune effector cell (IEC) therapy, such as CAR-T cell therapy or BsAb therapy. • Initial symptoms may be mild, such as loss of attention and/or slurred speech or tremors. • Further evaluation to investigate other possible causes should include review of concomitant medications or recent use of CNS-active drugs (e.g., opiates, benzodiazepines). Investigation may include a head CT or brain MRI, and a lumbar puncture to investigate infectious causes. Management: It may occur with or without CRS. **Treatment:** • Grade 1 (mild): Close neurological monitoring, supportive care. • Grade ≥2: Corticosteroids (Dexamethasone or Methylprednisolone) are initiated. • Tocilizumab is generally not effective for ICANS (because the IL-6 antibody does not cross the blood-brain barrier well). • Seizure prophylaxis/treatment: Levetiracetam is preferred. • Intensive care support in severe cases.

Keywords: CRS, ICANS, management, treatment.

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Abstract 031

GRAFT VERSUS HOST DISEASE PROPHYLAXIS

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Graft−versus−host disease (GvHD) is an important complication that can be observed after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The incidence of Acute GvHD (aGvHD) is around 30%-50% in HLA fully matched allo-HSCT. aGvHD is also common in haploidentical and matched unrelated donor transplantation. The mechanism underlying tissue damage in aGvHD is massive inflammatory cytokine secretion. Proinflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6] are seen, as well as the increased expression of the receptor repertoire (pattern recognition receptors) on antigen-presenting cells. The most important risk factor for GvHD is HLA mismatch. Other risk factors include sex disparity between donor and recipient, the intensity of the conditioning regimen, increased age, multiparous female donors, ineffective GvHD prophylaxis, and the source of the graft. A study showed that aGvHD was