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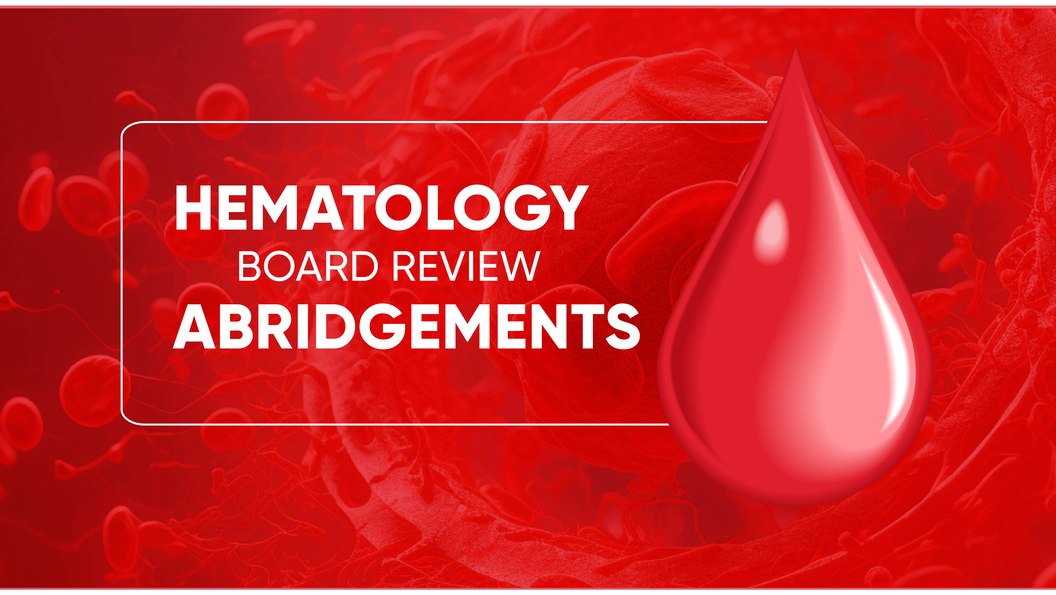

2025 Innovation Approaches to Managing Lymphomas – Abstract Paper

B-cell non-Hodgkin lymphomas (B-NHL)

B-cell non-Hodgkin lymphomas (B-NHL) are a heterogeneous collection of malignancies characterized by distinct biologies, natural histories and management. Optimal diagnosis is essential and requires sufficient tissue for histologic and immunophenotypic analysis, as well as for cytogenetic and molecular testing in selected subtypes. Following diagnosis, all patients undergo staging, typically with PETCT, and classified according to the Lugano criteria. Diffuse large B-cell lymphoma (DLBCL) is the most common subset of B-NHL and is clinically aggressive, but usually curable with initial therapy. Diagnosis of DLBCL includes assessment of cell of origin (GCB versus non-GCB) and FISH assessment for double hit lymphoma (DHL) characterized by rearrangements of MYC and BCL2 and/or BCL6. Upfront treatment options for DLBCL include R-CHOP and polatuzumab-R-CHP, the latter preferred for patients with high risk IPI scores. Selected subsets of patients may be managed differently, such as with dose-adjusted EPOCH-R in patients with DHL or primary mediastinal B-cell lymphoma, or R-mini-CHOP in very elderly adults. For patients with relapsed/refractory disease, novel agents and immunotherapies have transformed the treatment landscape with anti-CD19 CAR T-cells, anti-CD20 bispecific antibodies, Tafasitamab-lenalidomide, polatuzumab-bendamustine-rituximab, and loncastuximab tesirine all available. Selection of relapsed therapy is personalized to the patient based on the type of prior therapy received, response to prior therapy, age, comorbidities and preferences.

Follicular lymphoma is the prototypical indolent B-NHL typically characterized by waxing and waning painless lymphadenopathy. This disease is not considered curable in most cases, but is highly treatable. Localized disease which occutrs uncommonly may, however, be cured with radiation therapy. Given the indolent behavior and lengthy natural history with favorable prognosis, treatment is only indicated for non-localized FL if the disease is bulky, symptomatic, or threatening organ or bone marrow function. Standard initial treatment of high tumor burden disease is typically chemoimmunotherapy where the monoclonal antibody obinutuzumab has a modest benefit in terms of PFS over rituximab. Maintenance anti-CD20 monoclonal antibody therapy also prolongs progression without impact on overall survival. Second line therapy following chemoimmunotherapy is usually with lenalidomide-rituximab. In the 3rd line or later setting, numerous options are available and thus personalized to the patient with options including anti-CD20 bispecific antibodies, anti-CD19 CAR T-cells, tazemetostat, and zanubrutinib-obinutuzumab.

Mantle cell lymphoma usually presents at advanced stage and not considered curable with conventional therapies. Some cases may behave indolently, including the leukemic non-nodal variant. High risk features in MCL include TP53 mutation, high MIPI score, elevated Ki67, and blastoid/pleomorphic morphology. Young and fit patients are typically treated with intensive chemoimmunotherapy combined with the BTK inhibitor ibrutinib followed by maintenance ibrutinib and rituximab. Older patients may receive bendamustine-rituximab, most recently with the addition of the BTK inhibitor acalabrutinib. In the setting of relapse, patients who have not previously received a covalent BTK inhibitor should receive either zanubrutinib or acalabrutinib. Patients progressing on a covalent BTK inhibitor can receive either anti-CD19 CAR T-cell therapy or the non-covalent BTK inhibitor pirtobrutinib.

Hodgkin lymphomas

Hodgkin lymphomas (HL) most commonly refers to classic Hodgkin lymphoma (CHL) which accounts for 95% of cases, while 5% represent a distinct disease known as nodular lymphocyte predominant HL (NLPHL). Diagnosis requires sufficient tissue for histologic and immunophenotypic analysis of both the tumor cells as well as the surrounding microenvironment which accounts for the majority of tumor cellularity. Staging is with PETCT per the Lugano criteria where stages I and II are typically combined as limited stage disease and stages III and IV as advanced stage disease. Bulky stage I-II disease may also be treated as advanced stage disease. NLPHL usually presents as localized disease and can be effectively managed with surgical excision alone or radiation therapy. Advanced stage disease is most commonly treated with R-CHOP. NLPHL can relapse late or transform to DLBCL, so patients should be followed life long and biopsied if there is suspicion for relapse. Treatment for limited stage CHL remains ABVD with or without radiation therapy. Radiation therapy should be avoided in patients with a negative interim PETCT scan who can receive 4 total cycles of ABVD alone. Patients with a positive interim PET scan can have treatment intensified to escalated BEACOPP or BreCADD followed by radiation therapy. Advanced stage CHL may be treated with the nivolumab-AVD or BreCADD regimen, both of which are highly effective, but BreCADD is associated with significantly more toxicity. Nivolumab-AVD is certainly preferred in older patients. Elderly patients who are not candidates for anthracycline-containing therapy may receive brentuximab in combination with dacarbazine or nivolumab. Relapsed/refractory disease is treated with second line chemotherapy, usually combined with a PD-1 inhibitor, or brentuximab-nivolumab, followed by high dose chemotherapy and autologous stem cell transplant in eligible patients. Maintenance brentuximab vedotin can be included for high risk patients due to improvement in progression-free survival.

T cell Lymphomas

The T/NK-cell lymphomas are clinically, transcriptionally, and genetically heterogeneous and remain diagnostically and therapeutically challenging. In addition to a tissue biopsy, accurate classification often requires clinical and laboratory correlation.

PTCL, NOS and nodal TFH-derived PTCL (nTFHL) are the most common peripheral ("mature") T-cell lymphomas. The nTFHL are CD4+ and express TFH markers (e.g. ICOS, PD-1, CD10, BCL-6, CXCL13) and are often characterized by a distinct tumor microenvironment, with post-endothelial venule, follicular dendritic cell (FDC) and B-cell immunoblast expansion. The frontline standard of care for these patients includes anthracycline-based chemotherapy (i.e. CHOP, CHOEP, BV-CHP) and consideration of consolidation with high-dose therapy and autologous stem cell transplantation (HDT-ASCT) in first remission. The anticipated 5-year overall survival with this approach is ≈50%. Of note, ECHELON-2 was a randomized controlled trial comparing CHOP vs. BV-CHP. Most (70%) patients enrolled had systemic ALCL (sALCL), for which the anticipated ORR with single-agent brentuximab is 86%. In contrast, most of the remaining patients enrolled were PTCL, NOS/nTFHL, for which the anticipated ORR with single-agent brentuximab is substantially lower (41%). Among these non-ALCL patients enrolled in ECHELON-2, a significant improvement in survival was not observed with BV-CHP (HR for PFS in sALCL vs. non-sALCL, 0.55 vs. 0.96, respectively).

Systemic ALCL are clinically, molecularly and genetically classified according to site of involvement (e.g. breast-implant associated) or by genetic alterations (e.g. NPM-ALK, DUSP22, TP63). For most patients with sALCL, BV-CHP is the standard of care (ECHELON-2) and risk-stratification (IPI, genetic subgroup) informs decision-making for consolidation with HDT-ASCT.

For many T/NK-cell lymphomas, anthracycline-based strategies are suboptimal and not appropriate. In some cases, asymptomatic patients (e.g. in T-LGL, T-PLL, smoldering ATLL) may be observed. For others, non-anthracycline-based regimens are appropriate (e.g. ICE and allogeneic stem cell transplantation in HSTCL, asparaginase-based regimens in ENKTCL).

In patients with relapsed/refractory PTCL or advanced-stage CTCL, clinical trial participation or treatment with novel agents is preferred. Multiagent salvage regimens, as utilized in aggressive B-cell lymphomas (e.g. ICE, DHAP) are generally not recommended. Allogeneic stem cell transplantation may be curative in appropriately selected patients.

Treatment in CTCL is determined by stage and the extent of involvement across tissue compartments. Patients with patch/plaque (limited) stage disease are treated with skin-directed therapies ("lotions and light"), whereas patients with advanced stage disease (tumors, and/or blood, nodal, or visceral involvement) are treated with biological response modifiers (e.g. interferon, ECP) or novel agents (e.g. brentuximab, mogamulizumab, HDAC inhibitors) in a multidisciplinary fashion, and apart from allogeneic stem cell transplantation with palliative intent.

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