Overview of Blood Cancers

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Objectives

By the end of the presentation, the participants will be able to:

- Describe the major types of hematologic malignancies
- Discuss the important issues for navigation
Hematologic Diseases

- Malignant
  - Leukemias
    - Acute Myeloid Leukemia (AML)
    - Acute Lymphoid Leukemia (ALL)
    - Chronic Myeloid Leukemia (CML)
    - Chronic Lymphocytic Leukemia (CLL)
  - Lymphomas
    - Hodgkin Lymphoma
    - Non-Hodgkin Lymphoma
      - Aggressive-diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, mantle cell lymphoma, HIV-associated lymphomas, Peripheral T-cell lymphoma (PTCL)
      - Indolent follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma (SLL)

Hematologic Malignancies

- Multiple Myeloma
- Myelodysplastic Syndrome
- Myeloproliferative Disorders
  - Essential Thrombocythemia
  - Polycythemia Vera
  - Primary Myelofibrosis
  - Systemic Mastocytosis
- Myelodysplastic/Myeloproliferative Neoplasms
  - Chronic Myelomonocytic Leukemia
  - Atypical Chronic Myeloid Leukemia
  - Juvenile Myelomonocytic Leukemia

Benign Hematologic Disorders

- Anemias
  - Iron Deficiency
  - Folate or B12 deficiencies
  - Malignancy related (including MDS)
- Sickle Cell Anemia
- Hypogammaglobulinemia
- Coagulopathy
- Myelosuppression—neutropenia, thrombocytopenia

History of Identification of Hematologic Malignancies

- First hematologic malignancy—Hodgkin’s Disease, in 1832 by Thomas Hodgkin
- 1898 first description of malignant cells in Hodgkin’s Disease by Carl Sternberg
- In 1902, Dorothy Reed fully described the cells, termed Reed-Sternberg cells

Hematopoiesis
WHO Classification of Lymphoid Neoplasms

WHO Classification of Myeloid Neoplasms

Myeloid Neoplasms

Acute myeloid leukemia (AML) and related neoplasms
- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
  - Therapy-related AML
- AML, not otherwise specified
- Acute leukemias of ambiguous lineage

Myeloproliferative neoplasms (Ph negative) and chronic myeloid leukemia
- Essential thrombocytopenia
  - Polycythemia vera
- Primary myelofibrosis
- Systemic mastocytosis
- Chronic myeloid leukemia
  - Chronic neutrophilic leukemia
  - Chronic eosinophilic leukemia

Myelodysplastic syndromes (MDS)
- Refractory anemia with ringed sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts, type 1
- Refractory anemia with excess blasts, type 2
  - MDS with isolated del (5q)
  - MDS, unclassifiable

Myeloproliferative/myelodysplastic syndromes
- Chronic myelomonocytic leukemia
- Atypical chronic myeloid leukemia
- Juvenile myelomonocytic leukemia
- Myeloproliferative/myelodysplastic syndromes—unclassifiable

Diagnosis of Hematologic Malignancies

- **Scans**
  - CT Scan
  - PET/CT
  - Skeletal survey for Multiple Myeloma
  - May include MRI
- **Biopsy of lymph node or other tissue**-Core biopsy minimum or excisional biopsy (FNA inadequate tissue for diagnosis)
- **Bone Marrow Biopsy**
- **Laboratory Studies**
  - CBC, CMP, LDH, uric acid
  - May include quantitative immunoglobulins, beta-2 microglobulin, hepatitis panel, HIV, HTLV
  - May include spinal tap
Diagnostic Tests Used in Hematologic Malignancies

- Microscopy—for visualization of cells to determine morphology
- Immunohistochemistry—identifies specific molecules
- Flow cytometry—detects presence of intracellular proteins or proteins expressed on cell surface
- Immunophenotyping—used with flow cytometry to detect specific antigens on cells
- Fluorescence in situ hybridization (FISH)—characterizes structural chromosomal abnormalities and identifies chromosomes of uncertain origin
- Cytogenetics—analyzes chromosomes during metaphase. Identifies chromosomal abnormalities such as translocations, inversions, deletions and extra copies of chromosomes
- Polymerase chain reaction (PCR)—reveals specific genetic flaws on cells and is highly sensitive and specific
- Gene expression profiling—measures activity of genes

Non-Hodgkin Lymphoma

- 5th most common malignancy in US (both males and females)
- Accounts for 4% of new cancer diagnoses
- 70,130 in US were diagnosed with NHL in 2012
- In 2012, approximately 38,940 deaths due to NHL
- Median age at diagnosis is 66 years
- Highest incidence in Caucasians, lowest in American Indians/Alaska Natives
- Estimated 460,000 individuals are alive in US with history of NHL
- Risk factors: chronic infection (HIV, EBV, Hepatitis B, Hepatitis C, Human herpesvirus 8, Helicobacter pylori), immunodeficiency, autoimmune disorders, environmental and occupational exposures

Diffuse Large B-Cell Lymphoma (DLBCL)

- Most common lymphoid malignancy
- Comprises 30-50% of all NHLs
- Heterogeneous with multiple morphologic variants
- Increasing number of clinical subtypes
- May be transformed from an indolent lymphoma
- Usually presents as rapidly enlarging mass in a nodal or extranodal site
- Occurs more frequently in older adults
- Median age in 70s
- Patients may be asymptomatic
- Symptoms are highly dependent on the site of involvement
- Most patients have nodal disease (10% with involvement of Waldeyer’s ring, 30% with extranodal involvement)
- Most common extranodal sites are bone marrow and gastrointestinal tract

Diffuse Large B-Cell Lymphoma

- **B Symptoms:**
  - Fevers
  - Weight loss
  - Night sweats

- **Diagnosis**
  - CD19, CD20, CD22, CD79a, PAS5, CD45
  - CD 10 in 25-50% of cases
  - CD5 in 10% of cases (may exhibit poorer prognosis)
  - Ki67 (proliferation rate) usually greater than 40% but may be greater than 90% in some cases
  - Most common chromosomal translocations include:
    - BCL6 gene
    - BDL2 gene
    - MYC (associated with inferior prognosis)
    - Other: TP53 (17p), MUM1, and PAX5

Diffuse Large B-Cell Lymphoma

- 2008 classification recognized new subtype: B-cell lymphoma, unclassifiable with features intermediate between DLBCL and Burkitt lymphoma
- Double hit or triple hit lymphomas demonstrate multiple chromosomal abnormalities involving MYC, BCL6 and BCL2. Appear to have poorer prognosis as compared to classic BL and DLBCL.
- Staging with Ann Arbor Staging System
  - I-Involvement of single lymph node region
  - II-Involvement of two or more lymph node regions or lymph node structures on the same side of the diaphragm
  - III-Involvement of lymph node regions of lymphoid structures on both sides of the diaphragm
  - Disseminated disease

NHL International Prognostic Index (IPI)

• Five pre-treatment adverse factors:
  • Older age
  • Poor performance status
  • Elevated LDH
  • More than one extranodal site
  • Higher Stage

• Identifies prognostic subgroups

Diffuse Large B-Cell Lymphoma
Gene Profiling

- Two molecular signatures of DLBCL through gene expression
  - Germinal Center
    - CD10+, BCL6+, MUM1+
    - 5 year OS 76%
  - Activated B-cell
    - CD10-, MUM1+, BCL6-/+ 
    - 5 year OS 34%
- Gene profiling not incorporated in WHO classification system since it is not readily available in community

Management of DLBCL

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)—standard for all age groups
- Chemotherapy not as well tolerated in older patients
- R-miniCHOP can be useful in older patients (median age in study was 83 years) with median OS of 29 months
- In patients with cardiac disease, may need to replace anthracycline (doxorubicin)
- Studies underway to investigate addition of newer agents with R-CHOP (e.g., ECOG study of R2-CHOP vs R-CHOP)
- Recurrent disease—autologous transplant is standard of care in individuals up to 70 years (perhaps older)

Follicular Lymphoma

- A heterogeneous disease
- Second most common NHL in US
-Accounts for 22%-25% of new cases
- 70% of indolent lymphomas
- A chronic indolent NHL
- Characterized by a response to initial treatment, followed by relapses
- Occasionally associated with transformation to high-grade NHL (usually DLBCL)

Follicular Lymphoma

- Graded into three levels (I-III) depending on size and percentage of large cells present
  - Grades I and II—contain small cells or a mixture of large and small cells. Commonly indolent in growth pattern. Incurable in majority of patients
  - Grade III—contains many large cells. Has aggressive growth pattern. Treated same as DLBCL.
- Typically diagnosed in older patients—median age 60 years
- More common in Caucasians, rare in Asians
- A chronic and relapsing disease

Follicular Lymphoma

- Typically patients present with sub-acute or chronic asymptomatic peripheral lymphadenopathy with years of persisting or intermittent symptoms.
- Waxing and waning lymphadenopathy is hallmark
- Occasionally spontaneous remissions may occur
- Bone marrow involvement at diagnosis is common (50%)
- 20% of patients have splenic involvement
- Approximately 70%-80% of patients are diagnosed with stage III or IV disease
- About 20% have B symptoms

Follicular Lymphoma International Prognostic Index (FLIPI)

- Unfavorable Prognostic Factors
  - Age ≥ 60 years
  - Greater than 4 nodal sites
  - Elevated serum LDH
  - Hemoglobin <12 g/dl
  - Ann Arbor stage III or IV

- Allows stratification into low-, intermediate-, or high-risk disease. Correlates with overall survival

FLIPI-Manikin used for counting the number of involved areas.

Follicular Lymphoma

- No consensus on treatment approach
- Variety of treatment options ranging from observation (watch and wait) to high-dose chemotherapy.
- GELF Criteria for Treatment of Follicular Lymphoma
  - Involvement of ≥3 nodal areas, each with a diameter of ≥3 cm
  - Any nodal or extranodal mass with a diameter of >7 cm
  - Disease-related symptoms, including B symptoms
  - Lymphoma-related cytopenias (WBC <1,000 cells/mcL and/or platelets <100/mcL)
  - Leukemia (>5000 cells/mcL)
  - Splenomegaly
  - Pleural effusions or ascites

Treatment Options for Follicular Lymphoma

- R-Bendamustine
- R-CHOP
- R-CVP
- F + R
- R-FND
- Radioimmunotherapy
- Rituximab
- Autologous hematopoietic cell transplant
- Investigational agents (clinical trial, off-label therapies)

Hodgkin Lymphoma

- Characterized by presence of large abnormal lymphoid cells called Reed-Sternberg cells
- Rare—represents 0.5% of cancers, 11% of lymphomas
- Occurs most frequently in adolescents and young adults with a second peak in older adults
- Usually presents as localized disease
- Estimated 9,060 new cases in 2012
- Approximately 174,908 people with history of HL
- Highly curable
- Mortality has been decreasing in both men and women in past four decades

Hodgkin Lymphoma

- 2008 WHO divides HL into two disease entities:
  - Classical HL (95% of HL)
    - Nodular Sclerosis (75% of Classical HL)
      - EBV present in 10% - 40% of Nodular sclerosis HL cases
      - Best overall survival
    - Mixed-cellularity (20%-25% of Classical HL)
      - EBV present in nearly 75% of cases)
    - Lymphocyte-rich (5% of Classical HL)
      - Median age higher than other subtypes of Classical HL
      - 70% are male
    - Lymphocyte depleted (rarest Classical HL subtype-less than 1%)
      - Most common subtype associated with HIV
      - More aggressive than other subtypes
  - Nodular lymphocyte predominant HL (5% of HL)
    - Malignant cell is a popcorn cell or lymphocyte predominant cell
    - Express CD20 and lack CD15 and CD30
    - Can transform to an aggressive B-cell lymphoma in 5-20% of cases

Symptoms of Hodgkin Lymphoma

- Systemic Symptoms are common
  - B symptoms (fevers, night sweats and weight loss) in up to 40% of patients
- Pruritus
  - In up to 85% of cases
  - May be one of the first clinical manifestations of HL
  - Not generally associated with rash
  - Etiology unknown
- Alcohol-induced pain

International Prognostic Score for Hodgkin Lymphoma

- Albumin < 4 g/dl
- Hemoglobin < 10.5 g/dl
- Male sex
- Stage IV disease
- Age > 45 years
- WBC count > 15,000/mcL cells
- Lymphocytes <600/mcL or < 8% of WBC count

Management of Hodgkin Lymphoma

- ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)
- Radiation therapy
- Autologous transplant in relapsed disease
- Brentuximab vedotin
- ICE (ifosfamide, carboplatin, etoposide)
- DHAP (cisplatin, cytarabine, dexamethasone)
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- GCD (gemcitabine, carboplatin, dexamethasone)
- IGEV (ifosfamide, gemcitabine, vinorelbine, prednisone)

Multiple Myeloma

- Incurable disorder of bone marrow plasma cells
- Second most common hematologic malignancy in US—1% of all cancers
- Approximately 20,520 cases diagnosed in 2012
- Approximately 10,610 died from disease in 2012
- Approximately 71,213 men and women living with MM
- Plasma cells responsible for producing intact immunoglobulins
- One clone of a normal protein (monoclonal protein or M protein) is overproduced
- Five types of immunoglobulins—IgA, IgM, IgD, IgG, IgE
- Malignant plasma cell secretes cytokines, which lead to organ damage

Multiple Myeloma

- Men more likely to develop MM than women
- Risk of developing MM increases with age
- Average age at diagnosis is 70 years in US
- Higher risk of MM in African Americans compared to Caucasians
- Five-year survival is 39.7%
- Etiology unknown—no clear modifiable or environmental risk factor
- Most common risk factor for MM is the presence of monoclonal gammopathy of undetermined significance (MGUS)

Classification of Plasma Cell Disorders

- **MGUS**
  - Characterized by increased plasmacytosis and presence of monoclonal protein

- **Smoldering Multiple Myeloma**
  - Increased BM plasmacytosis (greater than 10%)
  - Presence of monoclonal protein in blood or serum
  - Absence of end-organ damage
  - Treated with observation alone

- **Solitary Plasmacytoma**—two types
  - Those that arise from bone (medullary)
  - Those that arise in soft tissues (extramedullary)—most often in head and neck (nose, paranasal sinuses, nasopharynx and tonsils)
  - Presenting symptoms vary depending upon tumor site

Multiple Myeloma

- Diagnostic Criteria:
  - Monoclonal plasma cells in the bone marrow >10% and/or presence of a biopsy proven plasmacytoma
  - Monoclonal protein present in serum and/or urine
  - Myeloma-related organ dysfunction
- CRAB
  - Calcium elevation in blood
  - Renal insufficiency
  - Anemia
  - Lytic bone lesions or osteoporosis*

* If solitary plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then >30% plasma cells is required in the bone marrow

Diagnostic Work-up for Multiple Myeloma

- Complete blood count with differential
- Chemistry panel
- Serum protein electrophoresis (SPEP)
- Quantitative immunoglobulins
- Immunofixation
- B2 Microglobulin
- 24-hour urine protein electrophoreses (UPEP)
- Serum-free light chain
- Bone marrow biopsy with FISH and cytogenetics
- Skeletal survey
- MRI in certain cases

International Staging System of Multiple Myeloma

- **I**—Serum B2 microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL
- **II**—Not stage I or III
- **III**—Serum B2 microglobulin ≥ 5.5 g/dL

Decisions Regarding Treatment based on Eligibility for Transplant

Newly Diagnosed MM Patient

Transplant Ineligible*
- Bortezomib
- Lenalidomide
- Melphalan
- Thalidomide
- Other

Relapsed or Refractory

Transplant Eligible
- Induction Therapy Non-alkylator based
- Early Autologous Transplant
- Delayed Autologous Transplant Extended Induction

Treatment Regimens for Multiple Myeloma

- TD (thalidomide, dexamethasone)
- RD (lenalidomide, dexamethasone)
- VAD (vincristine, doxorubicin, dexamethasone)
- VRD (lenalidomide, bortezomib, dexamethasone)
- CyBorD (bortezomib, cyclophosphamide, dexamethasone)
- Dexamethasone
- MP (melphalan, prednisone)
- VMP (melphalan, prednisone, bortezomib)
- MPT (melphalan, prednisone, thalidomide)
- MPR (melphalan, prednisone, lenalidomide)
- DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide)
- VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, prednisone)
- Carfilzomib, dexamethasone, lenalidomide
- Pomalidomide
Maintenance Therapy in Multiple Myeloma

• Goal of maintenance therapy is to improve PPFS and OS with limited tolerable toxicity
• Defined as the continuation of drug administration following the achievement of a remission or a plateauing of response

Myelodysplastic Syndrome

- Heterogeneous group of bone marrow disorders characterized by dysplasia, ineffective hematopoiesis and peripheral cytopenias
- Not defined as a cancer until after 2001
- Predominant in men
- Median age 77 years
- Two distinct groups:
  - De Novo-no identifiable cause
  - Treatment Related

Etiology of MDS

- Age
- Male
- Environmental factors such as smoking and benzene exposure (Solvents and agriculture chemicals)
- Autoimmune disorders
- Viral illnesses

WHO Classification of MDS

- Refractory Cytopenia with Unilineage Dysplasia
- Refractory Anemia with Ringed Sideroblasts
- Refractory Cytopenia with Multilineage Dysplasia
- Refractory Anemia with Excess Blasts
- Myelodysplastic Syndrome, Unclassifiable
- Myelodysplastic Syndrome with Isolated Del (5q)

International Prognostic Scoring System

- **Bone Marrow Blasts**
  - <5
  - 5-10
  - 11-20
  - 21-30

- **Cytogenetics**
  - Good: normal, -Y, del (5q), del (20q)
  - Intermediate: other abnormalities
  - Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies

- **Cytopenias**
  - 0/1
  - 2/3

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Management of MDS

- Antithymocyte globulin
- Azacitidine
- Cyclosporine
- Decitabine
- Lenalidomide
- Thalidomide
- Clinical Trials

ASH Choose Wisely

- Don’t transfuse more than the minimum number of red blood cell units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range.
- Don’t test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility).
- Don’t use inferior vena cava filters routinely in patients with acute VTE.
- Don’t administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (ie, outside setting of major bleeding, intracranial hemorrhage or anticipated emergent surgery).
- Limit surveillance computed tomography scans in asymptomatic patients following curative-intent treatment for aggressive lymphoma.

Navigation of Patients with Hematologic Malignancies

- Acute leukemias are treated as emergency for initiation of treatment
- Obtain diagnostic work-up test results for initial appointment
- Slides from lymph node biopsies, bone marrow biopsies or other sites of disease needed for secondary review
- For patients with low counts-obtain CBC results from multiple years
- Be aware if all hematologists will see patients with specific disorder (eg, benign hematologic issues, acute leukemia)
- Biopsies may be non-diagnostic but that does not mean patient does not have lymphoma or other hematologic malignancy
Take-Away Message

- Lymphomas are the most common hematologic malignancies
- There are over 50 types of lymphomas.
- It is important to subtype the lymphoma due to variances in management strategies between subtypes of lymphomas
- DLBCL is the most common NHL
- Hematologic malignancies can be divided into those that are curable and those that are chronic, incurable disorders
- Nurse Navigators need to be knowledgeable regarding the various hematologic disorders to adequately prepare the patients for their initial consultation and for referral to alternate care providers
- Nurse Navigators who assist patients with hematologic disorders need to be knowledgeable regarding transplant
Resources for Patients with Hematologic Malignancies

- Lymphoma Research Foundation (www.lymphoma.org)
- Leukemia and Lymphoma Society (www.lls.org)
- MDS Foundation (www.mds-foundation.org)
- Cutaneous Lymphoma Foundation (www.clfoundation.org)
- Multiple Myeloma Research Foundation (www.themmmrf.org)
- International Myeloma Foundation (www.myeloma.org)
- American Cancer Society (www.cancer.org)
- Chronic Disease Fund (www.cdfund.org)
- Patient Access Network (www.panfoundation.org)