

Lecture 34 – Immune Malignancies

- leukemia – malignant immune cells found circulating in the blood
- lymphoma – malignant immune cells are noncirculating
- myeloid – hematopoietic progenitor of dendritic cells (DCs), monocytes, neutrophils, eosinophils, basophils, platelets, and erythrocytes
- Lymphoid – hematopoietic progenitor of natural killer (NK) cells, B and T lymphocytes

Leukemic diseases

- Chronic Myeloid leukemia (CML) – malignant clonal disorder of hematopoietic stem cell
 - 3 phases of disease
 - 1) indolent (slow growing)
 - 2) accelerated – after 3 to 5 yrs
 - 3) blast crisis – large # of blast cells in blood and bone marrow; cells proliferate uncontrollably and fail to mature; patient experiences fatigue, anorexia, splenomegaly
 - CML diagnosed by detection of Philadelphia chromosome – results from translocation of BCR-ABL kinase between chromosomes 9 & 22
 - CML patients also have high levels of myeloperoxidase due to high # of myeloid cells
 - Treatment
 - 1) imatinib – inhibits BCR-ABL kinase
 - 2) chemotherapy
 - 3) bone marrow transplant
 - 4) IFN- α (interferon-alpha)
- Acute Lymphoblastic Leukemia (ALL) – malignant disorder of lymphoid stem cells
 - Most common cancer of childhood
 - Diagnosed by immunophenotyping (esp. by flow cytometry) – most ALL cells share phenotype w/ early precursors of B cells
 - Treatment – try to eradicate all leukemic cells and precursors to prevent infiltration of CNS and meninges doesn't occur
 - 1) aggressive chemotherapy (esp. for mature B-cell ALL) & radiotherapy
 - 2) bone marrow transplant
 - 3) broad spectrum antibiotics for patients that have fever b/c it may be from infection
- Chronic Lymphocytic Leukemia (CLL) – malignant proliferation of monoclonal B cells
 - Most common type of leukemia, mostly in the elderly
 - Characterized an excessive # of small lymphocytes in blood

- Express CD19 (surface marker for immature B cell) and don't secrete antibodies
- CLL can be distinguished from other forms of lymphocytosis (i.e. from viral infection) by measuring surface light chains
 - in normal cells the ratio of kappa and lambda is 3:2
 - in malignant cells there is only one type of light chain expressed
- a small percentage of patients w/ B-cell CLL secrete monoclonal immunoglobulin in serum – this group has a much worse prognosis
- The goal of treatment is to control symptoms and infections but it doesn't prolong survival

Mature B-cell Malignancies

- Hodgkin's Lymphoma
 - Have peculiar large cells that comprise ~1% of tumor
 - Hodgkins cells (mononucleated)
 - Reed/Sternberg cells (multinucleated) – germinal center B cells that lack surface immunoglobulin
 - All H/RS cells have monoclonal Ig rearrangements – but there is a defect in Ig gene transcript machinery, so no Ig transcripts
 - Mutated I κ B α gene in H/RS cells – NF-kB signalling is impaired
 - Epstein-Barr virus (EBV) detected in ~ 1/2 of Hodgkin's tumors
 - Disease results in depression of cell-mediated immunity – more prone to bacterial, fungal, and protozoal infections
 - Radiotherapy used to treat localized disease – very effective

- Non-Hodgkin's Lymphoma (NHL)
 - Bone marrow examination is most important in NHL b/c bone marrow involvement indicates a poor prognosis
 - Cell lineage of tumor is determined by staining tissue w/ labeled monoclonal antibodies to diff surface antigens
 - The most common NHLs are: Diffuse large B-cell lymphoma (DLBCL), Follicular lymphoma, and Burkitts lymphoma; all are derived from germinal center B cells
 - 1) DLBCL is most common type of NHL and is clinically heterogenous, although only one therapy is used to treat it (chemotherapy, 40% effective)
 - It is important to distinguish between diff forms of DLBCL by gene expression profiling (microarray analysis) b/c they have diff outcomes in response to chemotherapy
 - 2) Follicular lymphoma – derived from mature naïve B cells in follicular lymph nodes; malignant cells home to lymph nodes and spleen
 - Usually involves the translocation of the oncogene bcl-2 from chromosome 18 to 14
 - Lymphoma often associated w/ EBV

- Treated w/ chemotherapy and radiotherapy but the prognosis is still poor
 - Most effective treatment is self bone marrow transplant
- 3) Burkitt's lymphoma – arise from malignant germinal center B cells
- EBV-associated malignancy in children
 - Lymphoma commonly has t(8:14) translocation of c-myc (oncogene)
 - In most cases it can be cured
- Multiple Myeloma – malignant proliferation of plasma cells
- Characterized by recurrent infections, renal failure, fractures/bone pain (due to osteolytic bone lesions), and anemia (b/c of crowded bone marrow)
 - More common among the elderly
 - Monoclonal gammopathy, usually IgG or IgA since plasma cell has already undergone class switching
 - Bence-Jones proteins (monoclonal light chains) in urine
 - In the bone marrow there is a close interaction between malignant plasma cells and stromal cells – mutual stimulation of IL-6 needed for growth of myeloma cells
 - Treatment (although patient usually only survives a few years)
 - 1) IFN- α and IFN- γ to inhibit IL-6
 - 2) Monoclonal antibodies to IL-6
 - 3) Thalidomide – inhibits interactions between plasma and stromal cells in bone marrow
- Waldenstrom's Macroglobulinemia
- Usually presents after age 50, follows relatively benign course
 - Characterized by rise in serum viscosity b/c of increased monoclonal IgM
 - Symptoms: headaches, confusion, dizziness, changes in visual acuity, sometimes sudden deafness
 - Treat by vigorous plasmapheresis to reduce serum IgM, viscosity reduced
 - Also treat w/ chemotherapy to control monoclonal proliferation
- Hairy Cell Leukemia
- Many patients have pancytopenia – reduced RBCs, WBCs, and platelets
 - "hairy cell" – late-stage B cell w/ characteristic rxns to monoclonal antibodies; usually have rearranged immunoglobulin genes
 - Treatment:
 - 1) After splenectomy # of platelets and WBCs normalize
 - 2) Immunotoxin (monoclonal antibody against CD22) gives complete remission to most patients
 - 3) Recombinant IFN- α

T cell Lymphomas and Leukemias

- T cell lymphomas usually derived from mature T cells b/c immature T cells are programmed to die unless they survive positive selection
- Cutaneous T-cell lymphoma (CTL)
 - Mycosis fungoides
 - Most common type of CTL
 - Skin gets flat patches, thin plaques, or tumors
 - Commonly of CD4+ T helper type
 - T cells home to skin, are in activated state, have clonal dominance, accumulate in skin, lymph nodes, and blood
 - Patch of skin lesions prefer non-sun-exposed areas
 - Sezary syndrome – describes mycosis fungoides patients w/ erythroderma and atypical circulating lymphocytes (sezary cells)
 - Sezary cells have convoluted nuclei
 - Prognosis for sezary syndrome is much worse than for other CTL patients
- Adult T-cell Leukemia/Lymphoma (ATL)
 - Associated with the retrovirus HTLV-1; endemic to Japan and Caribbean
 - ATL is an aggressive systemic disorder, often w/ skin and neurological involvement