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The "Low-Down" on High Risk Hodgkin Lymphoma: The Role of Brentuximab

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Objectives

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- Describe the pathophysiology and staging of Hodgkin lymphoma
- Identify the historical chemotherapy regimens used to treat Hodgkin lymphoma in children
- Understand the rationale behind HLHR13 combination therapy
- Describe the mechanism of action and appropriate administration of brentixiamab vedotin
- Appraise potential adverse events related to brentuximab vedotin

2

Riddle Me This

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What did the antibody go to the Halloween party as?

http://vignette4.wikia.nocookie.net/austinally/images/a/a4/Cute_little_cartoon_ghost_on_halloween_trying_to_scare_someone_0515-1008-2503-2117_SMU.jpg/revision/latest?cb=20120923142027

3

Bullet-Point Immunology

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- Immunoglobulins (Ig) are expressed on the surface of immature and mature B cells
- Each immunoglobubin contains light chains (kappa or lambda) and heavy chains connected by disulfide bonds (-S=S-)
- Constant regions (F_c) on the heavy ($C_{H1,2,3}$) and light chains (C_L) determine immunoglobulin class and function
- Variable regions on the heavy (V_H) and light chains (V_L) comprise the antigen binding fragment (F_{ab})
- Activation of B cells into plasma cells leads to rapid immunoglobulin (antibody) production against specific antigenic epitopes, which are released, and bind to antigens, marking them for immune destruction
- Each activated B cell clone manufactures a unique antibody directed against a single epitope or site→ **monoclonal antibody**
- The combined activation of multiple B cells producing different antibodies directed against an antigen → **polyclonal response**

4

Check Out My Abs (Antibodies)

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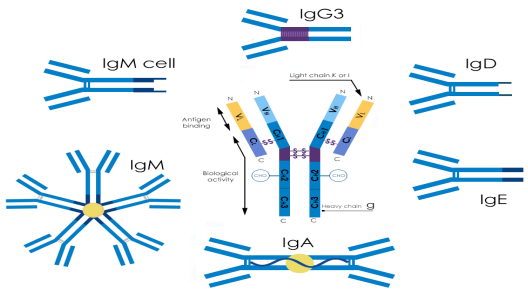

http://a.static-abcam.com/CmsMedia/Media/antibody-structure-and-isotopes.png

5

Don't Get Mad, Get mAbs

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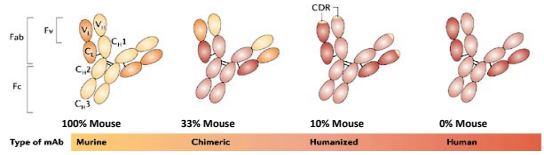
- Monoclonal antibodies (mAbs) are unique, specific antibodies produced by clones of a single parent B cell
- Each mAb has monovalent affinity for a solitary epitope on an antigen
- Production can occur in vivo through the use of mice, Chinese hamster ovaries (CHO), and human cell lines; or in vitro via cell culture and recombinant phage assay
- Genetic engineering and recombinant DNA (rDNA) technology has enabled the creation of chimeric, humanized, and fully human monoclonal antibodies
- Therapeutic applications range from laboratory testing (e.g. ELISA, immunohistochemistry) to the treatment of disease (autoimmune disorders, anticoagulation, GVHD, **cancer**)

6

A Rose Among Thorns

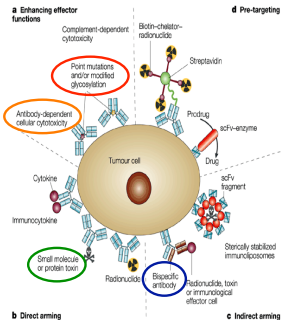
- Murine-derived monoclonal antibodies can lead to an IgE-mediated allergic response against the immunogenic fragments derived from mice
- **Human Anti-Mouse Antibodies (HAMA)**
  - Lead to a loss of therapeutic efficacy and to toxicity (infusion reactions → anaphylaxis)
- Decrease the risk of host antibody development through the incorporation of increasing amounts of human protein during mAb production



Nature Reviews Cancer 6, 714-727

"Magic Bullet"

- **Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)**
- **Complement-Dependent Cell-Mediated Cytotoxicity (CDCC)**
- **Addition of other therapeutic modalities**
  - Linkage of small-molecule drugs, radionuclides, toxins, or proteins
- **Bispecific Antibodies**
  - Bispecific T-cell Engagers (BiTEs)



Nature Reviews Cancer 1, 118-129

What's in a Name?

- United States Adopted Names Council (USANC) is the regulatory body responsible for choosing generic names for therapeutic substances
- Suffix **-mab** signifies the drug is a monoclonal antibody, **-pab** signifies a pooled polyclonal antibody product

What's the Source?	
Infix	**Source**
-o-	Murine
-xi-	Chimeric
-zu-	Humanized
-u-	Fully Human

What's the Target/Mechanism?	
Infix	**Target/Mechanism**
-tu-/-t-	Tumor
-li-/-l-	Immunomodulator
-ci-/-c-	Cardiovascular
-ki-/-k-	Interleukins
-so-/-s-	Bone
-ba-/-b-	Antibacterial
-fu-/-f-	Antifungal
-vi-/-v-	Antiviral

http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/naming-biologics/monoclonal-antibodies.page?

Rapid Fire Recognition

Can you identify the source and target of these monoclonal antibodies?

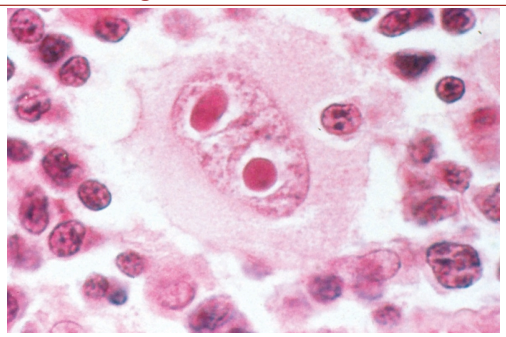
Ri-tu-xi-mab
Ecu-li-zu-mab
Ab-ci-xi-mab
Pani-tu-m-u-mab
Beva-ci-zu-mab
Tosi-tu-m-o-mab
Deno-s-u-mab
Muromomab

Hodgkin Lymphoma (HL)

- Accounts for ~7% of childhood cancer and ~1% of childhood cancer deaths
- Most common in adolescents with a peak incidence at 15-19 years old
- Males are more commonly diagnosed than females (5:4 ratio)
- Associated with Epstein-Barr virus activation in 25-50% of cases
- Characterized by the presence of Reed-Steinberg cells
  - Multinucleated cells with prominent eosinophilic inclusions = "owl's eyes"
  - CD15+, **CD30+**, CD20-, CD45-
- Two subtypes:
  - Classical HL (90-95%): Derived from germinal center B cells, but fail to express many normal genes with a loss of antibody production
  - Nodular lymphocyte predominant HL (5-10%): Retain functional germinal activity and have hypermutation of Ig producing genes

Crit Rev Hematol/Oncol 2013; 85: 216-237

Reed-Steinberg Cells



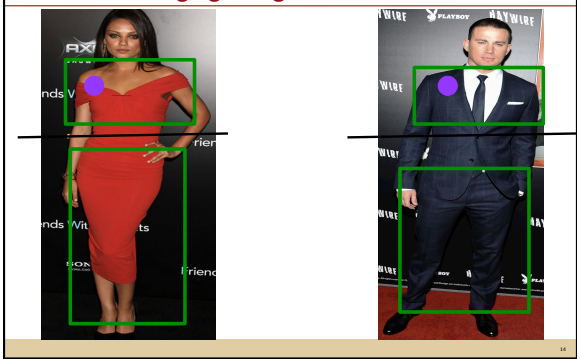
https://s3.amazonaws.com/classconnection/972/flashcards/4319972/png/screen_shot_2014-11-19_at_120808_am-149C673FCD04948S3CE.png

Ann Arbor Staging

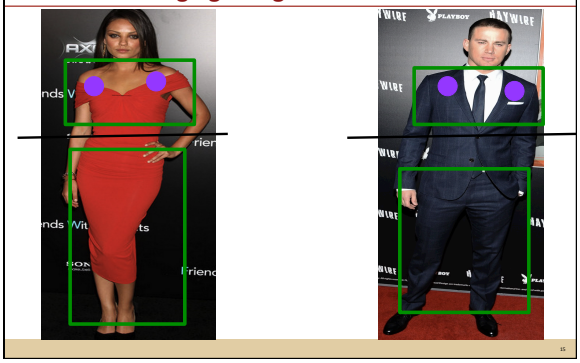
Stage	Description
Stage I	• Single lymph node region or single extralymphatic organ or site without lymph node involvement
Stage II	• Two or more lymph node regions on the same side of the diaphragm alone OR with contiguous extralymphatic involvement
Stage III	• Two or more lymph node regions on opposite side of the diagphragm
Stage IV	• Additional noncontiguous extralymphatic involvement with or without associated lymph node involvement
Subclassifications	• **A:** "B" symptoms absent OR **B:** "B" symptoms present • **E:** Non-extensive extranodal disease • **X:** Bulky disease (node or mass > 10cm in largest diameter or mediastinal mass > 1/3 x size of the thorax at T5/6)

http://training.seer.cancer.gov/lymphoma/abstract-code-stage/staging.html

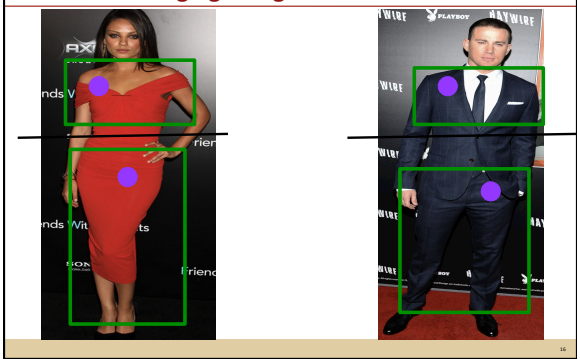
Ann Arbor Staging: Stage I



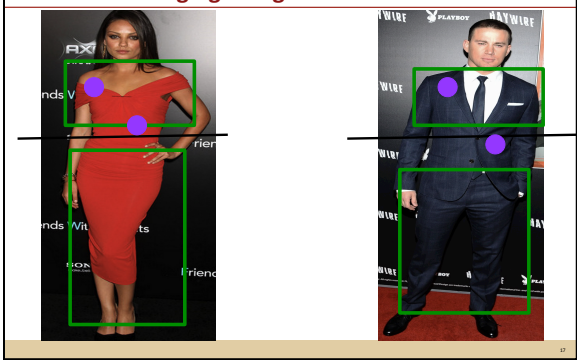
Ann Arbor Staging: Stage II



Ann Arbor Staging: Stage III



Ann Arbor Staging: Stage IV



Historical Treatment of HL

- 1960s: MOPP (Meclorethamine, Oncovin (vincristine), Procarbazine, Prednisone) given as 4 week cycles x 6 cycles with XRT
  - 5-year OS of 87%
  - BUT… azospermia in >90% of males and age-related risk of ovarian failure in females
- 1975: ABVD (Adriamycin (doxorubicin), Bleomycin, Vinblastine, Dacarbazine) given as 4 week cycles x 2-8 cycles with IFRT
  - 5-year OS of 90% with a decreased risk of infertility
  - BUT… predominant adverse effects are cardiotoxicity and pulmonary toxicity, especially in combination with radiotherapy

Risk Adapted Therapy

- Risk Adapted Therapy for Intermediate and High Risk HL
  - Intermediate risk:
    - Stage IA, IIA with bulky disease, >3 sites, bulky LAD, hilar LAD, >3 nodal regions, extranodal extension to contiguous structures
    - Stage IIIA
  - High (Unfavorable) Risk (HR)
    - Stage IIB, IIIB, IV ("B" symptoms + the above or advanced disease)
- Multiple regimens including 4 MOPP/4 ABVD, Stanford V, ABVE-PC, DBVE+PC BEA**COPP**, and **COPP**-ABV have resulted in similar OS of 90-97% with EFS of 80-87% for HRHL patients
  - **COPP (Cyclophosphamide,Vincristine, Procarbazine, Prednisone) has a high risk for azospermia development in boys!**

To Radiate or Not to Radiate?

- COG AHOD0031: Intermediate risk patients treated with dose-dense **ABVE-PC** x 2 cycles followed by response assessment
  - **ABVE-PC: Doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide**
  - Rapid Early Responders (RER) with a CR received 2 additional ABVE-PC cycles **f/b either 21Gy of IFRT or no additional therapy**
  - Slow Early Responders (SER) randomized to either 2 cycles of ABVE-PC or 1 cycle of DECA f/b 2 cycles of ABVE-PC and ALL received 21Gy IFRT
  - OS: 98.7% for RER and 96.9% for SER (p=0.02)
  - **More importantly, no significant different in EFS for RER randomized to IFRT or no IFRT**

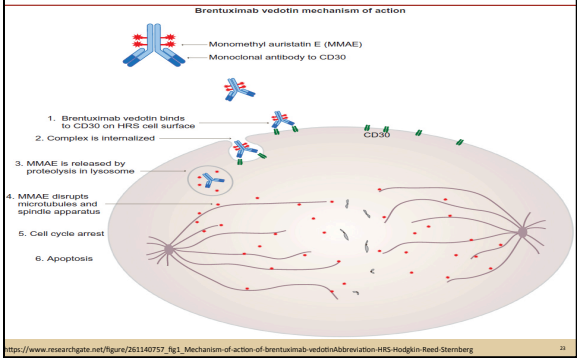
Across the Pond

- The German Society of Pediatric Oncology/Hematology began substituting different agents for procarbazine in OPPA induction and COPP consolidation based regimens
- GPOH-HD 2002: Unfavorable risk patients with Stage II_E B, III_E A/B, III B, IV A/B
  - Girls received 2 cycles of OPPA (VCR, procarbazine, prednisone and doxorubicin), f/b 4 cycles of COPP (cyclophosphamide, VCR, procarbazine and prednisone)
  - **Boys received the same regimen, except procarbazine was replaced by etoposide OPPA induction → OEPA, and by dacarbazine in COPP consolidation → COPDac**
  - **In intermediate and unfavorable risk patients, there was no difference in EFS between boys and girls (90.2% vs. 84.7%, p = 0.12)**

Brentuximab vedotin (Adcetris)

- Brentuximab vedotin is a chimeric antibody-drug conjugate containing an anti-CD30 monoclonal antibody linked to monomethylauristatin E (MMAE, vedotin)
- CD30 is a transmembrane receptor highly expressed on Reed-Steinberg cells in patients with HL
- After binding to CD30, brentuximab is internalized and transported to lysosomes where is it selectively cleaved, releasing MMAE into the cytoplasm
- MMAE exerts antineoplastic effects by inhibiting tubulin polymerization, leading to M-Phase arrest and apoptosis

A Picture is Worth 1000 Words



https://www.researchgate.net/figure/261140757_fig1_Mechanism-of-action-of-brentuximab-vedotinAbbreviation-HRS-Hodgkin-Reed-Sternberg

Rationale for Brentuximab

- Approved for use in adults with refractory HL or ALCL given at 1.8mg/kg (max 180mg) every 3 weeks as monotherapy
- **ECHELON-1:** Ongoing trial in adults assessing combination therapy with ABVD or AVD + brentuximab given biweekly at 1.2mg/kg (max 120mg)
  - BUT… 40% developed significant pulmonary toxicity in the ABVD cohort → ABVD arm terminated early and all patients were switched to AVD
- Small numbers of children treated with monotherapy in Phase I trials
- **COG AHOD1221** is a currently ongoing Phase I/II trial evaluating brentuximab + gemcitabine for relapsed HL
- **Given the risk of neuropathy with both single agent VCR and brentuximab, brentuximab was substituted for VCR in OEPA → AEPA and COPDac → CAPDac**

What About Post-SCT Relapse?

- **AETHERA Trial in relapsed/refractory HL after autologous stem cell transplant (ASCT)**
  - 329 adult patients with unfavorable-risk relapsed or primary CHL who underwent ASCT were randomized to either:
    - Brentuximab 1.8mg/kg IV q3 weeks x 16 cycles (starting 30-45 days post ASCT)
    - Placebo IV q 3 weeks (starting 30-45 days post ASCT)

Median Progression Free Survival (HR 0.57, p = 0.0013)	
Brentuximab vedotin	**42.9 months**
Placebo	24.1 months

  - **ASBMT and NCCN recommend post-ASCT maintenance therapy for 1 year in high-risk patients with primary refractory or relapsed disease <12 months after frontline therapy**

Lancet 2015;385:1853-1862

25

St. Jude Approach to HRHL

Agent	Dosage	Route	Schedule
AEPA x 2 Cycles (each cycle lasts 28 days)			
Brentuximab	1.2mg/kg (max 120mg)	IV over 30 minutes	***Days 1, 8, 15***
Etoposide	125mg/m^2	IV over 1-2 hours	Days 1-5
Prednisone	***60mg***/m^2/day/TID (max ***30mg***)	PO	Days 1-15
Doxorubicin	40mg/m^2	IV over 1-6 hours	Days 1, 15
CAPDAC x 4 Cycles (each cycle lasts 21 days)			
Cyclophosphamide	500mg/m2	IV over 1 hour	Days 1, 8
Brentuximab	1.2mg/kg (max 120mg)	IV over 30 minutes	***Days 1, 8***
Prednisone	***40mg***/m^2/day/TID (max ***20mg***)	PO	Days 1-15
Dacarbazine	250mg/m^2	IV over 15-30 min	Days 1-3

26

Brentuximab Administraton

- Infusion should be over 30 minutes. Do NOT administer via IV push or bolus.
- Do NOT use an in-line filter
- Final product does NOT need to be protected from light DURING ADMINISTRATION
- Routine premedication should NOT be administered
- Because infusion reactions may occur during or up to 60 minutes after the infusion, patients must be observed for at least 1 hour following the infusion
- Patients who develop Grade 1 or 2 infusion reactions may be pretreated with acetaminophen and diphenhydramine 30-60 minutes prior to brentuximab infusion
  - Steroid pretreatment is discouraged and must be approved by the PI
- Compatible with NS, 5% dextrose, and LR in concentrations of 0.4-1.8mg/mL

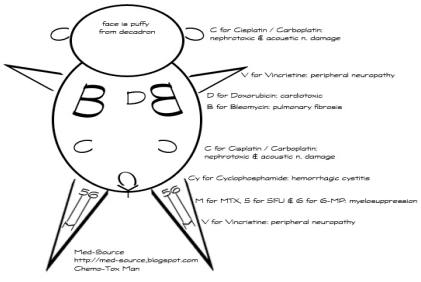
27

Order of Operations

- **AEPA**
  - Hour 0-0.5: Brentuximab
  - Hour 0.5-1.5: Etoposide
  - Hour 1.5-2.5: Doxorubicin
- **CAPDac**
  - Hour -2-0 OR when urine parameters met: Pre-hydration with D5½NS at 200mL/m^2/hr
  - Hour 0-0.5: Brentuximab
  - Hour 0.5-1.5: Cyclophosphamide
  - Hour 1.5-2: Dacarbazine
  - Hour 1.5-5.5: Post-hydration with D5½NS at 125mL/m^2/hr
- **Ensure reaction medications (diphenhydramine, hydrocortisone, epinephrine) are ordered!**

28

Adverse Events



29

Adverse Events

- **Expected Side Effects**
  - Diarrhea, nausea, constipation, vomiting
  - Fatigue, fever, chills, edema
  - **INFUSION RELATED REACTIONS**
  - Myelosuppression, neutropenia, thrombocytopenia, anemia
  - Upper respiratory infection, cough
  - **Peripheral sensory or motor neuropathy**, dizziness, headache
  - Anorexia
  - Arthralgia, back pain, myalgia
- **Less Common Adverse Effects**
  - Anaphylaxis

30

Questions?

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