Morning Rounds: Cases and Therapeutics

9/9/2021

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Learning Objectives

- Describe key components of a patient history
- Understand pathophysiology, clinical manifestations, and treatment of diffuse large B-cell lymphoma (DLBCL)
- Apply concepts to develop an assessment and plan for a patient

History of Present Illness (HPI)

CC: Inpatient chemotherapy administration

HPI: AH is a 51 y.o. male with PMH of refractory extranodal DLBCL with bone marrow and CSF involvement and HIV who presents as a planned admission for chemotherapy. Seen at bedside this PM. Feels well with no complaints. Is curious about the “schedule” for his eye. States that he has difficulty moving and opening his L eye. Otherwise states that he is here for chemotherapy. Explicitly denies having any medical concerns.

Oncological History

Dx with DLBCL

Gastric/duodenal involvement

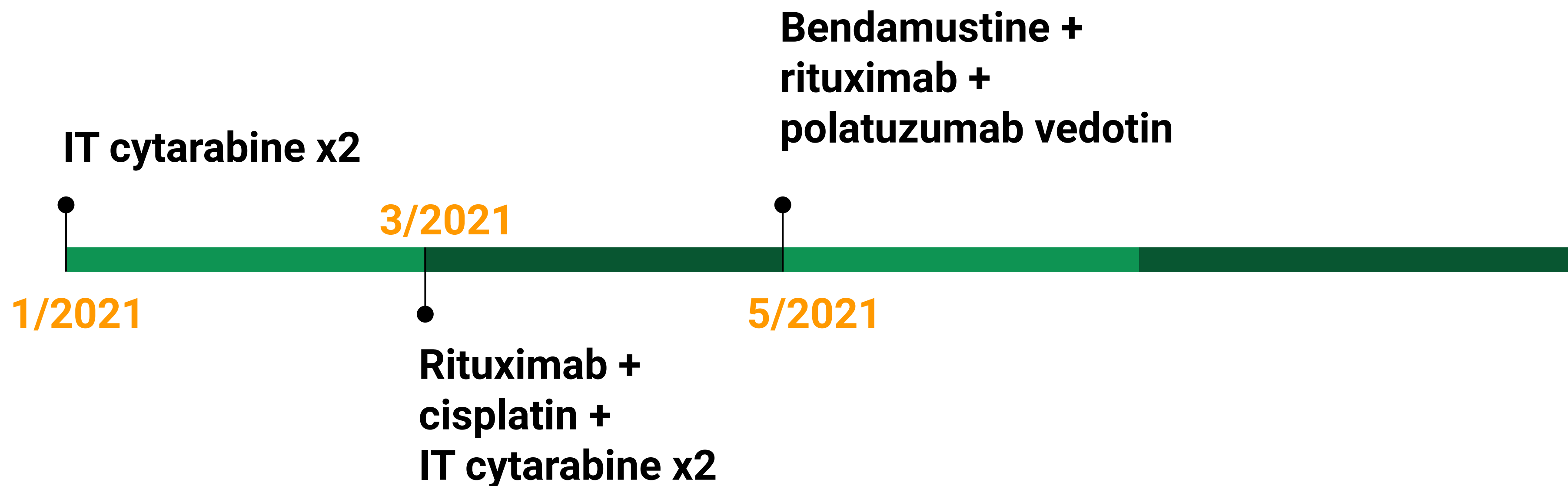
S/P DA-EPOCH-R through 5/2020

Relapsed DLBCL w/ CNS and right testicle involvement

S/P right radical orchiectomy

R-ICE + HD-MTX (+)CNS

Oncological History cont.



Oncological History cont.

Admitted for HA, vision changes 2/2 POD of lymphoma into CNS

6/2021 - 7/2021

6/4: LP (+) CNS

6/15: C1D1 MATRix

6/22: BMBx (+); c/b neutropenic fever/typhilitis requiring MICU

C2D1 MATRix

7/2021

9/3/2021

Admitted for C3D1 MATRix(?)

Past Medical History (PMH)

Abducens (sixth) nerve palsy, left	6/16/2021
Acquired abduction deformity of foot	3/19/2021
Acquired early latent syphilis	3/19/2021
Acute gonorrhea of genitourinary tract	3/19/2021
Acute kidney injury	6/13/2021
Acute tension-type headache	6/13/2021
Chronic hepatitis B infection	
Condyloma acuminatum	3/19/2021
Enteritis due to Giardia species	3/19/2021
Essential hypertension	3/19/2021

PMH cont. & PSH

- **Hepatitis B infection associated with human immunodeficiency virus infection** 3/19/2021
- **HIV infection** 3/19/2021
- Idiopathic gout 10/1/2013
- **Large cell lymphoma** 6/13/2021
- **Neutropenic colitis** 6/14/2021
- **Secondary syphilis of skin** 12/24/2009
- Shortness of breath 6/14/2021

PSH: s/p right radical orchiectomy (10/2020)

Social History

- Never smoker, no e-cigarettes
- No EtOH use
- Denies illicit drug use

- Lives alone
- Not currently working, peer counselor before
- Not currently sexually active

Family History

- No family history of cancer
- Mother, father alive

Allergies

- NKA reported

Medications PTA

Medication	Directions	Indication
acyclovir 400mg tablet	1 tablet PO BID	Herpes zoster prophylaxis
allopurinol 300mg tablet	1 tablet PO once daily x 14 days	Tumor lysis syndrome prophylaxis
bictegravir/emtricitabine/TAF 50-200-25mg tablet	1 tablet PO once daily	HIV, HBV
dexamethasone 4mg tablet	10 tablets PO daily x 4 days	CNS involvement of lymphoma, antiinflammatory
filgrastim-sndz 300mcg/0.5mL SubQ injection	Inject 0.5mL SubQ once daily	Neutropenia, hematopoietic growth factor
fluconazole 200mg tablet	1 tablet PO once daily x 14 days	Candida prophylaxis
levoFLOXacin 500mg tablet	1 tablet PO once daily x 14 days	Bacterial prophylaxis
metoprolol tartrate 25mg tablet	1 tablet PO Q12H	Essential hypertension
prochlorperazine 10mg tablet	1 tablet PO QID PRN N/V	Nausea and vomiting
sulfamethoxazole/trimethoprim 800-160mg tablet	1 tablet PO three times a week MWF	*Pneumocystis jirovecii* pneumonia prophylaxis
thiamine 100mg tablet	1 tablet PO once daily	Vitamin B-1 supplementation

Labs

	9/6/2021 05:31	8/30/2021 11:43 (O)	8/23/2021 13:17 (ED)	8/8/2021 04:44 (D)	7/30/2021 18:17 (A)	7/7/2021 03:48 (D)
WBC (3.9-12.0 k/uL)	25.6	19.6	2.0	2.0	3.7	0.5
Hgb (13.2-18.0 g/dL)	7.5	8.6	4.5	8.0	9.2	8.4
Plts (150-450 k/uL)	15	14	4	74	108	13
SCr (0.5-1.5 mg/dL)	1.19	1.65	1.35	0.97	1.08	0.99
Uric Acid (4.0-8.0 mg/dL)	4.2	-	-	3.1	5.6	2.0
LDH (90-180 u/L)	7,190	2,264	1,107	2,554	2,397	177
TBili (<=1.2 mg/dL)		0.7	0.5	0.7	0.5	0.4

Labs

	9/6/2021 05:31	**8/23/2021 13:17 (ED)**	**7/30/2021 18:17 (A)**	**7/7/2021 03:48 (D)**	**6/14/2021 12:11**
CD4 (438-1501 cells/uL)	146	74	240	<35	
HepB S Ag	Negative				Negative
HepB S Ab	9.6				3.6
Hep B Core Total Ab	Positive				Positive
Hep B Core IgM					Negative
Hepatitis C Ab	Negative				

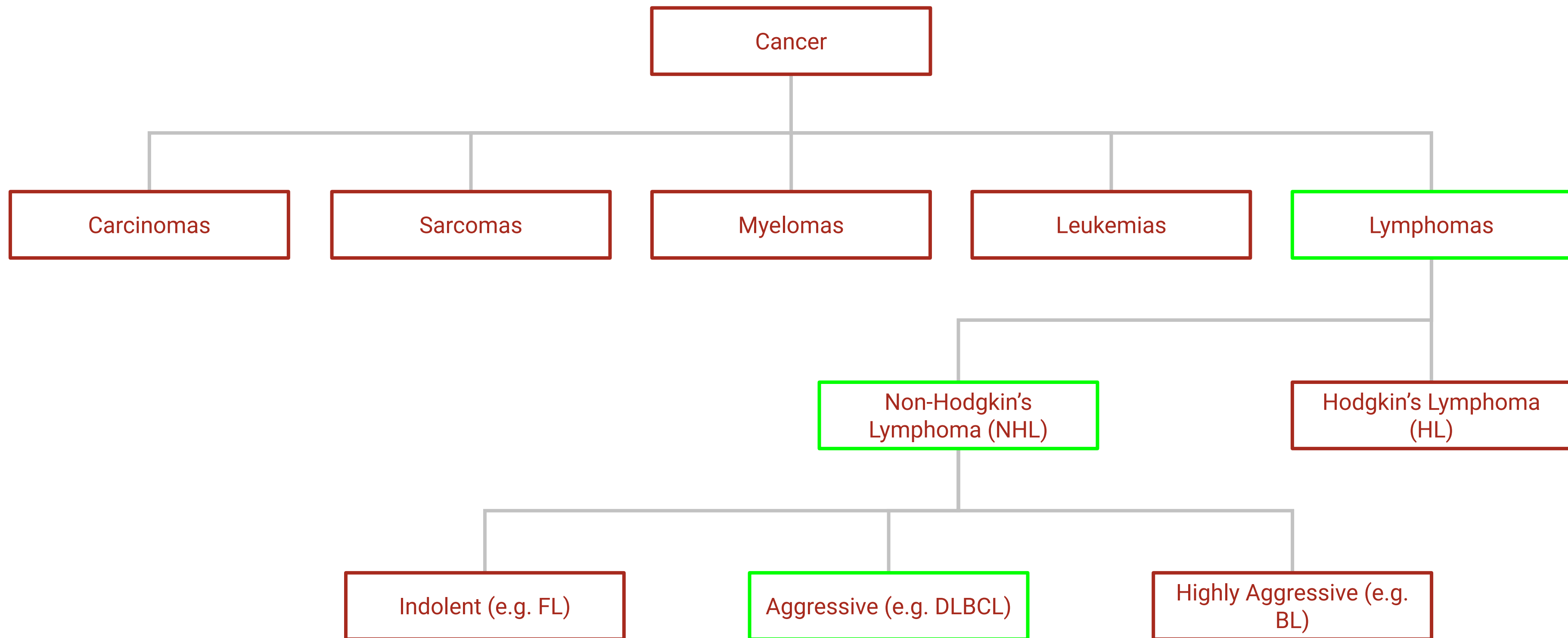
Pathology

- 1/10/20 Gastric and duodenum biopsy
  - High grade B-cell lymphoma, not otherwise specified with MYC rearrangement
  - Negative for CD20 (focal weak patchy, <5%) and BCL-6
  - Co-expression CD10, MYC, and EBER with Ki-67 proliferation index: 100%
- 7/23/20: CSF (-) lymphoma
- 9/30/20: CSF (+) lymphoma
- 10/1/20: right testicular mass and spermatic cord orchiectomy
  - High grade B-cell lymphoma, GC-type w/ c-MYC rearrangement, CD20 (-), EBER (+)
  - CD20 (-), BCL6 (-), focal variable BCL2 immunoreactivity
- 6/4/21: CSF
  - Dim CD19(+), dim CD20(+), bright CD10(+)

Imaging

- 9/18/20: PET-CT
  - Pathological hypermetabolism in right testicle/scrotum and retroperitoneal LAD
- 12/31/20: PET-CT
  - Significant progression of disease
- 7/31/21: CT
  - Progression of disease - increased size of bilateral axillary lymph nodes and right paracardiac lymph nodes
- 8/3/21: CT lumbar spine
  - Involvement of right L5 and right S1 nerve roots with tumor
  - Retroperitoneal adenopathy remains present

What is Diffuse, Large B-Cell Lymphoma (DLBCL)?



SEER Training Modules, *Cancer Classification*. U.S. National Institutes of Health, National Cancer Institute. 4 Sept 2021 <*https://training.seer.cancer.gov/*>

NHL

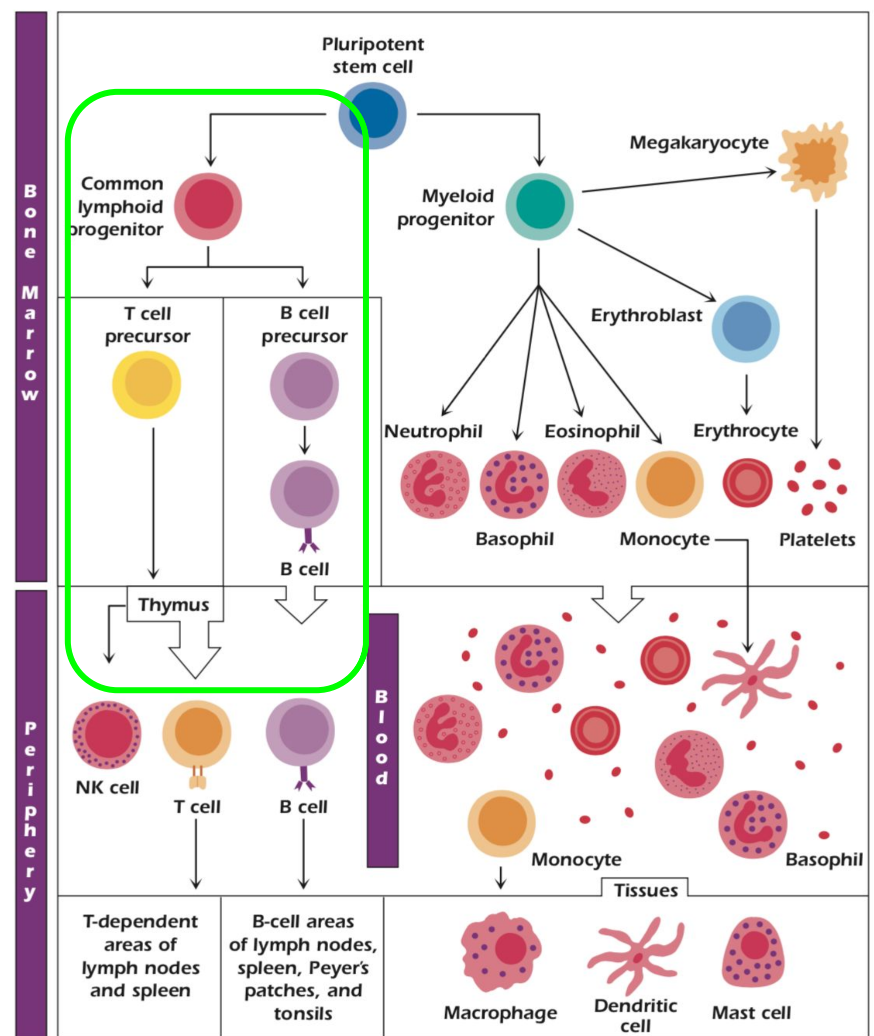
- In 2017, estimated 72,240 new cases of NHL in U.S. (~4% of all new cancers)
    - 9th in cancer-related death in U.S.
    - Male predominance, higher incidence for Caucasians than AA
- Conditions associated with development of lymphoma
    - Immunodeficient states
    - Autoimmune and inflammatory disorders
    - Chemicals and drugs
    - Infectious agents

Devita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology, 11th ed. (2019), Wolters Kluwer, Philadelphia.

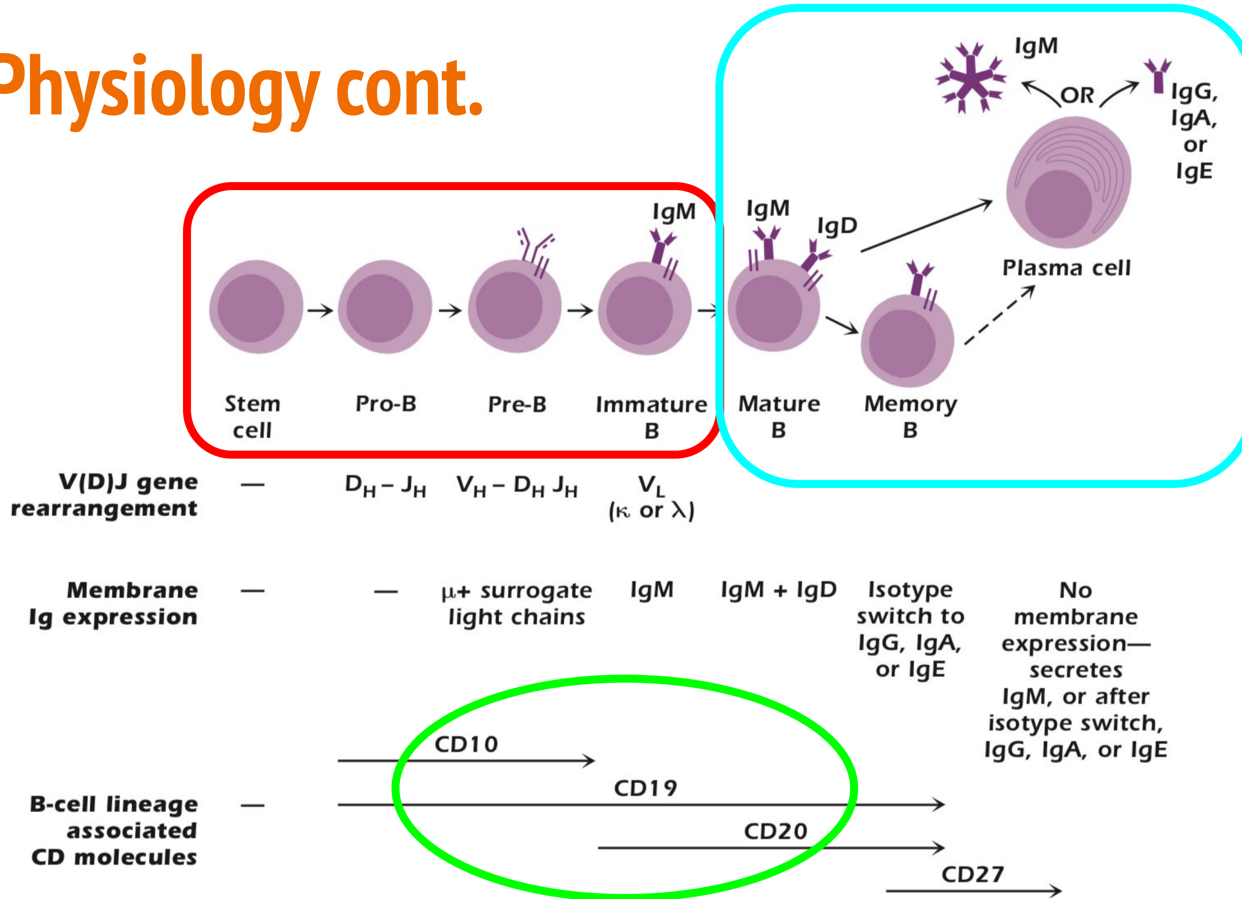
Normal Physiology

- Innate vs adaptive immunity
- Lymphoid lineage (T & B cells)
- B cell development
    - Primary vs. secondary lymphoid organs
    - B cell maturation in germinal centers
        - Antigen-driven affinity maturation: somatic hypermutation & clonal expansion
        - Class switch recombination

Coico & Sunshine, “Immunology: A Short Course,” 7th Ed. (2015), Wiley, New York.



Normal Physiology cont.



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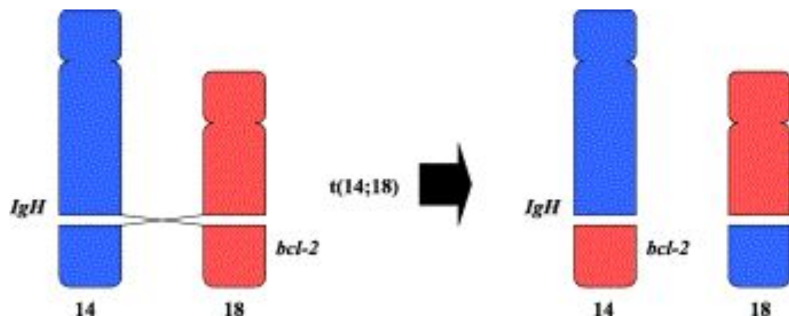
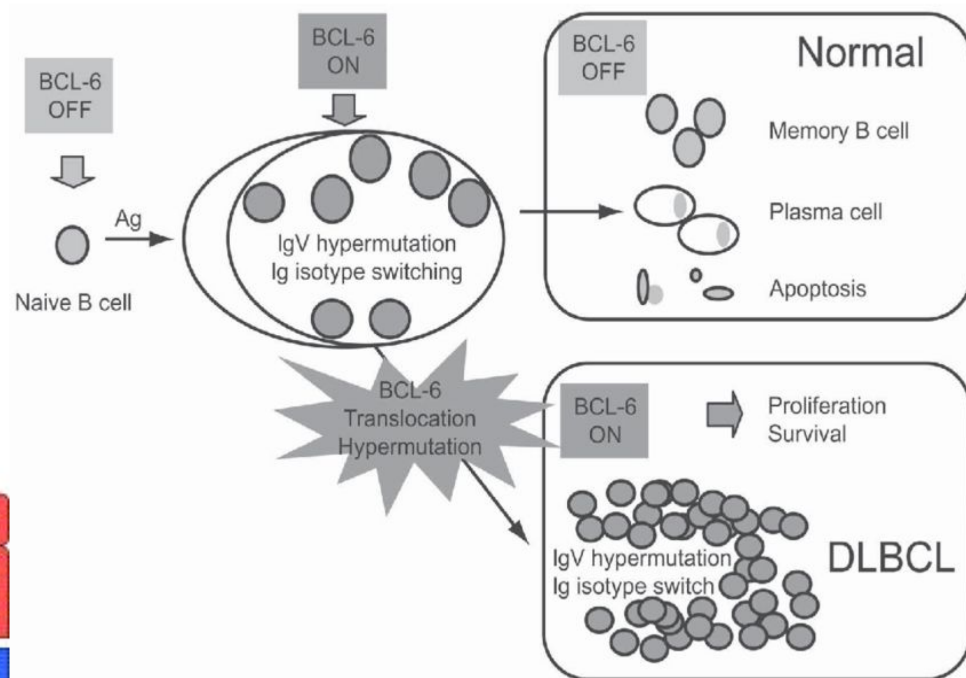
Pathophysiology

- Majority of B-NHLs derive from GC experienced B cells
- Common mechanisms of oncologic lesions





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DLBCL

- Most common histologic subtype of NHL
  - Similar patient characteristics and risk factors
- Diffuse proliferation of large cells with high mitotic rate
  - Large size of tumor cells
- Tumor cells generally express: CD19, CD20, CD79a
  - CD10 and BCL6 expression - GC origin
  - Common rearrangements of *MYC, BCL-2, BCL-6*

Devita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology, 11th ed. (2019), Wolters Kluwer, Philadelphia.

Clinical Features of DLBCL

- Highly invasive, with local compression of bone vessels, airways, involvement in peripheral nerves, and destruction of bone
- Stage IV disease; B sx; elevated serum LDH
- 40% with extranodal disease
    - Testicular, paranasal sinus, epidural, and presence of multiple extranodal sites associated with high risk of CNS dissemination
    - 10-20% bone marrow involvement and strong correlation with risk of CNS spread

Devita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology, 11th ed. (2019), Wolters Kluwer, Philadelphia.

Staging

Stage	Description
I	Single lymph node or single extranodal site
II	2+ lymph nodes or structures on same side of diaphragm; limited extralymphatic
III	Lymph nodes on both sides of diaphragm; limited extralymphatic; or both
IV	Diffuse or disseminated; 1+ extralymphatic organs or tissues

A or B - systemic B sx

Devita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology, 11th ed. (2019), Wolters Kluwer, Philadelphia.

International Prognostic Index (IPI)

Age > 60, LDH > ULN, Ann Arbor stage III or IV, number of extranodal > 1, ECOG performance status >/= 2

# of Factors	Risk Group	3-Y OS (%)
0 - 1	Low	91
2	Low intermediate	81
3	High intermediate	65
4 - 5	High	59

Devita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology, 11th ed. (2019), Wolters Kluwer, Philadelphia.

HIV-Associated NHL

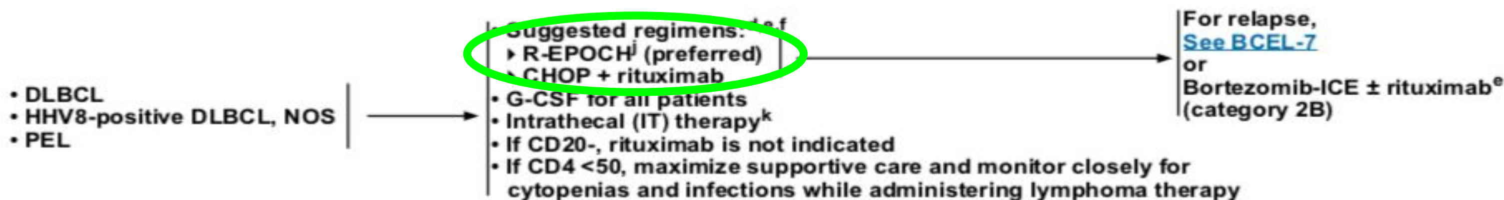
- Systemic AIDS-related NHLs generally highly aggressive
  - 75% DLBCL, 20% BL, etc.
  - Extranodal common: GI, skin and soft tissue, liver, lung, heart, bone marrow, CNS
- About 30% of AIDS-related lymphomas have deregulation of *BCL6* and similar have *MYC* abnormalities
- Risk factors: depressed CD4 count, high HIV viral load, lack of effective ART

Devita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology, 11th ed. (2019), Wolters Kluwer, Philadelphia.

Assessment and Plan

Dose-Adjusted R-EPOCH (da-R-EPOCH)

- AIDS-Related B-Cell Lymphomas



- For patients with CD4 count >50 cells/uL with high growth fraction disease (Ki67 > 80%), non-GCB cell of origin, double-hit cytogenetics, OR high IPI, da R-EPOCH over CHOP (despite limited clinical data)

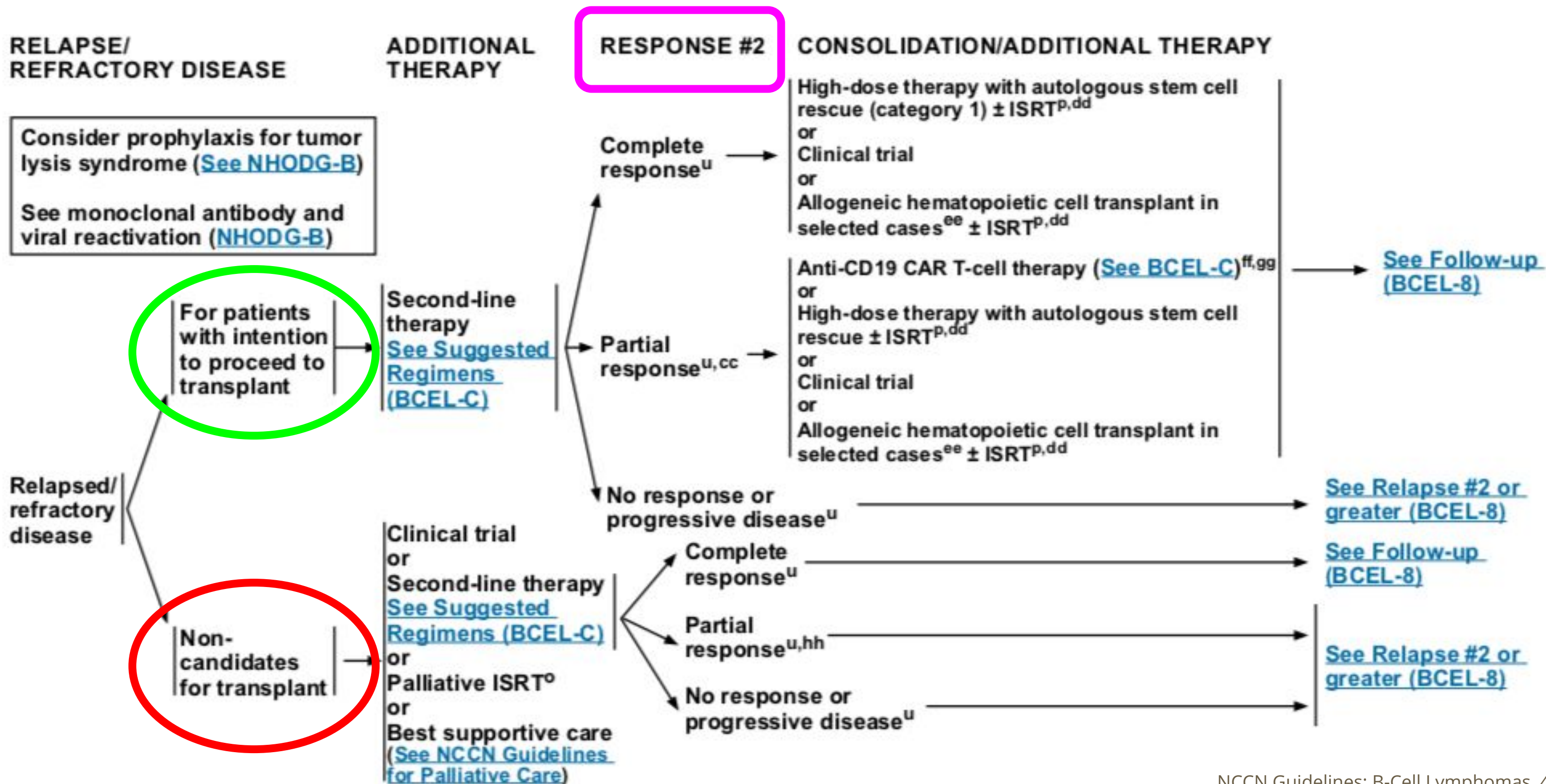
NCCN Guidelines: B-Cell Lymphomas, 4.2021. (2021), NCCN.
Kaplan LD and Ai W. HIV-related lymphomas: treatment of systemic lymphoma. UpToDate. (2021).

da-R-EPOCH

Drug	Mechanism	Notable Adverse Events
RiTUXimab	Binds to CD20 and mediates B-cell lysis	Reactivation of hepatitis B, fever, chills, urticaria, bronchospasm
Etoposide	Topoisomerase II inhibitor; acts on S and G2 phases of cell division	Myelosuppression
Prednisone	Antiinflammatory, immunomodulatory	Impaired wound healing, hyperglycemia
VinCRIStine	Inhibit microtubules during M phase	Peripheral neuropathy
Cyclophosphamide	Alkylating agent cross-linking nucleic acids and inhibiting protein synthesis	Hemorrhagic cystitis, alopecia, myelosuppression
DOXOrubicin	Anthracycline topoisomerase II inhibitor, blocks nucleotide replication and action of DNA and RNA polymerases	Cardiotoxicity, alopecia, myelosuppression

NCCN Guidelines: B-Cell Lymphomas, 4.2021. (2021), NCCN.
Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA.

Relapsed/Refractory Disease



NCCN Guidelines: B-Cell Lymphomas, 4.2021. (2021), NCCN.

R/R DLBCL Regimens

SECOND-LINE AND SUBSEQUENT THERAPY[d,i,j]
(intention to proceed to transplant)

Preferred regimens (in alphabetical order)
- DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab — 3rd
- DHAX (dexamethasone, cytarabine, oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab — 2nd

Other recommended regimens (in alphabetical order)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

- Suggested CNS prophylactic therapy (Optimal management is uncertain)
  - Systemic high-dose methotrexate (3–3.5 g/m² for 2–4 cycles) during or after the course of treatment and/or — 2nd
  - Intrathecal methotrexate and/or cytarabine (4–8 doses) during or after the course of treatment

SECOND-LINE AND SUBSEQUENT THERAPY[d,i,j]
(non-candidates for transplant)

Preferred regimens (in alphabetical order)
- GemOx ± rituximab
- Polatuzumab vedotin ± bendamustine ± rituximab[k,l] — 4th

Other recommended regimens (in alphabetical order)
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- Gemcitabine, vinorelbine ± rituximab (category 3)
- Rituximab
- Tafasitamab[m] + lenalidomide

Useful in certain circumstances
- Brentuximab vedotin for CD30+ disease
- Bendamustine[k] ± rituximab (category 2B)
- Ibrutinib[n] (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

NCCN Guidelines: B-Cell Lymphomas, 4.2021. (2021), NCCN.

MATRix Regimen

Drug	Mechanism	Notable Adverse Events
Methotrexate	Interferes with DNA synthesis, repair, and cellular replication	Stomatitis, nephrotoxicity, myelosuppression, hepatotoxicity
Cytarabine	Antimetabolite; inhibits DNA synthesis in S phase of cell division	Pulmonary toxicity, hyperuricemia
Thiotepa	Releases radicals disrupting DNA bonds and causing breakage of links	Myelosuppression, inflammatory disease of mucous membrane
RiTUXimab	Binds to CD20 and mediates B-cell lysis	Reactivation of hepatitis B, fever, chills, urticaria, bronchospasm

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Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA.

C3D1 MATRix - 9/6/2021

- Labs: CBC w/ diff, CMP, LDH, Uric Acid
- Hold and notify if: ANC < 1000, Plts < 100, Hgb < 8
- Pre-Medications:
  - acetaminophen 650mg, diphenhydramine 50mg
- Chemotherapy:
  - riTUXimab 700mg in NaCl 0.9% 610mL IVPB
  - Start infusion at a rate of 100mg/hr; if there is no infusion-related reaction, increase the rate by 100mg/hour increments every 30 minutes, to a maximum rate of 400mg/hour.
  - If pt has chills, rigors, fever, n/v, d/c infusion, wait for symptom to resolve, and restart at ½ the prior rate. For hypotension, angioedema, hypoxia, or bronchospasm, d/c infusion, provide care, call MD.
- Emergency Meds:
  - diphenhydramine 25mg (if received premed) or 50mg, hydrocortisone sod succinate 100mg, famotidine 20mg, EPINEPHrine PF 0.3mg, NaCl 0.9% bolus 1,000mL

C3 D6-10 MATRix (proposed)

- Labs: CBC w/ diff, CMP, LDH, Uric Acid, UA, APTT, Protime-INR, Methotrexate level
- Hold and notify if: ANC < 1500, Plts < 100, Hgb < 8, CrCl < 50, any toxicity >/= 3
- Pre-Medications:
  - ondansetron 16mg, dexamethasone 10mg in D5W 50mL IVPB
  - dexamethasone 0.1% ophthalmic solution
- Chemotherapy:
  - methotrexate 937.5mg in NaCl 0.9% 287.5 mL IVPB, over 15 min
  - methotrexate 5,612.5mg in NaCl 0.9% 1,224.5 mL IVPB, over 3 hours
  - cytarabine 3,750mg in NaCl 0.9% 250 mL IVPB, over 60 min
  - thiotepa 56mg in NaCl 0.9% 105.6 mL IVPB, over 30 min
- Supportive Care:
  - leucovorin injection 28mg IV Q6H, starting 25 hours after treatment for 12 doses
- PRN Meds:
  - prochlorperazine injection 10mg IV Q6H PRN, N/V
- Emergency Meds:
  - acetaminophen 650mg, diphenhydramine 50mg, hydrocortisone sod succinate 100mg, famotidine 20mg, EPINEPHrine PF 0.4mg, meperidine 25mg
- Take-Home Meds:
  - filgrastim-sndz (Zarxio) 300mcg/0.5mL, SubQ once daily x 10 days

9/7 Discharge

“Planned to have MATRIX chemotherapy but given thrombocytopenia and overall poor prognosis decided to not pursue further treatment. Had frustrations regarding prolonged hospital stay. Patient expressed clear wishes to go home, not enroll with hospice at this time, and manage his life independently with occasional family support.”

F/u with MD, palliative care outpatient

Recall... Medications PTA

Medication	Indication
acyclovir 400mg tablet	Herpes zoster prophylaxis
allopurinol 300mg tablet	Tumor lysis syndrome prophylaxis
bictegravir/emtricitabine/TAF 50-200-25mg tablet	HIV, HBV
dexamethasone 4mg tablet	CNS involvement of lymphoma, antiinflammatory
filgrastim-sndz 300mcg/0.5mL SubQ injection	Neutropenia, hematopoietic growth factor
fluconazole 200mg tablet	Candida prophylaxis
levoFLOXacin 500mg tablet	Bacterial prophylaxis
metoprolol tartrate 25mg tablet	Essential hypertension
prochlorperazine 10mg tablet	Nausea and vomiting
sulfamethoxazole/trimethoprim 800-160mg tablet	*Pneumocystis jirovecii* pneumonia prophylaxis
thiamine 100mg tablet	Vitamin B-1 supplementation

Devita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology, 11th ed. (2019), Wolters Kluwer, Philadelphia.

Discharge (Updated) Medication List

allopurinol 300mg tablet, 1 tablet PO once daily

bictegravir/emtricitabine/TAF 50-200-25mg tablet, 1 tablet once daily

dexamethasone 4mg tablet, 10 tablets daily x 4 days

metoprolol tartrate 25mg tablet, 1 tablet PO Q12H

prochlorperazine 10mg tablet, 1 tablet PO QID PRN N/V

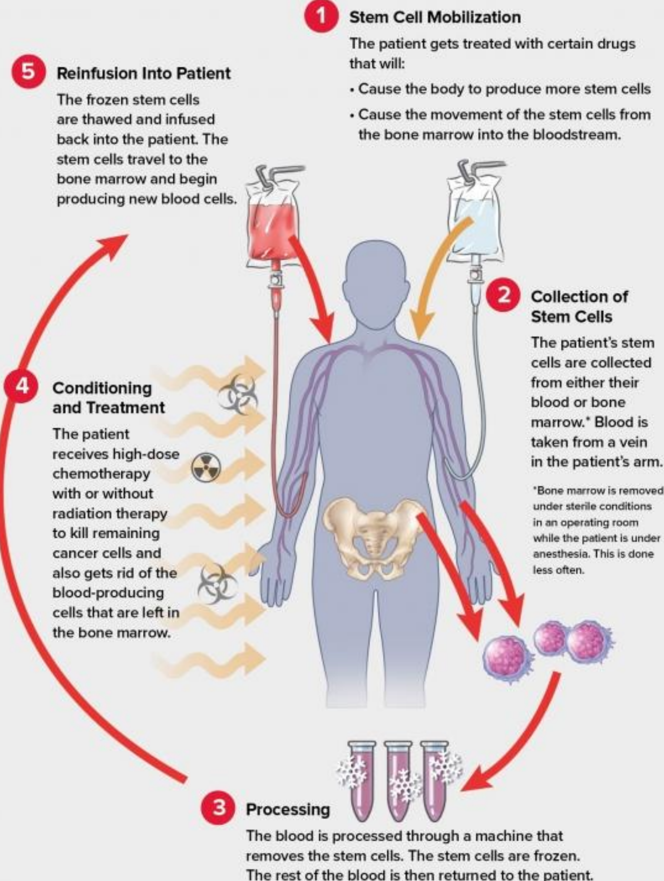
sulfamethoxazole/trimethoprim 800-160mg tablet, 1 tablet PO three times a week on MWF

thiamine 100mg tablet, 1 tablet PO once daily

What Next?

- Chemotherapy
- Autologous stem cell transplantation
- Anti-CD19 CAR-T cell therapy
- Clinical trials or palliative care
  - Selinexor

Fancher KM. Non-Hodgkin and Hodgkin Lymphomas. (2021). [Presentation]. ASHP and ACCP.



CAR T-cell Therapy

Remove blood from patient to get T cells

T cell

Make CAR T cells in the lab

Insert gene for CAR

T cell

Chimeric antigen receptor (CAR)

CAR T cell

Grow millions of CAR T cells

Infuse CAR T cells into patient

CAR T cells bind to cancer cells and kill them

Cancer cell

Antigens

CAR T cell

Cancer cell

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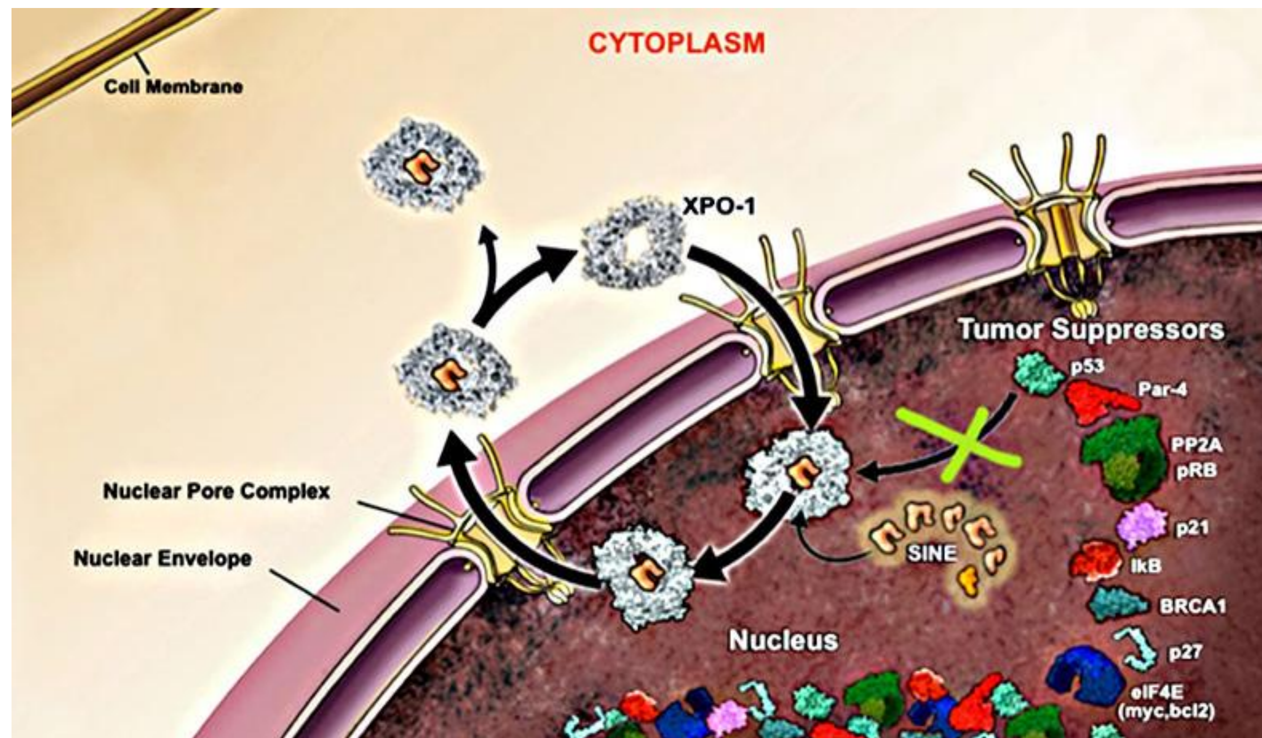
https://www.lls.org/treatment/types-treatment/stem-cell-transplantation/autologous-stem-cell-transplantation
https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy

Selinexor

- Recent approval for r/r DLBCL after 2 lines of systemic therapy
- MOA: inhibition of XPO-1



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https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selinexor-relapsedrefractory-diffuse-large-b-cell-lymphoma

A&P

- r/r DLBCL
  - Palliative intent: selinexor 60mg/dose twice weekly on days 1 and 3 each week; continue until disease progression or unacceptable toxicity
  - Add ondansetron for moderate-to-high emesis prevention
  - Counsel patient on adequate fluid and caloric intake
  - Monitor for POD, CBC w/ diff, CMP and s/sx of infection, bleeding, neurotoxicity, ocular toxicity, GI toxicity
- HIV (AIDS) and HBV
  - Continue Biktarvy
  - Monitor CD4 count and s/sx of infection

Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA.

What Questions Do You Have?

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