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Pulmonary Long-Term Toxicities

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Pulmonary Toxicity in Lymphoma Survivors

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Disclosure Information

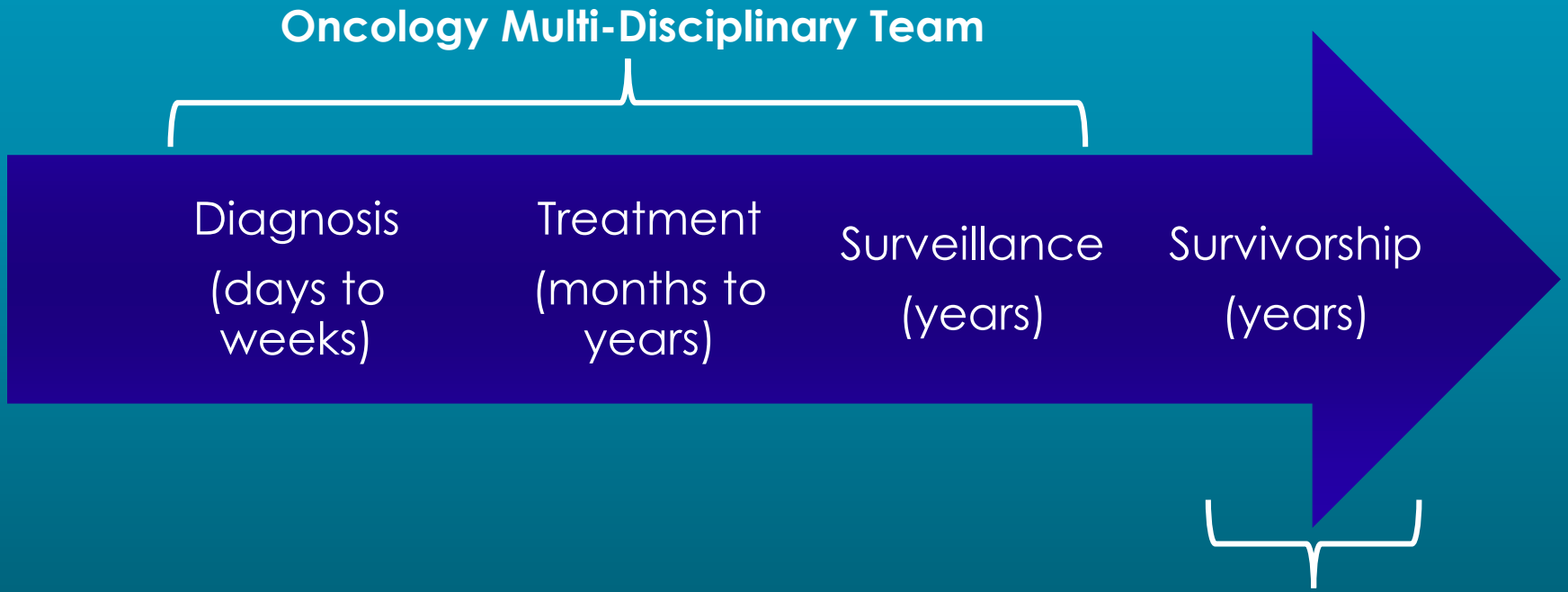
- I have no relevant financial relationships to disclose
- I will discuss the following off-label and/or investigational use in my presentation:
  - Imatinib

Overview/Objectives

- Present the background and challenges with managing pulmonary toxicity in the lymphoma survivor
- Discuss pulmonary toxicity in select populations: Hodgkin lymphoma, Non-Hodgkin lymphoma, Stem cell transplant
- Provide final recommendations for monitoring, prevention, and management


Lymphoma
Treatment Spectrum
Busulfan
Axicabtagene
Prednisone
Fludarabine
Vinblastine
Doxorubicin
Bendamustine
Procarbazine
Ifosfamide
Vorinostat
Thiotepa
Cyclophosphamide
Dexamethasone
Obinutuzumab
Gemcitabine
Carmustine
Brentuximab
Methotrexate
Dacarbazine
Vincristine
Vinorelbine
Romidepsin

Timeline of the Lymphoma Survivor



Challenges with Survivorship

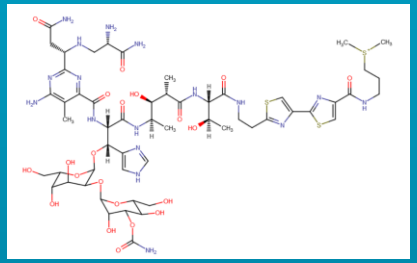
- Patients typically followed ~5 years post-treatment by oncologist with survivorship specific training/knowledge
- Thereafter, may only be followed by general practitioner that may not have expertise on the nuances of cancer survivorship care
- General guidelines exist but disease-specific formal recommendations from leading bodies are lacking

Hodgkin Lymphoma

- ~8,000 new diagnoses per year with bimodal age distribution (15-30 and >55 years)
- "Textbook" survivorship platform given overwhelming cure rates >80%
- Balancing long term adverse outcomes while maintaining excellent survival benefits has been main emphasis of research in HL
- Standard of care (potentially) uses two pulmonary toxic modalities: Bleomycin and radiation

NCCN Guidelines Version 3.2018. Hodgkin Lymphoma

Bleomycin Induced Lung Injury



- Bleomycin
  - Glycopeptide antibiotic derived
  - from streptomyces species
  - Creates reactive oxygen species which drives antitumor effect and pulmonary toxicity through inflammation and recruitment of fibroblasts
  - Lungs (and skin) lack enzyme bleomycin hydrolase which breaks down drug, leading to relative overexposure compared to other tissues
  - Specific polymorphism in bleomycin hydrolase gene may predispose certain patients to pulmonary fibrosis

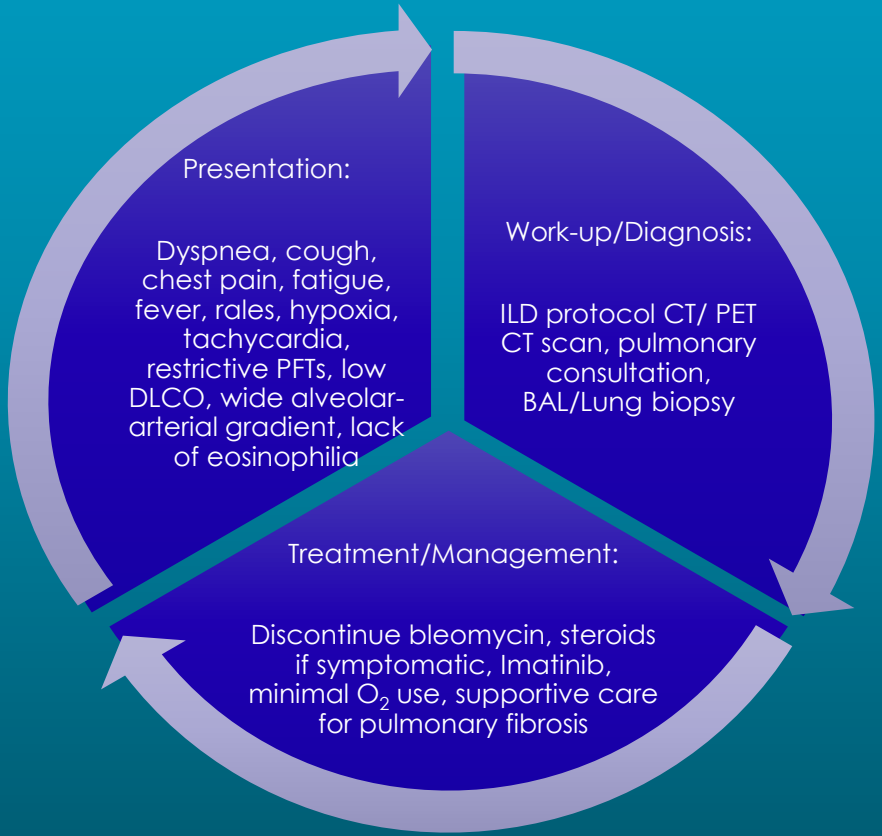
Sleijfer S. Chest 2001
Jona A, et al. PLoS One, 2016.

Bleomycin Induced Lung Injury

- Associated with cumulative doses >400 units
- Risk factors: smokers, renal dysfunction, age >70 years, chest RT and/or stem cell transplant
- Exacerbating causes: Oxygen and excessive IVF exposure in the setting of anesthesia
- Treatment of acute pneumonitis associated with better pulmonary fibrosis outcomes long term

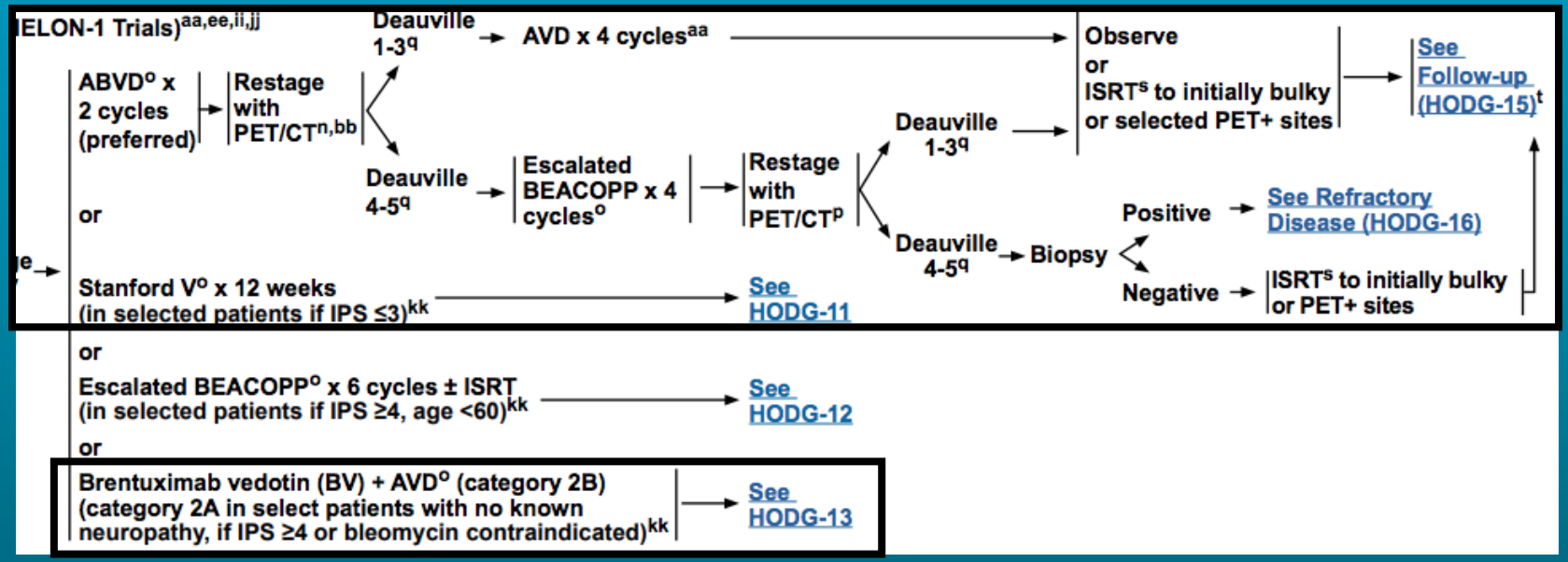
Sleijfer S. Chest 2001

Bleomycin Induced Lung Injury



Sleijfer S. Chest 2001
Patterson GJ. NCCN 2015

An Ounce of Prevention: Bleomycin sparing approaches



NCCN Guidelines Version 3.2018. Hodgkin Lymphoma
RATHL study: Johnson PW, et al. NEJM 2016
ECHELON-1: Connors JM, et al. NEJM 2018

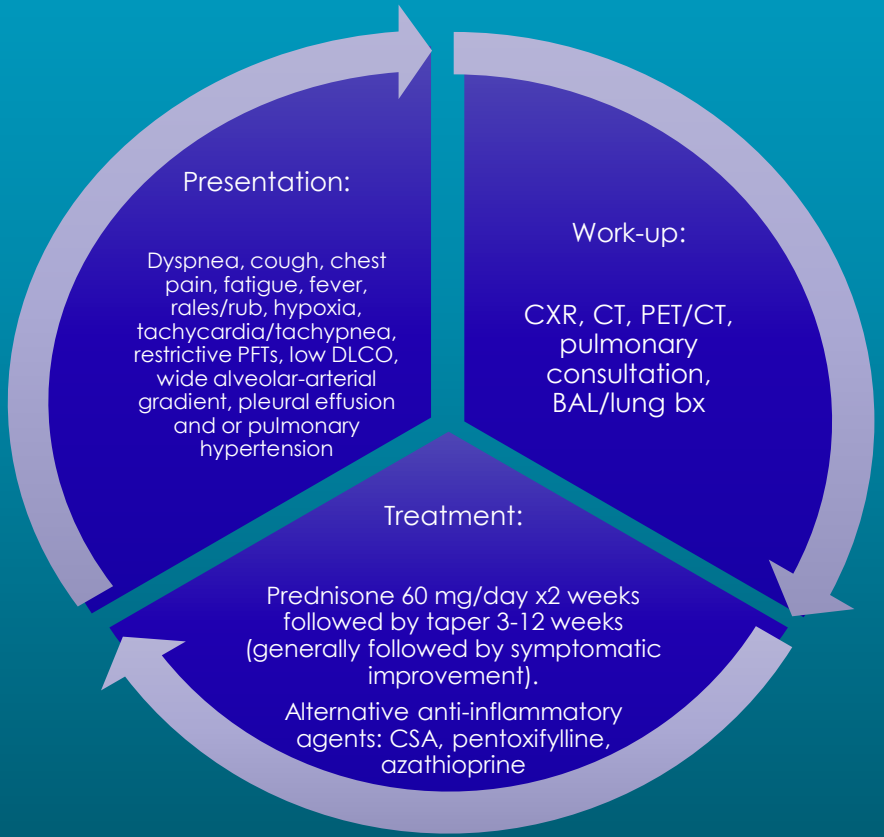
Conclusion

- Considerably less bleomycin being used
- Tobacco/smoking should be avoided
  - Many cessation resources available
- Judicious IV fluids/O_2 use in anaesthia setting in bleomycin exposed patients
- Scuba diving to be avoided in patients with bleomycin induced lung injury/decreased PFTs post-treatment

Radiation Induced Pulmonary toxicity

- Generally occurs 6 months after completion of RT
- Cytokine mediated fibrosis
- Risk Factors: Lung volume in RT field, dose, concurrent RT sensitizing chemo, prior RT, smoking/COPD

Radiation Induced Pneumonitis



Non-Hodgkin Lymphoma

- Long term pulmonary toxicity generally uncommon or is perhaps under-reported
- Pneumonitis during treatment due to monoclonal antibody (rituximab), chemotherapy (cyclophosphamide, gemcitabine), and small molecule inhibitors (ibrutinib) have all been described but generally do not result in long term or delayed pulmonary dysfunction
- Pulmonary infection in the treatment period is common due to immunosuppression but unclear if these events result in long term toxicity

Autologous Stem Cell Transplant

Infectious	Non-Infectious

• Pneumonia
  • Bacterial
  • Fungal
  • Viral
	• Pulmonary edema
	• Diffuse alveolar hemorrhage
	• Engraftment syndrome
	• Idiopathic pneumonia syndrome

- Infectious tend to be acute with non-infectious being later term
- Pneumonia (and other infection) may occur long term in those with hypogammaglobulinemia – repletion with IVIG is recommended
- Risk of death due to pulmonary complication is similar to that of patients without pulmonary toxicity by one year

Afessa B, et al. Chest 2012
Stenehjem JS, et al. Acta Onc 2017

Allogeneic Stem Cell Transplant

- Idiopathic pneumonia syndrome
  - AKA interstitial pneumonitis
  - Risk factors: chest RT, MTX, bleo, busulfan, GVHD
- Bronchiolitis obliterans syndrome (BOS)
  - Often considered as lung GVHD
  - Diagnosed with PFTs (FEV1/FVC <0.7, FEV1 <75% predicted) + air trapping/bronchiectasis on CT + absence of infection
  - Treated with immunosuppressive agents: Corticosteroids, CNIs (tacrolimus), sirolimus, ATG

Majhail NS, et al. BBMT 2012

Allogeneic Stem Cell Transplant

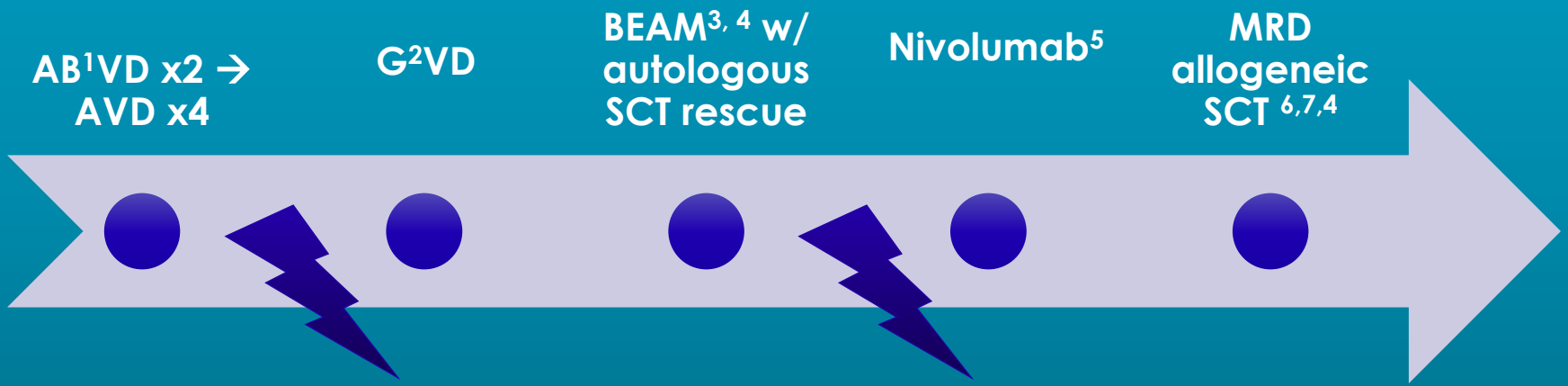
- Cryptogenic organizing pneumonia
  - Formerly called BOOP
  - Presentation: Cough, fever, dyspnea
  - Diagnosis: CXR (patchy infiltrates), PFTs (restrictive pattern), consider biopsy
  - Treatment: Corticosteroids (long tapers)
- Sino-Pulmonary infection
  - Possibly due to poor immune/graft function vs. immunosuppressive drugs
  - Vaccinations
  - Repletion of immunoglobulins with IVIG

Majhail NS, et al. BBMT 2012

Case

- CH is a 24 y/o F presenting to oncology clinic as a referral from PCP for B-symptoms and lymphadenopathy
- No other significant PMH
- Vitals, labs wnl outside of elevated LDH
- Medications: OCP, ibuprofen prn
- CH undergoes biopsy and PET imaging and is diagnosed with Stage IV classic HL

CH's (complicated!) treatment course – Count the risk factors for pulmonary toxicity



1. Bleomycin induced lung injury
2. Gemcitabine induced pneumonitis
3. Chemotherapy related pulmonary toxicity: BCNU (fibrosis), cytarabine, etoposide (pneumonitis), melphalan (pnuemonitis and fibrosis (rare))
4. Pulmonary infection in setting of neutropenia/immunosuppression
5. Autoimmune mediated pneumonitis
6. Pulmonary toxicity from induction chemotherapy agents (Busulfan, cyclophosphamide, TBI…)
7. Long term pulmonary complications from lung GHVD, BOS, IPS, etc.

Recommendations on Monitoring and Prevention

- Smoking cessation!
- Optimization of concurrent chronic lung disease (COPD, asthma)
- Management of concurrent cardiac disease (CHF)
- Consider baseline PFTs in survivorship phase
- Promote healthy behaviors
  - Exercise, nutrition, weight management, immunizations
- Surveillance and management with cancer survivorship team

Future Directions/Questions

- Long toxicity in NHL/T-cell lymphoma survivors likely unreported
- ?Long term toxicity in older adult survivors
- Influence of CAR-T and/or CRS

- Need for survivorship clinics
- RN/APP lead? But multidisciplinary collaboration is necessary

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