HODGKIN LYMPHOMA

DR. AMRIT KAHLON

HEMATOLOGIST, BC CANCER – ABBOTSFORD CENTER

FEBRUARY 18, 2021

CONFLICT OF INTEREST DISCLOSURE

I have received educational grant funding from Janssen

I have received speakers fees and advisory board honoraria from Janssen, Celgene and Sanofi Genzyme

OBJECTIVES

Review epidemiology and pathogenesis of Hodgkin lymphoma

Review clinical presentation of Hodgkin lymphoma

Recognize diagnostic criteria

Summarize key therapeutic options

Review post-treatment follow-up recommendations

MY QUESTIONS

Do you take care of Hodgkin lymphoma patients in your practice?

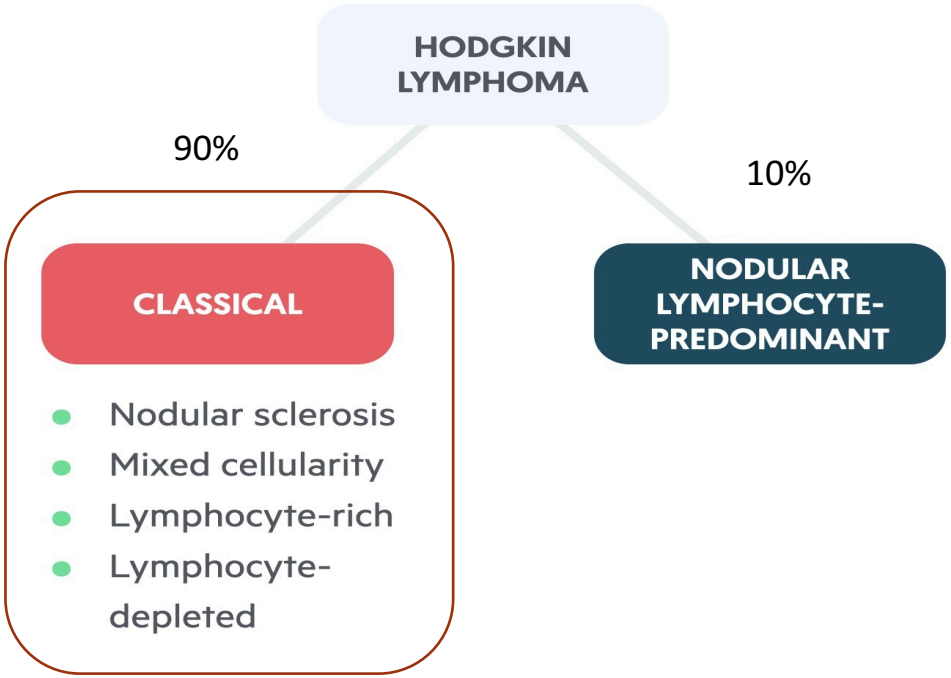
1. Yes
2. No

MY QUESTIONS

What type of care do you provide?

1. Making the diagnosis
2. Discussing the diagnosis
3. Managing acute side effects of chemotherapy
4. Post-treatment follow up care
5. 1 or 2 or 4
6. All of the above

EPIDEMIOLOGY



Overall incidence is low

- Annual age adjusted incidence in populations of European ancestry ~2-3% per 100,000
- HL is one of the most common cancers in young adults

RISK FACTORS

Immunosuppresion
- In the HIV population, cHL is one of the most common non-AIDS defining cancers and is almost always EBV positive
- Autoimmune disorders

Genetic risk factors
- Genome wide association studies in populations of European ancestry have identified 18 genetic risk variants primarily in immune related genes

Familial risk
- 3-5 greater risk with a family history of HL
- Very high incidence in identical twins (~100 fold) compared to fraternal twins

Socioeconomic status
- Higher socioeconomic status associated with NSHL and younger age at diagnosis
- Lower socioeconomic status associated with MCHL and LDHL and older age at diagnosis

EBV
- Varies by age, geographic region, and immuno-competence

Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61
UpToDate. Hodgkin lymphoma: Epidemiology and risk factors.

EPIDEMIOLOGY

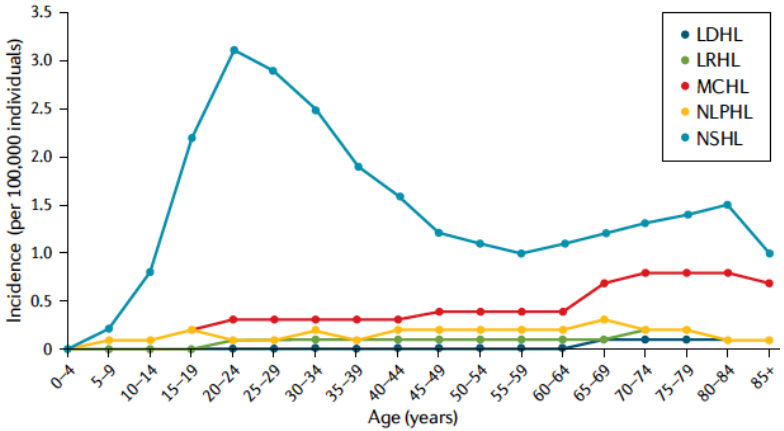


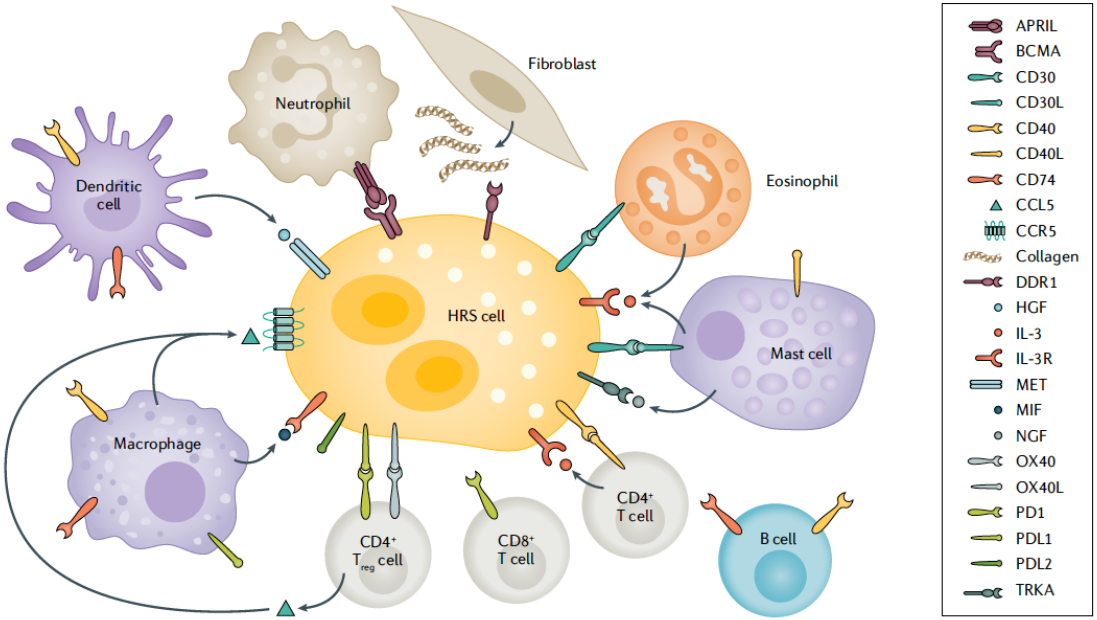
Fig. 2 | **Relationship between age and subtype of Hodgkin lymphoma.** The graph is based on 2000–2015 average annual age-specific incidence rates from the Surveillance, Epidemiology, and End Results (SEER) Program and shows the early and late peaks (the childhood peak cannot be detected on this scale) in nodular sclerosis Hodgkin lymphoma (NSHL) and the late peak in mixed cellularity Hodgkin lymphoma (MCHL). LDHL, lymphocyte-depleted Hodgkin lymphoma; LRHL, lymphocyte-rich Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma.

TRIMODAL AGE SPECIFIC PATTERN

- 15-35 years
  - EBV negative NSHL
  - Associated with high socioeconomic status, European ancestry, and slightly higher incidence in female sex
- Two smaller peaks in age <15 yrs and elderly adults >50 yrs
  - EBV positive MCHL
  - Associated with low socioeconomic status, non-European ethnicity, and male sex

Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61

PATHOPHYSIOLOGY



- Hodgkin and Reed-Sternberg cells
  - Develop from malignant transformation of developing B lymphocytes
- Aberrant autocrine and paracrine signaling by HRS cells
  - Attracts inflammatory tumor micro-environment
- Tumor micro-environment
  - Inflammatory cell infiltrate
  - Support growth and survival of HRS cells
  - Allows immune evasion of tumor cells

Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61
UpToDate. Pathogenesis of Hodgkin lymphoma.

CLINICAL PRESENTATION

Lymphadenopathy
- Supra-diaphragmatic lymphadenopathy
  - Neck – 60-80%
  - Axillary – 30%
  - Inguinal – 10%
- Isolated sub-diaphragmatic lymphadenopathy is uncommon (<10%)
- Mediastinal mass
  - Asymptomatic, cough, SOB, retrosternal chest pain, uncommonly pericardial/pleural effusion or superior vena cava syndrome

Constitutional (”B”) symptoms – 40%
- Fevers (>38C), drenching night sweats, unexplained weight loss of >/=10% of body weight within 6 months
- Pel-Ebstein fever
  - Uncommon but characteristic cyclic rise and fall in fever over 1-2 weeks

Pruritus – 10-15%

Alcohol induced pain - <10%

Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61
UpToDate: Clinical presentation and diagnosis of classical Hodgkin lymphoma in adults

CLINICAL PRESENTATION

Spread is contiguous via lymphatic channels before involving more distant or non-adjacent sites/organs

- Spleen, bone/bone marrow, lung, liver
- Rare – GI, CNS, skin, nephrotic syndrome (minimal change disease)

Laboratory abnormalities

- Anemia
- Hypercalcemia
- Eosinophilia
- Other – lymphopenia, hypoalbuminemia, thrombocytosis, leukocytosis

Disease tempo

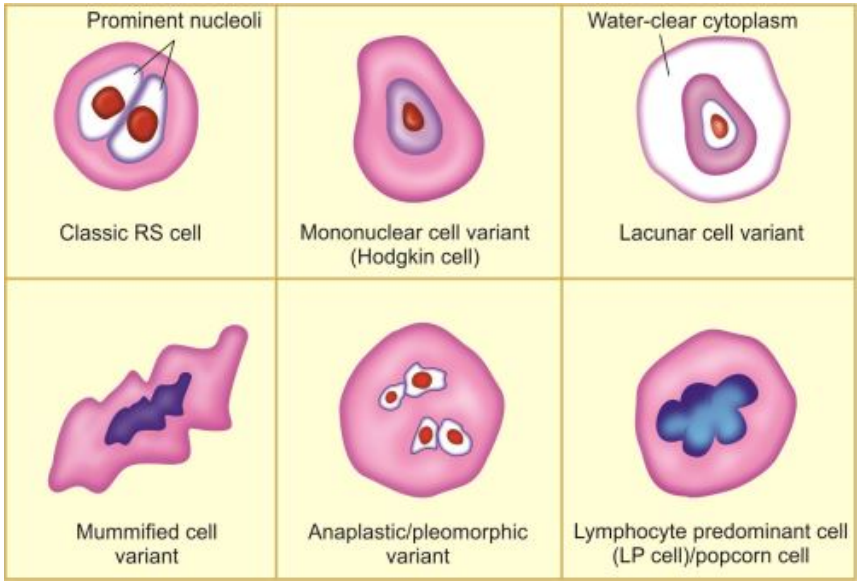
- Slow but can be variable

Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61
UpToDate: Clinical presentation and diagnosis of classical Hodgkin lymphoma in adults

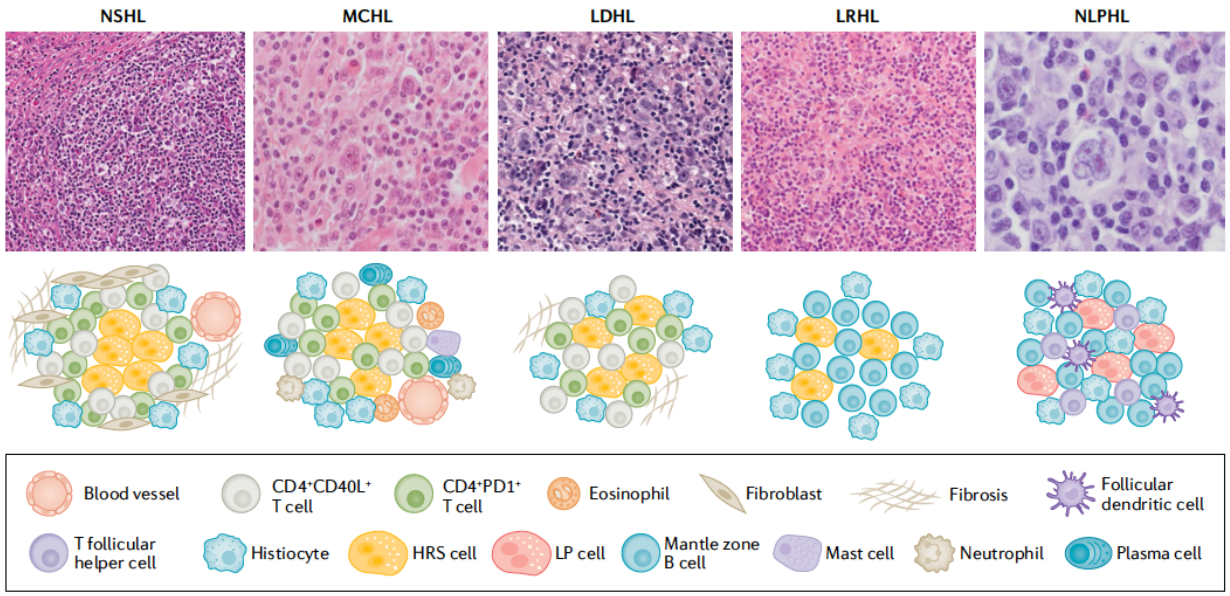
DIAGNOSIS

Lymph node biopsy

- Excisional biopsy preferred to core needle biopsy
- Identification of HRS or LP cells in the proper histological microenvironment
  - HRS variants (mononuclear variants, lacunar cells, necrotic forms, are useful for identifying cHL subtypes
- Immuno-histochemical staining: CD3, CD15, CD20, CD30, CD45, PAX-5, EBV by EBER and LMP1
  - **CD 30 positive, variable CD 15 positive, CD 45 negative**



DIAGNOSIS/CLASSIFICATION



- CLASSICAL HODGKIN LYMPHOMA (90%)
  - Nodular sclerosing HL(NSHL) – 70%
  - Mixed cellularity HL (MCHL) – 20-25%
  - Lymphocyte rich HL (LRHL) – 3-5%
  - Lymphocyte depleted HL (LDHL) – rare
- NON-CLASSICAL HODGKIN LYMPHOMA (10%)
  - Nodular lymphocyte depleted HL (NLPHL)

Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61

STAGING

History and physical (lymphadenopathy, abdominal organomegaly)

Laboratory investigations: CBC, renal, calcium, albumin, liver function tests, HIV, hepatitis B and hepatitis C serology

Imaging

- CT neck, chest, abdomen, and pelvis
- PET scan
  - Upstages 41% of patients from detection of extra-nodal disease especially bone and bone marrow disease
  - Downstages 10% of patients

Bone marrow biopsy

- No longer routinely done if PET scan staging available
- If PET unavailable, bone marrow done if
  - B symptoms
  - WBC < 4 x 10*9/L, HGB < 120 g/L (women), HGB < 130 g/L (men), PLT <125 x 10*9/L

STAGING

Box 2 | **Cotswold modification of the original Ann Arbor staging system for Hodgkin lymphoma**

Stages

Stage I: Single lymph node region (I) or single local extralymphatic site (IE)
Stage II: Two or more lymph node regions on the same side of the diaphragm (II) or one or more lymph node regions with local extralymphatic extension, all on the same side of the diaphragm (IIE)
Stage III: Lymph node regions on both sides of the diaphragm (III), which may be accompanied by local extralymphatic extension (IIIE)
Stage IV: Diffuse involvement of one or more extralymphatic organs or sites

Additional variables

A: Free from the presence of B symptoms (persistent otherwise unexplained fever, night sweats or weight loss of >10% of body weight over 6 months)
B: Presence of any B symptoms
X: Bulky nodal disease: mediastinal nodal mass of one-third or more of the intrathoracic diameter or ≥10 cm in diameter

MANAGEMENT – ABVD CHEMOTHERAPY

Originally developed in 1975

- 4 drug intravenous regimen (doxorubicin, vinblastine, bleomycin, dacarbazine)
- It is delivered as an outpatient every 14 days in 28 day cycles

Alternative chemotherapy regimens

- BEACOPP chemotherapy
  - Developed by the German Hodgkin's Lymphoma Study Group (GHSG)
  - Consists of oral prednisone and IV bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine
  - Compared with ABVD, BEACOPP improves PFS but did not demonstrate a clear OS advantage
    - ABVD vs. BEACOPP: 7 year PFS 73% vs. 85% (p=0.004), OS 84% vs. 89% (p=0.39)
  - Increased toxicity with BEACOPP compared to ABVD
- Stanford V
  - Not commonly used
  - Combines a brief intensive chemotherapy regimen with radiation therapy using less doxorubicin and bleomycin
  - No PFS or OS difference compared to ABVD

Bonadonna G et al. Cancer 1975; 36(1):252.
Viviani S et al. NEJM. 2011;365(3):203.
UpToDate. Initial treatment of advanced (stage III-IV) classical Hodgkin lymphoma

ABVD – SIDE EFFECTS

Neutropenia (34%), nausea/vomiting (13%), alopecia (34%)
- Severe infections (2%), anemia (5%) and thrombocytopenia (3%) are rare

Bleomycin induced pulmonary toxicity (20-30%)
- Develops sub acutely while on therapy or up to six months post treatment
  - Mortality rate of 4.2% and decreased 5 year OS (63% vs. 90%)
- Acute reactions: fever, hyperpyrexia syndrome, anaphylactoid reactions
- Late bleomycin-related pulmonary toxicity – pulmonary fibrosis
  - Risk factors include age >40 yrs, mediastinal radiation, use of GCSF, exposure to high FiO2, cigarette smoking
  - Symptoms include dry cough and shortness of breath on exertion
  - Pulmonary function testing can show a significant decline in DLCO

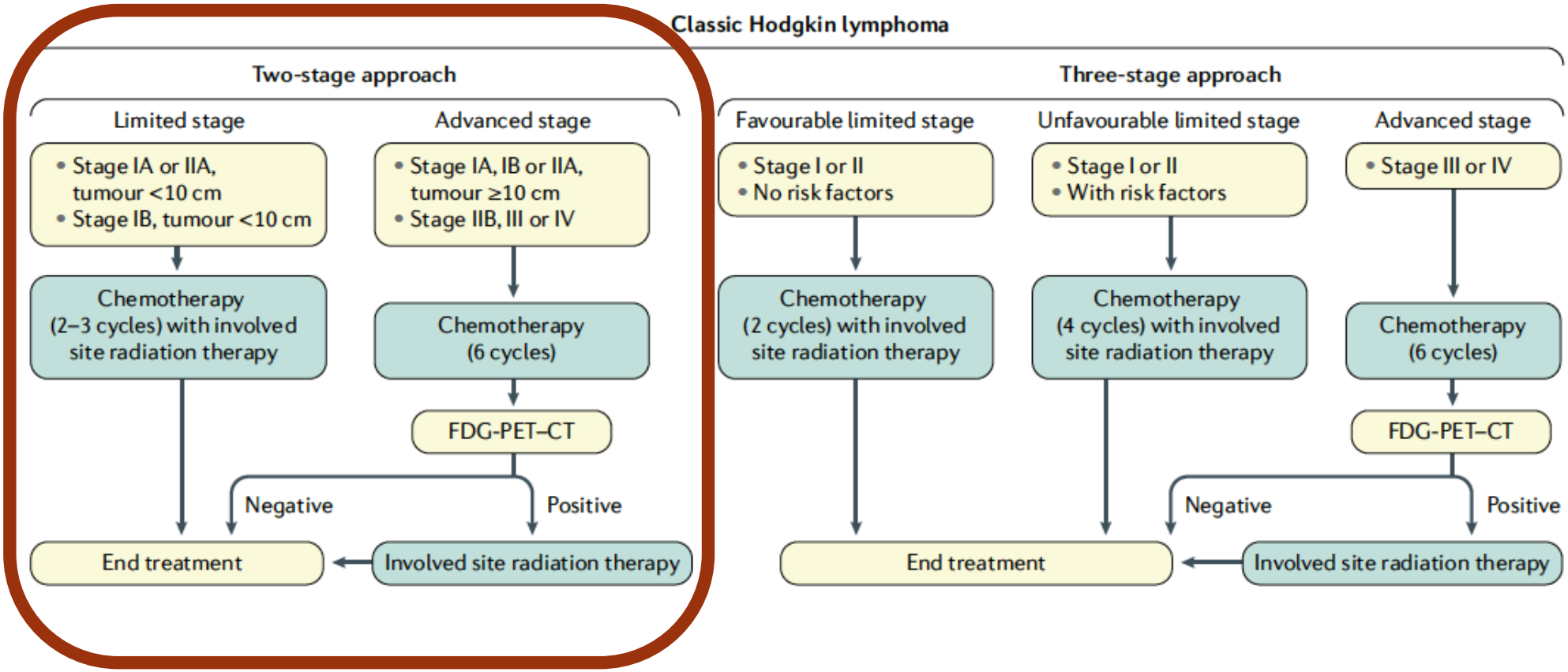
Doxorubicin associated cardiomyopathy
- Associated with total dose >400 mg/m2 (ABVD 6 cycles 300 mg /m2)
- 7.8 x higher risk of myocardial infarction compared to age adjusted normal population

Vinblastine associated peripheral neuropathy

Fertility is generally preserved
- Most studies show a low impact on ovarian reserve and fertility
- Azoospermia and oligospermia tend to recover to normal values post treatment
- Fertility preservation should still be discussed in higher risk patients

.
UpToDate. Initial treatment of advanced (stage III-IV) classical Hodgkin lymphoma

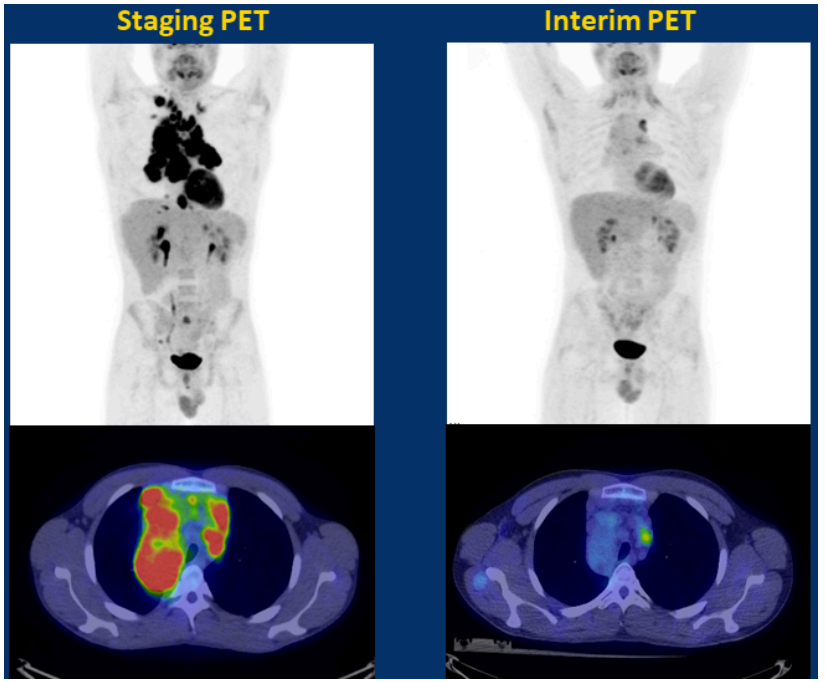
MANAGEMENT – TRADITIONAL



Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61

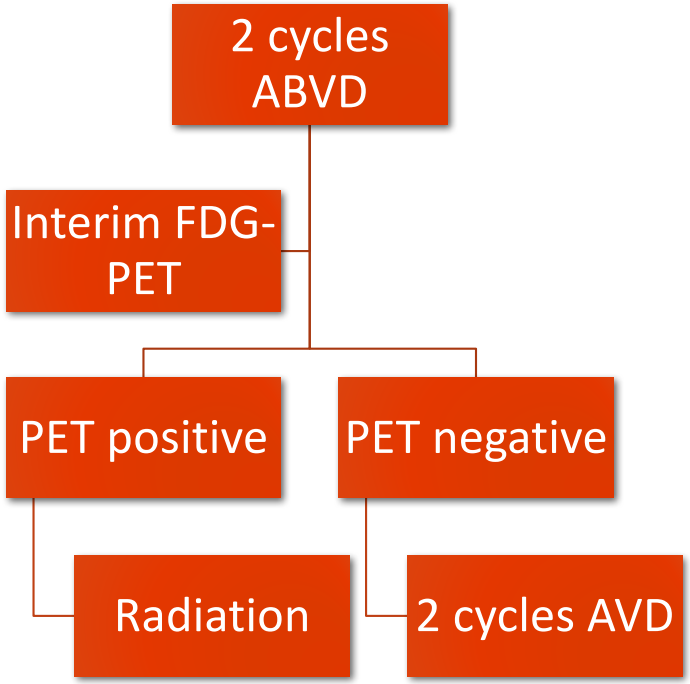
PET ADAPTED APPROACH

- FDG avid PET is used to measure the response after initial brief chemotherapy to identify patients with a high quality response to permit de-escalating intensity of therapy to reduce toxicity
  - Omit radiation
  - De-intensify chemotherapy
- Interim FDG avid PET following 2 cycles of chemotherapy are used in limited and advanced stage disease
- FDG avid PET is used at the end of treatment to distinguish between fibronecrotic debris and active lymphoma in residual masses



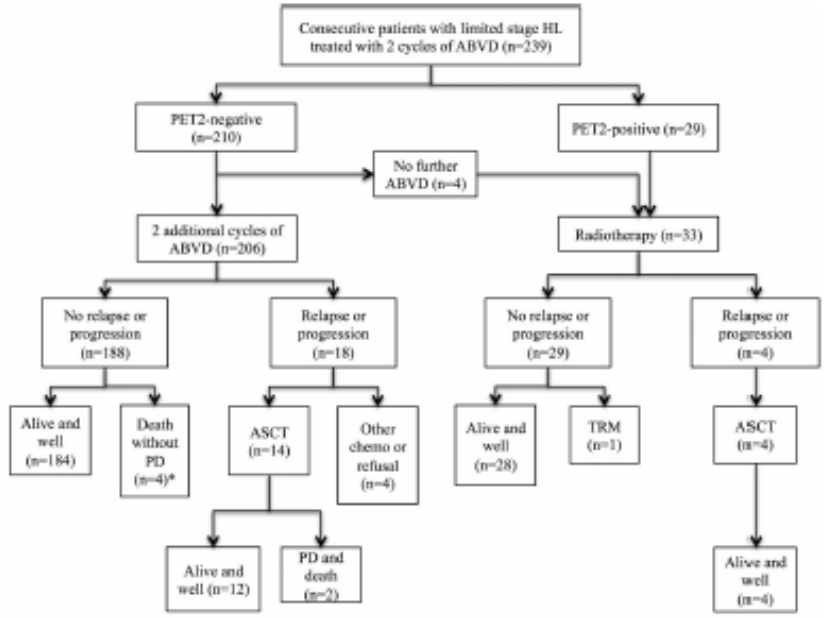
Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61

PET ADAPTED APPROACH LIMITED STAGE DISEASE



- Adopted by BC Cancer in 2005
- Rationale was to minimize the long-term toxicity of radiation for patients with chemosensitive disease
- Retrospective review of BC data from July 2005-April 2016 published December 2018

Interim PET-directed therapy in limited-stage Hodgkin lymphoma initially treated with ABVD



* 3 unrelated, 1 TRM

Figure 1. PET2 results, treatments, and outcomes. HL: Hodgkin lymphoma; PD: progressive disease; ASCT: autologous stem cell transplantation; TRM: treatment-related mortality (i.e., mortality related to ABVD +/- radiotherapy).

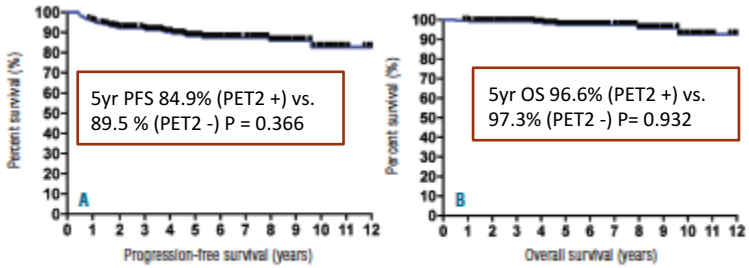
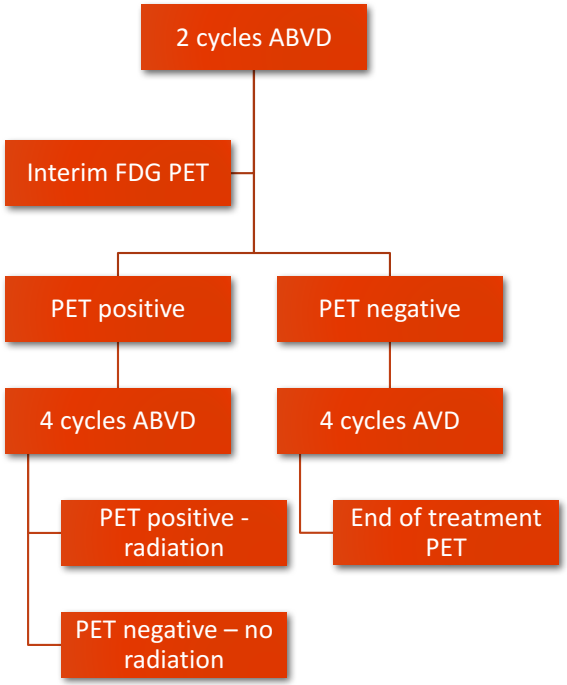


Figure 2. Outcomes for 239 patients with limited stage Hodgkin lymphoma managed with PET2-guided treatment. (A) Progression-free survival. (B) Overall survival.

- 239 prospectively diagnosed limited stage HL
- 88% were PET2 negative post 2 cycles ABVD
- Median follow up of 5.5 years (10 mo – 12 yrs)
  - 22 relapses at a median time to relapse of 14 mo (5 mo – 5.3 yrs), 9% ABVD alone and 12% ABVD + RT
- No statistically significant difference in PFS or OS in PET2 positive and PET2 negative groups

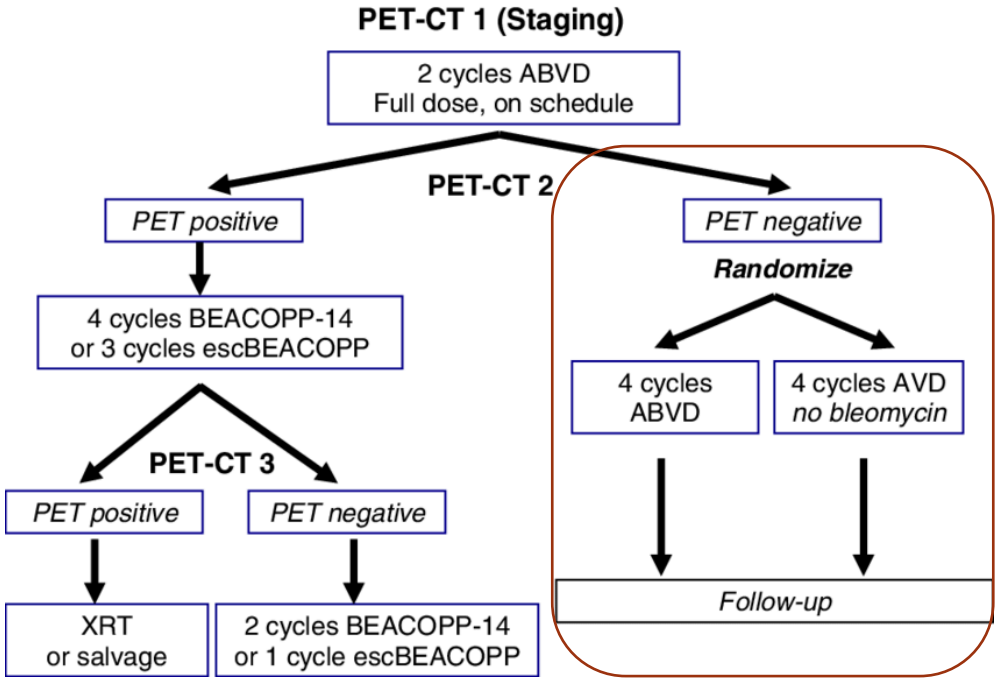
Villa et al. Haematologica 2018;103:e590

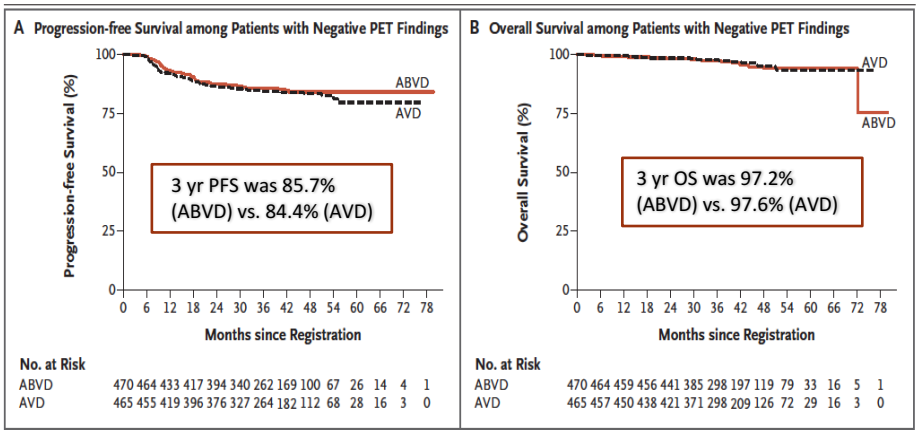
PET ADAPTED APPROAC ADVANCED STAGE DISEAE



- Rationale was to minimize long-term toxicity of bleomycin and radiation for patients demonstrating chemosensitive disease
- Approach based on evidence from Response Adapted Therapy in Hodgkin Lymphoma (RATHL) trial (2016)

Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma





- Prospective trial to test a response adapted approach based on PET2 after 2 cycles ABVD and modifying treatment based on results
- 83.7% of patients had a negative PET2

Johnson et al. NEJM 2016;374:2419-29

PROGNOSIS

Overall approximately 90% of patients in the age range of 16-70 years can anticipate being cured

- 50% of relapsing patients will be cured with HDT/ASCT

Limited stage disease

- Cure rates are 90-95% for non-bulky stage IA or IIA disease
- A risk stratification model for limited stage disease is not commonly used

Advanced stage disease

- Cure rates are 70-80% for advanced stage disease
- International Prognostic Score (IPS) provides validated estimates of probable PFS and OS

VOLUME 30 · NUMBER 27 · SEPTEMBER 20 2012

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

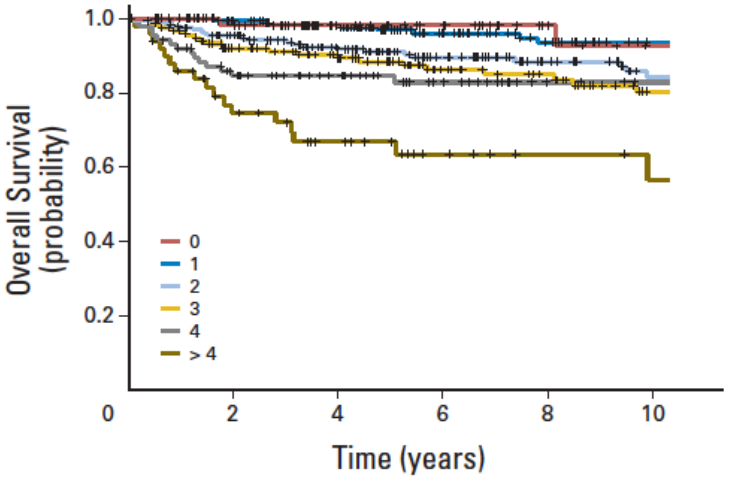
International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: Altered Utility in the Modern Era

Alden A. Moccia, Jane Donaldson, Mukesh Chhanabhai, Paul J. Hoskins, Richard J. Klasa, Kerry J. Savage, Tamara N. Shenkier, Graham W. Slack, Brian Skinnider, Randy D. Gascoyne, Joseph M. Connors, and Laurie H. Sehn

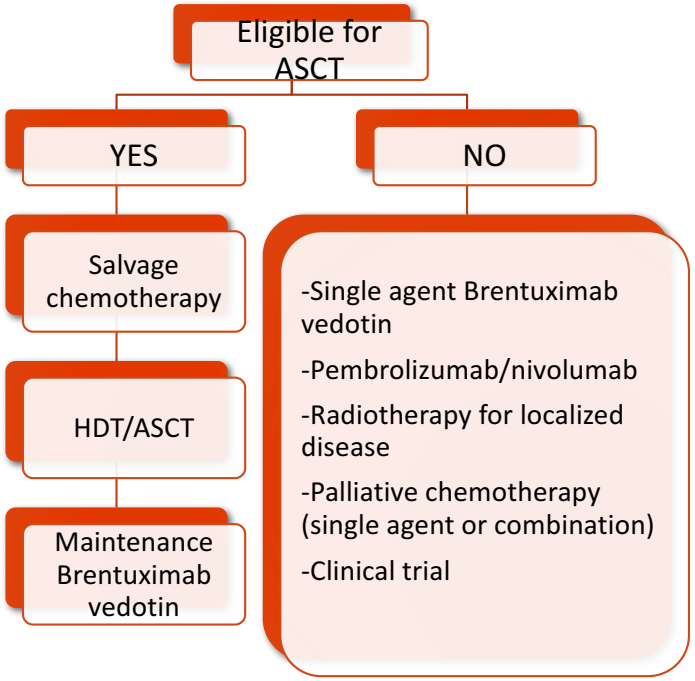
- IPS is the most widely used risk stratification index for HL
- Initially published in NEJM in 1998
  - Is based on patients treated before 1992 with a variety of chemotherapy regimens +/- radiation
  - Predicted 5 yr FFP and OS ranging from 42%-84% and 56%-89% respectively
- BC Cancer validated the score in a more recently treated patient population and published results in 2012
  - Included 740 patients treated between 1980 to 2010
  - The IPS remained prognostic for both FFP and OS
  - 5yr FFP and OS ranged from 62%-88% and 67%-98% respectively

The International Prognostic Score for Hodgkin lymphoma

One point is given for each of the characteristics below present in the patient, for a total score ranging from zero to seven
Serum albumin <4 g/dL
Hemoglobin <10.5 g/dL
Male gender
Age >45 years
Stage IV disease
White blood cell count ≥15,000/microL
Absolute lymphocyte count <600/microL and/or <8 percent of the total white blood cell count



RELAPSED HODGKIN LYMPHOMA



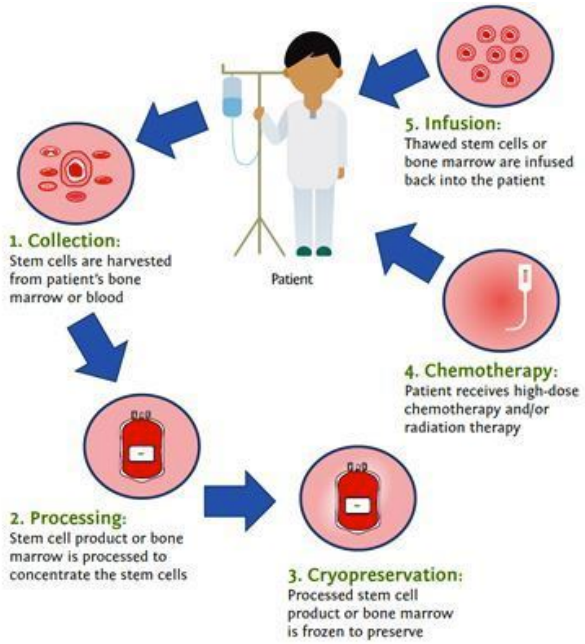
AUTOLOGOUS STEM CELL TRANSPLANT ELIGIBLE HL

- Salvage regimen (GDP, ICE, DHAP)
  - Gemcitabine/dexamethasone/cisplatin most commonly used in BC
  - No head to head trials to establish superiority of one regimen over another
  - 2-3 cycles delivered prior to proceeding with transplant to demonstrate chemo-sensitive disease

- Maintenance Brentuximab vedotin
  - Brentuximab is given IV in 3 week cycles for 16 cycles
  - AETHERA trial: maintenance Brentuximab post ASCT can prevent approximately 1/3 of relapses expected to occur post ASCT

Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61
Moskowitz et al. Blood. Dec 2018. 132(25), 2639.

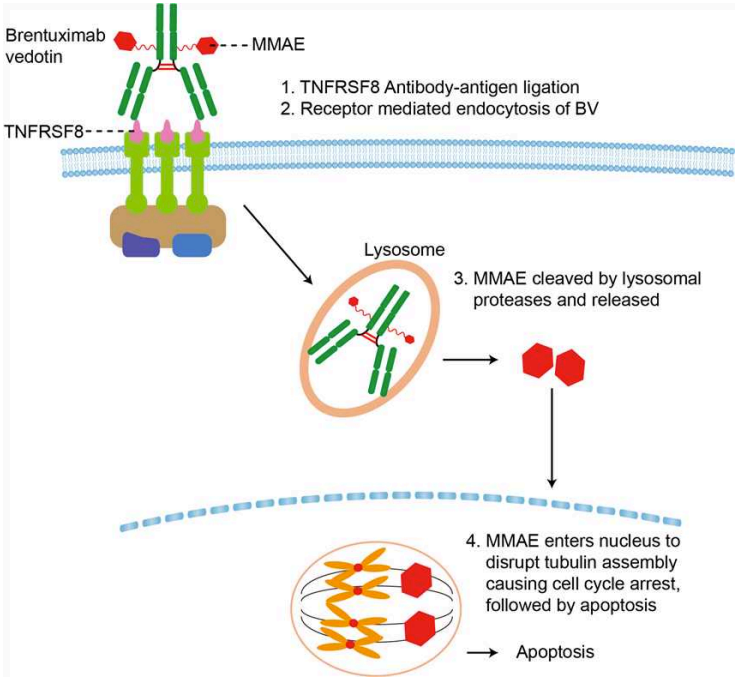
HIGH DOSE THERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT



- A number of HDT regimens are in use
  - BEAM, CBV – none has emerged as superior
- With current supportive care ASCT related mortality is expected be <5%
- Long-term toxicities
  - Infertility in women >25 years and men of any age
  - 5-10% risk of developing second neoplasms
  - Hypothyroidism
- Five independent factors associated with outcome
  - Time to relapse < 3mo, stage IV disease at relapse, performance status (ECOG >!), largest individual tumor $\geq$ 5 cm, lack of CR to second-line chemotherapy

Connors, JM et al. Nature Reviews Disease Primers. 2020. 6:61

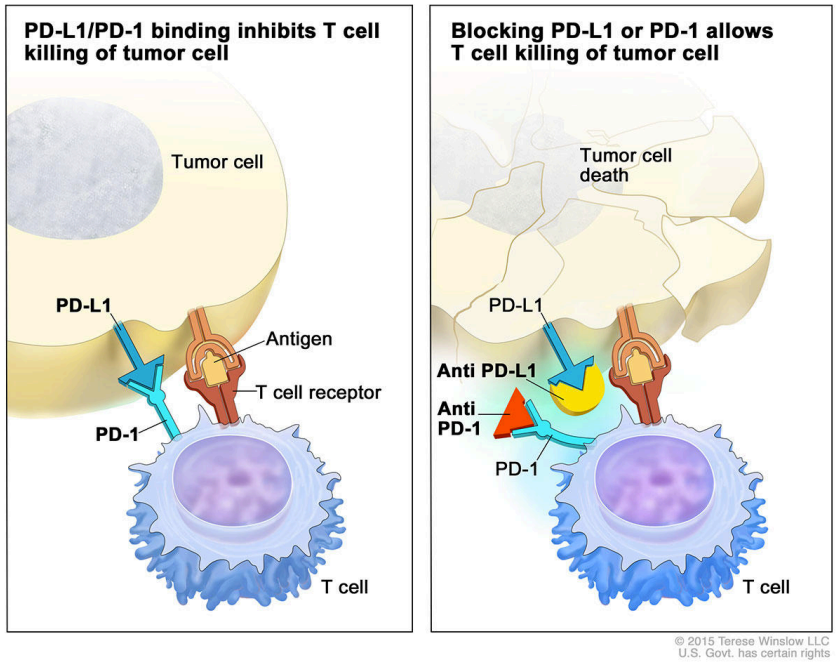
ANTIBODY DRUG CONJUGATES BRENTUXIMAB VEDOITIN



- Approved 2011 for relapse post ASCT
  - ORR 75% and CR 34%
- Maintenance therapy post transplant
  - AETHERA trial
- Newer 1st line combination AVD-Bv for stage III/IV CHL
  - ECHELON-1 trial demonstrated improved 2yr PFS of 82.1% (AVD-Bv) vs. 77.2% (ABVD)
  - Greatest benefit for patients with stage IV or 2 or more sites of extra-nodal involvement
- Main toxicities – peripheral neuropathy

Domingo-Domenech, EVA and Anna Sureda. J Clin Med. 2020 May; 9(5): 1384.

IMMUNE CHECKPOINT INHIBITORS



- Nivolumab and pembrolizumab available for use in Canada
  - Pembrolizumab approved for use up to 2 years
  - Nivolumab approved for use until disease progression or unacceptable toxicity
- Nivolumab being trialed in 1st line treatment with AVD and in combination with brentuximab and AVD and in combination with brentuximab alone in relapsed/elderly setting
- Main toxicities: autoimmune complications

Domingo-Domenech, EVA and Anna Sureda. J Clin Med. 2020 May; 9(5): 1384.

ALLOGENEIC STEM CELL TRANSPLANT

Limited role in Hodgkin lymphoma

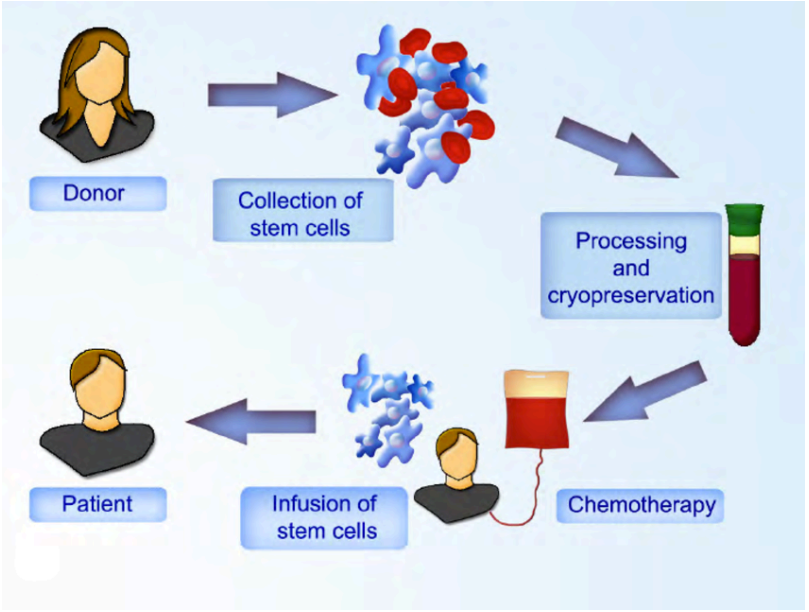
- Higher non-relapse associated mortality (NRM) (>15%)
  - Acute and chronic graft vs. host disease (GVHD)
  - Severe opportunistic infections in the context of GVHD

Remains a reasonable option for selected fit patients

- Only curative strategy for patients with HL that relapse after auto-SCT
- Disease status at transplantation plays the most important role
  - 4 yr PFS and OS was 18% and 41% in the global population
  - 4 yr PFS and OS improved to 40% and 60% respectively for patients allografted with chemosensitive disease

Newer agents such as brentuximab vedotin and the immune checkpoint inhibitors have provided new options for bridging patients to potentially curative allogeneic stem cell transplant

The timing of allogeneic transplant after brentuximab vedotin and immune checkpoint inhibitor therapy remains a topic of discussion



Domingo-Domenech, EVA and Anna Sureda. J Clin Med. 2020 May; 9(5): 1384.

SURVIVORSHIP CARE

RELAPSE SURVEILLANCE

MANAGEMENT OF LONGTERM COMPLICATIONS

RELAPSE SURVEILLANCE

Relapse Surveillance

- 5 year risk of relapse from diagnosis for all patients is 18.1%
  - 72% of relapses occur within the first 2 years of diagnosis
  - The risk of relapse diminishes to 5.6% at 2 years from diagnosis
  - For advanced stage patients remaining relapse free at 2 years, the 5 year risk of relapse is 7.6% and for three years post diagnosis is comparable to limited stage patients at 4.1%
- Patients are now being transitioned to surveillance follow up through their primary care provider at 2 years post completion of treatment
  - Clinic visits every 6 months for year 2-5 post treatment and annually after year 5
    - History
    - Physical exam including lymph node and spleen exam
    - Blood tests (CBC, LFTs, creatinine, LDH, calcium, albumin)
    - Chest x-ray (for patients with thoracic disease) every visit for 2 years and then every other visit (BC recommendation)

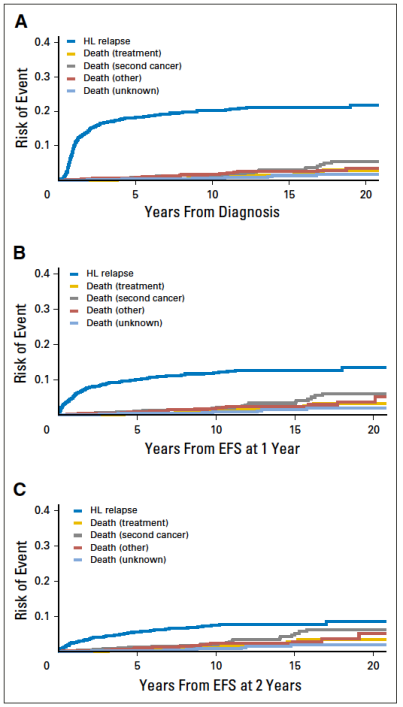


Fig 1. The risk of relapse compared with the risk of death from all causes for all patients with classical Hodgkin lymphoma (HL) at (A) diagnosis (n = 1,402), (B) event-free survival (EFS) at 1 year (n = 1,257), and (C) EFS at 2 years (n = 1,156).

Hapgood et al. J Clin Oncol. 2016. 34:2493-2500
BC Cancer. Cancer management guidelines. Hodgkin lymphoma

LATE COMPLICATIONS OF THERAPY

Secondary malignancies – leading cause of death in survivors of Hodgkin lymphoma

- Increased risk of solid tumors appears approximately 5 years after completing therapy and continues to rise for at least 20 years
  - Lung, colon and breast are most common secondary malignancies
  - Skin, thyroid, esophagus, colon, and sarcomas occur typically in the areas of radiation
  - Solid tumors are more frequent than hematologic malignancies
    - The risk of AML peaks at 5-9 years post treatment
- Screening
  - No general consensus regarding optimal screening program
  - BC recommendations
    - "Although uncommon, certain secondary neoplasms occur with increased frequency in patients who have been treated for Hodgkin lymphoma. These include acute myelogenous leukemia, thyroid, breast, lung and upper gastrointestinal carcinoma and melanoma and cervical carcinoma-in-situ. It is appropriate to screen for these neoplasms for the rest of the patient's life because they may have a lengthy induction period."
    - Annually
      - TSH level (only if thyroid irradiated)
      - Mammography for women beginning 10 years after diagnosis of Hodgkin lymphoma or at age 40 years, whichever comes first
      - Pap smear

UpToDate. Approach to the adult survivor of classical Hodgkin lymphoma.
BC Cancer. Cancer management guidelines. Hodgkin lymphoma

LATE COMPLICATIONS OF THERAPY

Cardiovascular disease – most common non-malignant cause of death

- Coronary artery disease, valvular disease, pericardial disease, arrhythmia, cardiomyopathy, and peripheral artery disease
- Increased risk emerges soon after completion of treatment and remains elevated for the survivors lifetime
- Risk factors
  - Pre-existing heart disease is the most significant predictor of post-HL therapy cardiac complications
  - Others: chemotherapy (doxorubicin), radiation therapy, traditional cardiac risk factors
- Screening
  - Cardiac exam and auscultation for heart murmurs, carotid bruits
  - Screening and management of cardiac risk factors
    - Blood pressure monitoring, screening for diabetes, dyslipidemia
    - Smoking cessation
    - Nutritional counselling/obesity control
  - Counsel patients to report symptoms such as fatigue

LATE COMPLICATIONS OF THERAPY

- Significant psychosocial impact which can be persistent and severe
  - Cognitive
  - Emotional functioning
  - Role functioning
  - Social functioning
  - Fatigue
  - Dyspnea
  - Sleep disturbance
  - Financial problems
- Impact can be influenced by baseline impact and age
  - Higher tumor burden at associated with impaired baseline scores
  - Impact is independent of chemotherapy type
- More literature is required to better assess the long-term psychosocial impact of cancer treatment

Kreissl, S et al. JCO. 2020. 38(25). 2839.


QUESTIONS