Welcome!

• To join the call dial (866) 740-1260, passcode 3754894#.
• All participants are placed on mute for the duration of the webinar.
• If you have questions, type them in the chat box at the bottom left hand side of your screen. They will be answered at the end of the presentation.
• This conference is being recorded for future use.
• The recording will be made available on the ASPHO website afterwards.
Dilemmas and Decisions in Limited Stage Hodgkin Lymphoma
Frank Keller, MD and Kara Kelly, MD
Hodgkin Lymphoma

- HL affects 4,960 men and 4,100 women in the US
  - Accounts for 1,190 deaths/year
- Most common AYA cancer
  - Age 0-14: 380 (4%)
  - Age 15-19: 800 (15%)
- Tendency to occur in the productive years of life
  - Considerable source of cancer related morbidity and mortality
Cure rates for Hodgkin Lymphoma are among the highest for pediatric oncology: SEER: 5 yr Survival 96% ± 0.4%
Overall survival in 5-year survivors of childhood Hodgkin lymphoma by sex


©2011 by American Society of Hematology
Survivors of Pediatric HL Experience Significant Morbidity as Adults

• Childhood Cancer Survivor Study
  – Survivors (n=10,397) HL 1,876 (18%)
  – Siblings (n=3,034)

• Relative Risk of a Chronic Health Condition among HL subset
  – Grade 1-4: 4.6 (4.2–5.1)
  – Grade 3-4: 10.2 (8.3–12.5)
  – ≥2 Conditions: 8.7 (7.4–10.2)

Major Challenges

• The major challenge in Hodgkin Lymphoma is to optimize the balance between overall survival and treatment related toxicity as:
  – More than 90% of patients are cured with risk-based combined-modality therapy, yet these therapies are frequently associated with risks for significant long term toxicities;
  – Innovative approaches are needed for those patients who have a high risk of failure with current therapies.
Many Unresolved Issues

• No consensus chemotherapy or radiotherapy approach
• No standard risk stratification
• Imaging standards outdated and lacking evidence
• Biology not advanced enough to guide treatment, even in retrieval setting
• Poor predictors of risk for acute and late effects
Histologic Subtypes

• **Classical** (85-90%)
  (CD15+, CD20-, CD30+, CD45-)
  – **Mixed cellularity** (30%)
  – **Nodular sclerosis** (Children 40%, Adolescents/Young Adults 70%)
  – Lymphocyte depletion - rare, HIV
  – Lymphocyte rich

• **Nodular Lymphocyte Predominant** (10-15%)
  (CD15-, CD20+, CD30-, CD45+)
  – Males, <10 years old
  – Localized disease

WHO/Updated REAL Classification
Schematic of the crosstalk between malignant Hodgkin Reed-Sternberg (HRS) cells and the tumor microenvironment in classical Hodgkin's lymphoma.

Steidl C et al. JCO 2011;29:1812-1826
Biomarkers in Diagnostic FFPET

**HRS Cell**
- EBV positive (≥ 45 years old)
- IHC: BCL2 positive
- IHC: Cytotoxic molecules positive
- IHC: MHC class II
- IHC: γc-MET
- IHC: HGal
- IHC: Topo-IIα
- IHC: COX2
- FISH: ABCC1 amplified
- RNA ISH: CSF1R positive

**Whole Biopsy**
- qRT-PCR: 11 genes

**Tumour Microenvironment**
- Treg cells
  - IHC: FoxP3
- CTL/NK cells
  - IHC: TIA-1
  - IHC: GzB
- B cells
  - IHC: CD20
  - IHC: BCL11A
- FDCs
  - IHC: CD21
- Macrophages
  - IHC: CD68
  - IHC: CD163

**IHC:**
- FoxP3
- Galectin-1
- TIA-1

Ann Arbor Staging

I: 1 lymph node region or single extra-lymphatic organ or site

II: Multiple regions or sites on 1 side of diaphragm

III: Multiple regions or sites on 2 sides of diaphragm

IV: Marrow, liver, lung, bone – not by direct extension

“E” : direct extension from node to adjacent extranodal tissue

**Bulk:** Mass/thoracic diameter>0.33
    - Nodal area >6 cm

“B” : Drenching night sweats, fever, 10% weight loss
## What Do We Consider Low Risk HL?

<table>
<thead>
<tr>
<th>Region</th>
<th>Risk</th>
<th>IA</th>
<th>IB</th>
<th>IIA</th>
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<th>IIIA</th>
<th>IIIB</th>
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<td>Consortium</td>
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E = Extranodal extension  
X = Bulky disease (peripheral > 6cm and mediastinal);  
mX = mediastinal bulk
Childhood Hodgkin International Prognostic Score (CHIPS) = sum of Stage 4 + Mediastinal Mass + Low Albumin + Fever

AHOD0031, by CHIPS1

Survival Distribution Function

STRATA: chips1=0 Censored chips1=0 chips1=1 Censored chips1=1 chips1=2 Censored chips1=2 chips1=3 Censored chips1=3

The world's childhood cancer experts

- Schwartz C et al, SIOP 2011; ASH 2011
Interim PET is predictive of outcome with ABVD – Impact in other treatment regimens is less clear

- Timing
- Definition of Response
- Variability – Need for central review
- Additive Role of Anatomic Response

*J Nucl Med May 1, 2013 vol. 54 no. 5 683-690*
# 5 Point Scale for Interpretation of Interim FDG-PET

<table>
<thead>
<tr>
<th>Score</th>
<th>PET/CT Result</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>No uptake above background</td>
</tr>
<tr>
<td>2</td>
<td>Uptake ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake &gt; mediastinum but ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>Uptake moderately increased compared to the liver at any site</td>
</tr>
<tr>
<td>5</td>
<td>Uptake markedly increased compared to the liver at any site</td>
</tr>
<tr>
<td>X</td>
<td>New areas of uptake unlikely to be related to lymphoma</td>
</tr>
</tbody>
</table>

![Images of PET/CT results](image_url)

- **Score 4**  
  Uptake > Liver  
  Positive by Deauville 5PS
- **Score 3**  
  Uptake ≤ Liver  
  Negative by Deauville 5PS

COG: 5-point Scale is More Predictive

Interim therapy PET (PET2) response assessment using 5-point score visual Deauville criteria, using PET score ≥ 4 (>reference liver) as PET positive.

Event-free survival (EFS) according to treatment groups (TGs)

Mauz-Körholz C et al. JCO 2010;28:3680-3686
Recent Trials Including Low-Risk Classical Hodgkin Lymphoma

- Stanford, Dana Farber, St. Jude consortium,
  - VAMP, Donaldson: *J Clin Oncol*, 2002*
  - VAMP, Metzker: *JAMA*, 2013*
- French Society of Paediatric Oncology,
  - VBVP, Landman-Parker: *JCO*, 2000
- German Society of Paediatric Oncology,
  - OPPA, Schellong: *JCO*, 1999
  - OPPA/OEPA, Mauz-Korholtz: *JCO*, 2010*
- Children’s Oncology Group,
  - COPP/ABV Hybrid, Nachman: *JCO*, 2002*
  - DBVE, Tebbi: *Pediat Blood & Cancer* 2006*
  - AVPC, Keller: *Blood*, 2010 (Abstract)*
  - ABVE-PC, Friedman: *JCO*. 2014*
- UK NCRI Lymphoma Clinical Studies Group
  - ABVD, Radford, Blood, 2012 (Abstract)*
- EORTC/LYSA/FIL,
  - ABVD, Raemaekers: *JCO*, 2014*
VAMP + IFRT

- Eligibility: Stage I and II, No mediastinal bulk, age <21, No peripheral Node > 6 cm.
- VAMP: Vinblastine, Doxorubicin, Methotrexate, Prednisone on 28 day cycle x 4
- RT: 15 Gy IFRT for CR (2 cycle), 25 Gy for others
- CR: disappearance of all measurable or assessable disease by CT scan.

VAMP + IFRT

• Patients:
  – n=110, median age 13 yrs
  – Histology: classical HL: 70%, NLPHEL: 30%
  – 4.5% with systemic symptoms

• Outcomes:
  – CR Rate after 2 cycles: 45%
    • cHL-30%, NLPHEL-84%
  – 10 yr EFS/OS 89.4%/96.1%
  – EFS: NLPHEL: 100%, cHL: 85.4% (p=0.04)
    • EFS for CR 95%, others 84.5% (p=0.02)

Overall survival (OS) and event-free survival (EFS) distributions for lymphocyte predominant Hodgkin's disease (LPHD; n = 33) versus classical Hodgkin's disease (HD; n = 77) of children with low-risk Hodgkin's disease treated with vinblastine, doxorubicin, ...
VAMP Subsequent Study

• Eligibility: IA and IIA without mediastinal bulk, no more than 3 sites of disease,

• CR: included PET or Gallium, 75% reduction of the lesions or return of nodes to normal size.

• Treatment: VAMP X 4. CR after 2 cycles: no RT, others 25.5 Gy IFRT

• Outcomes:
  – 64% were cHL, 36% NLPHL
  – CR rate: cHL- 37.5%, NLPHL- 81%
  – cHL(n=56) 5 yr EFS/OS = 89.1%/100%
  
Figure Legend:
Complete Response (n = 47) vs less than complete response (n = 41) after treatment with vinblastine, doxorubicin, methotrexate, and prednisone (VAMP) with or without low-dose, involved-field radiotherapy. Curves have been truncated at 8 years. The P value was derived using Cox proportional hazards regression. Error bars indicate 95% CIs.
Recent Trials Including Low-Risk Classical Hodgkin Lymphoma

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OPPA/OEPA (GPOH HD 2002)

• TG1:
  – Stages IA, IB and IIA

• OPPA (girls) or OEPA (boys) x2
  – Vincristine, Prednisone, Procarbazine and Doxorubicin or Etoposide to substitute for Procarbazine on a 4 week cycle

• RT: 19.8 Gy IFRT, (boosts to 30 and 35Gy) if < CR after chemotherapy

• CR: Volume reduction > 95%

OPPA/OEPA (GPOH HD 2002)

• Patients:
  – TG1: n=195
  – Median age 14 years.
  – NLPHEL excluded from analysis

• Outcomes:
  – CR rate after 2 cycles: 30%
  – 5 yr EFS/OS for TG1: 92%/99.5%
    • No difference in no RT and IFRT.

• OEPA now standard for girls and boys.

Recent Trials Including Low-Risk Classical Hodgkin Lymphoma

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COPP/ABV Hybrid (CCG 5942) +/- IFRT

- Group 1: Stage IA, IB or IIA
  - No hilar adenopathy, less than four nodal regions; no mediastinal bulk or node or nodal aggregate > 10 cm.

- COPP/ABV hybrid x 4:
  - Cyclophosphamide, Vincristine, Prednisone, Procarbazine, Doxorubicin, Bleomycin and Vinblastine on a 4 week cycle

- RT: Randomization +/- 21 Gy IFRT for those in CR after 4 cycles of chemotherapy.

- CR: At least 70% decrease in tumor volume, and resolution of Gallium avidity.

COPP/ABV Hybrid (CCG 5942) +/- IFRT

• Patients:
  – Group 1: n=294
  – NLPHL ~ 9% of total cohort, proportion in Grp 1 not stated

• Outcomes:
  – 83% CR after chemotherapy for entire cohort, Grp1 not reported (~80%)
  – Grp 1: 3 & 10 yr EFS/OS:
    • Overall: 95%/100%
    • As randomized: no RT: 91%/100%  IFRT: 97%/100%
    • As treated:    no RT: 89%/100%  IFRT: 100%/100%

Recent Trials Including Low-Risk Classical Hodgkin Lymphoma

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DBVE (POG 9426) + IFRT

- Eligibility: IA, IIA, IIIA\textsubscript{1}, without mediastinal bulk
- DBVE: Doxorubicin, Bleomycin, Vincristine, Etoposide on a 4 week cycle. Randomized to +/- dexrazoxane
- RT: 25.5 Gy IFRT after 2 (CR) or 4 cycles of chemotherapy.
- CR: disappearance of all areas of active disease
  - included a negative gallium scan.
  - Mediastinum < 50% original size

DBVE (POG 9426) + IFRT

- **Patients:**
  - n=255, median age 13 years
  - Histology: classical HL 89%, LPHL 11%

- **Outcomes:**
  - 45% CR after 2 cycles and proceeded to IFRT
  - 8 yr EFS/OS: 86.3%/96.5%
  - No difference in early responder vs. slow responder

AVPC (AHOD0431)

- Eligibility: IA, IIA,
  - no mediastinal bulk, no peripheral LN conglomerate > 6 cm

- AVPC:
  - Doxorubicin, Vincristine, Prednisone, Cyclophosphamide
give on a 3 week schedule

- RT:
  - 21 Gy IFRT if less than CR after 3 cycles of chemotherapy

- CR:
  - 80% decrease in axial plane,
  - resolution of PET or Gallium scan
AVPC (AHOD0431)

• Patients: n=278
  – cHL only

• Outcomes
  – CR after 3 cycles: 63%
  – 4 yr EFS/OS 79%/99.6%
  – 4 yr EFS: MC 95.1%, NS 75.6% (p=0.0099)
    • 69% of MC histology achieved CR after chemotherapy alone
  – 4 yr ITFS: 89%

EFS by CR vs. PR

- **CR**: 4 yr EFS 78%
- **PR**: 4 yr EFS 83%

EFS: PET 1 Positive vs. Negative

PET1 Positive: 4 yr EFS 68%

PET1 Negative: 4 yr EFS 88%

Keller, et al. 2013 Haematologica : 98(s2);37
## Recent Trials Including Low-Risk Classical Hodgkin Lymphoma

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ABVE-PC (AHOD0031)

• Eligibility:
  – IA and IIA with bulk, IB, IIB, IIIA and IVA

• ABVE-PC
  – Doxorubicin, Bleomycin, Vincristine, Etoposide, Prednisone and Cyclophosphamide on a 3 week schedule
  – Additional randomization +/- DECA for SER patients

• RT:
  – 21 Gy IFRT if not RER at 2 cycles (60% decrease in axial plane) and CR at 4 cycles (80% decrease in axial plane and PET or Gallium negative)
  – RER/CR randomized +/- 21 Gy IFRT if RER/CR

Friedman, et al. 2014. JCO 32: 3651-3658
ABVE-PC (AHOD0031)

- **Patients**: n=1734
  - Classical and NLPHL included (5.7%)

- **Outcomes**
  - 4 yr EFS/OS: 85%/97.8%
  - 79% RER, 44% RER and CR
  - 4 yr EFS for +/- IFRT: 87.9%/84.3%
  - 4 yr EFS for RER/SER: 86.9%/77.4%
  - 4 yr EFS for Stage I: 91.2%, for stage II 84.7%

Friedman, *et al.* 2014. JCO 32: 3651-3658
# Recent Trials Including Low-Risk Classical Hodgkin Lymphoma

<table>
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Phase III RAPID Study Design

Eligibility (n = 602)

Histologically confirmed classic HL
Stage IA/IIA by CT scan
No mediastinal bulk or B symptoms
No prior treatment

ABVD x 3 cycles
Response
PET scan (n = 571)

4th cycle ABVD then IFRT

PET +ve (n = 145)
IFRT 30 Gy (n = 209)†

PET -ve (n = 420)*
No further treatment (NFT) (n = 211)

* 6 pts not randomized
† 25 pts did not receive treatment

# Events at a Median Follow-Up of 48.6 Months

<table>
<thead>
<tr>
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<th>PET−, IFRT (n = 209)</th>
<th>PET−, NFT (n = 211)</th>
<th>PET+ (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive without PD</td>
<td>194 (92.8%)</td>
<td>190 (90.0%)</td>
<td>125 (86.2%)</td>
</tr>
<tr>
<td>PD</td>
<td>8 (3.8%)</td>
<td>20 (9.5%)</td>
<td>12 (8.3%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>7 (3.3%)</td>
<td>1 (0.5%)</td>
<td>8 (5.4%)</td>
</tr>
</tbody>
</table>

- 74.6% pts PET-negative after 3 cycles of ABVD

PFS in the PET-Negative Population

3-year PFS: 94.5% vs 90.8%
HR 1.51 in favor of IFRT, \( p = 0.23 \)

3-year PFS: 97% vs 90.7%
HR 2.39 in favor of IFRT, \( p = 0.03 \)

## Recent Trials Including Low-Risk Classical Hodgkin Lymphoma

<table>
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<th>Trial Details</th>
<th>EFS/OS</th>
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Study design of European Organisation for Research and Treatment of Cancer, Lymphoma Study Association, and Fondazione Italiana Linfomi H10 20551 trial of patients age 15 to 70 years with untreated supradiaphragmatic clinical stage I/II Hodgkin lymphoma (ex...)

Raemaekers J M et al. JCO 2014;32:1188-1194
EORTC H10 Trial

• Patients:
  • N=1137 (444 Favorable, 693 Unfavorable)

– Design:
  • Non-inferiority design

– Outcomes:
  • Favorable: 85.8% negative PET after 2 cycles
    – 1 yr PFS: Standard 100%, Experimental 94.9%
  • Unfavorable: 74.8% negative PET after 2 cycles
    – 1 yr PFS: Standard 97.3%, Experimental 94.7%
  • Interim futility analysis showed statistical significance for PFS in both favorable and unfavorable early PET-negative groups

Raemaekers, et al. 2014. JCO 32:1188-1194
# Recent Trials Including Low-Risk Classical Hodgkin Lymphoma

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Limited Stage Classical Hodgkin Lymphoma

• Conclusions:
  – There is no standard of care established for limited stage pediatric classical HL.
  – Most recent pediatric trials have delivered IFRT to the majority of limited stage patients.
  – Early response assessment is promising as a way to predict sufficiency of chemotherapy
    • Optimal modality and timing of response assessment is not determined and may vary by treatment regimen
  – The balance between optimal EFS and long term morbidity/mortality remains undefined and may vary with treatment regimen.
Limited Stage Classical Hodgkin Lymphoma

• Conclusions:
  – In our opinion, acceptable standards of care for the treatment of children and adolescents with limited stage, low risk cHL include:
    • ABVE-PC as per AHOD0031
    • VAMP with no RT for CR after 2 cycles
    • OEPA with no RT for CR after 2 cycles
    • ABVD x 3 with no RT for CR after 3 cycles (UK RAPID)
  – Limited Stage Mixed Cellularity HL may be treated with AVPC x 3 and IFRT for the approximately 30% that are not CR after chemotherapy
Limited Stage Nodular Lymphocyte Predominant Hodgkin Lymphoma

- NLPHL tend to do well on limited stage trials in pediatrics:
  - VAMP, Donaldson: *J Clin Oncol*, 2002:
    - EFS: NLPHL 100%, cHL 85.4%
    - POG experience- OS 100%
    - CCG5924 EFS: NLPHL 97%, cHL 84%
Limited Stage Nodular Lymphocyte Predominant Hodgkin Lymphoma

• Surgery only:
  – Mauz-Korholtz: *Cancer* 2007
    • PFS after surgical CR 67%
  – Appel: *Klin Padiatr* 2014 (Abstract O_10)
    • IA, IIA, no bulk. N=185
    • 4yr EFS after single node surgical CR 79% (28% of total)
    • AVPC x 3 for IA with surgical residual or IIA or recurrence after observation:
      – 4 yr EFS 86.8%.
      – 8% required IFRT after AVPC x 3
Limited Stage Nodular Lymphocyte Predominant Hodgkin Lymphoma

• Conclusions
  – Single node completely resected disease may be observed
  – Limited disease without adverse features may be treated with AVPC x 3, with possible RT for minority that do not achieve remission
  – More advanced disease usually treated according to an appropriate Hodgkin protocol.
THANK YOU!

QUESTIONS?
Please type them in the chat box at the bottom left hand side of your screen.
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Diagnostic Pearls in Vascular Anomalies

Wednesday, April 8, 2015
3pm CST

For more information about the upcoming webinars and other ASPHO webinars, visit www.aspho.org/webinar
ASPHO’s 2015 Annual Meeting

Registration is now open!

ASPHO’s 28th Annual Meeting

May 6-9, 2015
Phoenix, AZ

For more information about the upcoming annual meeting, visit www.aspho.org/meetings/annual-meeting/2015/overview