Update on Hodgkin Lymphoma

Matthew J Matasar, MD, MS
Physician, Lymphoma and Adult BMT Services
Director, Lymphoma Survivorship Clinic
Memorial Sloan Kettering Cancer Center
New York, NY

Welcome and Introductions
Update on Hodgkin Lymphoma

Disclosures
Matthew J Matasar, MD, MS is on the Advisory Board and has received research grants from Genentech and Spectrum Pharmaceuticals.

Update on Hodgkin Lymphoma

Dr. Matt Matasar
Assistant Member, Lymphoma and Adult BMT Services
Medical Director, Lymphoma Survivorship Clinic
Memorial Sloan Kettering Cancer Center
@drmatasar
Roadmap

Overview of Hodgkin lymphoma

Treatment of newly diagnosed Hodgkin lymphoma

Treatment of relapsed or refractory disease

Emerging and novel therapies

Survivorship care

In The Beginning…

(1798-1866)
What are the signs of Hodgkin lymphoma?

- Non-tender lymph nodes enlargement (localized)
  - Neck, collarbone, armpit most commonly
  - Middle of chest (mediastinum) on X-rays or scans
  - Groin or pelvis less common
- “B symptoms”
  - Recurring fevers
  - Drenching night sweats
  - Unexplained weight loss (10%)
- Other symptoms
  - Fatigue, itchiness without rash
  - Cough, chest pain, or shortness of breath
  - Aching pain in chest or areas of swollen nodes after drinking alcohol
### “Staging” Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Stage : Favorable</td>
<td></td>
<td></td>
<td>Advanced Stage</td>
</tr>
<tr>
<td>Early Stage : Unfavorable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Roadmap

- Overview of Hodgkin lymphoma
- Treatment of newly diagnosed Hodgkin lymphoma
- Treatment of relapsed or refractory disease
- Emerging and novel therapies
- Survivorship care
Treatment of Hodgkin lymphoma

Early stage favorable HL
GHSG: HD10 Study

1,190 patients with early stage (stage I/II), no risk factors


**RAPID trial**

Stage I/II, no bulk, no B symptoms

- ABVD x3
- PET (central lab)
  - PET + Deauville 3-5
  - PET - Deauville 1-2

- ABVD x1 ➔ IFRT
- Randomization
  - IFRT, 30 Gy
  - No further treatment

“Deauville” criteria for PET scan results

<table>
<thead>
<tr>
<th>Score</th>
<th>FDG-PET / CT scan result</th>
</tr>
</thead>
<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 more than liver uptake, at any site</td>
</tr>
<tr>
<td>5</td>
<td>Markedly increased uptake at any site or new sites of disease</td>
</tr>
</tbody>
</table>

(For RAPID: Score of 1 or 2 = PET negative)

RAPID’s results in the PET-negative patients

PFS

A. Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Progression-free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>36</td>
<td>70</td>
</tr>
<tr>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>72</td>
<td>40</td>
</tr>
<tr>
<td>84</td>
<td>30</td>
</tr>
<tr>
<td>96</td>
<td>20</td>
</tr>
<tr>
<td>108</td>
<td>10</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
</tr>
</tbody>
</table>

Rate ratio, 1.52 (95% CI, 0.84–1.89)
p = 0.26

OS

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>36</td>
<td>70</td>
</tr>
<tr>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>72</td>
<td>40</td>
</tr>
<tr>
<td>84</td>
<td>30</td>
</tr>
<tr>
<td>96</td>
<td>20</td>
</tr>
<tr>
<td>108</td>
<td>10</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
</tr>
</tbody>
</table>

Rate ratio, 0.33 (95% CI, 0.15–1.08)
p = 0.7

PET scans identify a group of patients with favorable early-stage Hodgkin lymphoma with an excellent outcome after ABVD x 3...but cure rate may be slightly lower than more definitive therapy.

How should patients with relapsed disease after “RAPID” treatment be managed?
Treatment of advanced stage HL

ABVD x 6

- CR
- PR (PET -)
- PR (PET +)
- Special cases residual (PET +)

Observation
Observation
Biopsy: If + ...

Maybe XRT ? (HD15)

What about “interim PET”? 

Andrea Gallamini et al. Haematologica 2014;99:1107-1113
RATHL Trial

Stage II (adverse), III-IV
IPS 0-7

PET2 +
Deauville 4-5

Treatment
intensification...

PET2 -
Deauville 1-3

Randomization

ABVD x4
AVD x4

Follow-up

PET2

Johnson PW, et al 13th ICML; 2015; Abst 008

How’d the PET2 Negative Patients do?

<table>
<thead>
<tr>
<th></th>
<th>ABVD N=469</th>
<th>AVD N=466</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>65%</td>
<td>69%</td>
</tr>
<tr>
<td>Deaths (N)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>3 yr PFS</td>
<td>85.4%</td>
<td>84.4%</td>
</tr>
<tr>
<td>3 yr OS</td>
<td>97.1%</td>
<td>97.4%</td>
</tr>
<tr>
<td>Severe lung disease</td>
<td>3.6%</td>
<td>0.6% (p=.002)</td>
</tr>
</tbody>
</table>
Roadmap

Overview of Hodgkin lymphoma

Treatment of newly diagnosed Hodgkin lymphoma

Treatment of relapsed or refractory disease

Emerging and novel therapies

Survivorship care

Treatment of relapsed / refractory HL

ABVD

Relapse/Refractory

Platinum-based regimen

Response

No Response

Gemcitabine-based regimen

Response

No Response

Cure!

ASCT

No Response/Relapse

3rd line regimen (BV) Investigational agents
Results of pre-transplant regimens in HL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>PR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGEV</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>mini-BEAM</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>ASHAP</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>MINE</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Dexa-BEAM</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>ICE</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>DHAP</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>GVD</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>GDP</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>ESHAP</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

% response rate

ASCT for relapsed / refractory HL

(1) PET negative, ENS negative: 46 pts; 42 censored
(2) PET negative, ENS positive: 30 pts; 20 censored
(3) PET positive: 21 pts; 6 censored

Time in Months

EFS Probability

Moskowitz C H et al. Blood 20012
Brentuximab vedotin: ADC (Antibody-drug conjugate)

1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. Toxin is released
4. Toxin disrupts cell mitosis
5. Mitosis fails
6. Cell death

ADC: Antibody-drug conjugate

**Response adapted salvage therapy**

45 patients

Brentuximab Vedotin 1.2mg/kg
6 weekly doses over 2 months

- **PET-**
  - 27%
  - Transplant

- **PET+**
  - 73%
  - Augmented ICE chemo
  - 69% PET negative
  - Transplant

Overall: 76% achieved PET- CR and proceeded to transplant
Bendamustine + Brentuximab

LaCasce A et al. ASH 2015

<table>
<thead>
<tr>
<th>Best clinical response prior to transplant</th>
<th>N=48</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission (CR)</td>
<td>40 (83)</td>
<td></td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>6 (13)</td>
<td></td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Objective response rate ([CR + PR])</td>
<td>46 (96)</td>
<td></td>
</tr>
</tbody>
</table>
The AETHERA study

329 patients were randomized at 78 sites in North America and Europe

AETHERA: Results

Progression-free survival

Overall survival


Who benefits the most?

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Event / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat population</td>
<td>135 / 329</td>
</tr>
<tr>
<td>Response to salvage therapy pre-ASCT</td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>41 / 123</td>
</tr>
<tr>
<td>Partial remission</td>
<td>51 / 113</td>
</tr>
<tr>
<td>Stable disease</td>
<td>43 / 93</td>
</tr>
<tr>
<td>HL status after frontline therapy</td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>89 / 196</td>
</tr>
<tr>
<td>Relapse &lt;12 months</td>
<td>40 / 107</td>
</tr>
<tr>
<td>Relapse ≥12 months</td>
<td>6 / 26</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>113 / 272</td>
</tr>
<tr>
<td>≥45</td>
<td>22 / 51</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84 / 173</td>
</tr>
<tr>
<td>Female</td>
<td>51 / 156</td>
</tr>
<tr>
<td>ECOG status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>76 / 184</td>
</tr>
<tr>
<td>1</td>
<td>59 / 144</td>
</tr>
<tr>
<td>Systemic treatments pre-ASCT</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>68 / 180</td>
</tr>
<tr>
<td>&gt;2</td>
<td>67 / 149</td>
</tr>
<tr>
<td>FDG negative pre-ASCT</td>
<td></td>
</tr>
<tr>
<td>FDG positive pre-ASCT</td>
<td></td>
</tr>
<tr>
<td>B symptoms after frontline therapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38 / 87</td>
</tr>
<tr>
<td>No</td>
<td>97 / 239</td>
</tr>
<tr>
<td>Extramedal involvement pre-ASCT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 / 107</td>
</tr>
<tr>
<td>No</td>
<td>81 / 222</td>
</tr>
</tbody>
</table>

**Roadmap**

Overview of Hodgkin lymphoma

Treatment of newly diagnosed Hodgkin lymphoma

Treatment of relapsed or refractory disease

Emerging and novel therapies

Survivorship care

---

**Brentuximab for newly diagnosed HL**

Stage Ila bulky, IIB, III-IV

![Brentuximab Cycle Diagram](image)

- Brentuximab Vedotin A(B)VD
- Cycle 1, Cycle 2, Cycle 3
- 6 Cycles +/- XRT

Younes A et al, Lancet Oncology 2013
ABVD or AVD + brentuximab vedotin

<table>
<thead>
<tr>
<th></th>
<th>ABVD with brentuximab vedotin</th>
<th>AVD with brentuximab vedotin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>11 (44)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>9 (36)</td>
<td>0</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>PET negative results</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>% CR at end of therapy</td>
<td>95%</td>
<td>96%</td>
</tr>
</tbody>
</table>


OS (mos)

Connors J et al, ASH 2014
ECHELON-1: ABVD vs. BV-AVD

Newly diagnosed HL
Stage III/IV HL

Randomize

Standard ABVD x 6 cycles

AVD + brentuximab x 6 cycles

N=1240
Primary outcome measure: Modified progression free survival

Immunotherapy in HL: “Checkpoint inhibitors”

Adapted from Stathis & Younes: Ann Oncology 2015
Results in Relapsed HL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Schedule</th>
<th>N</th>
<th>% ORR</th>
<th>% CR</th>
<th>Response following brentuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>10 mg/kg IV every 2wks</td>
<td>29</td>
<td>66%</td>
<td>21%</td>
<td>66% (n=19)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>3 mg/kg IV every 2wks</td>
<td>23</td>
<td>87%</td>
<td>17%</td>
<td>70% (n=16)</td>
</tr>
</tbody>
</table>

Nivolumab and Pembrolizumab

Illustration showing change from baseline in individual patient data (N = 23) with categories for complete remission, partial remission, and stable disease.
Novel agents in relapsed cHL

- High response rates
- Potentially combinable at full doses

Updated from Batlevi and Younes, Hematology Am Soc Hematol Educ Program. 2013

Hodgkin Lymphoma: Future Directions

Brentuximab vedotin

PD1/PDL1 antibodies

Chemo therapy

PI3Ki mTORi

Brentuximab Vedotin + PD1/PDL1 antibody

HDACi

Memorial Sloan Kettering Cancer Center.
Roadmap

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Survivorship care

Goals of survivorship

Maximize health and quality of life and

minimize preventable health problems related to your cancer and its treatment
High quality survivorship care

- Testing for relapse
- Preventing late effects
- Diagnosing late effects
- Managing the late effects you have
- Caring for other health conditions
- General preventive care / wellness
- Coordinating with other providers

Late effects of treatment for cancer

- Medical effects
  - Other cancers
  - Medical effects
    - Heart
    - Lungs
    - Endocrine (hormones)
    - Infections
- Psychosocial effects
  - “Chemo brain”
  - Anxiety and depression
  - Work, sexuality, insurance
Late Effects

- Host Factors
  - Gender
  - Race/Ethnicity
  - Socioeconomic

- Health Behaviors
  - Tobacco
  - Diet
  - Alcohol
  - Exercise

- Treatment Events

- Hereditary (genetic) Factors

- Tumor Factors
  - Histology
  - Biology
  - Site

- Treatment
  - Radiation
  - Chemotherapy
  - Surgery

Pre-cancer Conditions

Aging and Co-morbid Conditions

Hudson and Oeffinger 2004

Cancer treatments can cause cancer?!

All treatments have side effects:

- "off-target" (lung injury from bleomycin), or
- "friendly fire" (lung injury from radiation to the chest)

Any treatment that damages DNA (a common way that anti-cancer treatments work) can lead to "friendly fire" oncogenesis (cancer development)
Breast cancer and radiation therapy

- Breast cancer after radiation therapy involving breast tissue in young women:
  - Age <20: 34% lifetime risk
  - Age 20-29: 22% lifetime risk
  - Age 30+: 3.5% lifetime risk

Breast cancer surveillance guidelines

<table>
<thead>
<tr>
<th>NCCN</th>
<th>COG (adapted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Initiate 8-10y post-RT or age 40, whichever first</td>
<td></td>
</tr>
<tr>
<td>- Annual mammogram + breast MR if age ≤30 at RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Initiate 8y post-RT or age 25, whichever last</td>
</tr>
<tr>
<td></td>
<td>- Annual mammogram + breast MR</td>
</tr>
</tbody>
</table>

Awaiting readout of two trials of prophylactic tamoxifen (standard and low-dose)
## Other cancers after Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Risk factor(s)</th>
<th>Screening standard?</th>
<th>NCCN guidelines</th>
<th>COG guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Lung RT +/- alkylator</td>
<td>Case-by-case</td>
<td>&quot;Consider chest imaging&quot;</td>
<td>&quot;As clinically indicated&quot;</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastric RT, Procarbazine</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>Pancreas RT +/- alkylator</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Abdominal RT</td>
<td>Yes</td>
<td></td>
<td>Coloscopy every 5y starting 10y post-RT</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>RT</td>
<td>Yes</td>
<td></td>
<td>Yearly skin exam of RT field</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Thyroid RT</td>
<td>Yes*</td>
<td></td>
<td>Yearly thyroid palpation</td>
</tr>
</tbody>
</table>

### Late effects: Heart health

- Heart (cardiac) health risks in survivors:
  - Coronary artery disease and heart attack
  - Valvular heart disease
  - Stroke
  - Congestive heart failure
- Risk factors from treatment include:
  - Radiation in the area of the heart and neck
  - Doxorubicin
  - All the other normal risk factors for heart disease!
Late effects: Heart health

Prevention: Promote heart health in every way you can control

Guidelines aren’t very specific. But:

– **Definitely:** Maintain a low cholesterol, normal blood pressure, and get regular cardiovascular exercise
– **Discuss:** Early stress testing, baby aspirin
– **Future:** Cardiac CT angiography or cardiac MRI for screening?

Cardiac CT coronary angiogram
Cardiac MRI

- Coronary artery disease
  - Subendocardial
  - Mid-myocardial
  - Transmural

- Scarring (fibrosis)
  - Epicardial

Survivorship care plans

**Survivor**
- Visit right doctors
- Self-manage care

**Oncologist**
- Create, deliver, discuss survivorship care plan

**Primary care provider**
- Know what care the survivor needs
- Communicate with oncologist
Survivorship Care Plan ingredients:

Plans for future medical care and self-care
- Understanding risk related to the cancer therapy, lifestyles, genetics, and other health conditions
- Screening for late effects
- Prevention and counseling
- Promoting healthy behaviors
- Avoiding risky behaviors

Whom to visit, for what, and how often

Acknowledgements

- **MSK Lymphoma Service**
  - Anas Younes, MD
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  - Emily Tonorezos, MD

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  - R01 CA151899
Update on Hodgkin Lymphoma

Question & Answer Session

The speakers’ slides are available for download at www.LLS.org/CE

The Leukemia & Lymphoma Society (LLS) offers:

• Live, Online Chats provide a friendly forum to share experiences with others.
  ➢ WEBSITE: www.LLS.org/chat

• What to ask: For a list of suggested questions to ask about certain topics, download and print any of the following guides.
  ➢ WEBSITE: www.LLS.org/whattotalk

• Free education materials: www.LLS.org/publications

• Information Resource Center: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  ➢ EMAIL: infocenter@LLS.org, TOLL-FREE PHONE: (800) 955-4572