First Line Management of Classical Hodgkin Lymphoma

George Follows
Cambridge University Hospitals NHS Foundation Trust

gorge.follows@addenbrookes.nhs.uk
The controversial areas

• Early stage non-bulky / favourable
  – A move to European classification
  – RT versus no RT and the role of PET
  – ABVD cycle number (and ? Escalated BEACOPP use)

• Advanced stage
  – Choice of chemotherapy
  – Role of RT consolidation
  – Role of PET

• Elderly HL
<table>
<thead>
<tr>
<th>EORTC</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No large mediastinal adenopathy</td>
<td>No large mediastinal adenopathy</td>
</tr>
<tr>
<td>ESR &lt; 50 without B symptoms</td>
<td>ESR &lt; 50 without B symptoms</td>
</tr>
<tr>
<td>ESR &lt; 30 with B symptoms</td>
<td>ESR &lt; 30 with B symptoms</td>
</tr>
<tr>
<td>Age ≤ 50</td>
<td>No E-disease</td>
</tr>
<tr>
<td>1-3 lymph node sites involved</td>
<td>1-2 lymph node sites involved</td>
</tr>
</tbody>
</table>

EORTC, European Organisation for the Research and Treatment of Cancer; GHSG, German Hodgkin’s Study Group

**Table 1 - Favourable prognosis Stage I-II Hodgkin Lymphoma**
<table>
<thead>
<tr>
<th>EORTC</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>presence of one or more of the following</td>
<td>presence of one or more of the following</td>
</tr>
<tr>
<td>Large mediastinal adenopathy</td>
<td>Large mediastinal adenopathy</td>
</tr>
<tr>
<td>ESR ≥ 50 without B symptoms</td>
<td>ESR ≥ 50 without B symptoms</td>
</tr>
<tr>
<td>ESR ≥ 30 with B symptoms</td>
<td>ESR ≥ 30 with B symptoms</td>
</tr>
<tr>
<td>Age &gt;50</td>
<td>E-disease</td>
</tr>
<tr>
<td>≥ 4 lymph node sites involved</td>
<td>≥ 3 lymph node sites involved</td>
</tr>
</tbody>
</table>

Table 2 - Unfavourable prognosis Stage I-II Hodgkin Lymphoma

(analysis of HD10 and HD11 patients with EORTC and NCIC prognostic tool identified very similar splits in PFS and OS. Klimm et al Ann Oncol. 2013 Oct 22. [Epub ahead of print])
• Note, the UK has historically tended to treat early stage patients with bulk disease or B symptoms with advanced stage protocols, and have not separated favourable and unfavourable early stage HL.

• In contrast there are large trials with high quality data and generally excellent outcomes supporting the favourable / unfavourable split.
Early stage non-bulky / favourable HL

German HD10

ABVD x 2 + 20 Gy IFRT became the international standard of care

GHLSG HD10

Early stage non-bulky / favourable HL Canadian HD6 trial

From 2005 JCO analysis of the same trial
We evaluated 399 patients. Median follow-up is 4.2 years. In comparison with ABVD alone, 5-year freedom from disease progression is superior in patients allocated to radiation therapy (P = .006; 93% v 87%)
Early stage non-bulky / favourable HL

Children and adolescent data - multinational trial GPOH-HD95 JCO 2013 Dörffel W et al

- Large multinational European trial with 1000+ patients. 10 year f-up
- TG1 / TG2 / TG3

![Graph A](image1.png)

**A**

Progression-Free Survival Probability (%)

<table>
<thead>
<tr>
<th>TG 1</th>
<th>RT (n = 262), 19 events, pPFS (10 years): 92.2 ± 1.7%</th>
<th>No RT (n = 66), 2 events, pPFS (10 years): 97.0 ± 2.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[P = 0.21\]

![Graph B](image2.png)

**B**

Progression-Free Survival Probability (%)

<table>
<thead>
<tr>
<th>TG 2</th>
<th>RT (n = 211), 18 events, pPFS (10 years): 91.4 ± 1.9%</th>
<th>No RT (n = 43), 13 events, pPFS (10 years): 68.5 ± 7.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[P < 0.001\]
Early stage - ? Role of PET

UK RAPID trial

3 x ABVD → PET

RT vs No RT

ABVDx1 + RT

N= 602 patients
94 centres UK

Median age 34 years
(16 to 75)

Median f-up 60 months
Early stage - ? Role of PET

• ITT on 420 PET negative patients:
  – no statistical benefit from RT

• Per protocol on 392 patients:
  – PFS 97.1% (RT) vs 90.8% (no RT) p=0.02

• OS no difference between arms
Early stage - ? Role of PET

• 12/420 deaths in PET negative group

• 8/145 deaths in PET positive group

• Median follow-up 5 years, only:
  – 5 deaths from HL
  – 2 /301 deaths in < median age group
  – 18 / 301 deaths in > median age group
    (2 young deaths, 1x DLBL, 1 x RT-related)
EORTC/LYSA H10

• Early stage favourable an unfavourable trial
• All patients 2 x ABVD then PET
• Complex sub-dividing thereafter
EORTC/LYSA H10

N = 1950!!
EORTC/LYSA H10

1059 iPET2 negative patients

- 3 x ABVD + ISRT
- 4 x ABVD

**Favourable**
EORTC/LYSA H10

1059 iPET2 negative patients

- **Favourable**
  - 3 x ABVD + ISRT
  - 4 x ABVD

- **Unfavourable**
  - 4 x ABVD + ISRT
  - 6 x ABVD
EORTC/LYSA H10

361 iPET2 positive patients – median 4.5 years f-up

2 x ABVD + 2 x escB + INRT

3 - 4 x ABVD + INRT
Early Stage Unfavourable – HD14

German trial

• >1500 patients

ABVD x 4 + 30Gy IFRT

vs

escalated BEACOPP x 2 + ABVD x 2 + 30Gy IFRT
Early Stage Unfavourable – HD14

N = 1528

escB x 2 + ABVD x 2 + IFRT30Gy

ABVD x 4 + IFRT30Gy

B

Progression-Free Survival (probability)

\[
\begin{array}{c|cc|cc}
\text{5-year PFS (\%)} & 89.1 & 86.3 \text{ to } 91.9 \\
\text{95\% CI (\%)} & 93.7 \text{ to } 97.1 \\
\end{array}
\]

\[P < .001\]

C

Overall Survival (probability)

\[
\begin{array}{c|cc|cc}
\text{5-year OS (\%)} & 96.8 & 95.2 \text{ to } 98.4 \\
\text{95\% CI (\%)} & 95.8 \text{ to } 96.6 \\
\end{array}
\]

\[P = .731\]
Early stage Second cancers

- **HD10 – 7.5 years f-up**
  - 1190 patients 4.6% second cancers at 7.5 years median f-up

- **NCIC HD6 – 12 years f-up**
  - ABVD only – 1/196 (0.5%) second cancer at 12 years f-up (seems very low!)

- **GPOH-HD95 (paediatric trial)**
  - No RT - 1/165 = second cancer
  - RT - 20 / 746 = second cancer (2.7%). 14 of 17 solid cancers in RT field

- **EORTC/LYSA H10 – 5 years f-up**
  - No RT – 16/540 = 3.0% second cancer
  - RT – 26/1385 = 1.9% second cancer
Early stage HL

• The facts:
  – Whole cohort survival very good
  – Young patients death rate very low indeed
  – Think about ABVD cycle number
  – Think very carefully about each case where RT is withheld (Role for including other risk assessments such as TMTV – not discussed)
Advanced Stage Hodgkin Lymphoma

• Choice of chemotherapy
  – ABVD vs escalated BEACOPP vs others

• Who should get radiotherapy consolidation

• Can we use PET to guide decision making for points 1 and 2
The ABVD – escBEACOPP consensus

• ABVD and escalated BEACOPP will both cure the majority of advanced stage HL patients
• The majority of advanced stage HL patients do not need radiotherapy consolidation
• Escalated BEACOPP is a more ‘effective’ HL therapy
• Escalated BEACOPP is a more ‘toxic’ HL therapy
• The ‘relative gain’ for escBEACOPP is more for higher risk patients
The ABVD – escBEACOPP controversies

• Should escBEACOPP be reserved for poorer risk patients?

• How should we optimally escalate / de-escalate between the two?

• Will the addition of BV to either regimen have a role to play in the UK?
Advanced Stage Hodgkin Lymphoma

• The German escalated BEACOPP journey

HD9
(8 x escB)
10 year f-up 2009

HD15
(6 x escB)

HD18
(4 x escB)
5 year f-up 2017
HD18

• All patients started with 2 x escalated BEACOPP

• iPET2 randomised (D1/2 = negative = 50%)
  – PET + : variations with rituximab (made no difference)
  – PET - : total 4 cycles vs 6 or 8 cycles
HD18 – iPET did not affect outcome

HD18 – 4x eBEACOPP as good as 6/8 if iPET neg

Subsequent analysis: iPET D3 probably neg

<table>
<thead>
<tr>
<th></th>
<th>3y estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deauville 1-3</td>
<td>94.2%</td>
</tr>
<tr>
<td>Deauville 4</td>
<td>87.6%</td>
</tr>
<tr>
<td>Difference</td>
<td>-6.6%</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>2.27 (1.35-3.84)) p=0.002</td>
</tr>
</tbody>
</table>

Borchman et al – ASH 2017
If an HD18 approach is taken

- ¾ of patients finish within 12 weeks with only 5% relapse risk
- ¼ patients take 18 weeks with 10-15% relapse risk

- ? Fertility / fatigue / second cancers
RATHL

- All patients start with ABVD x 2

- iPET2 negative (D1-3) randomised B or no B

- iPET2 positive ALL move to escBEACOPP.
  - No RT mandated (was this incorrect?)
RATHL – median FU 52mo

**PFS**

- ABVD - AVD = 1.2% (-3.7 to +4.8) within pre-defined non-inferiority margin of 5%

**OS**

- 5yr PFS of 81.6% (79 – 84)
- 5yr OS 95.1% (93-96)

Trotman et al ICML 2017
16% of patients were iPET+ (DS 4,5) and intensified to eBEACOPP/14
RATHL TRAIL
OS stratified by iPET2 result
1088 PATIENTS • 18–59 YEARS

Median follow-up 58 months

Overall survival (%)

5yOS (%)  95% CI
iPET2 NEG  98.0  94.6–97.5
iPET2 POS  87.2  80.3–91.8
RATHL 18–59  95.1  93.4–96.4

# at risk

<table>
<thead>
<tr>
<th>iPET2 NEG</th>
<th>iPET2 POS</th>
</tr>
</thead>
<tbody>
<tr>
<td>855</td>
<td>163</td>
</tr>
<tr>
<td>832</td>
<td>144</td>
</tr>
<tr>
<td>803</td>
<td>135</td>
</tr>
<tr>
<td>738</td>
<td>114</td>
</tr>
<tr>
<td>481</td>
<td>74</td>
</tr>
<tr>
<td>221</td>
<td>39</td>
</tr>
</tbody>
</table>
**EECN vs. RATHL**  
(18–59)  
PFS whole cohort

### Progression-free survival (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Years</th>
<th># at risk</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>RATHL</td>
<td></td>
<td>1088944849765507244</td>
<td>85</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ABVD EECN</td>
<td></td>
<td>177158140124119110</td>
<td>92</td>
<td>78</td>
<td>57</td>
<td>45</td>
<td>28</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>escB EECN</td>
<td></td>
<td>44 44 36 26 18 11 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Comparison

- **EECN ABVD vs RATHL**: HR (95% CI) 1.13 (0.79–1.62) p-value 0.490
- **EECN eBEACOPP vs RATHL**: HR (95% CI) 0.25 (0.06–1.00) p-value 0.050
- **EECN eBEACOPP vs EECN ABVD**: HR (95% CI) 0.22 (0.05–0.91) p-value 0.019
Within the **RATHL 18–59 cohort**...

22.1% of **IPS 3+** patients were iPET2 positive
12.9% of **IPS 0-2** patients were iPET2 positive

<table>
<thead>
<tr>
<th>endpoint</th>
<th><strong>EECN ABVD</strong></th>
<th><strong>RATHL 18–59</strong></th>
<th><strong>EECN eBEACOPP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole cohort</td>
<td>79.2 (177; 72.3–84.5)</td>
<td>81.3 (1088; 78.6–83.6)</td>
<td>95.5 (44; 83.0–98.8)</td>
</tr>
<tr>
<td>IPS 0-2</td>
<td>84.7 (106; 76.2–90.3)</td>
<td>83.8 (728; 80.7–86.4)</td>
<td>90.9 (11; 50.8–98.7)</td>
</tr>
<tr>
<td>IPS 3+</td>
<td>71.9 (69; 59.5–81.1)</td>
<td>76.2 (359; 71.0–80.7)</td>
<td>97.0 (33; 80.4–99.6)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>73.6 (59; 60.0–83.2)</td>
<td>76.8 (305; 70.9–81.4)</td>
<td>98.9 (32; 79.8–99.6)</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole cohort</td>
<td>92.9 (177; 87.8–95.9)</td>
<td>95.1 (1088; 93.4–96.4)</td>
<td>97.2 (44; 81.9–99.6)</td>
</tr>
<tr>
<td>IPS 0-2</td>
<td>98.1 (106; 92.5–99.5)</td>
<td>96.3 (728; 94.3–97.6)</td>
<td>85.7 (11; 33.4–97.9)</td>
</tr>
<tr>
<td>IPS 3+</td>
<td>84.5 (69; 72.9–91.4)</td>
<td>92.6 (359; 89.1–95.1)</td>
<td>100 (33; N/A)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>92.6 (59; 81.3–97.2)</td>
<td>92.1 (305; 88.1–94.8)</td>
<td>100 (32; N/A)</td>
</tr>
</tbody>
</table>
Escalated BEACOP with dacarbazine

- Appealing – as per the BRECADD protocol
- Paediatric data suggests equivalence between dacarbazine and procarbazine (but we can’t be certain)
- Toxicity is likely to be less
- First 10 patients completed. All well in PET negative remission. No radiotherapy
  - iPET2 D2=3, D3=5, D4 =2
  - 5 patients stopped at 4 cycles
Will BV impact on frontline Rx - ECHELON-1
218 study sites in 21 countries worldwide

- Inclusion criteria
  - cHL stage: III or IV
  - ECOG PS: 0, 1 or 2
  - Age: ≥18 years
  - Measurable disease
  - Adequate liver and renal function

Screening CT/PET scan → 1:1 randomization (N=1334) → ABVD x 6 cycles (n=670) → EOT CT/PET

A+AVD x 6 cycles (n=664)
Brentuximab: 1.2 mg/kg IV infusion
Days 1 & 15

Follow-up
Every 3 months for 36 months, then every 6 months until study closure

End-of-Cycle-2 PET scan
- Deauville 5; could receive alternate therapy per physician’s choice (not a modified PFS event)

Connors JM et al (2017) NEJM ;
Connors JM et al ASH 2017 Abstract no 0006
Primary EP – a controversy begins...

- Primary endpoint: modified PFS per IRF
  - A modified PFS event was defined as the first of: PD, Death OR:

- PET6 = D3-5 after completion of frontline therapy followed by subsequent anticancer Tx

<table>
<thead>
<tr>
<th>Event</th>
<th>PET6 = D1–5</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx</td>
<td>Tx</td>
<td>No event</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>PET6 = D3–5</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx</td>
<td>Tx w/o “Cheson” progression</td>
<td>No event</td>
</tr>
</tbody>
</table>

Connors JM et al (2017) NEJM;
Connors JM et al ASH 2017 Abstract no 0006
## Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline patient characteristics</th>
<th>A+AVD N=664</th>
<th>ABVD N=670</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>Not Hispanic or Latino, %</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>White, %</td>
<td>84</td>
<td>83</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>35 (18–82)</td>
<td>37 (18–83)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, years, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>45–59</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>60–64</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>≥65</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

| Median time since initial diagnosis, months | 0.92 | 0.89 |

<table>
<thead>
<tr>
<th>Region, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Europe</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Asia</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline disease characteristics</th>
<th>A+AVD N=664</th>
<th>ABVD N=670</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Arbor stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>IV</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>IPS risk factors, %*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>2–3</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>4–7</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>B symptoms, %</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>Bone marrow involvement, %</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Sites of extranodal involvement, %†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>&gt;1</td>
<td>29</td>
<td>29</td>
</tr>
</tbody>
</table>

*Percentages do not total 100% due to rounding; †Unknown/missing data for 5% and 4% in the A+AVD and ABVD groups, respectively; IPS, International Prognostic Score
HR 0.77 (95% CI: 0.60–0.98)
Log-rank test p-value: 0.035

Median follow-up (range): 24.9 months (0.0–49.3)

Connors JM et al (2017) NEJM;
Connors JM et al ASH 2017 Abstract no 0006
Many difficult issues

- Small difference in mPFS (really an EFS)
- Very short f-up for a HL trial
- More toxicity
- If we accept more toxicity, why not escB?
- ? Long term effects
- Cost

Trial design (no response adaptive therapy)
FUTURE TRIALS

• Exploring prognostic tools
• Reducing chemotherapy and radiotherapy exposure
• Early recognition of the poorest prognostic patients to change therapy early

Many complex designs are possible - ASK GRAHAM!