RATHL:
Risk-adapted Treatment of Patients with Hodgkin’s lymphoma

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Haematology and Brain

International clinical trials day 19th May 2017
Objective

- To outline the design and major findings of the RATHL trial
- Plenary presentation Lugano 2015
- Published NEJM 2016
- Three oral presentations and a poster Lugano 2017

Background to HL

• Hodgkin lymphoma (HL) develops when B lymphocytes (WBC) grow abnormally

• In HL see an accumulation of Reed-Sternberg cells under the microscope

• Patients present with:
  • Swollen lymph node (commonly in neck)
  • B symptoms (fever, night sweats, weight loss)
  • Pain when drinking alcohol (rare)

• HL accounts for ~ 15% of lymphomas

• Annual incidence of 2.7 per 100,000

• UK incidence - 2000 people diagnosed / year

http://medical-dictionary.thefreedictionary.com/Reed-Sternberg%2Bcell
Background to HL

- Very sensitive to chemotherapy or radiation therapy
- 6 x cycles of ABVD expected to cure ~80%
- Established as SOC for all patients in 1990s but has side effects:
  - Bleomycin-related pulmonary toxicity
    - In patients >60 years the incidence is 10-27% and is fatal in ¼ patients
- ~20% relapse – German group shown BEACOPP may cure more but has side effects:
  - Infertility
  - Secondary malignancies (MDS/AML)
- Aim to de-escalate treatment in best responders to avoid toxicity (omit bleomycin) and escalate treatment (to BEACOPP) in poor responders
The role of Positron Emission Tomography

- A form of functional imaging
- Uses radioactive glucose (¹⁸F-fluoredoxyglucose or FDG) to show areas of high metabolic activity

CT scan  PET scan  PET-CT scan
Response assessment – the Deauville criteria

1 = no uptake
2 = uptake ≤ mediastinum
3 = uptake > mediastinum but ≤ liver
4 = moderately increased uptake > liver
5 = markedly increased uptake > liver and/or new lesions related to lymphoma

X = new areas of uptake unlikely to be related to lymphoma
RATHL schema


No response/PD
Off trial, salvage

Negative
Deauville 1-3

Randomise

Arm A
ABVD x4

Arm B
AVD x4

PET scan

Positive
Deauville 4+

BEACOPP-14 x4 or
esc-BEACOPP x3

PET scan

Negative
Deauville 1-3

BEACOPP-14 x2 or
esc-BEACOPP x1

Positive
Deauville 4+

RT/salvage regimen
Advanced stage Hodgkin’s Lymphoma (RATHL) schema


No response/PD
Off trial, salvage

PET scan

ABVD x2

Negative
Deauville 1-3

Randomise

Arm A
ABVD x4

Arm B
AVD x4

PET scan

Positive
Deauville 4+

BEACOPP-14 x4 or esc-BEACOPP x3

PET scan

Negative
Deauville 1-3

BEACOPP-14 x2 or esc-BEACOPP x1

Positive
Deauville 4+

RT/salvage regimen

Cancer Research UK and UCL Cancer Trials Centre
Eligibility

• Inclusion:
  • Newly diagnosed HL previously untreated
  • >18 years
  • Clinical stage IIB, IIIA, IIIB, or IV, or clinical stage IIA with adverse feature (see protocol for details)
  • Performance status 0-3
  • Informed consent
  • Agree to use adequate contraception

• Exclusion:
  • Cardiac contraindication to doxorubicin (see protocol for details)
  • Neurological contraindication to chemotherapy
  • CNS or meningeal involvement by lymphoma
  • Poorly controlled diabetes mellitus
• Starting assumptions:
  • 75% PET-negative after 2x ABVD
  • 3 year PFS 95% in PET-negative group

• 1200 patients recruited
  • 900 patients randomised to ABVD or AVD

• 3 year follow-up

• Primary endpoint = 3 year PFS

• Non-inferiority design
  • 90% power to exclude AVD being >5% worse than ABVD
Updated analysis January 2017

**NEJM publication:** median follow-up 41 months

**Updated analysis for Lugano 2017:** median follow-up 51.7 months

One extra patient (PET negative, randomised to AVD) excluded due to misdiagnosis – this was picked up on review of their diagnostic material at relapse
Recruitment

68 stopped before PET2
- PET error  n=53
- Withdrawn  n=2
- Declined randomisation  n=1
- Died  n=1
- Larceny and drug abuse  n=1
- Moved  n=1
- Declined to participate  n=1
- Toxicity/AE  n=6
- Treatment delay  n=1

2 not randomised
- Toxicity/AE  n=1
- Second cancer  n=1

N=1202

1214 recruited

Eligible, consenting patients are registered
N=1202

PET scan

ABVDx2
N=1202

ABVD
Arm A
N=470
Started treatment  n=468
Did not start (AEs)  n=2

AVD
Arm B
N=700

12 found to be ineligible
- Misdiagnosis  n=5
- Early stage disease  n=3
- Thyroid cancer  n=1
- Not fit enough  n=3

PET scan

N=1134

Negative
Deauville 1-3
N=936

Positive
Deauville 4+
N=182

Randomise

BEACOPP
N=172
BEACOPP-14  n=94
BEACOPP-ESC  n=78

ABVD
Arm A
N=464
Started treatment  n=457
Died before C3  n=1
Opted for ABVD  n=2
Declined  n=3
Stopped all treatment  n=2

AVD
Arm B
N=264

16 excluded due to a PET error
- ABVD  n=4
- AVD  n=11
- Not randomised (PET+)  n=1

PET scan

N=182

2 not randomised
- Toxicity/AE  n=1
- Second cancer  n=1

N=936

N=172
## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PET negative</th>
<th>PET Positive (BEACOPP)</th>
<th>All eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABVD</td>
<td>AVD</td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>32 (18-679)</td>
<td>32.5 (18-76)</td>
<td>32 (18-70)</td>
</tr>
<tr>
<td>Sex, N(%)</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>261 (55.5)</td>
<td>209 (44.5)</td>
<td>655 (54.5)</td>
</tr>
<tr>
<td></td>
<td>251 (54.1)</td>
<td>213 (45.9)</td>
<td>547 (45.5)</td>
</tr>
<tr>
<td>Stage, N(%)</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>195 (41.5)</td>
<td>157 (33.4)</td>
<td>118 (25.1)</td>
</tr>
<tr>
<td></td>
<td>196 (42.2)</td>
<td>140 (30.2)</td>
<td>128 (27.6)</td>
</tr>
<tr>
<td></td>
<td>73 (42.4)</td>
<td>34 (19.8)</td>
<td>65 (37.8)</td>
</tr>
<tr>
<td>B symptoms, N(%)</td>
<td>737 (61.3)</td>
<td>287 (61.1)</td>
<td>276 (59.5)</td>
</tr>
<tr>
<td>Performance status, N(%)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>340 (72.3)</td>
<td>111 (24.0)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td></td>
<td>354 (76.3)</td>
<td>96 (20.7)</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td></td>
<td>123 (71.9)</td>
<td>40 (23.4)</td>
<td>6 (3.5)</td>
</tr>
<tr>
<td></td>
<td>889 (74.0)</td>
<td>271 (22.6)</td>
<td>27 (2.3)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>11 (2.3)</td>
<td>8 (1.7)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td></td>
<td>27 (2.3)</td>
<td>14 (1.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>≥4</td>
</tr>
<tr>
<td></td>
<td>219 (47.2)</td>
<td>224 (48.5)</td>
<td>579 (48.6)</td>
</tr>
<tr>
<td></td>
<td>84 (49.4)</td>
<td>52 (30.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>404 (33.9)</td>
<td>208 (17.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>579 (48.6)</td>
<td>208 (17.5)</td>
<td></td>
</tr>
</tbody>
</table>
**Efficacy: PET negative patients**

<table>
<thead>
<tr>
<th></th>
<th>ABVD</th>
<th>AVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received at least 6 cycles, (%)</td>
<td>97.9</td>
<td>97.6</td>
</tr>
<tr>
<td>Consolidation RT (%)</td>
<td>2.8</td>
<td>4.3</td>
</tr>
<tr>
<td>PFS events (N)</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Deaths (N)</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td><em>Hodgkin’s lymphoma</em></td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td><em>First line TRM</em></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><em>TRM salvage</em></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><em>Cardiac</em></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Second malignancy</em></td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><em>Other: not related to HL or treatment</em></td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
Efficacy: PET negative randomised patients

HR (95% CI): 1.08 (0.79 – 1.48), p=0.62

3-year PFS ABVD: 85.4% (91.9 - 88.4)
3-year PFS AVD: 84.0% (80.3 – 87.1)

3-year PFS difference:
1.2% (-3.7 to 4.8)

3-year PFS difference (per protocol):
0.7% (-4.1 to 4.6)
Baseline prognostic factors

- Higher **age**, **stage** and **IPI score** were significantly associated with inferior PFS (though IPI was no longer significant in a multivariable analysis)

- Risk of progression/death almost doubled with stage III or IV disease (no interaction with randomised treatment)

Stage III: HR 1.89 (95% CI 1.29 – 2.78)
Stage IV: HR 1.99 (95% CI 1.34 – 2.96)
## Toxicity: PET negative patients

<table>
<thead>
<tr>
<th>Grade 3+ adverse events</th>
<th>ABVD</th>
<th>AVD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>6 (1.28)</td>
<td>15 (3.29)</td>
<td>0.041</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (2.99)</td>
<td>5 (1.10)</td>
<td>0.042</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>22 (4.70)</td>
<td>10 (2.19)</td>
<td>0.037</td>
</tr>
<tr>
<td>Pulmonary/Upper Respiratory</td>
<td>15 (3.21)</td>
<td>3 (0.66)</td>
<td>0.005</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>9 (1.92)</td>
<td>1 (0.22)</td>
<td>0.012</td>
</tr>
<tr>
<td>Any grade 3+ Clinical AE*</td>
<td>143 (30.56)</td>
<td>96 (21.05)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Pulmonary function (DLCO, % of normal)

<table>
<thead>
<tr>
<th>Pulmonary function end of treatment</th>
<th>ABVD</th>
<th>AVD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-11.6% (-13.3 to -10.0)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>-4.3% (-5.9 to -2.7)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Lung function year 1</td>
<td>-0.5% (-2.7 to 1.8)</td>
<td>4.2% (2.2 to 6.1)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Excludes blood and bone marrow and laboratory events*
Efficacy: PET positive patients

3-year PFS BEACOPP: 67.2% (59.4 – 73.8)

3-year OS BEACOPP: 87.5% (81.2 – 91.7)
Efficacy: All patients

3-year PFS: 82.2 (79.9 – 84.3)

3-year OS: 95.7% (94.3 – 96.7)
Conclusions

• Bleomycin can be safely removed from ABVD in patients who are PET2 negative; PFS results now fall within the 5% margin and AVD patients experienced fewer pulmonary AEs and had better lung function

• Although not randomised, PET+ patients escalated to BEACOPP did better than historical data

• The overall PFS results were slightly higher (82.2%) than the previous two trials (75% and 80%) and were achieved with a fraction of the consolidation RT, (previous studies: 38% and 53%, RATHL: 6.5%)

• PET negative patients did not do as well as expected; further work should be done to further refine the risk adapted approach i.e. should some patients be escalated upfront (Using stage? Quantitative PET*? A gene expression profile*)

• The RATHL approach has become standard of care in many centres

*Lugano 2017 abstracts.
Acknowledgements

All patients and their families

131 participating centers in the UK, Italy, Australia, New Zealand, Norway, Sweden and Denmark.

The PET review teams in London, Modena, Sydney, Lund, Aarhus

Cancer Research UK & UCL Cancer Trials Centre