Malignant lymphomas
Modern classification and management of the most frequent entities

Treatment of Early Stage Hodgkin Lymphoma

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Conflict of Interest Disclosure

I hereby declare the following potential conflicts of interest concerning my presentation:

• Consultancy:
  – Seattle Genetics, Takeda Oncology,

• Research Funding:
  – Takeda Oncology,

• Honoraria:
  – Takeda Oncology,
Background

The outcome for patients with cHL has improved dramatically over the last 60 years, so that the disease is now considered one of the most curable forms of cancer through the use of highly effective chemotherapy, with radiotherapy in a proportion of cases.

These high cure rates however come at a cost of substantial long-term treatment-related morbidity and mortality.
Cumulative incidence of 2nd cancer in 3 different periods

<table>
<thead>
<tr>
<th>2nd cancer</th>
<th>SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>4.2</td>
</tr>
<tr>
<td>G.I.</td>
<td>4.6</td>
</tr>
<tr>
<td>Esophagus</td>
<td>9.5</td>
</tr>
<tr>
<td>Lung</td>
<td>6.4</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>15.1</td>
</tr>
<tr>
<td>Sarcoma S.T.</td>
<td>12.0</td>
</tr>
<tr>
<td>Breast (F)</td>
<td>4.7</td>
</tr>
<tr>
<td>Thyroid</td>
<td>14.0</td>
</tr>
<tr>
<td>Hemolympho</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Solid line: study population  
Dashed line: normal age-matched population  

Hodgkin Lymphoma Management
Considerations for Individual Treatment

Survivorship starts with initial treatment selection
Assess the risk

| A | Prognostic factors that identify patients at low or high risk for recurrence help in optimizing therapy for patients with limited or advanced stage disease. |
Patient Allocation
(According to EORTC and GHSG)

Anatomical staging and clinical/biological risk factors still determine treatment decision!

**Early Favourable (20%)**
- Stage I-II without Risk- Factors*

**Early Unfavourable (25%)**
- Stage I-II with Risk Factors*

**Advanced (55%)**
- Stage II B#
- Stage III-IV, IIB LMM

* Risk Factors: B-symptoms; High ESR; Bulky tumour; >3 lymph node areas; Extranodal disease; # B-symptoms & Extranodal disease or bulky tumour

The approach

<table>
<thead>
<tr>
<th>A</th>
<th>Assess the risk</th>
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<tbody>
<tr>
<td>B</td>
<td>Check for available therapies</td>
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<td>C</td>
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</table>
EF HL: 30 or 20 Gy IF-RT?

Median observation time = 79 months

Arm difference in 5y-PFS = -0.6%
95% CI [-3.6%; 2.5%]
p= 0.93
EF HL: 4 or 2 cycles ABVD?

HD10, CT-comparison

- arm difference in 5y-PFS = -2.3%
- 95% CI [-5.3%; 1.2%]
- p=0.24

Progression Free Survival

Time [months]

Pts. at Risk
4xABVD  596  569  546  519  492  442  339  233  135  59  6
2xABVD  594  566  541  509  484  416  321  230  135  54  9
OS, all arms (HD10)

Median observation time = 79 months

HD10, all evaluable patients

5y-OS difference arm A vs arm D: -0.4%
95% CI [-3.4%; 2.7%]

2x ABVD + 20Gy IFRT is the standard for early favorable HL

GHSG - HD13: enrollments and primary endpoint

Early-stage favourable HL
1710 patients randomized

2*ABVD
30 Gy IF-RT
Arm A
646 Pts (09/2009)

2*ABV
30 Gy IF-RT
Arm B
198 Pts (02/2006)

2*AVD
30 Gy IF-RT
Arm C
648 Pts (09/2009)

2*AV
30 Gy IF-RT
Arm D
167 Pts (09/2005)

Conclusion: Dacarbazine cannot be omitted from ABVD!

ABVD vs. AVD: “Impact of bleomycin within the ABVD regimen?
“Efficacy: non-inferiority test with margin of 1.72 for Hazard Ratio (corresponding to 6% difference in 5y-FFTF)”

Behringer et al., Lancet 2015
GHSG - HD13: final analysis

ABVD vs. AVD: “Impact of bleomycin within the ABVD regimen?”

5 year estimate [95%-CI]
2xABVD+IF: 93.1% [90.7% to 95.5%]
2xAVD+IF: 89.2% [86.3% to 92.2%]
difference: 3.9% [0.1% to 7.7%]

Hazard Ratio [95%-CI]
1.50 [1.00 to 2.26]

non-inferiority margin of 6% not excluded
➤ non-inferiority cannot be concluded

Pts. at Risk

<table>
<thead>
<tr>
<th></th>
<th>ABVD</th>
<th>AVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>566</td>
<td>571</td>
</tr>
<tr>
<td>12</td>
<td>533</td>
<td>541</td>
</tr>
<tr>
<td>24</td>
<td>500</td>
<td>496</td>
</tr>
<tr>
<td>36</td>
<td>437</td>
<td>439</td>
</tr>
<tr>
<td>48</td>
<td>326</td>
<td>320</td>
</tr>
<tr>
<td>60</td>
<td>207</td>
<td>213</td>
</tr>
<tr>
<td>72</td>
<td>120</td>
<td>117</td>
</tr>
</tbody>
</table>

Behringer et al., Lancet 2015
GHSG - HD13: overall survival

5 year estimate [95%-CI]
2xABVD+IF: 97.6% [96.1% to 99.1%]
2xAVD+IF: 97.6% [96.2% to 99.0%]
difference: 0.0% [-2.1% to 2.1%]

Hazard Ratio [95%-CI]
1.33 [0.67 to 2.63]

Pts. at Risk
ABVD 566 554 538 502 397 277 173
AVD 571 560 541 508 396 288 180

Behringer et al., Lancet 2015
GHSG - HD13: conclusions

• Dacarbazine cannot be omitted without considerable loss of efficacy

• Bleomycin cannot be omitted with the predefined non-inferiority margin of 6%

• Reduction in FFTF does not translate into poorer OS

• Moderate reduction in acute toxicity when omitting Bleomycin (leucopenia) and Dacarbazine (nausea or vomiting)

• 2xABVD+20Gy IFRT remains the standard for early favorable HL!
Early unfavorable HL: HD14 trial

Stages I, IIA with RF a-d; IIB with RF c,d

- ABVD
- ABVD
- ABVD
- ABVD

BEACOPP escalated
BEACOPP escalated

- ABVD
- ABVD

30 Gy IF
30 Gy IF

A

Freedom From Treatment Failure (probability)

5-year FFTP (%)

Arm A: 87.7, 95% CI: 84.8 to 90.6
Arm B: 94.8, 95% CI: 93.1 to 96.6

P < .001

No. at risk

Time (months)

B

Progression-Free Survival (probability)

5-year PFS (%)

Arm A: 89.1, 95% CI: 86.8 to 91.9
Arm B: 95.4, 95% CI: 93.7 to 97.1

P < .001

No. at risk

Time (months)

C

Overall Survival (probability)

5-year OS (%)

Arm A: 96.8, 95% CI: 95.2 to 98.4
Arm B: 97.2, 95% CI: 95.8 to 98.6

P = .731

No. at risk

Time (months)
“2+2”, demonstrated superiority in terms of PFS but not OS compared to 4xABVD in the combined modality setting.

ESMO Guidelines For The Treatment Of Early Unfavorable HL: 4xABVD or 2 cycles of Beacopp_{esc} + 2 cycles of ABVD (<60 Years)

(Eichenauer Et Al. Annals Of Oncology Advance Access Published July 25, 2014)
Early favorable HL: UK RAPID trial

Stage IA/IIA; no bulk
602 pts registered

Initial treatment: 3xABVD
Re-assessment: NR/PD: off study
CR/PR: PET

Randomisation
420 pts
- IFRT
- Follow-up

PET+ (DS 3-5) 25%
4th cycle ABVD + IFRT

PET- (DS 1&2) 75%

Randomisation
RAPID study: outcome of iPET negative patients

3 year PFS for IFRT: 94.6%; (95% C.I.: 91.5-97.7%),
Non inferiority margin: 87.6%
3 year PFS for NFT: 90.8%; (95% C.I. 86.9-94.8%).
Early Positron Emission Tomography Response–Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial

Marc P.E. André, Théodore Girinsky, Massimo Federico, Oumédaly Reman, Catherine Fortpied, Manuel Gotti, Olivier Casasnovas, Pauline Brice, Richard van der Maazen, Alessandro Re, Véronique Edeline, Christophe Fermé, Gustaaf van Imhoff, Francesco Merli, Rédâa Bouabdallah, Catherine Sebbar, Lena Specht, Aspasia Stamatoullas, Richard Delarue, Valeria Fiaccadori, Monica Bellei, Tiana Raveloarivahy, Annibale Versari, Martin Hutchings, Michel Meignan, and John Raemaekers
PET NEGATIVE

M. Andre et al., J Clin Oncol 2017: 35(16):1786-1794
### H10 PET negative: sites of relapse

<table>
<thead>
<tr>
<th>Site of progression/relapse</th>
<th>Favourable</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Unfavourable</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Std. ABVD+INRT</td>
<td>Exp. ABVD, no RT</td>
<td>Std. ABVD+INRT</td>
<td>Exp. ABVD, no RT</td>
<td>N=2/238</td>
<td>N=30/227</td>
<td>N=16/292</td>
<td>N=30/302</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initially involved</td>
<td>0</td>
<td>22</td>
<td>5</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initially uninvolved</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td></td>
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Median time to relapse
- N(%): relapses <= 24 months
  - 36 months
  - 12 months
  - 7/16 (44%)
  - 27/30 (90%)

Marc Andre et al., J Clin Oncol 2017: 35(16):1786-1794
Response adapted therapy in early HL. The H10 trial by EORTC/LYSA/FIL PET+ group: escBEACOPP versus ABVD

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; HL, Hodgkin lymphoma; Involved-nodal radiotherapy; PET, positron emission tomography

Marc Andre et al., J Clin Oncol 2017: 35(16):1786-1794
Prognostic value of early PET patients randomized for standard CMT

N = 954
PET positive N = 192 (20.1%)

**Progression-Free Survival**

- HR (95% CI) = 5.7 (3.6, 9.1), p<0.001
- 5 yr PFS: 77% vs. 95%

**Overall Survival**

- HR (95% CI) = 6.7 (3.2, 14.1), p<0.001
- 5 yr OS: 89% vs. 98%

Raemaekers et al
13th ICML, Lugano, June 17-20, 2015
Conclusions Intergroup H10 Trial

✓ Patients with early PET positive scan (after two cycles of ABVD) significantly benefit from intensification of ABVD to BEACOPPesc followed by IN-RT
  • 5 yr PFS increase from 77% to 91%

✓ In patients with early PET negative scan, the non-inferiority objective of omitting IN-RT could not be met (interim analysis sustained)
  • Though overall outcome was excellent
Early favorable stages: GHSG HD16-study

CS I/II without RF

2 x ABVD PET (+/-)
20 Gy IF

Experimental arm

2 x ABVD PET-
Follow up
20 Gy IF

2 x ABVD PET+

„Early unfavorable“ stages: GHSG HD17-trial

Randomization

Experimental arm

2x BEACOPPesc
2 x ABVD
PET (+/-)

Follow up

30 Gy IF

2x BEACOPPesc
2 x ABVD

PET

PET -
Follow up

PET +
30 Gy IN
<table>
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<td>B</td>
<td>Check for available therapies</td>
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<tr>
<td>C</td>
<td>Make the right choice</td>
</tr>
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</table>
Early HL: new standard of care?

- INRT effectively prevents local relapse.
- Early PET (after 2 cycles of ABVD) is prognostic and facilitates early PET adapted treatment.
- **Early PET positive**: significant benefit from intensification of chemotherapy in combined modality setting: consider as new standard of care.
- **Early PET negative**: omitting INRT after ABVD is defensible, albeit at the cost of higher “early” relapse rate.
- Early PET adapted treatment should become the new standard of care in early HL.

What is next?
Prognostic value of baseline total metabolic tumor volume (TMTV) for patients with early stage Hodgkin’s lymphoma (HL) enrolled in the standard arm of the H10 (EORTC/LYSA/FIL) trial (N=258).

AS Cottereau et al, 2017, submitted
Anticipating interim PET after the 1st ABVD cycle

Stage I 10
Stage IIA 34
Stage IIB 24
Stage III 24
Stage IV 34
Total 126

• Interpretation key: 5-PS
• 14 PET1-positive patients converted to a negative PET2
• All PET1-negative patients (N=88) were also PET2-negative.
Radiotherapy Free Treatment IN Good prognosis nonbulky early stage Hodgkin Lymphoma (RAFTING study)

Writing committee

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JM Zaucha (PL)
B Malkowski
I Kryachok (UA)
M Federico (I)
A Biggi (I)
S. Chauvie (I)
S. Viviani
A. Versari (I)
RAFTING Study: Trial Design

Early favorable: I-IIA nonbulky HL

PET-0 → ABVD X 1 → PET-1

- MTV

ABVD X 2

- CMR

No CMR → INRT

PET-0 → ABVD X 2 → PET-1

+ MTV

INRT 30 Gy (15%)

Stringent follow up for 3 years

Early unfavorable: I-IIA nonbulky HL

PET-0 → ABVD X 1 → PET-1

- MTV

ABVD X 2

- CMR

No CMR → INRT

PET-0 → ABVD X 2 → PET-1

+ MTV

INRT 30 Gy (20%)

Stringent follow up for 3 years

MTV

- = DS 1-2-3

+ = DS 4-5

INRT
Brentuximab Vedotin Followed By ABVD +/- Radiotherapy In Patients With Previously Untreated Hodgkin Lymphoma: Final Results Of A Pilot Phase II Study

Massimo Federico, Stefano Luminari, Cinzia Pellegrini, Francesco Merli, Emanuela Anna Pesce, Stephane Chauvie, Letizia Gandolfi, Isabella Capodanno, Massimiliano Salati, Lisa Argnani, Pier Luigi Zinzani

Haematologica April 2016 101: e139-e141; Doi:10.3324/haematol.2015.138388
**Study Flow Chart**

**Screening**

- BV X 2 Cycles

**Disease Assessment PET2**

- Stage I-IIIA
  - ABVD x 3 cycles +/- RT*

- Stage IIIA
  - ABVD x 6 cycles +/- RT*

*On initial bulky sites or on responding sites with residual PET positivity

Presented by: Massimo Federico
BV Followed By ABVD +/- Radiotherapy In Patients With Previously Untreated Early Stage HL

• 12 patients were enrolled
• After the 2 cycles of BV, 10 patients (83%) achieved a CMR, and one achieved a partial metabolic response (ORR of 92%).
• Following BV, patients received 3-4 cycles of ABVD
• Additional RT was delivered to 5 patients.
• After the full treatment program, the ORR reached 100%.
• At a median follow up of 12 months, all patients were alive, with 11 still in complete remission, and one relapse.
• Median 1-year PFS (range 7–16 months) was 92% (95%CI: 55–99).

Case 009

- 28-year-old male;
- Treatment:
  - 2 x Brentuximab vedotin 1.8 mg/kg, Q3wk → CR (DS2 pictured)
  - 3 x ABVD → CR
  - Remission duration = 3+ mo

Presented by: Massimo Federico
Case 002

- 19-year-old female;
- Early unfavorable HL
- Treatment:
  - 2 x Brentuximab vedotin 1.8 mg/kg, Q3wk → PR (DS4 pictured)
  - 4 x ABVD → CR
  - RT IF 30 Gy → CR
- Remission duration = 4+ mo

Presented by: Massimo Federico
Brentuximab vedotin (SGN-35) associated with chemotherapy in untreated patients with stage I/II Unfavourable Hodgkin’s lymphoma

A RANDOMIZED PHASE II LySA-FIL-EORTC INTERGROUP STUDY

Study chairman : Marc André (Lysa)

Coordinators : Massimo Federico (FIL)
Igor Auer (EORTC)
Study design

RND ratio St/Exp 1:2
PET-based Response After 2 Cycles of Brentuximab Vedotin in Combination with AVD for First-Line Treatment of Unfavorable Early-Stage Hodgkin Lymphoma: First Analysis of the Primary Endpoint of BREACH, a Randomized Phase II Trial of LYSAFIL-EORTC Intergroup.

Conclusions

Today, a risk-adapted and response-oriented therapeutic approaches represent the landmark for planning initial therapy in Early Stage HL.

Novel targeted therapies may represent an additional opportunity to improve disease control while reducing the risk of long-term consequences.