Treatment of Hodgkin lymphoma
Clinical Case Discussion

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• Advisory boards/consultant: Roche, Celgene, Sandoz, Pfizer, Gilead

• Lectures: Gilead

• Travel grant: Takeda, Celgene, Janssen
Key points and unmet medical needs in HL

Rare haematological cancer of the young patient (M>F)
95% are cHL; 5% are nodular lymphocyte-predominant HL (NLPHL)
Staging refers to the Lugano update of the Ann Arbor system and includes:
• Ph and lab exams (including viruses)
• B symptoms evaluation
• CT scan and FDG-PET
• BMB no longer indicated with FDG-PET
• Lung and cardiac function tests, reproductive counseling

High cure rates (90-95%) but 10-30% early failures and excess of late events

BMB, bone marrow biopsy; cHL, classic Hodgkin lymphoma; CT, computed tomography; FDG-PET, fludeoxyglucose-positron emission tomography; Ph, Philadelphia

Cheson BD et al. JCO 2014, Barrington SF et al. JCO 2014 El-Galaly TC et al. JCO 2012
Early Favourable (stage I-II without risk factors*)

- 2-3 x ABVD + 20 Gy IFRT or ISRT

Early Unfavourable/intermediate (stage I-II with risk factors*)

- 4x ABVD + 30 Gy IFRT
- 2x ABVD + 2x escBEACOPP + 30 Gy IFRT or ISRT (< 60 years)

Advanced (stage IIB#, stage III-IV or stage IIB with LMM)

- 6-8x escBEACOPP (< 60 years) + IFRT to PET+ve residual lymphoma > 2.5 cm
- 6-8x ABVD and IFRT to residual lymphoma > 1.5cm

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

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplant; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ESR, erythrocyte sedimentation rate; HL, Hodgkin lymphoma; IFRT, involved field radiotherapy; ISRT, involved site radiotherapy; PET, positron emission tomography
Early Interim FDG-PET Is Prognostically Superior to IPS in Adv-Stage HL: Italian-Danish Study

Recommendations for initial evaluation, staging, and response assessment of HL and non-HL: the Lugano classification

PFS according to IPS group and PET results after two cycles of ABVD

Gallamini A et al. JCO 2007

5 point scale Deauville criteria

- **Score 1:** no uptake
- **Score 2:** uptake ≤ mediastinum
- **Score 3:** uptake > mediastinum but ≤ liver
- **Score 4:** moderately increased uptake > liver
- **Score 5:** markedly increased uptake > liver and/or new lesions related to lymphoma
- **Score X:** New areas of uptake unlikely to be related to lymphoma

Cheson BD et al. JCO 2014

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; FDG- PET, fludeoxyglucose-positron emission tomography; HL, Hodgkin lymphoma; IPS, International Prognostic Score; PFS, progression-free survival CMR Complete Metabolic response
The RATHL trial
Stage II (adverse), III, IV PS 0-3

PET 1 (Staging)
2 cycles ABVD
Full dose, on schedule

PET 2

PET 2-positive
4 cycles BEACOPP-14
or 3 escBEACOPP

PET3
PET3 +ve
RT or salvage regimen

PET3 -ve
2 cycles BEACOPP-14
or 1 escBEACOPP
No RT

PET 2-negative*
Randomise

4 cycles ABVD
4 cycles AVD

Follow-up (no RT)
*PET-negative = Score 1-3

Johnson P. NEJM 2016
In advanced HL, with a negative interim PET scan after two cycles of ABVD, it is safe to omit further bleomycin (↓ pulmonary toxicity) and reduce use of consolidation radiotherapy.

Escalating therapy to escBEACOPP or BEACOPP14 for the 16% interim PET-positive patients delivers a promising PFS (5yrs PFS 65.7% (58 – 73))

Overall results from RATHL: 5yr PFS 79.5% and OS 93.5%, support an interim PET-adapted approach, with reduced chemotherapy and less radiotherapy (6.5%)
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
Exploring the BEACOPP side of response adapted therapy

• Interim PET is not prognostic in advanced HL treated with BEACOPP due to the very low PPV

• The high NPV makes it reasonable to conduct response adapted trials investigating de-escalation strategies

• AHL2011-LYSA Casasnovas ASH 2015
  • Randomised comparison of escBEACOPP versus response adapted strategy (i.e. shift to ABVD after 2 escBEACOPP and negative iPET (DS 1-3)

• HD18-GHSG Borchmann EHA 2017
  • Randomised study comparing 4 versus 2 escBEACOPP in patients with negative iPET after 2 escBEACOPP

BOTH trials concluded in favor of Tx de-escalation in patients PET-ve after 2 escBEACOPP
Treatment of relapsed/refractory HL

2014 ESMO GUIDELINES

• For most patients with RR HL the treatment of choice consists of high dose chemotherapy followed by ASCT

• Several salvage regimens are available (DHAP, IGEV, ICE) to mobilise PBSC prior to ASCT

• Brentuximab vedotin represents an option in patients failing ASCT

• Allogeneic stem cell transplantation is an active option (RIC)

ASCT, autologous stem cell transplantation; DHAP, high-dose cytarabine, cisplatin, and dexamethasone; ICE, ifosfamide, carboplatin and etoposide; IGEV, ifosfamide, gemcitabine, vinorelbine; PBSC, peripheral blood stem cells; RIC, reduced-intensity conditioning; RR HL relapsed/refractory Hodgkin lymphoma
ESMO consensus conference on malignant lymphoma: general perspectives and recommendations for prognostic tools in mature B-cell lymphomas and chronic lymphocytic leukaemia

M. Ladetto¹*, C. Buske², M. Hutchings³, M. Dreyling⁴, G. Gaidano⁵, S. Le Gouill⁶, S. Luminari⁷,⁸, C. Pott⁹, A. Zamò¹⁰, E. Zucca¹¹ & the ESMO Lymphoma Consensus Conference Panel Members†

…the panel recognised that interim FDG-PET is prognostic when used after reinduction chemotherapy and before a preplanned high-dose therapy programme in relapsed or refractory HL... [III, A]
RR HL after ASCT or not eligible to ASCT

**brentuximab vedotin** (anti-CD30 MoAb conjugated with monomethil auristatin - MMAE)

Pivotal phase II study, single agent, RR HL after ASCT. ORR 75%; CRR 34%; mPFS 5.6m (CR 20m) Good safety profile. Younes A. et al. JCO 2012

Randomised data support the use of Brentuximab vedotin consolidation to improve the tumor control in High risk patients: AETHERA Trial Moskowitz CH et al Lancet 2015

Ph-II study of PET-adapted sequential salvage therapy with BV followed by augICE and/or ASCT at 1° relapse. (N=45; 28% PET–ve after 4 BV). Moskowitz AJ et al. Lancet Oncol 2015

Ph-II study of BV combination with bendamustine at 1° relapse (CRR 83%) La Casce Blood 2014

ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; CRR, complete response rate; ORR, objective response rate; MoAb, monoclonal antibody; RR HL relapsed/refractory Hodgkin lymphoma;
CHECKMATE 205: nivolumab in RR HL after ASCT and BV

- Nivolumab demonstrated:
  - **High response rate** per IRRC (66%)
    - A complete response in 9% of patients ($n = 7$)
  - **Durable response** (median duration of response 7.8 months)

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\text{PFS by IRRC in Cohort B}
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- Median PFS (95% CI): 10.0 (8.41–NE) months

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\text{24/80 events}
\]

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\text{6-month rate: 76.9%}
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ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; NE, not estimable

Response rate and duration of response, pembrolizumab and RR HL (keynote 0-87)

Multicohort study N=210

ORR 69.0% (95% CI, 62.3% to 75.2%), CRR 22.4% (95% CI, 16.9% to 28.6%).

CRR, complete response rate; ORR, objective response rate

Chen R et al, JCO 2017
allo-HSCT can be safely performed in patients after checkpoint inhibitors

OS, PFS, CIR, and NRM following HSCT in patients previously treated with a PD-1 inhibitor
Outcome of HL patients has greatly improved with currently available therapies; safety and treatment tolerability should now be considered as primary goals.

Interim FDG_PET has shown to be the strongest prognostic factor for outcome, driving the development of response adapted therapies.

- **ABVD lovers:**
  
  Randomised data support the choice to remove Bleomycin in adv HL from cycle 3-6 in i-PET−ve (DS 1-3).
  
  Randomised data support intensification to escBEACOPP in early stage who are i-PET+ve (DS 3-5).

- **BEACOPP lovers:**

  Non randomised data suggest that escalation to BEACOPP iPET+ve pts (DS 4-5) is a good option.

  Randomised but still non published data suggest that it is safe to de-escalate therapy (ABVDx4 of BEACOPPx2) in patients who are iPET negative.

CONCLUSIONS

Response adapted therapy will be included in the 2017 update of ESMO guidelines for HL!!
CONCLUSIONS

• In the R/R setting ASCT is still the treatment of choice for patients who are chemosensitive to salvage therapy (response adapted trials needed)

• BV and checkpoint inhibitors are currently available for the management of patients who relapse after ASCT but guidelines remain undefined.

• Relevant open questions for new agents in HL
  • Position in 1st line: ECHELON1 (BV) PhIII results at ASH 2017
  • Phase III studies at 1st relapse
  • Biomarker driven studies
  • Elderly patients
  • Long term data (efficacy and safety)
Other phase III response adapted trials in advanced HL (PET+ve patients)

**FIL-GITIL HD0607 Trial**

Failure Free Survival according to PET2 result

- Preliminary report on 500/783 registered pts
- PET+ = DS 4-5
- iPET+ 17.3%

Gallamini et al. XIII ICML Lugano 2015 Abstract #118

**HD0801 Trial**

Progression-Free Survival (%)

Zinzani PL et al JCO 2016

HL, Hodgkin lymphoma; PET, positron emission tomography
Hodgkin’s lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. A. Eichenauer¹, A. Engert¹, M. André², M. Federico³, T. Illidge⁴, M. Hutchings⁵, & M. Ladetto⁶
on behalf of the ESMO Guidelines Working Group*
Other phase III response adapted trials in advanced HL (PET+ve patients)

FIL-GITIL HD0607 Trial

Failure Free Survival according to PET2 result

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|     Years       | 0               | 1               | 2               | 3               | 4               | 5               |     Patients at risk (Event)|
|-----------------+-----------------+-----------------+-----------------+-----------------+-----------------+-----------------+-----------------+-----------------+
| TOT             | 500             | 417             | 338             | 271             | 222             | 194             | 3               |
| TOT NEG          | 271             | 151             | 121             | 96              | 78              | 67              | 3               |
| TOT POS          | 229             | 186             | 217             | 165             | 146             | 127             | 0               |
| PET2 NEG         | 290             | 240             | 200             | 160             | 120             | 90              | 3               |
| PET2 POS         | 210             | 146             | 135             | 105             | 78              | 50              | 0               |

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Reid W. Merryman et al. Blood 2017
PFS and OS in patients with positive PET2

- 16% patients PET2-positive
- 5 year PFS 65.7% (58-73), 5 year OS 85.1% (78-90)
- No significant difference between escBEACOPP and BEACOPP-14

BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival

Trotman J et al. XIV ICML Lugano 2017
ABVD versus BEACOPP in response adapted therapy

Use of checkpoint inhibitors to induce remission

Interim PET-CT and response adapted therapy

The safety of allograft following immunotherapy

Role of brentuximab Vedotin

Management of early relapse

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; PET-CT, positron emission tomography-computed tomography
Disease progression was considered a competing risk to TRM

TRM, treatment-related mortality

Carlo-Stella C et al, EBMT 2017 (unpublished information, with permission)
AHL 2011

Median follow-up = 16.3 months (0.1-37.4)

2y-PFS = 91.6%
2y-PFS = 88.3%

- 87% of patients were PET2 neg (DS1-3)
- 84% patients in the exp arm treated with 2 escBEACOPP + 4 ABVD

Casasnovas et al. ASH 2015