Early stage Hodgkin lymphoma

Martin Hutchings
Rigshospitalet, Copenhagen, Denmark
EORTC Lymphoma Group
What are the challenges of early stage HL?

- The large majority of patients are cured although not 100%
- Late effects of treatment are a serious concern and include second cancers, cardiovascular disease, chronic fatigue, muscle weakness, psychosocial problems etc.
- Radiotherapy is probably the dominant cause of the late treatment-related morbidity and mortality seen today in survivors of HL treated 15-50 years ago
  - Since then, both radiotherapy doses and field sizes have been reduced dramatically along with fundamental improvements in radiotherapy techniques
- But chemotherapy also has late effects, serious and potentially fatal:
  - Cardiovascular disease, chronic muscle weakness and fatigue (dose-dependent effects of doxorubicin)
  - Pulmonary disease (bleomycin)
HD7 trial for early favorable HL (FFTF)

*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved

**HD10 trial**

Comparison of CT and RT

**CS I/II without risk factors**

- **4 x ABVD**
  - 30 Gy IF

- **4 x ABVD**
  - 20 Gy IF

- **2 x ABVD**
  - 30 Gy IF

- **2 x ABVD**
  - 20 Gy IF

*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved*

HD10 trial
Comparison of CT and RT

HD10 trial
Comparison of CT and RT

HD11 trial for early unfavorable HL

HD14 study for early unfavorable HL (PFS)

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* large mediastinal mass; *b* extranodal disease; *c* high ERS; *d* 3 or more areas

Current standard of care of early stage HL

**Early favourable**

- 2 x ABVD + 20 Gy ISRT (GHSG HD10)
  - 8-year FFTF 86%
  - 8-year OS 95%

**Early unfavourable**

- 4 x ABVD + 30 Gy ISRT (GHSG HD11 and HD14)
  - 5-year FFTF 85%
  - 5-year OS 94%

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Early interim PET in early stage HL

- PET after 2xABVD is prognostic in early stage HL
  - when patients are given both chemotherapy and radiotherapy

257 stage I-II (A+B) patients
Central, blinded PET review according to Deauville

246 stage IA-IIA patients
Central, blinded PET review according to Deauville

Early interim PET in early stage HL

- PET after 2 cycles is also prognostic in early stage HL when patients are given chemotherapy only

99 patients with stage I-II non-bulky HL
Treated with 6 cycles of AVG
PET after 2 cycles predictive of PFS
3-year PFS for all patients 77%
2-year PFS if PET2-neg = 88%
2-year PFS if PET2-pos = 54%

The focus of recent years:

- Q1: Should omission of radiotherapy be standard in early PET-negative patients?
- Q2: Should treatment be escalated in early PET-positive patients?
Q1: Should radiotherapy be omitted in early PET-negative patients?

**Prospective, randomised trials:**

- UK/NCRI RAPID  Final analysis
- EORTC/LYSA/FIL H10  Interim analysis
- GHSG HD16  Still ongoing
UK/NCRI RAPID final analysis

- 602 patients included
- 420 patients PET-negative after 3 x ABVD randomised to IFRT or NFT
- Non-inferiority margin = 7%
- Median follow-up 60 months
- 3-year PFS
  - 3 x ABVD + IFRT = 94.6%
  - 3 x ABVD + NFT = 90.8%
  - Difference = -3.8% (95% CI: -8.8 to 1.3%)
- 3-year OS
  - 97.1% vs 99.0% (NS)
- Conclusions:
  - Study did not show non-inferiority
  - PET3 negative patients have a very good prognosis, regardless of consolidation radiotherapy

EORTC/LYSA/FIL H10 interim analysis

- 1950 patients randomised
- 1137 patients available for interim analysis
- Non-inferiority margin 10%
- Median follow-up 13 months
- PET2 negative, favourable:
  - 1-y PFS 94.9% if no RT
  - 1-y PFS 100% if INRT
- PET2 negative, unfavourable:
  - 1-y PFS 94.7% if no RT
  - 1-y PFS 97.3% if INRT

IDMC conclusion: Unlikely to show non-inferiority; advised to stop randomisation of PET2 negative patients

Authors’ conclusion: Cannot exclude non-inferiority of chemo only arm, but early outcome is excellent in both arms

Q1: Should omission of radiotherapy be standard in early PET-negative patients?

- NO, since

1. No prospective, randomised studies support this
2. Two large randomised studies investigating this very question have reached negative conclusions
What is the appropriate margin of non-inferiority for such a trial? How many babies can you throw out with the bathwater in order to save others from drowning in the bathwater?
Is one answer to John’s question true for all patients?

I am worried about 2nd cancers!

I am an elderly man with a weak heart

Disclaimer: These are fictional characters
Negative trials can be useful

- RAPID and H10 data will probably reveal much useful information to help us tailor therapy to the individual patient with early stage HL, based on
  - Age
  - Sex
  - Disease location
  - Comorbidity
  - Early response (incl. PET)
  - Patient preference
  - Etc.
Q2: Should treatment be escalated in early PET-positive patients?

- 1950 patients randomised
  - 754 favourable
  - 1196 unfavourable
- Median follow-up 4.5 years
- PET2 positive:
  - F: 54 patients (14%)
  - U: 138 patients (23%)

**Progression-Free Survival**

HR (95% CI) = 0.42 (0.23, 0.74)  
p=0.002 *  5-yr PFS: 91% vs. 77%

**Overall Survival**

HR (95% CI) = 0.45 (0.19, 1.07)  
p=0.062  5 yr OS: 96% vs. 89%

1. Raemaekers JM, et al. ICML Lugano 2015,
Q1: Should omission of radiotherapy be standard in early PET-negative patients?
   - No, but for some patients it may be appropriate

Q2: Should treatment be escalated in early PET-positive patients?
   - Yes, but for some patients it may be inappropriate

Q3: Should early sensitivity testing be part of future individualised therapy for early-stage HL?
   - Yes!
Thank you!