Response-adjusted therapy for Hodgkin Lymphoma (RATHL)
Principles for a trial in advanced Hodgkin Lymphoma

• ABVD will cure 70%
• eBEACOPP might cure more, but will probably make them sterile, and may risk MDS/AML
• Our retrospective data does not support the absolute need for maximum intensity at the start
• It is desirable to de-escalate treatment in the best responders to avoid late toxicity
• FDG-PET after 2 cycles appears highly predictive, particularly for treatment failure on ABVD
Inclusion criteria

- Classical Hodgkin Lymphoma by WHO
- Aged 18 or above
- Not previously treated
- Stages IIB - IV or stage IIA with adverse features (bulk, 3+ sites)
- All prognostic groups
2 cycles ABVD
Full dose, on schedule

PET positive

4 cycles BEACOPP-14
or 3 eBEACOPP

PET-positive
XRT or salvage regimen

PET-negative
2 BEACOPP-14
or 1 eBEACOPP
No XRT

PET negative

Randomize

CT2 + PET2

PET negative

4 cycles ABVD

Follow-up (no radiation)

RATHL

CT1 + PET 1(Staging)

IPS 0-7

CT2 + PET2

4 cycles ABVD
or 3 eBEACOPP

CT3 + PET3

PET-positive
PET-negative

2 BEACOPP-14
or 1 eBEACOPP
No XRT

4 cycles BEACOPP-14
or 3 eBEACOPP

Follow-up (no radiation)
RATHL: statistics

• Assumptions:
  – 75% PET-negative after 2 ABVD
  – 3 year PFS 95% in PET-negative group

• 1200 patients and 3 years follow up:
  – 900 patients randomised in ABVD vs AVD
  – Primary end-point 3 year PFS
  – 90% power to exclude AVD being 3-4% worse than ABVD
PET Protocol

- 350 - 550 MBq $^{18}$F-FDG for 2D acquisition
- 150-350 MBq for 3D acquisition

- Emission scan at 60, or maximum 70, minutes after injection

- Response scans (day 9-13) performed at the same time after injection as the baseline scan ± 10 minutes

- Attenuation corrected ‘half-body’ PET-CT scan to cover the area from the base of the brain to mid-thigh using the CT of the PET-CT scanner

- Perform head and neck scan if required to cover sites of disease.

- Patients scanned with arms above the head for the body scan (if tolerated) and by the side for head and neck scan if acquired
Central PET review

Standardised protocol drawn up by expert panel:

– Only full-ring dedicated PET-CT scanners
– Documented daily quality control procedure
– Tested and secure method to transfer anonymised scan data, and agreed file naming convention.
– It must be demonstrated that image quality is comparable between centres and standard uptake values can be reliably determined from the PET/CT images
Scoring

1 no uptake
2 uptake $\leq$ mediastinum
3 uptake $>$ mediastinum but $\leq$ liver

If mediastinal blood pool activity $\neq$ liver:
lesion uptake less than liver = score 2
lesion uptake equal to liver = score 3

4 moderately increased uptake compared to liver
5 markedly increased uptake compared to liver
Testing the reading of PET scans

• 100 scans read at 4 centres
  – St Thomas’s, Modena, Copenhagen, Lund
  – 50 baseline, 50 post cycle 2
• Agreement in 44/50 cases, 46/50 after discussion
• Kappa for neg vs pos 0.85
Current status of RATHL study

• Trial Opened August 2008
• Collaboration of Italian (GISL), Irish (ICORG), Australasian (ALLG) and Nordic groups
• Sites: UK 62, Italy 12, Norway 3 to date
• ALLG, Sweden, Denmark, Ireland with the lawyers
• 182 patients registered, 114 randomised
• 12/100 PET score 4/5
• 2 sub-studies:
  – Fertility/ ovarian cryopreservation: funded
  – Markers of bleomycin toxicity: under review
Patients not randomised

- Adverse events 2
- Patient choice 4
- Non-compliance 3
- Other 1
PET Centres: UK

- Aberdeen
- Newcastle
- Nottingham
- Cambridge
- Guy’s/ St Thomas’
- Royal Marsden
- St Bartholomew’s
- UCL

- Glasgow
- Preston
- Manchester
- Birmingham
- Coventry
- Cheltenham
- Oxford
- Mount Vernon
- Portsmouth
Conclusions

• Central review system is working…
• …and can be replicated internationally
• Recruitment is accelerating
• Rate of PET+ lower than expected
• Number of withdrawals is low