Incorporating PET into lymphoma trials: U.S. experience

Yvette Kasamon, MD
Assistant Professor of Oncology and Medicine
Johns Hopkins University
Objectives

- Describe integration of PET in response-adapted lymphoma trials and other trials (focus on U.S. experience)
- Consider options for managing post-therapy PET results on clinical trials
Traditional risk stratification

- **IPI (aggressive NHL)**\(^a,b\):
  - Age > 60
  - ECOG performance status ≥ 2
  - High LDH
  - Stage III or IV
  - > 1 extranodal site

- **IPS (advanced Hodgkin’s)**\(^c\):
  - Age ≥ 45
  - Stage IV
  - Male
  - Albumin < 4 g/dl
  - Hemoglobin < 10.5 g/dl
  - WBC > 15,000/mm\(^3\)
  - Lymphopenia

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a) NEJM 1993; 329: 987-994  
b) Sehn LH et al, Blood 2007;109:1857-1861, Fig 4  
c) Hasenclever, Diehl. NEJM 1998;339:1506-14, Fig 1A.
• Prognosis depends not only on whether PET becomes negative, but how quickly this occurs
• In thinking about lymphoma trials, what is the biologic basis of this observation?
First-order kinetics

Usual size at diagnosis

With 6 cycles, need at least 1.5 logs of cell kill per cycle

Cure

Kasamon YL et al, JNM 2007
PET likely can only measure the first 2-3 logs of cell kill (so negative PET does not mean absence of tumor).

Kasamon YL et al, JNM 2007
A true negative PET after 2 cycles implies an adequate rate of tumor kill.

Usual size at diagnosis

Lower detection limit of PET

Logs of lymphoma cells

Cure

Cycles of chemotherapy

Kasamon YL et al, JNM 2007
A true negative PET after 2 cycles implies an adequate rate of tumor kill

Kasamon YL et al, JNM 2007
A true positive PET after 2 cycles suggests cure is unlikely.

Usual size at diagnosis

Lower detection limit of PET

A true negative PET at end of therapy might be less predictive

Kasamon YL et al, JNM 2007
Why might midtreatment PET be superior to posttreatment?

Early PET result implies a certain rate of tumor kill
Considerations

- Recently, more variability in outcome than appreciated in previous series
- Subsets with positive interim scans do well – not as clear-cut as previously appeared
- Concern about false positives
- Variability with PET criteria and reproducibility of reads
Response-adapted therapy

- Changing chemotherapy based on early PET
- Using PET to guide # of cycles and to tailor radiation
Aggressive NHL, any stage, any IPI (n = 59)

(R)CHOP for 2 or 3 cycles

PET -
- Complete conventional therapy

PET +
- If no disease progression
  - (R)ESHAP or (R)ICE x 2
    - (NO BIOPSY)
  - High dose therapy and ABMT

Kasamon YL et al, BBMT 2009;15:242
Johns Hopkins PET assessment

NEGATIVE
- 0  no abnormal activity (tumor cold)
- 1+ minimal activity (tumor < mediastinal blood pool)
- 2+ equivocal (tumor = or near blood pool)

POSITIVE
- 3+ moderate activity (tumor clearly > blood pool)
- 4+ strong activity (tumor much greater than blood pool)
JHH trial: EFS by interim PET

PET neg pts (n = 26):
3-year EFS 82%

Transplanted PET pos (n = 28):
3-year EFS 65%

JHH trial: disease outcomes and impact of PET scale

All PET pos pts (n = 33): EFS by intention to treat
(3 pts with early progression, 2 consent withdrawals)

All PET pos pts: cumulative incidence of relapse/progression

IPI and midtreatment PET

IPI ≤ 2
(n = 36)

IPI ≥ 3
(n = 20)

21 PET+ 15 PET- 11 PET+ 9 PET-

• No association between interim PET and IPI (0-2 vs 3-5); P = 0.99

• If mid PET pos, tendency toward greater relapse risk with IPI ≥ 3 (HR 3.6, P = 0.07)
Johns Hopkins experience

- Early treatment intensification on basis of midtreatment PET is feasible in most pts
- Advantages of this approach, compared with conventional therapy, remain to be defined
- Relative contribution of BMT, compared with platinum- and etoposide-based salvage regimens, is uncertain
- Gradations of FDG uptake may be prognostic
Ongoing Johns Hopkins study

DLBCL (stage II bulky, III, or IV)

R-CHOP x 3

PET neg

complete R-CHOP

PET pos *

if no disease progression

R-ICE x 2

Rituximab + high dose (transplant dose)
cyclophosphamide without BMT

* 5-point scale with blood pool and liver references

PI: Lode Swinnen
MSKCC: Risk-Adapted Therapy for DLBCL

- DLBCL with risk factors
  - Accelerated R-CHOP x 4
    - Negative PET: ICE × 3
      - Observation
    - Positive PET with CT correlate: Biopsy
      - Negative biopsy: ICE × 3
      - Positive biopsy: (R)ICE × 3 ABMT

Moskowitz CH et al, JCO 2010
MSKCC: overall outcomes

OS 90%, PFS 79%

Moskowitz CH et al, JCO 2010
Separation by PET and Biopsy

Results

R-CHOP-14 x 4

PET and CT

97 pts

PET pos*

38 pts

Biopsy pos

5 pts (13%)

3 progression-free

Biopsy neg

33 Pts (87%)

26 progression-free

PET neg

59 pts

51 progression-free

* Uptake > local background, with CT abnormality
PFS according to interim PET

Moskowitz CH et al, JCO 2010
PFS according to PET and biopsy

PET Negative (n=59, censored 51)

PET Positive/Biopsy Negative (n=33, censored 26)

PET Positive/Biopsy Positive (n=5, censored 3)

Moskowitz CH et al, JCO 2010
**SUV in relation to biopsy result**

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**Table 3. Correlation Between SUV and Biopsy Result**

<table>
<thead>
<tr>
<th>Biopsy Result</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
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<tbody>
<tr>
<td>Negative</td>
<td>3.4</td>
<td>1.5</td>
<td>11.5</td>
<td>1.46</td>
<td>−0.2</td>
<td>3</td>
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<tr>
<td>(n = 33)</td>
<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>5.4</td>
<td>2</td>
<td>14</td>
<td>1.3</td>
<td>0.2</td>
<td>1.7</td>
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<tr>
<td>(n = 5)</td>
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<tr>
<td>P (Wilcoxon test)</td>
<td>0.25</td>
<td></td>
<td></td>
<td>0.36</td>
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</tr>
</tbody>
</table>

*Ratio SUV = \log \left( \frac{\text{initial SUV max at biopsy site}}{\text{interim SUV max at biopsy site}} \right)*

Moskowitz CH et al, JCO 2010
Considerations in trial planning

• Impact of regimen
  – IPI, revised IPI were also not prognostic
  – A moving target?

• Role of biopsy
  – Prognostic significance of PET previously established without use of biopsy
  – Limited prognostic data on midtreatment biopsy
  – Sampling error
  – All biopsies showed inflammation and/or necrosis
How positive is “positive”??
How positive is “positive”?  

5-year PFS: 89%  

59%  

16%  

Early interim PET  

Minimal residual uptake  

Negative  

Positive  

Time in years  

Cumulative progression-free survival  

Mikhaeel NG et al, Ann Oncol 2005;16:1514-1523, Fig 3A
Considerations in trial planning

- Reproducibility of reads in context of risk-adapted trials
E3404: Phase II Study of Response-Adapted Therapy for DLBCL

Baseline PET

R-CHOP x 4

PET during C3

PET pos → R-ICE x 2

PET neg → R-CHOP x 2

Central review of interim PET; designated + or – by visual assessment

PI: Lode Swinnen
ECOG criteria for interim PET (binary result)

- Evaluate only sites abnormal at baseline
- Pos sites must have anatomic correlate
- Abnormal = focal appearance and intensity > liver
- Marrow, spleen abnormal only if focal and clear
- Symmetric foci in chest abnormal only if remaining scan is pos
- New foci considered pos only if remaining scan is pos, or if new lesion is focal, very intense, and has CT correlate
E3404: PET read reproducibility

68-72% agreement (k: 0.4 – 0.5)

- 16 – 29% interim scans read as positive
- Consensus reached in 3 of 12 discordant cases

Horning SJ et al, Blood 2010;115:775
E3404: PET read reproducibility

- Similar reproducibility of ECOG & London criteria
- Sources of disagreement
  - Para-aortic, spleen, bone
  - CT correlates of residual “positive” sites often absent or equivocal

Horning SJ et al, Blood 2010;115:775
SUV vs. CT measurements

A

Percent Change in SUV_{bw max}

ICC -0.94

Jacene HA et al, JNM 2009;50:1760
SUV vs. CT measurements

Percent Change in Two-dimensional CT Size (WHO)
ICC – 0.33

Mean Percent Change in Two-dimensional CT Size of 4 CT Readers for 52 Individual Tumors

Jacene HA, JNM 2009;50:1760
Cycle 2 PET in DLBCL

3-point visual scale (65% accuracy)

Change in SUV max (76% accuracy)

Lin C et al, JNM 2007;48;1626
SUV analyses

• Potential for greater reproducibility
• Standardization critical
• Although no clear “cut-off”, further prospective studies are warranted – particularly correlating with visual criteria
• May help in prognosticating “minimal residual uptake”? 
Phase II US Intergroup trial (S0816): stage III-IV HL

CT1 + PET 1 (Staging)

2 cycles ABVD

CT2 + PET2

PET positive

6 cycles BEACOPP esc. (if HIV neg)

CT3 + PET3

Follow-up (no radiation)

PET negative

4 cycles ABVD

CT3 + PET3

Follow-up (no radiation)

IPS 0-7

(≥ 160 pts)

5-point scale, with exploratory SUV studies

Soon to open: CALGB risk-adapted trial in HL
COG study: high-risk pediatric HL

CR: Rapid early response

- ABVE-PC
- PET1

ABVE-PC

CR: Rapid early response

- ABVE-PC x 2
- CT
- Risk-adapted radiation *

PR or SD: Slow response

- PET2, CT
- Ifos/vino x 2
- ABVE-PC x 2
- CT, PET
- Risk-adapted radiation *

* Initial bulk disease, nonbulk disease with slow response
COG study: high-risk pediatric HL

• Response criteria
  – Modification of revised IWG criteria
    • CR: nodal size criteria and PET neg
    • PR: nodal size criteria, either PET neg or pos

• Endpoints
  – Maintain comparable overall survival in rapid and slow responders through risk-adapted therapy
  – Investigate whether PET1 identifies group distinct from “rapid early responders” (e.g. PET1+, PET2-), who might require augmented therapy
U.S. observational studies: example

- CALGB imaging protocol for de novo DLBCL
- Centralized PET review: 5-point visual scale and SUVs

Baseline PET/CT $\rightarrow$ R-CHOP vs R-EPOCH $\rightarrow$
PET/CT post cycle 2 and cycle 6 (no intervention)

**Negative**
- 0 no abnormal activity (tumor cold)
- 1+ minimal activity (tumor < background)
- 2+ equivocal (tumor = background)

**Positive**
- 3+ moderate activity (tumor > background)
- 4+ marked activity
Managing a positive post-therapy PET

• Extending course of chemotherapy?
  – Doubtful that additional cycles of same chemo will help, even if brisk CT response
Managing a positive post-therapy PET

• Extending course of chemotherapy?
• Adding radiation?
  – Radiation may complicate future therapies
  – Chemoresistance and radioresistance often coexist
  – **Should not assume radiation is natural next step**
  – Positive PET may identify subset who stand NOT to benefit from radiation
Radiation in residually PET+ pts

Retrospective analysis: NHL with positive PET after chemo

Hodgkin’s: PET and radiation

81 pts with HL, stage I-IV
(retrospective analysis)

Stanford V chemo (8-12 weeks)

PET 1 (staging)

PET 2
(before pre-planned radiation)

75 PET neg pre-xrt

6 PET pos pre-xrt

Advani R et al, JCO 2007;25:3902
Hodgkin’s: PET and radiation

81 pts with HL, stage I-IV
(retrospective analysis)

Stanford V chemo (8-12 weeks)

PET 1 (staging)

PET 2
(before pre-planned radiation)

75 PET neg pre-xrt

3 relapses

6 PET pos pre-xrt

4 relapses:
3 in-field, 1 at margin

Advani R et al, JCO 2007;25:3902
Managing a positive post-therapy PET

- Extending course of chemotherapy?
- Adding radiation?
- Intensifying treatment, possibly with BMT?
  - Before considering escalating therapy, outside a trial, confirm disease persistence
False positives: implications for trial planning

Transverse PET, lower thoracic region

Sugawara Y et al, JCO 1998; 16: 173
False positives after Hodgkin’s therapy: implications for trial planning

Inflammatory node (SUV 9.4)

Thymic hyperplasia (SUV 3.7)

Brown fat (SUV 13)

Castellucci P, Nuc Med Commun 2005; 26: 689
An 18 year old with HL

Baseline  |  End of chemo  |  3 mo after chemo
Negative mid-PET: de-escalate therapy?

- Studying this makes sense but...
- A true negative PET may not mean ultimate eradication of disease
- Caution with early cessation of chemo (many logs of tumor may remain, depending in part on timing of PET)
- (For same reason, focusing radiation on residual PET+ foci, while reducing toxicity, may be ineffective)
Usual size at diagnosis

Lower detection limit of PET

Cure
Considerations: trial design

• Potential to more precisely tailor treatment to the individual patient
  – Changing definition of disease response
  – Changing risk stratification

• Prognostic significance not as clear-cut as earlier series suggested

• Prognostic value may reflect efficacy of the chemotherapy regimen
Considerations: trial design

- Investigation of SUV criteria: prospective analysis, comparison to visual criteria
- Threshold for treatment modification
- Role of biopsy
- Reproducibility of reads
- Conservative strategy best outside of a trial