Interim PET-Hodgkin’s Disease

Fellows talk
Fellow: Shweta Jain
Faculty: Ajay Gopal
Why is this a Question?

Early
- ABVD + RT
- ABVD

Advanced
- ABVD
- Beaçoapp

iPET
- Pos
- Escalation
- Salvage
- Neg
- De-escalation

Salvage
Talk outline

Advanced cHL

• Observational data
  – Retrospective
  – Prospective

• Response adapted approaches
  – Observational
  – Phase II
  – RCT
Observational Data

• Retrospective
  – Gallamini et al. 2014 (ABVD)
  – Zinzani et al. 2012 (ABVD)

• Prospective
  – Gallamini et al. 2007 (Joint Italian Danish study) (ABVD)
  – Cerci et al. 2010 (ABVD)
  – Hutchings et al. 2014 (ABVD)
  – Markova et al. 2012 (Beacopp)
The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale

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Design

• International cohort, Retrospective, 17 centers
• Jan 2002- Dec 2009, n=260
• Advanced cHL
  – Stage IIb-IV HL or stage IIa adv
• ABVD 4-8 cycles +/- RT
• FPS, PET pos -4-5
• Primary end point
  – PET2 accuracy in predicting outcome and PFS

Results

• ABVD x 2 (n=260) → PET2
  – PET2 pos: 45 (17%) - PET2 neg: 215

• 3 year PFS*
  – PET2 pos: 28% -PET2 neg: 95%

• 3 year OS
  – PET2 pos: 87% -PET2 neg: 99%

• PET2 Accuracy: 91%, NPV 94%, PPV 73%

• 45 pts with progression or relapse- IPS was not reliable (33 pts PET2pos, 12 pts PET2 neg)

Figure 1. Kaplan-Meier plot showing progression-free survival according to IPS group and PET results after two cycles of ABVD.
Early interim $^{18}$F-FDG PET in Hodgkin’s lymphoma: evaluation on 304 patients

Pier Luigi Zinzani · Luigi Rigacci · Vittorio Stefanì · Alessandro Broccoli · Benedetta Puccini · Antonio Castagnoli · Luca Vaggelli · Lucia Zanoni · Lisa Argnani · Michele Baccarani · Stefano Fanti

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Design

• Retrospective, 2 Italian centers
• June 1997 to June 2009, n= 304 pts
• Aim: association b/w PET2 and clinical outcome at end of Rx and during follow up.
• cHL : early =147 , advanced =157
• Rx : ABVD +/- RT
• PET assessment : Gallamini criteria *

Results

• ABVD x 2 – PET2 (n=304)
  – PET2 neg : 251  - PET2 pos : 53

• Advanced stage (n =157)
  – PET2 neg : 123  - PET2 pos : 34

• 9 year PFS *
  – PET2 neg- 88.6%  -PET2 pos 28.7%

• 9 year OS *
  – PET2 neg- 96.4 %  -PET2 pos 50.5%

Fig. 4 PFS (a) and OS (b) curves for patients with advanced-stage HL in relation to the PET+2 results.


Andrea Gallamini, Martin Hutchings, Luigi Rigacci, Lena Specht, Francesco Merli, Mads Hansen, Caterina Patti, Annika Loft, Francesco Di Raimondo, Francesco D’Amore, Alberto Biggi, Umberto Vitolo, Caterina Stelitano, Rosario Sancetta, Livio Trentin, Stefano Luminari, Emilio Iannitto, Simonetta Viviani, Ivana Pierri, and Alessandro Levis
Design

- Prospective cohort
- Advanced cHL
  - Stage IIb-IV HL and Stage Ila adv
- ABVD- 6 cycles +/- RT
- PET assessment: Gallamini criteria *
  - Pos - bright uptake
  - Neg – no uptake
  - MRU – similar/equal/slightly higher than med. Pool-neg

Results

- ABVD x 2 (n=260) → PET2
  - PET2 neg: 210 - PET2 pos: 50
- 2 year PFS
  - PET2 neg: 95% - PET2 pos: 12.8%
- Accuracy 92%, NPV 92%, PPV 93%, Sensitivity 81%, Specificity 97%
- Multivariate regression analysis: No prognostic value of IPS when information from PET2 added
- Other Significant Prognostic factors: Stage IV disease

Fig 2. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group.

Log-rank P < .02

Fig 3. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group and positron emission tomography.

Log-rank P = .00

Our objective was to assess the prognostic value of $^{18}$F-FDG PET after 2 cycles of chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in Hodgkin lymphoma (HL) patients overall and in subgroups of patients with early and advanced stages and with low and high risks according to the International Prognostic Score (IPS). **Methods:**

Hodgkin lymphoma (HL) is highly sensitive to standard chemotherapy, radiation therapy, or combined-modality therapy, with long-term cure rates expected to be more than 80% in patients receiving the standard treatment (1–4).
Design

- Prospective Brazilian study
- Aim: assess prognostic value of FDG-PET
- Aug 2005-Dec 2007, n=104
- cHL: 43 early, 61 advanced (stage III-IV)
- Rx:
  - Stage I,II- ABVD-4-6 cycles
  - Stage III- ABVD- 6-8 cycles
  - Stage IV- ABVD 8 cycles
- PET assessment: Gallamini criteria *

Results

• ABVD x 2 -> PET2 (n=61)
  – PET2 neg : 40 -PET2 pos: 21
• 3 year EFS
  – PET2 neg : 90.5% -PET2 neg : 53.4%
• NPV 90%, PPV 57.1%, Sens 75%, Spec 80%
• Univariate analysis : PET2 was the only factor associated with treatment failure

FIGURE 3. Kaplan–Meier plot showing EFS for PET2 results.
In Vivo Treatment Sensitivity Testing With Positron Emission Tomography/Computed Tomography After One Cycle of Chemotherapy for Hodgkin Lymphoma

Martin Hutchings, Lale Kostakoglu, Jan Maciej Zaucha, Bogdan Malkowski, Alberto Biggi, Iwona Danielewicz, Annika Loft, Lena Specht, Dominick Lamonica, Myron S. Czuczman, Christina Nanni, Pier Luigi Zinzani, Louis Diehl, Richard Stern, and Morton Coleman

ABSTRACT

Purpose: Negative $^{18}$F-fluorodeoxyglucose (FDG) – positron emission tomography (PET)/computed tomography (CT) after two cycles of chemotherapy indicates a favorable prognosis in Hodgkin lymphoma (HL). We hypothesized that the negative predictive value would be even higher in patients responding rapidly enough to be PET negative after one cycle. This prospective study aimed to assess the prognostic value of PET after one cycle of chemotherapy in HL and to assess the dynamics of FDG uptake after one cycle (PET1) and after two cycles (PET2).
Design

• Prospective multicenter; US, Italy, Denmark
• 126 pts PET1, 89 pts PET1 and PET2
• Aim: prognostic value of PET1
• cHL : Early (n=44) and advanced (n=82)
• Rx
  – Early : ABVD x 2-4 + RT/ ABVD x 6
  – Advanced : ABVD x 6 +/- RT
• PET Assessment : FPS

Results

• ABVD x 1 PET1 (n=126)
  – PET1 neg : 89
  – PET1 pos : 37

• ABVD x 2 PET2 (n=89)
  – PET2 neg : 76
  – PET1 pos : 13

• 2 year PFS
  – PET2 : 90.2%
  – PET2 pos : 38.5%

• PET2 Accuracy: NPV 90.8 %, PPV 84.6%, Sens 61.1%, Spec 97.2%

Role of [18F]-fluoro-2-deoxy-D-glucose positron emission tomography in early and late therapy assessment of patients with advanced Hodgkin lymphoma treated with bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone

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Abstract
The prognostic value of positron emission tomography (PET) in early therapy response assessment, after completion of chemotherapy and 3 months after the end of treatment in become one of the most curable malignancies. Today the prognosis is excellent, with reported 10-year overall survival rates of 86% in patients with advanced HL after combined treatment modalities [1]. The German Hodgkin Study Group

Design

- Prospective, single center
- Aim: confirm and extend prognostic value of PET in early response assessment (PFS)
- Jan 2004- Feb 2008, n=69
- Advanced cHL (stage IIb-IV)
- Rx: Beacopp (esc-6-8, condensed) +/-RT
- PET4: after 4 cycles of Beacopp
- PET assessment * : pos residual mass and uptake slightly above the mediastinum

Results

• Beacopp x 4 – PET4 (n=69)
  – PET4 neg : 51
  -PET4 pos : 18
• NPV 94%

Figure 1. PET-4. Kaplan-Meier curves showing progression-free survival in interim PET-4 positive ($n = 18$) and negative ($n = 51$) patients after four initial cycles of BEACOPP_{escalated}. The log-rank test showed a significant intergroup difference ($p = 0.016$).
Risk adapted approaches

• Observational
  – Gallamini et al 2011 (GITIL) : retrospective

• Phase II
  – Pres et al 2016 (ABVD to Beacopp)
  – Ganesan et al 2015 (ABVD to Becopp)
  – Zinzani et al 2016 (HD0801 trial) (early Salvage SCT)

• RCT
  – Johnson et al 2016 (RATHL) (ABVD,AVD,Beacopp)
  – Casasnovas et al (interim analysis) (escBeacopp to ABVD)
Early chemotherapy intensification with BEACOPP in advanced-stage Hodgkin lymphoma patients with a interim-PET positive after two ABVD courses

Summary
Interim 2-[18F]Fluoro-2-deoxy-D-glucose Positron Emission Tomography performed after two chemotherapy cycles (PET-2) is the most reliable predictor of treatment outcome in ABVD-treated Hodgkin Lymphoma (HL)

Design

- GITIL, retrospective, 8 Italian, 1 North American center
- Jan 2006-Dec 2007, n=165
- Advanced cHL (Stage IIa-adv, stage III-IV)
- ABVD x2 → PET2
  - PET2 pos → Beacopp
  - PET2 neg ABVD x 4 cycles =/- RT
- PET assessment: FPS

Results

• 2 year FFS
  – PET2 neg : 92% -PET 2 pos : 65%
  Appeared that escalation with Beacopp improved the FFS in PET positive arm

(A)

Failure free survival

Months from diagnosis

All patients:

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US Intergroup Trial of Response-Adapted Therapy for Stage III to IV Hodgkin Lymphoma Using Early Interim Fluorodeoxyglucose–Positron Emission Tomography Imaging: Southwest Oncology Group S0816


Design

• US Intergroup, Prospective Phase II trial
• Sep 2010 to Dec 2012, n= 336
• Aim:
  – Improve 2 year PFS with response adapted Rx
  – Improve 2 year PFS of PET2 pos
• Advanced cHL- Stage III or stage IV

ABVD
Full dose, on schedule, no G-CSF
Closed 12/1/2012

PET/CT #1 (Staging)
N = 358 HIV negative (336 eligible and evaluable)

Two cycles ABVD
n = 331

PET/CT #2

n = 60 (18%)
PET positive

Six cycles eBEACOPP
n = 49 (+3 ABVD, +3 declined any protocol treatment)
Follow-up [no RT]

n = 271 (82%)
PET negative

Four cycles ABVD
n = 270
Follow-up [no RT]

PET/CT #3

PET/CT #3
Results

• Estimated 2 year OS : 98%, PFS : 79%

• 2 year estimate of PFS
  – PET2 Neg : 82% (CI 77-86) - PET2 pos : 64% (CI 50-75)

• Risk of disease progression for PET2 pos pts is 1.7 times higher than for PET2 neg (two sided p= 0.0442)

Phase II study of interim PET–CT-guided response-adapted therapy in advanced Hodgkin’s lymphoma

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Background: Combination chemotherapy ABVD (doxorubicin, bleomycin, vinblastine and dacarabazine) cures ~70% of patients with advanced Hodgkin’s lymphoma (aHL, stages IIIB, III and IV) while more toxic escalated BEACOPP (EB, combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) increases cure rates to 85%. Patients with a positive interim positron emission tomography–computed tomography

Design

• Phase II study, open label, single center
• Jan 2012 to Oct 2013, n= 50
• Advanced cHL (Stage IIb-IV)
• Rx ABVD x2- PET2
  – PET2 neg → ABVD x 4
  – PET2 pos → esc Beacopp x 4
• FPS scale assessment

Results

• 50 pts ABVD → 49 PET2
  – 41 PET2 neg → 39 pts ABVD x4 → PET → 34 remission, 5 progressed
  – 8 PET2 pos → 7 pts esc Beacopp →
    • 5 attained CR → 4 in CR at follow up, 1 relapsed after 6 months
    • 2 progressive disease

• Estimated 2 year EFS 75.7% (CI 68.4-83); OS 87.7% (CI 81.6-93.8)

• Univariate analysis- PET2 only factor that predicted EFS (bulky dis, IPS, type B symptoms)

Figure 1. (A) Kaplan–Meier survival curve showing the event-free survival (EFS, dotted line) and overall survival (OS, bold line) of the entire cohort. (B) EFS depending on the outcome of interim PET–CT scan carried out after two cycles of ABVD chemotherapy (bold line: PET-2-negative; dotted line: PET-2-positive). PET: positron emission tomography; CT: computerized tomography; ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine.
Interim Positron Emission Tomography Response–Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study

Pier Luigi Zinzani, Alessandro Broccoli, Daniela Maria Gioia, Antonio Castagnoli, Giovannino Ciccone, Andrea Evangelista, Armando Santoro, Umberto Ricardi, Maurizio Bonfichi, Ercole Brusamolino, † Giuseppe Rossi, Antonella Anastasia, Francesco Zaja, Umberto Vitolo, Vincenzo Pavone, Alessandro Pulsoni, Luigi Rigacci, Gianluca Guidano, Caterina Stelitano, Flavia Salvi, Chiara Rusconi, Monica Tani, Roberto Freilone, Patrizia Pregno, Eugenio Borsatti, Gian Mauro Sacchetti, Lisa Argnani, and Alessandro Levis

Phase II, HD0801 trial

• AIM: Early PET guided salvage with high dose chemo and ABMT- safe & effective

• Sep 2008- Apr 2013, 512 pts

• Advanced cHL (Stage IIb- IV)

• Rx – ABVD x 2 – PET2 pos- Salvage
  – High dose chemo : IGEV
    • PET neg → ABMT
    • PET pos → Mel- ABMT-> RIC HLA matched Allo
    • OR→ Melphalan- Beam ABMT

• PET assessment FPS- Juweid criteria

ABVD x 2 cycles → PET2

Results

• ABVD x2 → PET2 (n=512)
  – PET2 neg : 409 (80%) → ABVD x 4 (73 dis progression)
  – PET2 pos : 103 (20%) → 2 refused Rx, 20
    ABVD/different Rx – (21 pts showed dis progression)
• Salvage arm: 81 pts → IGEV x4
  – 43 pts PET neg → ABMT (Beam) → PET neg
  – 38 pts PET pos →
    • 24 pts tandem ABMT → 11 PET neg
    • 14 pts allo SCT → 4 PET neg
  – 23 pts PET pos

Patients proceeded to IGEV salvage (n = 81)

- Negative patients (n = 43)
  - BEAM-conditioned ABMT
    - Negative patients (n = 43)

- Positive patients (n = 38)
  - High-dose melphalan BEAM-conditioned ABMT (no HLA-matched donor) (n = 24)
    - PET-negative patients (n = 11)
  - High-dose melphalan reduced-intensity alloBMT (HLA-matched donor) (n = 14)
    - PET-negative patients (n = 4)

Patients on different salvage treatment (n = 5)

- Patients continued to four or more ABVD cycles (n = 15)
  - Complete response (n = 11)
  - Partial response (n = 1)
  - Disease progression (n = 3)
Results

• Estimated 2 year OS 97%, PFS 80%
• Estimated 2 year PFS
  – PET2 neg : 81% (CI 76- 84)
  – PET2 pos : 76% (CI 66-84)
    • * 81 on IGEV salvage : 74% (CI 62-82)

Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin’s Lymphoma

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Design

• Multicenter RCT, International
• Aug 2012 to Dec 2013
• Primary outcome : Non-inferiority PET2 neg de-escalation arm: 3 year PFS
• Advanced stage cHL
  (stage IIb-IV, IIa with adverse features)
• ABVD x 2 --> PET2
  – PET2 neg → 1:1 randomized
    • ABVD vs AVD without Bleomycin
  – PET2 pos → Beacopp
• PET assessment: 5PS

Results (PET2 neg)

• ABVD x 2 - PET2 (n= 1119)
  – PET2 neg : (n=937) → 1:1 randomized
    • ABVD (n= 470) vs AVD (n= 465)

• 3 year PFS
  • ABVD : 85.7% (CI 82.1-88.6)
  • AVD : 84.5% (CI 80.7-87.5)
  – 3 year OS
    • ABVD : 97.2% (CI 95.1-98.4)
    • AVD : 97.6% (CI 95.6-98.7)

• Hazard ratio favored ABVD for pts with type B symptoms : 1.76 (CI 1.04-2.97)

Results (PET2 pos)

- iPET positive- 182 pts → (22 deaths, 55 events of PD, relapse or death during follow up)

  94 Beacopp-14 vs 78 esc Beacopp

- 3 year PFS 67.5% (CI 59.7-74.2)

- 3 year OS 87.8% (CI 81.5-92.1)

- ? Higher iPET score- more likely to Rx failure

Interim Analysis AHL 2011

- AHL 2011 trial, phase III randomized trial
- May 2011- May 2014, 782 pts
- Advanced cHL (stage IIb-IV)
- Standard: esc Beacopp x 6 arm (n=401)
- Exp: esc Beacopp x 2- PET2 → (n=381)
  - PET2 neg → ABVD x 4
  - PET2 pos → esc Beacopp x 4

- Primary end point 5 year PFS, non-inferiority trial

Results

• Std esc Beacopp x 2 - PET
  – PET2 neg : 353 pts $\rightarrow$ esc Beacopp x 4
  – PET2 pos : 48pts $\rightarrow$ esc Beacopp x 4

• Esc Beacopp x 2 $\rightarrow$ PET
  – PET2 neg : 319 pts $\rightarrow$ ABVD x4
  – PET2 pos : 49 pts $\rightarrow$ esc Beacopp x 4

Results

• Estimated 2 year PFS (median follow up 16.3 months)
  – Std arm : 91.6%  -Exp arm : 88.3% (p=0.79)

• Estimated OS similar in both arms, regardless of PET2

• PET2 pos : significantly lower PFS in both randomized arms

Summary

• Interim PET scan: prognostic—regimen?
• Interim PET scan: Predictive—evolving

To do or not to do: do it with informed discussion

Questions?