Interim PET with emphasis on the effect of drugs

*What can we learn from animal studies?*

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Principles of response assessment

- **Chemosensitivity**
  - Responders vs non-responders

- **Chemoresistance**
  - Sufficient response?

**Graph**

- **Number of malignant cells** (Y-axis)
- **Time** (X-axis)

- **Diagnosis**
- **Chemo**
- **PET-detection**

- **False positive**
- **Quantification**
- **False negative**

- **Death**

**Symptoms**

- **Time**
- **Radiotherapy**
Early response assessment in DLBCL after 7 days of treatment

- Materials and methods
  - 29 patients
  - Newly diagnosed DLBCL
  - Treatment with R-CHOP
  - PET/CT after 7 days

<table>
<thead>
<tr>
<th>Table V.1. Patients Characteristics</th>
<th>Early PET negative (n=13)</th>
<th>Early PET positive (n=17)</th>
<th>Overall (n=30)</th>
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Early response assessment in DLBCL after 7 days of treatment

29 patients
- 17 patients positive on early PET
  - 2 refractory disease
    2 relapsed (12 and 23mths)
  - 13 disease free
    (follow-up 20 mths)
- 12 patients negative on early PET
  - No relapses (21 mts)

Visual: NPV=100%, PPV=24%
Quantitative: NPV=100%, PPV=29%

Despite a significant residual uptake on early PET, this patient obtained a complete remission at interim PET, and is still disease free after a follow-up of 29 months.
Early response in DLBCL after 7 days

Analysis based on tumor bulk

Analysis based on the worst responding lesion

Analysis based on tumor bulk after partial volume correction

Analysis based on the worst responding lesion after partial volume correction

Figure IV.7. Overview of the different relative parameters of FDG-decrease for the different analyses with corresponding outcome of the patient.

- No evidence of disease
- Primary refractory disease
- Relapse after 12mths
- Relapse after 23 mths
Principle of response assessment: influence of different treatments

- Diagnosis
- Chemo
- PET-detection
- Radiotherapy

- Number of malignant cells
- Time

- Death
- Symptoms

- Rapid regrowth
- Slow regrowth

- Aggressive cytotoxic
- Cytostatic drugs
Intensified therapies are associated with a fast response, but...

  - 2xBEACOPPesc
  - Sens 50%, more false negative lesions
  - PPV 60%, more false positive lesions

  - 45 pt advanced staged HL
  - 2xBEACOPPesc, followed by 4x ABVD
  - Sens 60% spec 79% NPV 87%, PPV 45%

→ a decrease in accuracy
   more false negative results
   more false positive results
Inflammation and its interference with early response assessment

Inflammation evoked by therapy
more effect of therapy -> more inflammation

- Diagnosis + chemo
- chemo
- chemo
- chemo
- chemo
- chemo
- chemo
- (radiotherapy)

Time

Number of malignant cells

PET-detection

Symptoms

Death
Is inflammation important in clinical practice?

- High false positive rate after radiotherapy

- Jacene et al, *JNM 2009*, 
  - RIT (Zevalin, Bexxar)
  - Continuous decrease in FDG-uptake 24 wks after therapy

  ➔ inflammatory changes with the recruitment of immune cells and high FDG-uptake
High incidence of false positive PET after rituximab in NHL

  - 51 pt DLBCL+MCL,
  - Midtherapy (2-4 cycles): PPV= 33%, Sp 68%
  - Posttherapy: PPV=19%, Sp 80%

  - 90 pt NHL, 37 rituximab, PPV 44%, Sp 70% after 2 cycles

- Moskowitz et al, *JCO* 2010,
  - PET after intensified RCHOP4 in 97 patients
  - 59 PET neg – consolidation with ICE, excellent prognosis
    \(\Rightarrow\) midtreatment negative = excellent prognosis
  - 38 PET positive – 33 biopsy negative (2 sample error)
    \(\Rightarrow\) high frequency of false positive midtreatment, outcome identical as PETnegative patients
False positive PET after rituximab in NHL

Baseline

RCHOP 3

RCHOP 6

→ inflammatory changes with the recruitment of immune cells?
Inflammation and its interference with early response assessment

Spaepen, EJNM 2003
SCID mice with cyclophosphamide, ex-vivo measurements
Inflammation and its interference with early response assessment

- Can we improve correlation of FDG-uptake with tumor response?
  1. By the administration of steroids?
  2. By the use of other PET-tracers: FLT as a marker of cellular proliferation?

- Materials and methods
  - SCID-mouse subcutaneous injected with lymphoma cell line
  - Treatment with chemo at day 0, half the mice hydrocortisone
  - Measurements of tracer-uptake by microPET
Does the presence of anti-inflammatory drugs (corticosteroids) influence the FDG-uptake and the cellular response after chemotherapy?

Cyclophosphamide
Cyclophosphamide + hydrocortisone

Alternatives for FDG? Proliferation tracers.

- Can we improve correlation of tracer uptake with tumor response by using FLT as a marker of *cellular proliferation*?
  - Wagner, *Cancer Research* 2003
    - High uptake in murine model lymphoma, correlation with BrdU in mice
    - Correlation with Ki67 in patients, high grade vs low grade lymphoma
Metabolism of Thymidine

Extracellular compartment

THYMIDINE

Passive diffusion
Facilitated transport

Intracellular extra-DNA compartment

THYMIDINE

catabolization

dTMP → dTDP → dTTP

de novo pathway

dUMP ↔ L-glutamine, CO₂, ATP, L-aspartate

Salvage pathway

DNA
Metabolism of FLT: marker of proliferation

Cancer: TK1 (x3-x4) degradation ↓

‘metabolic trapping’
Response evaluation by FLT-PET

Rectumca: FDG + FLT before, during and after CRT

FDG d0  |  FDG post CRT  |  FLT d0  |  FLT post CRT
Inflammation and early response assessment: is FLT more accurate?

Granta cell line (Mantle cell lymphoma) in SCID mouse

FDG and FLT-uptake after cyclophosphamide

Brepoels et al. JNM 2007
Illustration of the high specificity of FLT-PET compared to FDG-PET.

(A) PET before therapy shows an extensive lymphoma localization in the proximal tibia
(B) After chemotherapy and local radiotherapy, FDG-uptake is still clearly positive but post-radiotherapy changes cannot be distinguished from persistent lymphoma
(C) FLT-PET after therapy shows a focal uptake in the proximal tibiae which suggests persistent lymphoma (mark the high FDG-uptake in the bone marrow in the non-pathological tibia).

The patient relapsed several months later.
Alternatives for FDG? Proliferation tracers.

- Can we improve correlation of tracer uptake with tumor response by using FLT as a marker of cellular proliferation?
- Metabolism ≠ proliferation: cytostatic and cell cycle targeted agents?
  ➞ Is FLT more accurate in cell cycle targeting therapies?
Inflammation and early response assessment: is FLT more accurate?

Mantel cell lymphoma R/mTOR inhibitor

FLT d0

FLT d+7
Is FLT more accurate in cell cycle targeting drugs?

Early response assessment after therapy with mTOR inhibition.
(A) FDG-PET/CT before therapy (B) FLT-PET/CT before therapy (C) FLT-PET/CT one week after the first administration and (D) FDG-PET/CT after 6 weeks of therapy
The patient obtained a disease free status after a few months of therapy and is still in complete remission (36 months)
Inflammation and early response assessment: is FLT more accurate?

Granta cell line (Mantle cell lymphoma)

FDG and FLT uptake after cyclophosphamide

FDG and FLT uptake after temsirolimus

FDG and FLT uptake after cyclophosphamide
histology after mTOR treatment showed a decreased cyclin d1 expression shortly after therapy, which increased again on D+7

- Synchronization of the cells? Repair mechanisms?
- Close interactions of FLT uptake with cellular metabolism
Other more specific tracers?

- Apoptosis: annexin, caspase-3 ([18F]ICMT-11)
- Lymphoma specific tracers: Recombinant anti-CD20 antibody fragments,…
- $^{89}$Zr-Zevalin
- Methionine
- FET
Opportunities of animal studies

- No limitations on numbers of scans, radiation protection: time course of tracer uptake
- Standardization
- Different treatment regimes, evaluation of the different components of a regimen
- Histological confirmation possible, ex vivo measurements of enzymes, ....

A. FDG uptake after cyclophosphamide

<table>
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<tr>
<th>Day</th>
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<tbody>
<tr>
<td>D0</td>
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<tr>
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<tr>
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<td>D+14</td>
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But...

- Evaluation of therapy response, not of “sufficient” response. Prognostic significance?
- Human cell lines in immunodeficient mice: interference with the immune system? HL?
- Syngeneic mice: growth of lymphoma-like pathology, potential to evaluate the effect of new treatment strategies (E.g. vaccination studies, Chaise, 2007, cancer immunother)
- No new more accurate tracers compared to FDG have been developed, potential mainly because of their higher specificity
Animal studies allow the evaluation of

- Interaction of tracers with cellular metabolism
- Interaction of therapy with cellular metabolism
- Interactions of therapy with uptake of PET tracers

“I go home today. They cured me using this new miracle drug. I’m afraid it’ll be years before it’s approved for humans.”