Clinical Molecular Imaging of Cancer: Why, When and How?

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Personalized Medicine – Targeted Therapy

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Epidermal growth factor receptor (EGFR) mutations increase the sensitivity of lung cancer cells to gefitinib

Paez et al. Science (2004) 304:1497-1450, Figure 1, edited

Targeted therapy of cancer
Treatment of lung cancer patients with the EGFR kinase inhibitor gefitinib

Gefitinib can be radiolabeled with fluorine-18 without changing its chemical properties

Distribution of [18F]gefitinib in tumor bearing mice

Su et al. Eur J Nucl Med Mol Imaging. 2008;35:1089-1099. Figure 5, Table 2
The hallmarks of cancer

Oncogenes and Glucose Metabolism


Hanahan and Weinberg (2011)

Kreimer & Pouyetsepov. Cancer Cell 13:472-482 (2008) Figure 2 (edited)
Effect of EGFR kinase inhibition on tumor FDG-uptake

- Baseline: 2 x 1 mg Gefitinib
- Gefitinib sensitive (L758R Mutation)
- Gefitinib resistant (Ras Mutation)


Monitoring tumor response with FDG-PET

Early response on FDG-PET and Survival in patients with non-small cell lung cancer

Mileshkin et al. (2011) 17:3304-15, figure 2B
Zander et al. J Clin Oncol (2011) 29:1701-8, figure 2A

Role FDG-PET in treatment monitoring

- Genetically defined sensitivity (EGFR mutations amplification)
- Secondary Mutations
- Other Signaling Pathways
- PET response
- Change Treatment
- Continue Treatment

Trial of Erlotinib, Gefitinib (+/- "X")
- Total of Eotaxin, Gefitinib (="X")
- Outcome in an individual patient
- Drug efflux
- Ligand expression

Monitoring tumor response with FDG-PET
PET-Plan Study
Optimization of radiotherapy planning of patients with inoperable locally advanced non-small-cell lung cancer with F-18-FDG
Prospective randomized multicenter therapy optimizing trial
21 Centers, 396 Patients, start: Nov. 2009

- Arm A: CT based target volume delineation
- Arm B: PET based target volume delineation
- Dose escalation study.
- Dose limitation: tolerance of normal tissue
End point: Local tumor control

New Targets for PET
Peptide hormone receptors are excellent targets
- Expression on the cell surface
- Peptide hormones bind to these receptors with high affinity and specificity -> the receptors have a characteristic structure that can be recognized by an imaging agent
- Peptide hormones can serve as starting points for tracer development

Why peptides as radiopharmaceuticals?

Peptides labeled with radiometals can be used for diagnostic and therapeutic purposes.

Nuclear Medicine is more than Molecular Imaging

"This paper is a report of successful therapy of a case of metastatic adenocarcinoma of the thyroid treated by the principle of specific internal radiation with radioactive iodine."
Somatostatin receptors as a target for imaging and therapy

Metastatic NET before Therapy

Metastatic neuroendocrine tumor

After three cycles $^{177}$Lu-DOTA-TATE

Radionuclide therapy with $^{90}$Y-DOTA-TOC

Response rate: 34%

Voxel based dosimetry for calculation of tumor dose

89 \text{Lu-DOTATATE} therapy

Average dose 5.1 \text{Gy/GBq} = 76 \text{Gy/30 GBq}

Scheler, Fischer, Welld 2011

The bombesin receptor family

- Bombesin: 14 aa, found in toad bombina bombina
  Glp-Gln-Arg-Leu-Gly-Asn-Gln-Try-Ala-Val-Gly-His-Leu-Met-NH$_2$
- GRP: Gastrin releasing peptide 27 aa, human counterpart
  Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-NH$_2$

Bombesin receptors
- BB1 receptor (neuromedin B receptor)
- BB2 receptor (gastrin-releasing peptide receptor)
- BB3 receptor (orphan bombesin receptor)
- BB4 receptor (only amphibians)

GRP receptor expression in human prostate cancer

- GRP receptors are expressed in PIN (prostate intraepithelial neoplasia) and prostate cancer, but not in normal prostate or hyperplasia (n=36)

The bombesin receptor family

Bombesin based radioagonists were studied in preclinical models and patients.

Problems encountered
- Limited metabolic stability
- High uptake in the gastrointestinal tract
- Side effects like nausea, vomiting, cramps in clinical studies
- Potential mitogenic effects

Bombesin Antagonists as an Alternative?
- Promising preclinical and clinical results with somatostatin antagonists
- Bombesin antagonists are being developed for anticancer therapies
- Less/no side effects of bombesin antagonists expected

GRP receptor antagonist CBC-AR-06

CBC (stable chelator for Cu²⁺)  Spacer (PEG₈₄₄)  Statin-based bombesin antagonist (active group)

- \( ^{64} \text{Cu} \) half-life 12.7 h  PET imaging for several hours to allow for urinary clearance of the peptide
- \( IC_{50} \) CBC-AR-06 = 5.5 ± 1.3 nmol/L (assessed by in-vitro GRP receptor autoradiography using \( ^{125} \text{Tyr}-\text{Bombesin} \))

Results small animal PET/CT
Imaging of bombesin receptors in prostate cancer

Bombesin receptor autoradiography ex vivo

$^{64}$Cu-CBC-AR-06-PET/CT

4 h p.i.

Bombesin and Choline PET/CT in a patient with PSA recurrence

Choline PET/CT

0 6 SUV

Bombesine PET/CT

0 5 SUV

Combination therapy with the bombesin receptor antagonist $^{177}$Lu-RM2 and rapamycin

Dumont, Mansi, et al. WMIC 2011

Nude mice bearing PC3 xenografts

Percent survival

Days

100

50

0

100 150 200

Untreated

rapamycin + Mg

$^{177}$Lu-RM2 + Mg

rapamycin + RM2

Duranton, Manci, et al. WMIC 2011
PET imaging in oncology

Research
• Proliferation
• Hypoxia
• Apoptosis
• Receptors (Integrins, Bombesin, CXCR4, Folate)
• Metabolism (Glucose, amino acids, lipids, ...)

Regulatory approval
• Glucose metabolism (FDG)
• Described 1980, approved 2000, reimbursed (in Germany) ????

They all fly, but do they need the same regulations?

Airbus 380-800
Hang glider
Toy plane

Where to invest?

No reported side effects of PET
Radiopharmaceuticals in 81,801 applications

210,000 NSCLC/year in the US
~ 40,000 resections w/o PET ~ 17000 not curative w/PET ~ 5000 not curative

*extrapolation of the data of the PLUS study (van Tinteren 2002)