Personalisierte Medizin – zurück in die Zukunft

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The first molecularly targeted cancer therapy

Radioactive Iodine Therapy: Effect On Functioning Metastases of Adenocarcinoma of the Thyroid
Seidlin, Marinelli, Oshry. JAMA 1946

„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.“
Celebrated Patient BB

1943
Prior to Radioiodine Tx

1949
After Radioiodine Tx

Courtesy of Lenny Freeman, Montefiore Hospital

Siegel E. Cancer Biother Radiopharm 1999
Seidlin et al. JAMA 1946
Precision medicine for cancer

Theranostics - combining imaging and therapy

A non-specifically cytotoxic agent concentrates in the tumor tissue

“Conventional” precision therapy

A drug inhibits a target systemically, which is more toxic for cancer cells

Tumor cell death
“Conventional” precision medicine

Requires
• Understanding of the complex signaling networks
• Understanding of feedback mechanisms that may lead to resistance
• Continuous inhibition of the networks, i.e. continuous side effects
A 38-year-old man with BRAF-mutant melanoma and miliary, subcutaneous metastatic deposits.

Before vemurafenib

Week 16 on vemurafenib

Week 23 on vemurafenib

Wagle N et al. J Clin Oncol (2011) 29:3085-3096, Figure 2 edited
Theranostics

Requires

• Only the accumulation of sufficient amounts of radioactivity
• A limited number of treatment cycles
• Typically only mild side effects for a brief period of time
• Radiation doses to normal organs is dose limiting

\( ^{131} \text{I SPECT/CT} \) in thyroid cancer
Receptor imaging of malignant tumors
Somatostatin receptor imaging with $^{68}$Ga-DOTA-TATE

Carcinoid in the ilium
Treatment of NETs: NETTER 1 trial

• Randomized comparison of
  – $^{177}$Lu-DOTATATE
    (4 cycles of 7.4 GBq every 8 weeks)
    vs.
  – Octreotide LAR
    (60 mg every 4 weeks)
• 230 patients with grade 1-2 metastatic midgut NETs
• Median PFS (primary endpoint)
  – Not reached for $^{177}$Lu-DOTATATE
  – 8.4 months for Octreotide
• Deaths: 14 for $^{177}$Lu-DOTATATE vs. 26 for octreotide LAR
  ($p = 0.0043$, interim analysis)

Milliardeninvestition
Siemens kauft CTI

Die Medizintechnik-Sparte von Siemens will für rund eine Milliarde Dollar die US-Firma CTI Molecular Imaging kaufen.


Proposed Tender Offer by Novartis

Novartis Oncology Expertise to Facilitate Ongoing Development of Theragnostic Pipeline

October 30, 2017, Saint-Genis-Pouilly, France - Advanced Accelerator Applications S.A. (NASDAQ: AAAF) (AAA or the Company), a leader in nuclear medicine theragnostics, today announced that it has entered into a Memorandum of Understanding with Novartis, pursuant to which Novartis proposes to make a cash tender offer to acquire all the outstanding shares of AAA, including shares represented by American Depositary Shares (the "ADSS"), for $41 per ordinary share and $82 per ADS (each representing 2 ordinary shares), in a transaction that is valued at approximately $3.9 billion. This represents a 47% premium to the 30 volume-weighted trading days prior to the unaffected share price on NASDAQ on September 27, 2017.
PSMA PET in PubMed
Therapy of metastatic prostate cancer with a $^{177}$Lu PSMA I&T ligand

71y/o patient, s/p Doc/Abi/Enza/Ra-223

Before therapy
PSA = 755 ng/mL

Cycle 1

Cycle 2

Cycle 3

Cycle 4
PSA < 0.2 ng/mL

$^{68}$Ga-PSMA-11 PET/CT

Heck et al. J Urol (2016) 196:382–391, Figure 4, edited
Initial experience with $^{177}$Lu-PSMA-618 targeted therapy

- ** PSA change**
  - N = 99
  - 45%

- **Administered activities ($^{177}$Lu-PSMA-617)**

<table>
<thead>
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<th>Administered activity (GBq)</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
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</table>

- 145 patients recruited at 12 centers
- Metastatic castration resistant PC
- After Enza/Abi or docetaxel

First prospective trial of $^{177}$Lu-PSMA-617 for castration resistant prostate cancer

PSA decline > 50% in 57% of patients
> 30% in 70% of patients

Median OS: 13.5 months

Therapy of metastatic prostate cancer with a $^{225}$Ac labeled -PSMA ligand

Kratochwil, J Nucl Med 2016; 57:1941–1944, Figure 2
Castration resistant prostate cancer can present with FDG positive, PSMA negative metastases (and vice versa)

Despite the success of PSMA targeted imaging and therapy other targets need to be studied
Gastrin releasing peptide receptor (GRPr) a G protein coupled receptor as a theranostic target for prostate cancer

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

GRPR PET/CT (⁶⁸Ga-RM2, GRPr antagonist)

Final pathology
Gleason 7 (3+4)
Bilat
Dominant ant bilat
ECE+
SV -
LN -

Michaud et al. Eur Urol Oncol, in press
Tumor detection with GRPR PET/CT

- 64 areas in total evaluated: 55 areas with PCa, 9 areas without Pca (16 pts)
- ROC curves MRI, $^{68}$Ga PET-CT, Combined and SUVmax

Michaud et al. Eur Urol Oncol, in press
Dual modality GRPr ligands for Prostate Cancer Imaging

HZ220

IR650

GRPr
Antagonist

DOTA

Radioactivity uptake
in cell culture

Unblocked
Blocked

FACS

Unstained HZ220

PC3 cells

PET/CT

Fluorescence

Ex-vivo imaging

Unblocked
Blocked

In-vivo imaging