EAHP 2016
Seminar PH2
Cancer Therapy: review of the present and a look to the future

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Conflict of interest

• Founder and Scientific Advisor of OncoPeptides AB
• Chief Medical Officer of Vivolux AB
Three cornerstones in the treatment of cancer

• Surgery
• Radiotherapy
• Pharmacology
  - Chemotherapy
  - Antibodies (tumor associated antigens)
  - Low Mw targeted therapy
  - Immunology adaption
  - Hormonal therapy

(We will focus on pharmacology today)

Questions

• Is hematotoxicity the most common dose limiting effect of chemotherapy?
• Is adjustment by BSA an ideal method to reduce variability in PK among patients?
• Does the introduction of targeted agents increase the demands for validated molecular pathology assessments of tumor material for each patient?
Case

• A 38 years old woman discovers a tumor in her right breast
Surgery is the most important part of treatment (for most solid tumors)

However, it is not always possible to cut out everything (size, nerves, vessels etc)

Microscopic spread

It is very common that surgery is combined with pharmacologic therapy or radiotherapy, i.e. "adjuvant treatment"

• Breast cancer surgery: lumpectomy and sentinel node biopsy (or axillary clearance if mets)

In our case patient has a 20 mm ductal cancer; ER+, HER-2 neg, low proliferation (15 %) and 2 lymph node mets (of 9 nodes removed). The PATHOLOGY REPORT is very important for the decision of further therapy.

• The prognosis have significantly changed; histological a non-aggressive tumor, but pos lgl is a bad prognostic sign
How will it go?
(Premenopausal N1)

Prof Carl Blomqvist, Helsingfors
Universitetssjukhus, Finland

Our case

How to reduce the risk for Relapse even more?

Chemotherapy act on cell division!

- Alkylators/Platinum compounds
- Topoisomerase inhibitors
- Tubulin inhibitors
- Anti metabolites
CHEMOTHERAPY – Characteristics

Substances delivered into the systemic circulation iv or orally (sometimes used locally) acts on cancer cells by:
- Induction of apoptosis
- Inhibits metastasis
- Inhibits angiogenesis
- Anti inflammatory effect

DNA is the target:
How about selectivity for cancer cells vs normal cells? -> Side effects limit the use

Different diseases have different sensitivity to cancer drugs

<table>
<thead>
<tr>
<th>Extremely high sensitivity</th>
<th>Low sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Head-neck</td>
</tr>
<tr>
<td>Testicular</td>
<td>Esophagus</td>
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<tr>
<td></td>
<td>GI</td>
</tr>
<tr>
<td>High sensitivity</td>
<td>Malignant melanoma</td>
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<tr>
<td>Lymphoma</td>
<td>NSCLC</td>
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<tr>
<td>Ovarial</td>
<td>Prostate</td>
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<tr>
<td>SCLC</td>
<td>Resistant</td>
</tr>
<tr>
<td>Intermedite sensitivity</td>
<td>Primary liver (HCC)</td>
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<tr>
<td>Breast</td>
<td>Renal</td>
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<tr>
<td>Sarcoma</td>
<td></td>
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<tr>
<td>Anal</td>
<td></td>
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</tbody>
</table>
Chemotherapy – Narrow therapeutic window

Acceptable side effects, e.g.:
- hair loss
- nausea
- stomatitis

Unacceptable:
- Death
- Irreversible neuropathy
- Renal failure
- Liver failure

Discussable:
- Secondary neoplasms
- Infertility

Hematotoxicity is very common

What can be done:
Anemia
Transfusion, EPO

Thrombocytopenia
Transfusion

Leukopenia
Isolation, Antibiotics, or G-CSF
Dose-limiting toxicity often hematotoxicity

Increased risk for severe infections when neutropenia (ANC <0.5 x 10⁹/L)

"Neutropenic fever"

Side effects from organs with high cellular turnover

SIDE EFFECTS from CHEMOTHERAPY

- Hematology (low blood cell counts)
- Gastrointestinal: nausea, mucositis, diarrhea
- Alopecia, Dry skin
- Fatigue
- Cardiac
- Neurological
- Central nervous: Fatigue, Nausea
- Psycho/neurological: cognitive impairment
- Renal
- Hypersensitivity reactions
Nausea

Basic treatment: corticosteroids and methoclopramide
+5HT3 receptor antagonists
+NK1 receptor antagonist

A young patient with lymph node metastases is considered a "risk patient" is invariably offered adjuvant chemotherapy (and radiotherapy and antihormonal therapy).

She is (in Sweden 2005) treated with six cycles of chemotherapy every three weeks; FEC x3 followed by Docetaxel x 3.

3-4 weeks after the first cycle she looses her hair, she is nauseous and uses methoclopramide in addition to 5HT3 blocker and aprepitant during FEC. With docetaxel she has muscle and joint pains, fatigue and a discoloration of her nails.

She is informed to be very observant for increased body temperature, but completes her chemo without infections.

Our case
Dose reduction or delay allowed for low blood cell counts

Dosing of Chemo based on BSA....


Pharmaceutical Industry; need to find model to transfer Preclinical tox data (LD10 or LD50) to phase 1 dosing
Nomogram (from DuBois and DuBois)
Simple dosage/BSA calculator rulers
Smartphone or web apps

Variability – effects of BSA correction
### Guidelines for dosing from FASS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing by</th>
<th>Adjustment for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fixed BSA</td>
<td>Weight GFR</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>x</td>
<td>(x)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Methotrexate</td>
<td>(x)</td>
<td>(x)</td>
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<tr>
<td>Lomustine</td>
<td>(x)</td>
<td>(x)</td>
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<tr>
<td>Temocapronol</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Decarbazine</td>
<td>x</td>
<td>(x)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Fludarabine</td>
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<td>x</td>
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<tr>
<td>Cytarabine</td>
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<td>x</td>
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<tr>
<td>Fludarabine</td>
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<td>x</td>
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<tr>
<td>Gemcitabine</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Liposomat</td>
<td>x</td>
<td>(x)</td>
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<tr>
<td>Vinblastine</td>
<td>x</td>
<td>(x)</td>
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<tr>
<td>Vinorelbine</td>
<td>x</td>
<td>(x)</td>
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<tr>
<td>Paclitaxel</td>
<td>x</td>
<td>(x)</td>
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<tr>
<td>Docetaxel</td>
<td>x</td>
<td>(x)</td>
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<tr>
<td>Vincristine</td>
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<tr>
<td>Etoposide</td>
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<td>x</td>
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<tr>
<td>Doxorubicin</td>
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<td>Epotaxin</td>
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<td>x</td>
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<tr>
<td>Bleomycin</td>
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<td>x</td>
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<tr>
<td>Mitomycin</td>
<td>x</td>
<td>(x)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>(x)</td>
<td>(x)</td>
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<tr>
<td>Carboplatin</td>
<td>(x)</td>
<td>X</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>(x)</td>
<td>(x)</td>
</tr>
<tr>
<td>Imatinib</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Botetorbin</td>
<td>x</td>
<td>(x)</td>
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<tr>
<td>Eribulin</td>
<td>x</td>
<td>(x)</td>
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<tr>
<td>Sunitinib</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Sosatisenib</td>
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<td>x</td>
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<tr>
<td>Rituximab</td>
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<tr>
<td>Trastuzumab</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Alectuzumab</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>x</td>
<td>x</td>
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**Note:**

All doses of drugs may be reduced if side effects occur. Only Temozolomide (and maybe cetuximab) may be increased in the absence of side effects (according to the label).

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### How will it go? (Premenopausal N1)

- **CMF is an old chemo combination**
  - Percent survivors: 68, 62, 54, 41

- How to reduce the risk for Relapse even more?

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**Prof Carl Blomqvist, Helsingfors Universitetssjukhus, Finland**
How will it go?
(Premenopausal N1)

Percent survivors

Prof Carl Blomqvist, Helsingfors
Universitetssjukhus, Finland
There is a slow but steady progress in the treatment results

Different diseases have different results

Pancreas ca

Breast ca

Testis, non-seminoma
Prof Carl Blomqvist, Helsingfors
Universitetssjukhus, Finland

How will it go?
(Premenopausal N1)

Percent survivors

0 5 10

0 20 40 60 80 100

Only surgery

CMF+RT

CMF

FEC+RT

Er+/FEC+RT+Tamoxifen 5y

Prof Carl Blomqvist, Helsingfors
Universitetssjukhus, Finland
How will it go?
(Premenopausal N1)

Prof Carl Blomqvist, Helsingfors
Universitetssjukhus, Finland

Yesterday’s therapy?

-Surgery and radiotherapy are very important options for localized disease
-Chemotherapy curative for some (leukemia, lymphoma, testicular ca), very important as adjuvant treatment or in the palliative setting

Side effects are very common; myelosuppression most often dose limiting toxicity and if the cycle intensity important (e.g. R-CHOP14) G-CSF is used

Chemotherapy is most often given
- Intravenously
- In cycles of 3 weeks (1-4)
- With supportive therapy to reduce side effects
Is the future Target Specific Treatment…

…or Dirty Drugs…

"A dirty disease needs dirty drugs"
…or both?

Tomorrows therapy?

Still chemotherapy is needed!

New chemo is developed and marketed, but not as frequently as new targeted agents

E.g.
- Bendamustine
- Cabazitaxel
- Vinflunine
- Eribulin
- Trabectidin
- Abraxane
**Todays/Tomorrows therapy?**

**Targeted therapies**

- Tyrosin kinase inhibitors (TKI) and downstream targets, including mTor-inhibitors
- Angiogenesis inhibitors
- Antibodies
  i) Surface antigens
  ii) Receptors

**Tyrosine kinase coupled receptors**

Membrane bound TK-R are often mutated in cancers – gives a mitotic signal to the cancer cell.
Downstream signalling from RTK - Novel targets!

![Diagram of RTK signalling pathway]

Examples of TKI (growing field)

**Imatinib**: bcr/Abl, PDGFR, cKit (Ph+KML, Ph+ ALL, cKit+ GIST)

**Gefitinib**: EGFR (NSCLC EGFR+)

**Erlotinib**: EGFR (pancreas cancer, NSCLC)

**Sunitinib**: multi TKI (GIST, renal cancer, pNET)

**Sorafenib**: multi TKI (renal and liver cancer)

**Dasatinib**: bcr/Abl, PDGFR, cKit (KML, Ph+ ALL)

**Lapatinib**: HER-2 (Herceptin resistant HER2+ breast ca)

**Nilotinib**: bcr/Abl, PDGFR, cKit (imatinibresistant KML)

**Pazopanib**: multi TKI (renal cancer)

Some TKI are well tolerated (e.g. Imatinib); some have problematic side effects (hematotoxicity, nausea, diarrhea, skin and hair, cardiac etc).

Oral treatment continuous or with drug free intervals
mTor-inhibitors

Everolimus (Afinitor), Temsirolimus (Toricel)
renal cell cancer, mantle cell lymphoma
and some sarcomas

Side effects comparable to chemotherapy

Angiogenesis inhibition e.g. bevacizumab

TKI inhibiting VEGF-R
Sunitinib, Sorafenib

Talidomid
Lenalidomid
Myeloma, lymphoma.
Studies for solid tumors
Antibodies
-Surface antigens – cell specific

Rituximab binds to CD20 on B-lymphocytes and activates both the complement system and the cell mediated cytotoxicity to destroy the B-cell
– receptors (e.g. EGFR)

MOA
- blocking the TKR signal
- complement activation
- cell mediated cytotoxicity

Tomorrows therapy today – where are we going?
• Individualized therapy
• Genomics and proteomics are incorporated in the clinic
• Biomarkers
• New targets
• Antibody conjugates
• IMMUNOTHERAPY

Still very few cures after disseminated disease (?) but tendency to establish ‘chronic disease’
Therapy adapted for each individual patient (tumor)

- To some extent used already
  - ER status, HER-2 status
  - EGFR-status (+/-, mutated/un)
  - KRAS (colorectal)
  - bcr/abl (CML, AML)
  - cKit
  - CD20 (lymphoma)

What every Oncologist should know for each patient?
Multivariate analysis

Breast cancer – use of neoadjuvant chemo

Proliferation genes

Stroma genes


Therapy adopted to each situation

Point mutation
= Change TKI

Increased expression
= Increase the dose

Detailed analysis of each patient at diagnosis and progression
The techniques are available…
Some examples of novel targeted agents accompanied by biomarker assays

- ALK-inhibitors (crizotinib)
- BRAF-inhibitors (vemurafenib, dabrafenib)
- PARP-inhibitors
- Antibody conjugates (potent cytotoxins or radioisotopes)
ALK

- Anaplastic Lymphoma Kinase (EML4-ALK), fusion mutated oncogene
- 10% NSCLC
- Found also in lymphoma, sarcoma
- In development: PF02341066 (crizotinib), AF802, LDK378, TAE684


Crizotinib
1500 pat screened, 82 ALK-positive
Dose esc phase I
PARP

- DNA-repair
- Olaparib, Iniparib, Veliparib, MK-4827
- Single agent treatment or combos with DNA damaging chemo (e.g. platinum)
- In particular with BRCA mutated breast- and ovarian cancer (“synthetic lethality”)


One-armed phase II study in 33 (300 mg) + 24 (400 mg) patients
B-RAF

- Oncogene in growth factor signalling cascade, often mutated in melanoma, colorectal ca, NSCLC, papillary thyroid cancer and lymphoma

Antibody conjugates

• Tumor antibody coupled to very potent cytotoxin or radionuclide
• Most results with DM1 (=Emtansine) or Mertansine
  - Bivatuzumab mertansine (CD44 SCC)
  - Cantuzumab mertansine (CanAg colorectal)
  - Lorvotuzumab mertansine (CD56 myeloma, Ovarial ca, NSCLC)
  - Trastuzumab-DM1 (HER-2 breast ca)
  - Brentuximab vedotin = SGN-35 (CD30 lymphom)
Immunooncology
• The most rapidly expanding area of oncology right now.
  ➢ BCG-instillation for bladder cancer
  ➢ Allogenic stem cell transplantation
  ➢ Interferon
  ➢ Low dose radiotherapy or chemotherapy
  ➢ Vaccines (HPV16 etc)
  ➢ Monoclonal antibodies
  ➢ CAR-T and other T-cell therapies
  ➢ Immun-checkpoint inhibitors

Immune-checkpoint
➢ Regulates the immune defence
➢ Interplay between several co-stimulatory and inhibitory factors
➢ Essential to suppress autoimmunity
➢ But also a way for tumor cells to evade the immune system "camouflage"

Tumor cells make themselves invincible ("tumor escape")
Immune checkpoints

PD-1

• PD1 is a co-inhibitory factor expressed on activated T-cells
• When PD-1 interacts with PD-L1 and PD-L2 the effector T-cells are inhibited
• Expression of PD-L1 on tumor cells and/or stroma cells (macrophages) may suppress "immune surveillance" and facilitate cancer growth
Immune checkpoint inhibitors

- Ipilimumab – CTLA4
- Nivolumab – PD1
- Pembrolizumab – PD1

- Approved for malignant melanoma, squamous cell lung carcinoma
- Likely approved for many more indications during 2016-2017
- Numerous of antibodies in development incl those targeted against PDL1/L2

-Dramatic effects in some tumors
-Side effects common and may be problematic (pneumonitis, hepatitis, colitis, nephritis hypophysitis)
-Cost issue!
Questions

• Is hematotoxicity the most common dose limiting effect of chemotherapy?
• Is adjustment by BSA an ideal method to reduce variability in PK among patients?
• Does the introduction of targeted agents increase the demands for validated molecular pathology assessments of tumor material for each patient?

Thanks for listening!