Clinical aspects on drug development in oncology

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Plan for the lecture

• Declaration

• Is drug development for cancer fundamentally different?

• What is special with cancer drug development
  – The aims
  – The knowledge in cancer biology
  – The preclinical models
  – The targeted approach or dirty drugs
  – The adverse effects
  – The clinical trials
  – The benefit from new drugs
  – The need for companion diagnostics
  – The generalizability of the clinical trial findings
  – The costs
  – The ethics
  – The change of strategy
Declaration

• No experience from other therapeutic areas

• 3 year experience from assessment of cancer drugs at Swedish MPA

• Consultant in oncology with clinical work in GI-cancer

• Translational research with the aim to take potential drugs from the lab to the clinic

• Co-founder of 3 companies with cancer drugs in clinical phase 1 – 3

• These are my personal views on cancer drug development
Is drug development for cancer fundamentally different?

- Yes

  - Formidable task to eradicate the cancer cells without destruction of normal cells, tissue and organs

  - The cancer cells differ from normal cells in the expression of only a few genes

  - A very delicate balance between benefit and (even fatal) adverse effects

  - Some few (uncommon) cancer types “monogenic” driven and thus possible to selectively attack by a targeted drug
What is special with cancer drug development

The aims

- To eradicate microscopic disease before/after local treatment
  - Neoadjuvant/adjuvant treatment

- To eradicate/downsize macroscopic disease in a curative setting
  - As the only treatment
  - Combined with local treatment

- To control macroscopic disease in a palliative setting
  - Relief of symptoms
  - Prolong survival
What is special with cancer drug development
The knowledge in cancer biology

- Dramatic increase in knowledge in the fundamentals of cancer
  - Provides a background for development of new and better drugs

Hanahan & Weinberg, Cell 2011
What is special with cancer drug development
The preclinical models

- **Model: friend or foe**
The models

• Simple and therefore attractive

• Reflect some properties of cancer cells...

• ... but not the disease ....

• ... and also suffers from the general problem of reproducibility

• Model findings poorly predictive for clinical efficacy
What is special with cancer drug development
The targeted approach or dirty drugs?

The paradigm
The reality

"Universal" ("chemotherapy")
- Interacts with general cell function

"Cancer specific" ("targeted")
- Interacts with cancer specific function

Tissue specific – interacts with eg hormone receptor

Immune modulators
- specific/non-specific

Blood vessels
What is special with cancer drug development
The targeted approach or dirty drugs?

• Most useful drugs are ‘dirty’
  – Chemotherapeutics
  – New ‘nibs’
  – Immune checkpoint inhibitors

• Also targeted drugs produce adverse effects
  – Complex biology
  – Off target effects

• Eradication of cancer with minor adverse effects possible for a few uncommon ‘monogenic’ driven cancer types
What is special with cancer drug development

The adverse effects

• A delicate balance between benefit and harm
  – Given from the overall treatment aims and the nature of common cancers
  – Also true for ‘targeted drugs’

• Difficult to predict serious and even lethal Aes

• Preclinical toxicology does not tell everything

• Need for very careful dose-titration in early studies of new drugs
What is special with cancer drug development
The clinical trials

• Phase 1

  – Recruit patients with no standard treatment options left
    • Healthy volunteers in trials with new non-toxic drugs

  – Establish RPTD and DLT

  – The problem with therapeutic misconception
What is special with cancer drug development
The clinical trials

• Phase 2

  – Evaluate efficacy and tolerance, mostly after standard Rx

  – Effects dependent on patient selection

  – Non-comparative

  – Difficult to evaluate

  – Poorly predictive for clinical utility, no basis for approval

  – ‘Window of opportunity trials’
What is special with cancer drug development
The clinical trials

• Phase 3

  – Establish efficacy and safety in comparison with a standard Rx

  – Designed to show a small yet statistically significant effect in a selected patient population

  – Multicenter/multinational RCTs

  – Now sometimes blinded, but in reality not blinded

  – Patients with or without prior treatment

  – Findings not necessarily generalizable to patients in routine healthcare

  – High internal but low external validity
What is special with cancer drug development
The benefit from new drugs
What is special with cancer drug development
The need for companion diagnostics

- The classical broad drug indication based on diagnosis soon obsolete?

- A personalized approach necessary
  - But we are far from real PCM
  - The use of cancer drugs is stratified at best

- Has to rely on predictive (in contrast to prognostic) biomarkers

- Predictive biomarkers can be generated from
  - Preclinical models
  - Clinical trials

- Predictive biomarkers need to be validated in (randomized) clinical trials

- Procurement of biomarkers in clinical trials needs careful planning and performance
What is special with cancer drug development

The generalizability of the clinical trial findings

• Cancer drugs are mostly approved based on results from optimized ‘experiments’ in the clinic

• The benefit/risk balance is highly dependent on patient selection
  – Median OS in mCRC is 30 months in recent clinical trials but only 15 months in routine care

• Risk for overuse in routine care of drugs with modest or small effects
What is special with cancer drug development

The costs

- Treatment cost per month for new drugs often 30 – 50 tkr
- Cost per QUALY often 1 000 tkr
- Funding difficult and much discussed
- Selection of patients that benefit might be the key
What is special with cancer drug development
The ethics

• Patients are in an extremely difficult situation: lethal disease with no treatment left

• When is there enough support for drug use in a patient
  – Preclinical data
  – Clinical trial data
  – Drug approval
  – Clinical routine
  – Sliding indication

• How handle scientific support for anticancer effects for drugs in use for other indications?
  – The problematic moral panic in the footsteps of Macchiarini
What is special with cancer drug development
The change of strategy

Cancer: The Road to Amiens
David J. Stewart, Department of Thoracic-Head & Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX
Razelle Kurzrock, Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas M. D. Anderson Cancer Center, Houston, TX

"You don’t have to be a doctor to see that the difference between the two arms of this study is miniscule and of no real clinical benefit," commented Dr. Philip. "We need to make a distinction between what is statistically significant and what is meaningful for our patients."

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Incremental Advance or Seismic Shift? The Need to Raise the Bar of Efficacy for Drug Approval
Alberto Sobrero, Ospedale San Martino, Genova, Italy
Paolo Bruzzi, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy
What is special with cancer drug development
The change of strategy

• Roads to Amiens
  – More but smaller trials
    • Calculated risk to miss slightly better new drugs
  – Trials more realistic for routine healthcare
    • To sort out drugs that may really make a difference
  – Match the drug to the right patient
    • Based on biology, biomarkers and predictive tests
  – Agnostic instead of diagnostic drug indications
The End