PHARMACOLOGICAL ASPECTS OF CLINICAL TRIALS

DISCLOSURES

❖ Alex A. Adjei has reported no conflicts of interest
❖ Emiliano Calvo has reported no conflicts of interest
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❖ Ian Tannock has reported no conflicts of interest
❖ Joseph Tabernero has reported to have served on Advisory Boards for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho and Takeda
In drug development and clinical trials, what the body does to the drug (PK) is as important as what the drug does to the body (PD).

The development of targeted therapies has shifted focus to tumour biomarkers and de-emphasised the importance of PK.

However, the schedule and frequency of anticancer drug administration depends on PK. This is important in drug combinations and newer drug formulations, such as nab-paclitaxel and irinotecan.

**Pharmacodynamics** is the study of the biochemical and physiologic effects of drugs (especially pharmaceutical drugs), and how they affect an organism, whereas **pharmacokinetics** is the study of how the organism affects the drug. Both together influence dosing, benefit, and adverse effects.
PHARMACOKINETICS (PK)

Absorption
Distribution
Metabolism
Elimination
Pharmacokinetics

- Dose of drug administered
- Absorption
- Distribution
  - Drug in tissues of distribution
- Elimination
  - Drug metabolised or excreted

Pharmacodynamics

Drug concentration in systemic circulation

Drug concentration at site of action

Pharmacologic effect

Clinical response
  - Toxicity
  - Effectiveness

Drug in tissues of distribution
SOURCES OF PK VARIABILITY

**Patient-specific factors**
- Genetic regulation and/or differences in absorption, metabolic and excretion pathways
- Organ function: liver, kidney
- Age
- Sex
- Race
- Weight, height (BSA)
- Circadian rhythm

**Drug-related factors**
- Mode of administration
- Site of administration
- Drug–drug interactions
- Incompatibilities (parenteral preparations)
- Herbal and vitamin supplements
- Food–drug interactions
- Patient adherence
APPARENT VOLUME OF DISTRIBUTION ($V_d$)

\[
\text{Concentration} = \frac{\text{Amount of drug (dose)}}{V_d}
\]

\[
V_d = \frac{\text{Amount of drug (dose)}}{\text{Concentration}}
\]

Small $V_d$ = Low tissue binding

Large $V_d$ = Drug tightly bound
CLEARANCE (CL)

\[ CL = \frac{\text{Dose}}{\text{AUC}} \]
AREA UNDER THE CURVE (AUC)

Integration of Concentration vs. Time
Measure of systemic exposure
HALF-LIFE ($T_{1/2}$)

- Time required to clear 50% of drug
- Depends on Volume of Distribution ($V_d$) and Clearance (CL)
- Multiphasic (if you can capture the distribution phase)
- **Rule of thumb**: Drug is cleared in 5 half-lives

\[ t_{1/2} = V_d \times \ln(2) / CL \]
OTHER IMPORTANT PARAMETERS

Peak plasma concentration
Bioavailability
Duration above a threshold concentration
Free drug vs. Total drug
Cumulative dose
Bioactivation to active metabolite
Plasma protein binding
Variations in drug concentration within a tumour
MOLEcularly-targeted Drugs
SHIFT TOWARDS TARGET-BASED VS. COMPOUND-BASED DEVELOPMENT

Compound-based (backward)
- Interesting compound discovered with activity in *in vitro* models

Target-based (forward)
- Protein or gene targets identified on carcinogenesis pathway
- Drugs designed to interfere with these specific targets
- Immunotherapy agents – antibodies, vaccines, etc., are developed against specific proteins
COMPOUND-BASED VS. TARGET-BASED DRUG DEVELOPMENT

**Compound-based**
- Compound isolated
- Compound screened in cell culture
- Activity in animal models
- Mechanism
- Toxicology
- Clinical trials
  - Phase I
  - Phase II
  - Phase III

**Target-based**
- Target identified
- Target validated *in vitro*
- Compounds screened for target selectivity
- Toxicology performed
- Phase I, II, III clinical trials
Drugs are developed against specific targets in patient tumours

It is important in this context to also consider variations in drug exposure due to differences in drug transport, metabolism and elimination

Right drug – right patient – **right exposure** – whatever the dose
CLINICAL RATIONALE FOR DOSE MANAGEMENT

TOO HIGH
- Toxicity
- Premature treatment termination
- Higher treatment costs

TOO LOW
- Lack of therapeutic response
- Continued growth of cancer
- Higher cost of recurrence

Optimal Therapeutic Range
THERAPEUTIC DRUG MONITORING (TDM): ONCOLOGY

Anticancer drugs

- Busulfan
- 5-fluorouracil
- Taxanes
- Imatinib

Consideration may have to be given to TDM in order to truly personalise therapy and truly achieve effective anticancer drugs.

Therapeutic drug monitoring is the measurement of specific drugs at intervals in order to maintain an optimal concentration and benefit to the patient with minimal toxic side effects. Therapeutic drug monitoring is common in other fields of medicine, especially the use of antiepileptic medicines, some antibiotics, and immunosuppressants. In oncology, therapeutic drug monitoring has been used primarily with vancomycin, methotrexate, and carboplatin.
Critical part of the clinical development of new anticancer drugs

PK data can give important information as to mechanisms responsible for distribution, metabolism, and elimination

Allows assessment of degree of intra- and inter-patient PK variability

PD correlations between drug exposure and drug toxicity can be made

Provides insights into optimal dose and schedule for subsequent Phase II studies
THANK YOU!