Tumor Cell Drug Penetration for Individualized Cancer Treatment

Introduction

Imke H. Bartelink, PharmD PhD
Clinical Pharmacology Fellow
Department of Medicine/Munster lab
UCSF

Transitioning to
Senior pharmacometrician
MedImmune

i.h.bartelink@gmail.com
Why is drug distribution in tumor tissue heterogeneous?

- Target expression
- Tumor vasculature
- Drug properties
- Internalization
- Inflammatory microenvironment
- Cell metabolism
- Interstitial fluid
- Drug transporters
Study heterogeneity in drug distribution on multiple levels

Example of ado-trastuzumab emtansine (T-DM1), antibody drug conjugate in HER2 positive breast cancer

*Cilliers et al. AAPS Journal 2016, V 18; 5:1117–1130*
Tumor drug penetration correlates with treatment outcome

ZEPHIR study: $^{89}$Zr-Trastuzumab HER2+ imaging in 56 HER2+ mBC patients prior to T-DM1 predicts response

Example patients baseline

HER2+ pattern  HER2- pattern

HR = 4.5 95% CI 2.1–9.4, P < 0.0001

Learning/ discussion points

Techniques to determine drug penetration

• PET/CT, MALDI-MSI, fluorescence labeling
• Different techniques provide information on multiple scales
• Limitations and opportunities

Studies to improve drug penetration in tumor (cells)

Key challenges to implement tumor cell drug penetration to individualize therapy

• Integration of data of multiple sources → PKPD using spatial data
• Prospective studies needed

1. Cilliers et al. AAPS Journal 2016, V 18; 5; 1117–1130
Applying imaging for optimal development and precision dosing, multiscale approach needed

Extra slides
Can we individualize therapy to improve outcomes?

- Using imaging to determine tumor-absorbed doses
  - Somatostatin receptor-based molecular imaging
  - mIBG imaging
Information of drug penetration may guide patient selection

HER2 pattern + early metabolic response by FDG-PET
PPV and NPV 100%

Example patients

HER2+ pattern
HER2- pattern

Metabolic response: $\Delta$ FDG–PET/CT 2 weeks

Hypothesis: variability in response due to heterogeneity in microscopic distribution payload?

MALDI-MSI


HR(1) = 8.3,
HR(2)= 3.7
P < 0.0001
Vision of precision dosing

Prospective clinical studies

Tumor measurements

Models to guide personalized dosing

Diagnosis → Randomize → Standard Tx → Imaging optimized Tx

Randomize

Dose escalate

Dose de-escalate

Biopsy: baseline

macroscopic imaging: TE

Response imaging, plasma PK

Biopsy: microscopic measurements

Animal models

Prospective clinical studies

Tumor measurements

Models to guide personalized dosing

Diagnosis → Randomize → Standard Tx → Imaging optimized Tx

PK partition

3D tumor PK

Response models

Models of biomarker data (histology, genomics, pathology, drug transporters)

3D tumor growth models

Survival models
Example of imaging to optimize drug development

- Example of target engagement visualization to guide optimal biological dose (OBD)
  - 16-[18F]fluoro-dihydrotestosterone imaging in phase 1 of ARN-509, a Novel Antiandrogen
  - The approved dose was much lower than the traditional maximum

Pharmacokinetic models are needed to integrate information of drug penetration into clinical decision making.

Example model to predict tumor penetrance of payload T-DM1

*Cilliers et al. AAPS Journal 2016, V 18; 5; 1117–1130