Novel Formulation and Biopharmaceutical Challenges of Oral Cancer Therapy

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Synopsis

- Introduction
- Oral administration
- Cancer and chemotherapy developments
- Barriers requiring carriers
- Pharmaceutical nanolandscape
- Amorphous, anthracyclines and taxanes
- Nanotechnology issues
- Conclusions
Gavin Halbert

- Pharmacist, Chemist & Qualified Person
- Drugs into patients
- Range of research, formulation and product experience
- Drug delivery sympathies – practical realities

MMIC

CMAC

OrBiTo

Introduction
Formulation Unit

• Established in 1983 – unique within UK
• Develop novel anti-cancer drugs selected by Cancer Research UK
• Antibodies – Alkylating Agents – Antisense
• Drug Delivery Systems
  Liposomes
  ADEPT
Drug Delivery in Cancer Chemotherapy

• Long history of delivery/targeting drugs to cancer
  1958 – methotrexate conjugated to polyclonal antibody

• Early rationale
  Alleviation of toxicity

• Multiple systems tested
  Liposomes
  Microspheres
  Nanoparticles
  Polymeric conjugates

Oral Nanoparticulate Systems

• Uptake of nanoparticles after gastro-intestinal administration

Jani, P., et.al., J.Pharm.Pharmacol., 1990;42;821-826
Jani, P., et.al., J.Pharm.Pharmacol., 1989;41;809-812

Dawson, G.F., Halbert, G.W., Pharm.Res., 2000;17;1420-1425
Cancer and chemotherapy developments
Cancer Research

- Massive increase in biological understanding
- Imatinib – 2001 – targeted treatment
- Tumour heterogeneity
- Agile combination therapy
- Personalised therapy

Molecular Complexity

BCS Issues

- **Imatinib**
  - Solubility: 200mg/ml
  - Oral Bioavailability: 98%

- **Nilotinib**
  - Solubility: sparingly
  - Oral Bioavailability: 31%

- **Sorafenib**
  - Solubility (1:2 DMSO:PBS): 0.3mg/ml
  - Oral Bioavailability: 50%

Cancer and chemotherapy developments
Intestinal Solubility Variation

- Impact of simulated gastrointestinal fluid composition

Oral administration
Cancer Chemotherapy Therapy
Routes of Administration

• Oral therapy – always present
  Chlorambucil, tamoxifen
  Traditional formulation presentations
  Not always optimal

• Parenteral therapy – main route
  Alkylating agents, doxorubicin
  Bioavailability
  Acute therapy
  Toxicity, pharmacokinetics
Oral Therapy - Temozolomide

- **Dacarbazine**
  - IV administration
- **Temozolomide**
  - Oral administration

![Dacarbazine and Temozolomide structures](image)

Pro-drug approach
Advantages and switch to oral

“the most frequently reported attributes contributing to preference included convenience, ability to receive treatment at home, treatment schedule, and side effects.”

EeK, D., et.al., Patient Preference and Adherence 2016;10;1609-1621

Shih, Y-C.T., et.al., J.Clin.Oncol., 2015;33;2190-2196
Bioavailability

- Poor bioavailability - always an issue
- Chemical stability
- Poor solubility
- Efflux pumps

Methotrexate

Doxorubicin

Paclitaxel
Barriers requiring carriers
Gastrointestinal transit route

Reviews
Blanco, E., et.al., Nat.Biotechnol., 2015;33;941-951
Gastrointestinal transit route

- Solubility Dissolution
- Drug in solution → Intestinal Fluid → Portal Circulation → Liver
  - Un-dissolved → Un-absorbed → Degraded
  - Metabolised
  - Excreted → Kidney → Liver

- Intestinal Membrane
- Pumps

- Metabolism
- Excretion

- Tumour Vasculature
  - Normal Organs
  - Toxicity

- Stability

Barriers requiring carriers
How far do you need to go?

Use an excipient (carrier) to usurp or circumvent the barrier
Pharmaceutical nano-landscape
Pharmaceutical nano-landscape

Nanocrystals

Micelles

Figure 1: Schematic depiction of routinely used nanomedicine formulations. Note that most standard (chemotherapeutic) drug molecules are between 0.1 and 1 nm in hydrodynamic diameter.

Talelli, M., et.al., Nano Today 2015;10;93-117
Amorphous systems

- Are they nanobased?
  - Drug dispersed in polymer – nano sized domains
  - Molecular dispersion or solution
- Route to increased kinetic solubility
- Systems variability possible
  - Nano-crystalline to amorphous
  - Polymer characteristics
- Extreme particle size reduction
  - Down to the molecule
- NB also applicable for other systems

Review
Jermain, S.V., et.al., Int.J.Pharm., 2018;535;379-392

Martinez-Marcos, L., et.al., Int.J.Pharm., 2016;499;175-185
Development of polymeric systems

Hydrophilic

Hydrophobic

Polymer A

Polymer B

Drug

Direct chemical attachment

Physical mix

Additional Modifier

Additional molecules

Targeting Ligand

Reviews
Biswas, S et.al., Eur.J.PharmSci., 2016;83;184-202
Amorphous, anthracyclines and taxanes
Amorphous systems

- Increased interest
  Poorly soluble drugs
- Range of manufacturing techniques
  Hot melt extrusion, solvent precipitation
- Example marketed systems
  Vemurafenib
  Regorafenib
  Evorlimus
- Solubility assistance only

Dissolution of Albendazole

Solid dispersion
Native drug


Amorphous, anthracyclines and taxanes
PAMAM-Doxorubicin dendrimer

- Oral administration 20mg/kg in rat
- Particle size ≈ 4nm
- Doxorubicin
  \[ \text{Cmax (µM)} = 0.20 \]
  \[ \text{AUC (µg/mL)*h} = 0.78 \]
- Doxorubicin-PAMAM
  \[ \text{Cmax (µM)} = 7.63 \]
  \[ \text{AUC (µg/mL)*h} = 247 \]
- Doxorubicin IV
  \[ \text{Cmax (µM)} \approx 10 \]

Data from: Ku, W., et.al., J.Pharm.Sci., 2008;97;2208-2216

Relative not Absolute!
Surface decorated nanoparticles

- PLGA Nanoparticles
- Surface – polyethylene glycol or mannosamine
- Epirubicin @ 10mg/kg in rats
- Particle Size ≈ 250nm

Data from: Tariq, M., et.al., Int.J.Pharm., 2016;501;18-31
Docetaxel microemulsion

- o/w microemulsion oral in rats
  Capryol 90/cremophor/transcutol
- Droplet size ≈ 30nm

Po 10 mg/kg
iv 8mg/kg

Yin, Y-M., et.al., J.Cont.Rel., 2009;140;86-94

Amorphous, anthracyclines and taxanes
Paclitaxel nanomicelle

- Dual functional system – in rats
  Mucosal penetration & P-gp inhibition
- Particle size ≈ 250nm

Lian, H., et.al., Colloids and Surfaces B: Biointerfaces, 2017;155;429-439
Nanotechnology issues
Nanotechnology issues

- Complex systems
- Production
  - Solvent, dialysis, sonication, centrifugation
- Issues of scale up
  - Working volume approx 10mL
- Control of complex polymers
  - Synthesis and impact on properties
- Stability
  - Chemical and physical
- Cost of goods
  - Greater than drug costs?
- Toxicity

Realistic values ≈ $10^n$
Conclusions

- Not yet - “set the heather alight!”
  Struggling to break through
- Amorphous systems
  Increasing acceptance – solubility only – or maybe not?
- Experimental promise – not realized clinically
- Not simply drug – but whole system
  Efficacy, variability, biological interaction, manufacture and control
- Likely to arrive
  Bioavailability improvement
- Watch this space

Recent Quote
Despite the demonstrated advantages by the preclinical studies, further studies on improved understanding of the interactions of SLNCs with biological tissues of the target site is necessary for efficient designing functional nanoparticles for clinical applications. Mu, H., Holm, R., Expert Opinion Drug Delivery 2018;15;771-785

Reviews
Tran, S., et.al., Clin.Trans.Med., 2017;6;44
Ventola, C.L., P&T., 2017;42;742-755
Thank you

• Funder – Cancer Research UK

• Collaborators
  Many and varied
  Local, national and international

• Organisers - Invitation

• You for listening