Liposomal Formulations
Phase-I-studies with newly developed liposomal formulations: safety and efficacy issues

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Liposomal formulations: examples

Drugs with severe, harmful toxic effects
- Doxorubicin (DOXIL®/ Caelyx®)
  - ovarian and breast cancer
- Amphotericin B (AmBisome®/ ABELCET®)
  - systemic fungal infection
- Daunorubicin (DaunoXome®)
  - AIDS-associated Kaposi-Sarkom

Drug targeting
- Verteporfin (Visudyne®)
  - age-related macular degeneration
Liposomal formulations: examples

Extended release in target organ
- Morphine (DepoDur®)
  - post-surgical pain relief with single-dose epidural administration
- Cytarabine (DepoCyte®)
  - treatment of meningeosis lymphomatosa with intrathecal administration

Other locally applied products
- Amikacin (Arikace®)
  - treatment of lung infections by susceptible pathogens (e.g. P. aeruginosa) for inhalative administration

Phase-I-/BA/BE-studies

Relevance of systemic availability...
- predictive for efficacy?
- predictive for safety?

Focus on formulation types to overcome toxicity
coming along with systemic administration
- cancer
  - e.g. daunorubicin, doxorubicin, paclitaxel, mitoxantrone, vincristine, SN-38, cisplatin, camptothecin, topotecan, lutotecan, vinorelbine, ...
- infections
  - e.g. amphotericin B, amikacin, nystatin, ...
Rationale for Phase-I-Studies

During early development
- characterisation of formulation, i.e. determination of free and encapsulated fraction over time
- assessment of linearity / MTD etc.
- often not “First-in-human”

For scale up and post approval changes
- characterisation of influence of change on formulation, i.e. determination of free and encapsulated fraction over time

Assessment of Drug-Drug Interactions
- DDIs influencing the incorporated drug / other drugs

For generic development
- demonstration of bioequivalence (rate and extent of BA)

BE: Example Doxorubicin

Development rationale for originator
- favourable therapeutic index
  - less rapid clearance from plasma (t½↑, AUC↑)
  - advantageous tissue distribution pattern
- reduction of cardiotoxic side effects

Different liposomal concepts
- Caelyx®: PEGylated DSPC liposomes
  - monotherapy of metastatic breast cancer
  - advanced ovarian cancer
  - progressive multiple myeloma (combined with bortezomib)
  - AIDS-related Kaposi-Sarkom (low CD₄ counts)
- Myocet®: non-PEGylated EPC liposomes
  - first-line therapy of metastatic breast cancer
Prerequisites for BE-assessment

**Same drug product composition**
- qualitatively and quantitatively the same except
  - buffers
  - preservatives
  - antioxidants
  - lipid excipients are considered critical

**Active liposome loading process**
- quality by design approach

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**Equivalent liposome characteristics**
- composition
- state of encapsulated drug (equivalent precipitate)
- internal environment (volume, pH ...)
- morphology/ number of lamellae
- lipid bilayer phase transition
- liposome size distribution
- grafted PEG at the liposome surface
- electrical surface potential/ charge
- in-vitro leakage
Caelyx®: Side-effects

- **Cardiac toxicity**: Primarily in patients
- **Myelosuppression**: After two to three cycles of treatment
- **Infusion-related reactions**: Palmar-plantar erythrodysesthesia (PPE, hand-food syndrome)
- **GI-reactions**: nausea, vomiting, constipation, diarrhea
- **Neutropenia**: More common with Caelyx® than with doxorubicin
- **Alopecia**: More common with Caelyx® than with doxorubicin
- **Mucositis / Stomatitis**: More common with Caelyx® than with doxorubicin

Pre-clinical safety: mutagenic and carcinogenic

No Phase-I-study in healthy subjects acceptable!

US-FDA design requirements

**Clinical Study.**

1. Type of study: Fasting*
   - Design: Single-dose, two-way crossover in vivo
   - Strength: 50 mg/vial
   - Dose: 50 mg/m²
   - Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy.
   - Additional Comments: Patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of Doxil should not be entered into the study. Females should not be pregnant or lactating. Other exclusion criteria include: total cumulative dose of doxorubicin HCl approaches 550 mg/m²; patient is < 18 years of age or > 75 years of age, active opportunistic infection with mycobacteria, cytomegalovirus, toxoplasma, P. carinii or other microorganism if under treatment with myelotoxic drugs; clinically significant cardiac, liver or kidney disease.

   * If the health conditions of patients prevent fasting, the sponsor can provide a non-high-fat diet during the proposed study. Alternatively, the treatment can be initiated 2 hours after a standard (non-high-fat) breakfast.
Challenges for BE-trial - doxorubicin

Relatively high number of patients needed

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Dose/patient population</th>
<th>Reference product</th>
<th>Number analysed (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKD/08/038</td>
<td>50mg/m² ovarian cancer</td>
<td>Caelyx (Europe)</td>
<td>23</td>
</tr>
<tr>
<td>PKD/09/031</td>
<td>30mg/m² multiple myeloma</td>
<td>Caelyx (Europe)</td>
<td>26</td>
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<tr>
<td>PKD/09/030</td>
<td>50mg/m² ovarian cancer</td>
<td>Doxil (US)</td>
<td>41</td>
</tr>
</tbody>
</table>

Demands for trial (planning and performance)

- high number of subjects...
- ...to be recruited in a short time
- high level of standardisation
- ...to be realised only in a setting with adequate QMS (professional CPU)

Challenges for BE-trial - doxorubicin

Availability of subjects - breast and ovarian cancer

- high - at least in countries with a highly developed medical care system
- phase-I-cancer studies are often realised in Universities - there recruitment / performance might be limited:
  - infrastructure not optimum for the needs of the trial
  - high level of competition with other trials
  - often little interest of oncologists (catchwords: Citation Index of publication • scientific reputation • lack of therapeutic benefit)

AIDS-related Kaposi’s - sarcoma

- lower dose recommended: 20 mg/m²
- patients are more difficult to recruit – at least in countries with highly developed medical care system
PK of liposomal doxorubicin

Dosing regimen according to SmPC

- breast/ovarian cancer
  - once every 4 weeks (50mg/m²)
  - as long as the disease does not progress and the patient continues to tolerate treatment

- multiple myeloma
  - 30mg/m² on day 4 of bortezomib 3 week treatment regimen
  - as long as the patient responds satisfactorily and tolerates treatment

Gabizon et al, 1994
Caelyx® SmPC
Ethical considerations

Situation for the subjects
- no therapeutic benefit
- other benefits may play a role (e.g. knowledge of “own” systemic exposure, exchange with other patients concerned)
- high logistical burden due to duration of sampling
- financial compensation meaningful

Situation for subjects and oncologists
- relevant interference with treatment due to long $t_{1/2}$
- thus, relevant interference with safety and tolerability

Against the background of missing therapeutic benefit the missing clinical proof of efficacy / safety of the generic formulation is of particular relevance!

Conclusion: BE studies

Provided the product is of adequate quality
- BE-testing in a phase-I-trial is feasible – at least for the higher doses
- and commonly considered ethically justifiable

Study organisation and performance requires adequate recruitment infrastructure and professional Quality Management System
Assessor’s comment:
“The two original ("tissue") distribution studies submitted with this application were deficient in terms of the doses utilised, study duration, choice of analyte, data analysis methods and interpretation of results. (...)

“While the applicant concluded comparability of tissue distribution of the two products, there were major concerns regarding the reliability of the data and signals of a lack of equivalence between the two products.”

“There remains an outstanding major objection regarding the reliability of the data and signals of lack of equivalence between the two products.”
DDI-studies in brief

Quality of the formulation
- not an issue for already approved liposomal formulations
- for new products: „business as usual“

Situation for the subject
- therapeutic benefit may be given depending on whether the combination tested is part of regular treatment
- burden from procedures remains
- financial compensation may also be adequate

Situation for the oncologist
- depends on therapeutic benefit for the subject
- depends on scientific relevance

Maybe less question marks for the clinical performance itself compared to generics?

DDI-studies – design questions

Drug-Drug interaction
- relevance of liposomal “protection” of the drug?
- relevance against the background of flip-flop kinetics?

Drug-liposome interaction
- influence on release characteristics imaginable?
- drug uptake in liposomes imaginable?

Selection of study design
- single dose investigations adequate?
- duration of steady-state build-up phase for md studies?

Analyte of relevance
- free drug?
- encapsulated fraction?
- total drug?
Doxorubicin Drug Interactions

“A total of 359 drugs (1160 brand and generic names) are known to interact with doxorubicin”
- 68 major drug interactions
- 227 moderate drug interactions
- 64 minor drug interactions

Pharmacodynamic Interaction
“Caelyx® may potentiate the toxicity of other anti-cancer therapies“

Pharmacokinetic Interactions
- competitive biliary excretion
- CYP 3A4
- P-glycoprotein

Conclusion: DDI studies

Provided the expected DDI and the design is clear
- DDI-testing in a phase-I-trial is feasible
- and ethically justifiable

But only limited knowledge available so far
- which questions are to be answered?
- which type of design is adequate?

Decision criteria analogous to conventional DDI studies?