Phase I clinical trials in oncology

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### Phase I oncology trials vs other diseases: how are they different?

<table>
<thead>
<tr>
<th></th>
<th>Oncology</th>
<th>Most other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overriding concern</strong></td>
<td>Avoid or delay a fatal outcome</td>
<td>First do no harm</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>With advanced, refractory disease</td>
<td>Healthy volunteers</td>
</tr>
<tr>
<td><strong>Preferable dose</strong></td>
<td>Maximum tolerated</td>
<td>Minimum effective</td>
</tr>
<tr>
<td><strong>Direct subject benefit</strong></td>
<td>At therapeutic doses</td>
<td>None expected</td>
</tr>
</tbody>
</table>
# Phase I oncology trials vs other diseases: how are they similar?

<table>
<thead>
<tr>
<th></th>
<th>Oncology</th>
<th>Most other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>As limited as possible (ethics and cost)</td>
<td>As limited as possible (ethics and cost)</td>
</tr>
<tr>
<td><strong>Surrogates desirable</strong></td>
<td>For activity / efficacy</td>
<td>For safety</td>
</tr>
<tr>
<td><strong>Information obtained for later trials</strong></td>
<td>Toxicity, early signs of activity</td>
<td>PK/PD</td>
</tr>
<tr>
<td><strong>Move quickly to trials in</strong></td>
<td>Patients with target tumor</td>
<td>Patients with target disease</td>
</tr>
</tbody>
</table>
Objectives of phase I trials in oncology

Phase I trials in oncology are carried out in patients with the following objectives:

• **Statistical** - Reliable identification of the highest dose that is safe enough to be used in phase II trials

• **Clinical** - Treatment of small cohorts of patients who have failed all standard therapies

• **Ethical** - Treatment of patients who might benefit from new drug at doses that are close to therapeutic

Phase I trials of cytotoxic drugs

Parallel dose-effect curves for efficacy and toxicity, with efficacious doses only slightly lower than toxic doses

Very narrow therapeutic window

Dose producing substantial tumor shrinkage and acceptable toxicity
Phase I trials of cytotoxic drugs

The purpose of a phase I trial is to determine the maximum tolerated dose, i.e. the dose at which a given percentage of subjects experience toxicity (which is a surrogate for activity).
Classical design

- Initial low dose extrapolated from animal data (e.g. 1/10 LD_{10} in mice)
- Doses are increased according to a “modified Fibonacci series” (1, 2, 3.3, 5, 7, 9, 12, …) for which dose increments are decreasing (100%, 66%, 50%, 40%, 33%, 33%, …)
- Maximum Tolerated Dose (MTD) is dose for which a given proportion of patients (e.g. 33%) experience Dose Limiting Toxicity (DLT)
Classical design

- Dose-limiting toxicities (DLT) are usually pre-defined adverse events (depending on the mode of action of the drug) of grade 3 or 4 severity

<table>
<thead>
<tr>
<th>Scale</th>
<th>NCI/CTC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>mild</td>
<td>1</td>
</tr>
<tr>
<td>moderate</td>
<td>2</td>
</tr>
<tr>
<td>severe</td>
<td>3</td>
</tr>
<tr>
<td>life-threatening</td>
<td>4</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Toxicity Criteria
# Examples of NCI/CTC toxicity grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes  (total WBC)</td>
<td>WNL</td>
<td>&lt; LLN - 3.0 x 10^9 /L</td>
<td>≥2.0 - &lt; 3.0 x 10^9 /L</td>
<td>≥1.0 - &lt; 2.0 x 10^9 /L</td>
<td>&lt; 1.0 x 10^9 /L</td>
</tr>
<tr>
<td>SGOT (AST) (serum glutamic oxaloacetic transaminase)</td>
<td>WNL</td>
<td>&gt; 1 - 2.5 x ULN</td>
<td>&gt; 2.5 - 5.0 x ULN</td>
<td>&gt; 5.0 - 20.0 x ULN</td>
<td>&gt; 20.0 x ULN</td>
</tr>
<tr>
<td>Stomatitis / pharyngitis</td>
<td>none</td>
<td>painless ulcers, erythema, or mild soreness in the absence of lesions</td>
<td>painful erythema, edema, or ulcers, but can eat or swallow</td>
<td>painful erythema, edema, or ulcers requiring IV hydration</td>
<td>severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation</td>
</tr>
</tbody>
</table>

WNL = Within Normal Limits; ULN = Upper Limit of Normal
Classical design

Start at lowest dose

- Treat 3 patients at this dose
  - No DLT: Go to next higher dose
  - 1 DLT: Treat 3 more patients at this dose
    - No DLT: Go to next higher dose
    - 1, 2 or 3 DLT: MTD reached!
  - 2 or 3 DLT: MTD reached!
Continual reassessment method (CRM)

In the CRM, the dose given to the next patient is based on an assumed dose-effect relationship for dose-limiting toxicities.

The idea is to assume some initial (one parameter) relationship and to reassess this relationship in the light of the toxicities (DLT) observed in successive patients.

Continual reassessment method (CRM)

A model is chosen to describe the dose-response relationship

e.g. \( P_i = \frac{\exp(3+\alpha d_i)}{[1+\exp(3+\alpha d_i)]} \)
Continual reassessment method (CRM)

Example of a dose escalation using the CRM, constrained to start at dose level 1 and increase by only 1 dose level at a time. The target dose is level 4. Patients with a DLT are indicated by an open square.
A distinction must be made between agents that produce acute toxicity (cytotoxics) and agents that do not (cytostatics).

For cytotoxics, phase I trials aim at determining the Maximal Tolerated Dose (MTD). For cytostatics, phase I trials aim at determining the Optimal Biological Dose (OBD).

The most promising new agents in oncology are not traditional cytotoxics, but targeted therapies, therapeutic vaccines, immunotherapies, etc.
Oncology Drugs in Development Preclinical to Phase III (n = 374)

- Cytotoxics: 22%
- Vaccines: 8%
- Supportive care: 7%
- Others: 10%
- Antiangiogenic: 6%
- Hormones: 6%
- Gene therapy: 5%
- Monoclonal antibodies: 9%
- Signal transduction: 8%
- Novel agents*: 19%
- Others: 10% †

* Includes antisense, peptides, oligonucleotides
† Includes immunomodulators, radiosensitizers, chemoprevention

Source: PhRMA, New Medicines in Development for Cancer
The main drivers of the growth are:

- increase in patient numbers (ageing population)
- early intervention
- use of biologically targeted therapies
Phase I trials of cytostatics

Dose-effect curve much flatter for toxicity than for efficacy, with efficacious doses sub-toxic

Wide therapeutic window

Dose producing high biological activity and little toxicity
## Phase I trials of cytostatics

<table>
<thead>
<tr>
<th></th>
<th>Cytotoxics</th>
<th>Targeted agents</th>
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<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>MTD</td>
<td>OBD</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>All</td>
<td>Target-bearing</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Toxicity</td>
<td>Inhibition of target</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Dose escalation in small cohorts</td>
<td>Guided-dose escalations</td>
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