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Imaging fundamentals

Imaging in clinical trials

Overview

The drug development process

Stage	Goal
1. Basic research	Target identification
2. Discovery/lead optimization	Identify suitable molecule or prototype to interact with target
3. Preclinical studies	Mechanism of action, proof of principle in animals
4. Early clinical trials	Dosage, pharmacodynamics, safety, proof of concept
5. Late clinical trials	Efficacy and safety

Common terms and acronyms

- **Randomized:** each patient's treatment assignment is left to chance.
- **Controlled:** the treatment group with drug is compared to a group given either an active control (established drug; also known as an active comparator) or a placebo (sugar pill; negative control).
- **Blinded:** physicians, patients, and imaging readers are unaware of a patient's treatment group throughout the evaluation period.
- **Open-label:** a study in which there is no blinding; participants and physicians are aware of the treatment being given, and there is no placebo group.
- **IND:** Investigational New Drug
- **NDA:** New Drug Application

Oncology trial design

The primary endpoint in most oncology trials is patient survival:

- Overall Survival (OS): clinical endpoint; considered gold standard; not always practical due to high patient numbers and required time Progression-free Survival (PFS): measures time from treatment initiation to beginning of disease progression; most commonly used oncology endpoint

Another oncology trial endpoint:

- Objective Response Rate (ORR): proportion of patients with a reduction in tumor burden by a predefined amount

Disease progression is defined according to the chosen response criteria:

- The most widely used response criteria for solid tumors is RECIST1.1, which assesses tumor size by CT or MRI
  - — Tumor growth = disease progression; tumor shrinkage = response to treatment
- In RECIST1.1, tumor response is categorized according to defined parameters:
  - — CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
- Immunotherapies have their own unique response criteria: irRC and irRECIST among a growing number
  - — Immunotherapies typically exhibit a delayed response and tumors can enlarge prior to disease stabilization
  - — Tumor growth does not automatically define disease progression; imaging is performed again after a 12-week waiting period to test for response

Clinical trial phases

Overview of the Clinical Trials Process

	Preclinical testing		Phase 1	Phase 2	Phase 3	
Subjects	Laboratory and animal studies		20–100 Healthy volunteers	100–300 Patient volunteers	1,000–3,000 Patient volunteers	
Purpose	Assess safety & biological activity	FILE IND	Determine safety & dosage	Evaluate effectiveness & side effects	Verify effectiveness & monitor adverse long-term use	FILE NDA
Time Course	Year 1–2		Year 3	Year 4–5	Year 6–8	
New Drugs Passed	100%		70% of INDs	33% of INDs	27% of INDs	
	10,000 →	250 →		50 →	5 →	1

Imaging in clinical trials

Clinical trials attempt to answer the following questions:

- *Is the drug safe?*
- *What happens to the drug in the body?*
- *What happens to the body when the drug is taken*
- *Is the drug clinically effective?*
- *How should the drug best be administered?*

Clinical trial phases (continued)

Preclinical & FIM	• Preclinical testing involves animal and laboratory studies – Is the drug effective in living organisms? – Is the compound biologically active?	• At the conclusion of preclinical testing, an investigational new drug application (IND) must be filed with the regulatory agency – then the First in Man (FIM) Studies
Phase I ~1–2 Years	• Phase I evaluates drug safety and a safe dosing range: clinical efficacy is generally limited to establishing proof of principle. – Sometimes, Phase I is divided into Ia and Ib. Phase Ia studies are usually performed on healthy volunteers and phase Ib is on patients with the disease – Tumor size can also be used as a safety parameter, as any new drug that results in tumor growth will not proceed through the clinical trial process. • Pharmacokinetic (PK) and pharmacodynamic (PD) data is collected. –PK and PD: The evaluation and quantification of what the body does to a drug over time, tested at many doses (absorption, distribution, metabolism, and elimination)	• Imaging in Phase I can be used to: – Evaluate extent of disease using CT or MRI – Identify patient populations most likely to respond to treatment – Assess PK using PET – Test drug safety: kidney or liver damage using MRI – Make go/no go decisions on whether or not to proceed in clinical testing – Test novel imaging endpoints
Phase II ~2 Years	• Drug is given to a larger group of patients who have the disease – Does the drug work in the disease population? – At what dose is the drug effective? – Drug is tested at several doses using placebo controlled or active comparator design to determine the optimal dose to carry into Phase III studies	• Imaging studies in Phase II can be used to: – Detect early changes to pathophysiology as it relates to efficacy or safety – Stratify patients into treatment groups – Identify patient populations most likely to respond – Evaluate imaging biomarkers – Make go/no go decisions regarding entry into Phase III
Phase III ~3-5 Years	• Confirm efficacy results in a larger population: determine clinically meaningful drug benefit and requires the greatest amount of time, financial resources, strategic planning – Is the drug working and safe? • Identify adverse events: establishes a benefit-to-risk ratio (BRR) for the patient – BRR influences the decision to approve the drug for first-line, second-line, or salvage therapy – BRR must be comparable or better than current therapies in order to gain first-line treatment status.	• After Phase III testing, a new drug application (NDA) is filed with the regulatory agency. – The NDA contains all data from preclinical and Phase I-III studies; an NDA can be thousands of pages long and may require as long as 1-2 years to be reviewed by the regulatory agency • Imaging in Phase III is used to determine disease progression as an indicator of clinical benefit – This typically includes measuring changes in tumor size after treatment (compared to baseline) using CT or MRI for solid tumors; can also include measuring glucose metabolism by PET/CT (i.e., for lymphoma) – The way in which disease progression is measured is determined by response criteria, which are specific to type of tumor and/or drug class
Phase IV	After review and approval of the NDA, Phase IV postmarketing studies are initiated; also called post-marketing surveillance • Phase IV studies are conducted after the drug has already been approved by the regulatory agency to confirm safety and efficacy with long-term use	• Collects additional information for patients and healthcare providers that was not generated in Phase III trials – Phase IV studies must use current prescribing instructions – Used to study specific populations, monitor a longterm safety parameter, investigate a new efficacy endpoint, or explore new indications – Regulatory agencies can make approval contingent upon Phase IV studies that address specific safety concerns. – Phase IV imaging studies are used to further assess or confirm efficacy and safety

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