Early Phase Oncology Studies

Ethical Issues

Basic Facts

- Despite substantial recent improvement in the management of individual cancer, e.g., Immunotherapies, 50% with cancer die every year from it
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- In 2021 (the latest year for which there are global data), more than 10 million people died of cancer worldwide.

Aims of Early Phase Oncology Studies

- Early phase studies in oncology introduce an investigational new drug into human subjects
- Represent a challenging first step for the new drug on the road of clinical development
- Early phase studies are the bridge between basic science and clinical development,
- Provide pivotal information to select the:
  - **Right drug at the**
  - **Right dose for the**
  - **Right patients**
- To be investigated in the subsequent phases of clinical development

Ethical Issues

- Two fundamental ethical challenges are frequently raised about phase 1 cancer research:
- The risk-benefit ratio
- Informed consent

The risk-benefit ratio on Phase I Oncology studies

- ? Is there little benefit with substantial risks for patients in phase 1 oncology studies.
- Based on old data that 5% of patients in phase I trials experience tumour response
- The majority are partial responses only
- Only 0.3% to 0.7% are complete responses
- A 0.5% mortality rate
- Is it irrational or unethical for patients to participate in such studies?
- Due to:
  - Disclosure of information
  - Lack of understanding by research participants
- Are on phase I oncology studies uninformed, misinformed, and/or irrational?

Does 5% Response Rate cover better outcomes?

- Tumour Response does not always translate to improved Survival
- 35 year old data >60% compounds had >1 objective tumour response, shrinkage of >50%
- >30% of the drugs tested had greater than a 5% response rate
- Phase I studies in the 1970s, cisplatin for testicular cancer >50%
- 25% tumor completely disappeared, probably cured
- In Phase I, Imatinib mesylate (Gleevec) demonstrated complete hematologic RR of 98%, with 96% lasting beyond 1 year in CML

Objective of Most Phase I studies is NOT Tumour Response

- However, the designs of most Phase 1 trials are intended to minimize toxicity, which, ironically, ensures that the majority of participants are treated at doses that cannot produce responses in human tumours.
- 60% of participants appear to receive biologically inactive doses.
- Consequently, participants face little risk but also little chance of clinical benefits
- Novel design strategies that may allow more patients to be treated at biologically active doses, increasing the chances for a therapeutic response
- Less than 15% of phase 1 studies use these innovative methods

Is RR risk-benefit argument too narrow?

- Patients may not find the adverse effects in phase I studies vexing
- Nonphysical benefits to participation in phase 1 studies.
- Routine and regular physician contacts reduce psychological distress during a time of great uncertainty
- Well-being, in very sick terminally ill patients, is "not merely the absence of disease or infirmity" but includes psychological, social, and other dimensions
- Patients in phase I trials may have better quality of life than comparable patients receiving supportive care
- Enhancing QoL should be one of the goals of phase 1 oncology studies
- Risks -benefits of phase I trials not worse than those used by the FDA to approve oncology agents for clinical use.

What Standards Determines Risk-Benefit Ratio?

- To determine when a risk-benefit requires a standard of evaluation, appropriate for patients with advanced cancer who will most likely deteriorate and die.
- No standard criteria define a favourable risk-benefit ratio for Phase 1 oncology studies
- One approach would be to elucidate a standard based on socially accepted determinations of risk-benefit ratios already used for cancer treatments, such as in FDA approval of cancer agents.
- FDA-approved High dose IL-2 for metastatic renal cell carcinoma with a response rate of 14% (5% complete responses, 9% partial responses) with a median response duration of 20 months
- IL-2 has substantial toxic effects including a sepsis-like and pulmonary edema from capillary leak
- Topotecan with a 10% response rate for ovarian cancer
- Irinotecan for metastatic colon cancer on the basis of less than 2 months' prolongation of overall survival
- Gemcitabine for metastatic pancreatic cancer, despite a 5.4% response rate, because of quality-of-life benefits

Determination of Risk-Benefit in Cancer

- In non–terminally ill cancer patients, chemotherapy with limited benefits is widely accepted.
- In newly diagnosed stage I breast cancer, where 5-year overall survival is >90%, a 2 or 3 drug chemotherapy regimen lasting 4 to 6 months, with its adverse effects, offers an absolute survival benefit of just 1% to 2% is received by the vast majority of women
- For patients in whom all standard therapeutic interventions have failed, a slight chance of therapeutic benefit is not unreasonable.
- The risk benefit assessment requires consideration of the available alternatives

Who Decides What on a Risk-Benefit Ratio?

- The lack of explicit criteria means (IRB) members frequently rely on their intuitions to determine risk-benefit ratio for phase I oncology studies.
- But IRB members tend to be healthy individuals.
- Healthy IRB members and critics of such studies are likely to view studies with few benefits and greater risks as unfavourable, yet patients might view the same studies as having a favourable risk-benefit ratio
- Substantial data patients facing serious illnesses make very different assessments of their own condition and the risks they are willing to confront compared with healthy individuals.
- Studies found that cancer patients were willing to undergo intensive chemotherapy with substantial adverse effects for a 1% chance of cure
- Compared with 50% chance for oncology nurses, physicians, a 10% chance and the general public who needed a 50% cure rate
- IRB determinations of risk benefit ratios for phase I oncology studies would benefit from the position of Terminally ill cancer patients
- Such patients may not be narrowly focused on physical safety and might view risk-benefit ratios more favourably

Objections Based on Informed Consent

- Are there deficiencies in accurate information given, failure to understand the information, disclosure, understanding, and voluntariness in the informed consent process?
- ? “Informed consent documents make phase I studies sound like the cure for your cancer
- Are most terminally ill patients have deficient understanding of the objectives, benefits, and risks of phase I research
- Are cancer vulnerable, their judgment is clouded, and they are not to be trusted with their own decision making.

Informed consent and Disclosure

- Available data do not support the claim disclosure and consent are deficient
- In 272 phase I oncology consent forms 99% explicitly stated the study was research and in 86% this statement was prominent
- 92% indicated that safety testing was the research goal.
- Patients with advanced cancer who participate in phase I research may have a different set of values than do critics and are not coerced.
- 70% of patients understand that they may not directly benefit
- Some also receive comfort from knowing they are helping future patients

Do Terminally ill Cancer Patients Misunderstand?

- Are Patients With Cancer Able to Choose Freely?
- To categorize the choice of patients with advanced cancer to participate in phase 1 studies as inherently coerced is a serious confusion.
- However, being in a situation with limited and difficult choices does not itself constitute coercion.
- Many dying people want chemotherapy, even with a very low chance of benefit and a reasonable chance of toxic effects, because it offers them hope
- Fits with their life narrative to fight against the odds and to overcome challenges;
- To die without trying everything would be false to themselves and their values

Are Terminally ill Cancer Patients "Vulnerable"?

- Most important, even if terminally ill patients are vulnerable, this does not imply an inherent lack of capacity to give informed consent.
- The use of "vulnerability" has become a catch-all for many of the ethical issues raised at the end of life.
- Most people with advanced cancer are able to and do make rational, reasonable, and informed decisions.
- There will be some individuals who are unable to give adequate informed consent, just as is true for people without advanced cancer.

The Old Model

- Oncology Therapies mostly consisted of very toxic agents.
- Investigational drugs were tested in Phase I with a small, heterogeneous patient population
- To identify a safe dose
- Then moving into disease-specific, Phase II protocols to test the antitumor activity.

The field has progressed

- Elucidation of the full sequence of the human genome & the breakthroughs in molecular biology & immunotherapy,
- Very specific targeted therapies are tailored
- To the specific pathophysiology of different types of cancers.

The New Model

- Today Phase I protocols are increasingly incorporating preliminary evaluation of anti-tumor activity and the selection of the cancer population more likely to be targeted by the new drug.
- Study designs include a dose escalation cohort to determine the maximum tolerated dose (MTD) of the optimal biological dose (OBD),
- Followed by a dose expansion cohort with narrower eligibility criteria
- With focus on specific biomolecular features to confirm the recommended Phase II dose
- to obtain preliminary evidence of the anti-cancer efficacy in selected patient subgroups

Conclusion

- Phase 1 oncology trials are critical to improving the treatment of cancer
- Critics have raised ethical concerns about an unfavourable risk-benefit ratio and informed consent.
- A critical analysis of the risk-benefit ratio does not show it to be unfavourable.
- Empirical data on informed consent in phase 1 oncology trials do not support the notion that consent is uninformed.

Early Phase Oncology Studies are Ethical and Essential for the continual Innovation and Improvement of Patient Care

I recommend This Motion to The House