# Ethics of Phase I Oncology Trials

Manish Agrawal M.D., M.A.
Department of Clinical Bioethics
Medical Oncology Clinical Research Unit
National Institutes of Health

# Phase I Research

- Phase I research is research aimed at identifying the safety, toxicities and the appropriate dosing of a new drug or intervention for future efficacy studies (Phase II).

# 8 Requirements for Ethical Research

1) Collaborative partnership
2) Social value
3) Scientific validity
4) Fair subject selection
5) **Favorable risk-benefit ratio**
6) Independent review
7) **Informed consent**
8) Respect for human subjects

# What the Critics Say

" …Phase I cancer drug research, for example, may not be performed on terminally ill subjects under these guidelines because there is no reasonable probability that it will benefit the subjects."

-George Annas

# Another Critic

"Informed consent documents make phase one studies sound like the cure for your cancer"

LeRoy Walters (2000)

# Ethical Criticisms of Phase I Oncology Research

- Unfavorable Risk Benefit Ratio
- Informed Consent is flawed

# Risk/Benefit Ratio

- Critics argue that the risks outweigh the benefits
- Some even argue that there are risks with no benefits

# What are the Benefits?

Decoster et al. (1990)

Reviewing 211 trials involving 87 drugs and 6,639 patients between 1972-1987.

- Complete Responses 0.3%
- Partial Responses 4.2%
- Toxic deaths 0.5%

# What are the Benefits?

Estey et al. (1986)

Reviewing 187 trials involving 54 drugs and 6,447 patients between 1974-1982.

- Complete Responses 0.7%
- Partial Responses 3.5%

# What are the Risks?

- Toxic Death 0.5%

- Side effects- Neutropenia, hair loss, neuropathy; severity and prevalence is not quantified

# What are the Risks?

- Resource and time commitment from patients and families; due to frequent blood draws, radiological evaluations, physician visits, biopsies etc.

# Do the data as discussed tell the whole story?

# A Second Look at the Meta-analyses

Overall response rates may hide important response data:

- 30% of the drugs from the meta-analyses had response rates over 5%
- Only 39% of the trials had no objective responses
- The meta-analyses only looked at drugs from 1972-1987, the drugs used now are better.

# Some Notable Responses in Phase I Studies

Some remarkable therapeutic benefits in Phase I oncology trials

- Platinum had >50% response rate in testicular cancer
- Gleevac had >90% response rate in CML

# More Recent Data on Risks/Benefits

CTEP Database

- 477 trials between 1991 and 2002
- 10,867 patients for response
- 12,458 patients for toxicity

# Risk-Benefit Ratio

| | RR | CR | Deaths |
|---|---|---|---|
| **Overall** | 12.2% | 4.0% | 0.68% |
| **1 Invest. Agent** (21%) | 4.0% | 1.4% | 0.62% |
| **Multiple Invest Agent** (3.8%) | 15.1% | 1.1% | 0.43% |
| **Approved and Invest** (25%) | 18.7% | 7.3% | 1.2% |
| **Signal Trans** (10%) | 3.2% | 0.8% | 0.24% |

# Risk-Benefit Ratio

| | Death | Grade III Toxicity | Grade IV Toxicity |
|---|---|---|---|
| Total 12,458 | 0.68% | 79.3% | 22.8% |
| 1 Invest Agent 2,575 | 0.62% | 73.8% | 26.9% |
| Approved and Invest 3,099 | 1.2% | 60.6% | 21.8% |
| Sign Trans 1,213 | 0.24% | 73.9% | 17.0% |

# Risk-Benefit Ratio

- **125 Phase I studies published in 2002**
- **3,494 total patients but 2,830 evaluable**

| CR | PR | SD | Deaths |
|---|---|---|---|
| 4.6% | 14.0% | 24% | 1.3% |

# Benefits beyond Tumor Responses

"…Patients do not seem to be harmed by their experience of participating in a phase I trial and may experience benefits, albeit not in terms of tumor control"

Moore (2001)

# Benefits beyond Tumor Responses

- If we are going to consider non-medical risks, we should also consider non-medical benefits.

# Other Benefits Beyond Tumor Response

- Some data suggest that enrolling in Phase I research is beneficial to the quality-of-life of patients.
- Patients in Phase I had stable Quality Of Life and performance status over 1 course of therapy whereas similar patients receiving supportive care had declines in QOL.

Melink et al. (1992), Berdel et al. (1988)

# Psychological Comfort

- 65% of research participants said they believed they would receive psychological benefit from being in the phase I study.
  - Structure and routine of trials
  - Exercise some control
  - Help others in the future

Daugherty et al. (2000)

# Summary of Risks

- Risks may not be as bad as implied.
- 0.5% risk of death for a terminally ill patient may not be very high.
- It would be good to have more data on the risks of other side effects and morbidity rates.

# Summary of Benefits

- Benefits may be greater than implied.
- Many Phase I drugs trials have had >15% response rates and at least 2 notable cases have provided substantial therapeutic responses even cures.
- QOL may be better on a Phase I trial than supportive care.

# What do the Data Show?

- While the scientific objectives of phase I oncology studies do not include patient benefit, there do appear to be benefits.
- Are the benefits enough to make risk/benefit ratio favorable?

# Is the risk/benefit ratio favorable or unfavorable?

# Compare Results of Phase I Studies to FDA Approved Chemotherapy

- High dose IL-2 for metastatic renal cell

  Complete Response 5%

  Partial Response 9%

  Median duration of response is 20 months
- Gemcitabine approved for improvement in QOL for pancreatic cancer with response rate of only 5%

# Compare Results of Phase I Studies to FDA Approved Chemotherapy

- Topotecan is approved with 10% response rate for ovarian cancer.
- CPT-11 is approved for metastatic colon cancer on the basis of less than 2 month prolongation of survival
- 1% gain in absolute mortality for 4 cycles of adjuvant chemotherapy for Stage I breast cancer.

# Risk-Benefit Ratio Not Worse than Other Approved Therapy by FDA

- The risk-benefit ratio for phase I oncology studies is clearly not worse than risk/benefit ratios used by the FDA as a basis for approval of many chemotherapeutic agents.

# Who decides what is a favorable risk benefit ratio?

# Who decides?

- Who currently decides a favorable risk-benefit ratio in research?
  - Investigators
  - Bioethicists
  - Lawyers
  - Statisticians
  - Physicians
  - Policymakers

# Who Should Decide?

- Should the people who are facing life-ending illness have some input on whether a risk/benefit ratio is favorable for research studies?

# Patients Have Different Perceptions than Healthy People

- Substantial data demonstrates that patients facing serious illnesses make very different assessments of their own condition and the risks they are willing to confront compared to healthy individuals.
- Even families, consistently overestimate symptoms and underestimate patient satisfaction and quality of life

Epstein (1989), Zweibel (1989)

# Patients Willing to Undergo More Risk than Healthy People

- Patients need very small benefits to find cancer chemotherapy worthwhile.
- Cancer patients only needed only 1% chance of benefit to want an intensive chemotherapy regimen described with many side effects.
- Nurses needed 50% chance, and doctors needed a 10% chance, general public needed 50% chance of benefit.

Slevin et al. 1990

# A patient's perspective

We who are struggling to escape cancer do not, obviously, want to die of it. We do prefer death in the struggle to life under cancer's untender rule. The enemy is not pain or even death, which will come for us in any eventuality. The enemy is cancer, and we want it defeated and destroyed… This is how I wanted to die—not a suicide and not passively, but eagerly in the struggle.

George Zimmer

Phase I patient University of Chicago

# Patient's Perspective Should be Taken into Account

- Views of terminally ill cancer patients should inform IRB determinations of favorable risk-benefit ratios for phase I oncology studies.

- Including such patients might emphasize alternative study designs using higher doses that increase toxicities but also may increase the chance of benefits

# Ethical Criticisms of Phase I Oncology Research

- Unfavorable Risk Benefit Ratio
- Informed Consent

# Invalid Informed Consent

Disclosure

- Are Phase I informed consent documents distortive?

Understanding

- Do terminally ill patients understand information about Phase I research?

Voluntariness

- Are terminally ill patients able to choose freely?

# Invalid Informed Consent

Problems with disclosure of information

- Physicians do not provide appropriate or accurate information.

- Physicians stress and exaggerate the benefits while minimizing the risks of research participation.

# Invalid Informed Consent

Problems with patient understanding.

- Because they are terminally ill, patients cannot understand the true objectives, benefits and risks of Phase I research. Their understanding is clouded by their physical state and their hope for a cure.

- What clear thinking patient would opt to take toxic drugs rather than receive palliative care and comfort measures at the end of life?

# Invalid Informed Consent

- Because terminally ill patients are not given proper information by their physicians, because they cannot understand the information they are given, and because they are vulnerable, they cannot provide valid informed consent.

# Informed Consent

Can terminally ill patients provide informed consent?

- Do Phase I researchers misinform patients?
- Do Phase I informed consent documents misinform?
- Do terminally ill patients misunderstand information about Phase I research?
- Are terminally ill patients under a therapeutic misconception?
- Are terminally ill patients vulnerable?

# Do Phase I Researchers Misinform Patients?

# Do Physicians Misinform?

Tomamichel et al. (1995)

- Recorded informed consent interactions for 32 patients.
- Quantitative analysis indicated that 3 major information points were communicated in almost 80% of cases.
- Use of indirect patient responses was not as good.

# Do Physicians Misinform?

Daugherty et al. (1995)

18 Phase I oncologists at U of Chicago

| | |
|---|---|
| 1-2 months added survival | 10% |
| Complete and partial response | 15% |
| Complete response | 1% |
| Life-threatening toxicity | 10% |
| Death | 5% |

# Do Physicians Misinform?

Meropol et al. (2003)
48 physicians and 328 patients considering Phase I

| Discussed with Patients | **Physicians** | **Patients** |
|---|---|---|
| Possible side effects | 92% | 78% |
| Possible risks | 92% | 73% |
| Possible benefits | 90% | 79% |
| Change in length of life | 60% | 29% |

# Do Physicians Misinform?

- Benefit from experimental therapy 15%
- Adverse events experimental therapy 10%

# Do Physicians Misinform?

- Limited data suggests physicians do not misinform patients and if they do misinform they tend to over-estimate risks more than benefits.

# Do Phase I Informed Consent Forms Misinform?

# Informed Consent Forms

Are Phase I informed consent forms distorted?

- Do they over promise benefits?
- Do they minimize risks?

# Do Forms Misinform?

Data from a review of 272 Phase I informed consent documents from 1999.

- Only 29% of all Phase I oncology trials involve a previously untested drug in classic dose escalation design.

- 40% of Phase I trails had a therapeutic element. For instance, adding a new drug to a known effective drug.

Horng et al. (NEJM, 2002)

# Do Forms Misinform?

- 92% mention safety, dose determination, or toxicity as the purpose of the trial.

- 99% mention that the study is research or an experiment with most of these being prominent or highly prominent in the informed consent form.

# Do Forms Misinform?

- 6% explicitly mention that the research is not therapeutic.

- 96% refer to the chemotherapy agent as treatment or therapy.

# Do Forms Misinform?

- Median length of risk and benefit sections

| | |
|---|---|
| Risk | 35 lines |
| Benefit | 4 lines |

- 67% mention death as a possible risk
- 33% mention death more than once
- 83% mention possibility of serious harms

# Do Forms Misinform?

- One of 272 forms mention benefits will definitely accrue to subjects.

- Mention as possible benefits

| | |
|---|---|
| Cure | 5% |
| Life prolongation | 20% |
| Tumor shrinkage | 36% |
| Generalizable knowledge | 68% |

# Do Forms Misinform?

- 96% have separate alternatives section

- Mention as alternatives

| | |
|---|---|
| Palliative care | 56% |
| Standard therapy | 88% |
| No treatment | 65% |
| Other experimental therapy | 52% |
| Hospice | <1% |

# Do Forms Misinform?

While the documents are not perfect and can be improved, it is hard to say that informed consent documents:

- Over promise benefits and minimize risks
- Disguise the nature of the trial or that it is research
- Promise cure

# Do Patients with Advanced Cancer Misunderstand Information about Phase I Research?

# Do Patients Misunderstand?

Decoster et al. (1990)

- 91% of patients on Phase I trials had prior therapy:
  - 50% chemotherapy alone
  - 25% chemotherapy and radiation therapy
  - 11% radiation therapy alone

# Do Patients Misunderstand?

- Daugherty et al. (2000)

| | |
|---|---|
| Recall signing consent form | 100% |
| Recall explanation of study as research | 98% |
| Recall explanation of risks and side effects | 97% |
| Recall at least 1 specific side effect | 100% |
| Felt well informed | 96% |

Quality of the information transfer was associated with higher education.

# Do Patients Misunderstand?

Joffe et al. (2001)

Mailed survey of 207 Phase I, II, and III cancer patients.

50 in Phase I studies, but not distinguished in data analysis.

# Do Patients Misunderstand?

Joffe et al. (2001)

- 84% read the consent form carefully
- 87% had enough time to learn about the trial
- 93% sufficient time to ask questions
- 48% consent discussion last over 1 hour
- 44% consulted an outside physician

# Do Patients Misunderstand?

- Almost all patients participating in Phase I studies feel well informed and are satisfied by the informed consent process:

| Study | # of Patients | % Satisfied |
|---|---|---|
| Daugherty | 144 | 96% |
| Tomamichel | 31 | 96% |
| Joffe | 207 | 90% |

# Do Terminally Ill Patients have a Therapeutic Misconception about Phase I Trials?

# Therapeutic Misconception?

| Study | # Subjects | Results |
|---|---|---|
| Yoder | 37 | 70% to get best care |
| | | 85% shrink tumor |
| Tomamichel | 31 | 59% medical benefit |
| Cheng | 30 | 60% medical benefit |

# Therapeutic Misconception?

- Daugherty et al. (2000)

  Patients views of purpose of Phase I

  - Anticancer Response 61%
  - Toxicity Determination 27%
  - Combination 8%

# Therapeutic Misconception?

Meropol et al. (2003)

Maximum Benefit of Experimental Therapy

37% of studies only investigational agents

| | |
|---|---|
| Totally cure | 39% |
| Reduce cancer | 26% |
| Control cancer | 30% |
| Improve symptoms | 3% |
| Nothing | 2% |

# Therapeutic Misconception?

Joffe et al. (2001)

- 75% reported that the main reason for trials was to improve treatment of future patients
- 71% there may not be direct medical benefit to me
- 48% report treatments and procedures in the trial are standard for their cancer

# Elizabeth

"I know you want me to say that this trial is about safety. But the doctors wouldn't start the trial without hoping they could prove the drug would be effective in stopping cancer in future trials."

# Invalid Informed Consent

Disclosure

- Are Phase I informed consent documents distortive?

Understanding

- Do terminally ill patients understand information about Phase I research?

Voluntariness

- Are terminally ill patients able to choose freely?

# The Ethical Concern Raised about Voluntariness

- Some critics argue that terminally ill patients not only have clouded understanding and are not acting voluntarily but under compulsion by their impending death.

# Voluntariness

- No data on the voluntariness of the informed consent process in phase I cancer studies

# We Don't Ignore Other Decisions People Make at the End of Life

- Just facing terminal illness does not invalidate people's decisions
- We accept estate wills and DNR requests made by terminally ill patients as genuine

  We do not reject the consent of life-saving organ transplants as prima facie invalid because they are made by terminally ill patients who cannot think clearly

# Cannot Label Everyone with Advanced Cancer as Incompetent

- There will be some people with advanced cancer who are able to and do make rational , reasonable, informed decisions and some who can't just like those without advanced cancer
- But cannot conclude that all patients with advanced cancer are unable to give informed consent

# Summary

- Risk-Benefit ratio is not unfavorable
  - There are more benefits than ascribed by critics
  - The Risk-Benefit ratio is not clearly worse than some FDA approved therapy
  - Patients perspective should be taken into account when deciding about risk-benefit ratios
- Data does not suggest that consent is uninformed