Some ethical issues with phase I oncological trials

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History of cancer chemotherapy

- In 1940s Goodman, Gilman and Linskog found that nitrogen mustard can supress lymphomas;
- In 1950s were found that antifolates, e.g. methotrexate, can suppress acute lymphoblastic leukaemia and the solid tumor choriocarcinoma, also national program to develop anticancer drugs were created in the US.
- In 1960 the idea of combination chemotherapy were implemented
- Since 1990s more targeted anticancer drugs appear.

http://en.wikipedia.org/wiki/History_of_cancer_chemotherapy

Selection of research subjects

(Eisenhauer, Bonetti, Gelber, 2004)

- Due to high toxicity of volunteers usually do not participate in such studies;
- Cancer patients entering into trials do not have any proven efficient therapy;
- Research subjects should have adequate hepatic, renal, hematologic functions.

Ethical problems with phase I oncological studies

- Tension between scientific and therapeutic objectives;
- Appropriate risk-benefit relationship for participants;
- Validity of consent from terminally ill patients.

(Joffe ja Miller, 2006)

In general there are two clearly opposing parties to consider ethical issues of phase I anticancer clinical trials

Phase I: Pure science or rather more complex one?

- “Principal objective of phase I trials is to define a safe dose and schedule suitable for later efficacy testing. Additional objectives of most phase I studies are the gathering of pharmacokinetic data and the preliminary assessement of the effect of the agent.” (Van de Velde, Grochow, 2005)
- At the same time the compound under research has potential to be therapeutically effective for patients/research subjects, but with obvious uncertainty for doctors/researchers.

Informed consent

- Opponents to patient participation in phase I oncological trials have concerns to deficient disclosure in informed consent procedure.
- The number and character of empirical studies on the quality of informed consent has not been sufficient to express good quality opinions on the issue.
- Some empirical studies have shown that majority of research subjects were motivated to participate in trial due to the hope to get better treatment or medical care.
- Different studies showed that 30-80% of participants knew the experimental character of the study.
- Over 90% of research participants were satisfied with informed consent procedure.

Agrawal & Emanuel, 2003

Risk-benefit assessment I

- Risk-benefit analysis is a very common approach to study moral status of situation, incl. scientific research, in utilitarianist tradition.
- Some critics say that phase I oncological trials have little benefit and substantial risks for research subjects;
- Benefits seems to be more collective and risks mainly personal which may have influence on human dignity issue.

Risk-benefit assessment II

- According to several empirical studies the tumor response in phase I nonpediatric single-agent trials occurs in 4-6% of patients and 0.5% patients die due to the toxic effect of research compounds (Horstmann et al., 2005), i.e. both benefit and extreme risk are quite low.

Risk-benefit assessment III

There are scales to differentiate tumour response and levels of toxicity:

- **The WHO and RECIST** (Response evaluation criteria in solid tumours) **criteria** distinguish complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD);
- **Common Toxicity Criteria** (CTC) have grades 0-5: 0 = no adverse event or within normal limits; 1 = mild adverse event; 2 = moderate adverse event; 3 = severe and undesirable adverse event; 4 = life-threatening or disabling adverse event; 5 = death related to adverse event

Risk-benefit assessment IV

- Horstmann et al (2005) studied 460 phase I oncological trials between 1991-2002 with 11 935 participants;
- 10.6 % of all participants had complete (3.1%) or partial (7.5%) response varying from 3.0% to 19.5% in different studies;
- Among all participants the death rate was 0.49%. In subgroup of 168 studies with 3465 research subjects 14.3% (4.3-34%) had grade 4 toxic events.

Some conclusions

- More exact conceptualizations may help to clarify ethical analysis of phase I studies
- New trial designs and more targeted research compounds can reduce tensions of classical phase I trials with cytotoxic compunds.
- The topic has practial importance at least in (East) European context to think about creating some common standards or guidelines for such type of studies.

References

- Agrawal M., Emanuel E.J. Ethics of Phase 1 Oncology Studies: Reexamining the Arguments and Data. *JAMA, 2003* 290: 1075-1082.
- Eisenhauer EA, Bonetti M, Gelber D. The principles of clinical trials. In: Cavalli, Hansen, Kaye, eds. Textbook of Medical Oncology, 2004.
- Horstmann E, McCabe M, Grochow L, Yamamoto S, Rubinstein L, Budd T, Shoemaker D, Emanuel E, Grady C. Risks and Benefits of Phase I Oncology Trials 1991-2002. *New England Journal of Medicine*. 2005; 352(9), 895-904.
- Joffe S, Miller FG. Rethinking Risk-Benefit Assessment for Phase I Cancer Trials. *J. Clin Oncol.* 2006, 24(19), 2987-2990.