Innovative Therapies for Children with Cancer

ITCC European consortium

Introductory course in paediatric drug development - Utrecht

ETHICS OF CONDUCTING EARLY PHASE TRIALS IN CHILDREN

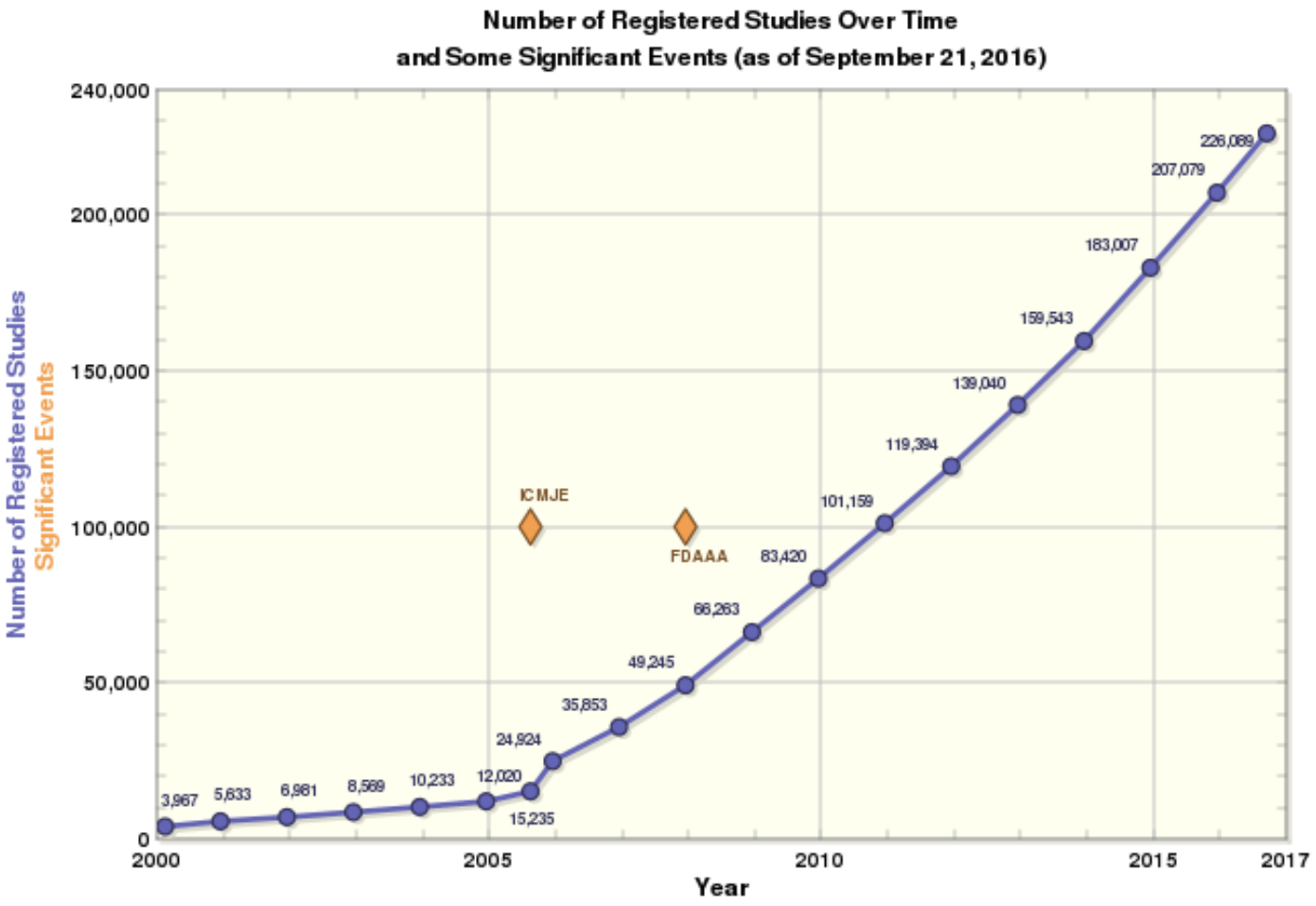
Luca Bergamaschi MD

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI – MILANO

S.C. Pediatria Oncologica

October 15th , 2018

Increasing number of clinical trials



Source: https://ClinicalTrials.gov

Changes in drug development

- Improved understanding of mechanisms of tumorigenesis

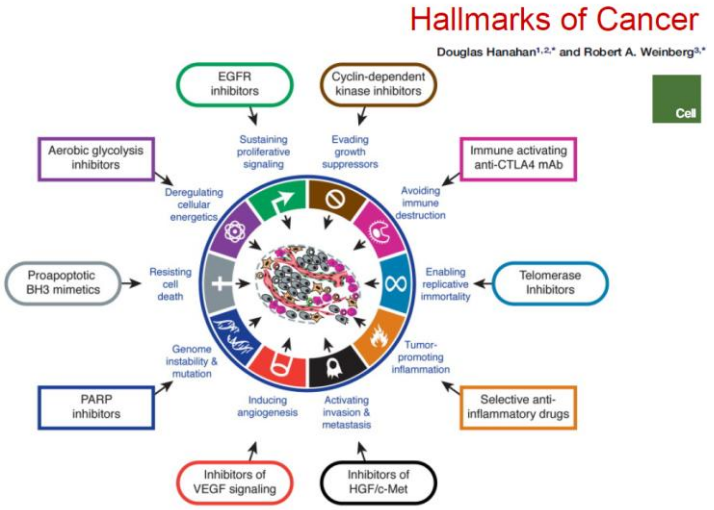
- Increasing number of new anticancer compounds

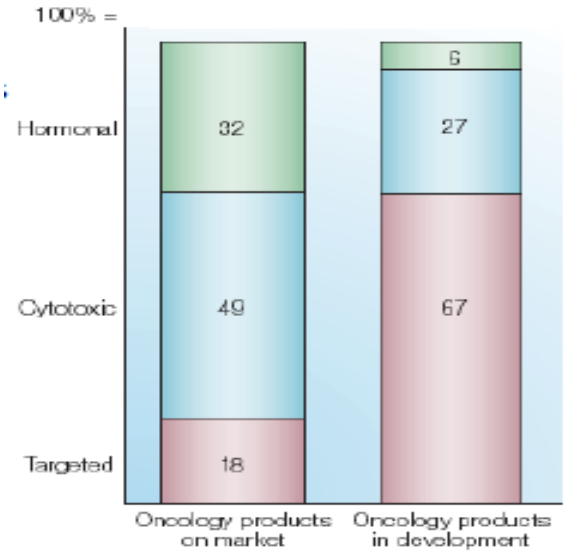
  >1000 new molecules every year
  targeted therapy, immunotherapy
  new mechanisms of action

- Only 5% demonstrate efficacy for regulatory approval

- Strategies to optimize and expedite the development

- Need for regulatory principles to guide research

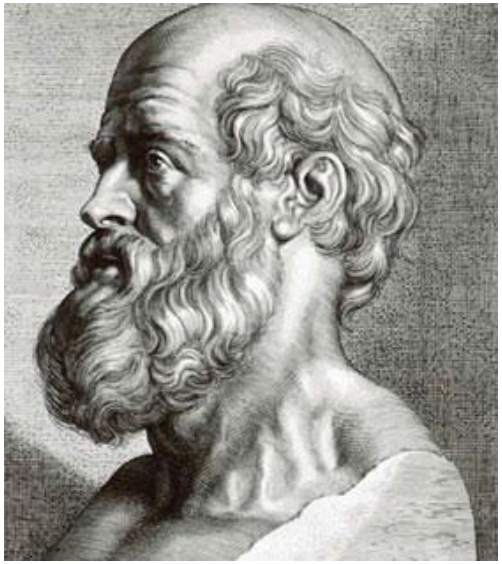


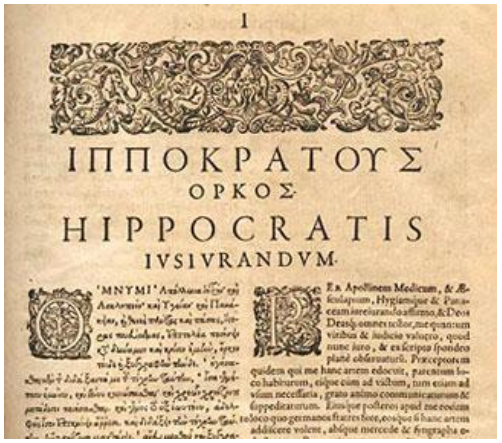


Ethics in medical profession

Hippocratic oath

"…I will apply, for the benefit of the sick, all measures which are required, avoiding those twin traps of overtreatment and therapeutic nihilism…."





- Ethical principles are present and rule every clinical decision

- Often decisions are complex, particularly when we consider research and clinical trials

Balance between two souls

PEDIATRIC ONCOLOGIST

CAREGIVER

RESEARCHER

Regulatory aspects

After the second world war, there was an emerging need of ethical rules to conduct experimentations on human beings:

- ***Nuremberg Code*** *(1947)*
- ***Declaration of Helsinki*** *(1964)*

Nuremberg Code (1947)

1. **Required is the voluntary, well-informed, understanding consent of the human subject in a full legal capacity.**
2. The experiment should aim at positive results for society that cannot be procured in some other way.
3. It should be based on **previous knowledge** (like, an expectation derived from animal experiments) that justifies the experiment.
4. The experiment should be set up in a way that **avoids unnecessary physical and mental suffering** and injuries.
5. It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.
6. The **risks** of the experiment should be **in proportion to** (that is, not exceed) the expected humanitarian **benefits**.
7. Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.
8. The staff who conduct or take part in the experiment must be fully trained and scientifically qualified.
9. The human subjects must be **free to immediately quit the experiment** at any point when they feel physically or mentally unable to go on.
10. Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous.

Declaration of Helsinki (1964)

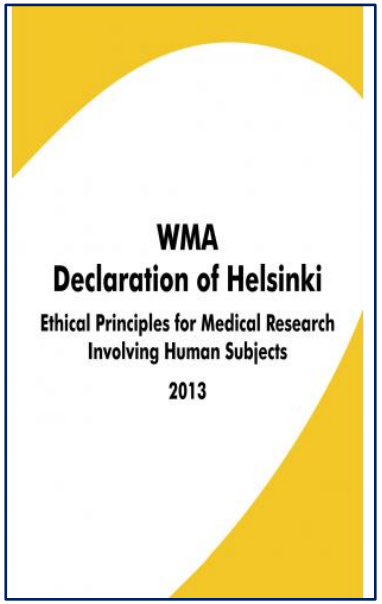
- Written by World Medical Association (7 revisions)
- The cornerstone document on human research ethics
- Technical and executive aspects

BASIC PRINCIPLES

- Respect for the individual, their right to self-determination and the right to make informed decisions

- Subject's welfare must always take precedence over the interests of science and society

- Special vigilance for vulnerable individuals



Declaration of Helsinki (1964)

OPERATIVE PRINCIPLES

- Research should :
  - be based on a thorough knowledge of the **scientific background** and a careful assessment of **risks and benefits**
  - have a reasonable likelihood of benefit to the population studied
  - be conducted by suitably **trained investigators** using **approved protocols,** subject to **independent ethical review** and oversight by a properly convened committee

- The protocol should address the ethical issues and indicate that it is in compliance with the Declaration

- Studies should be discontinued if the available information indicates that the original considerations are no longer satisfied

- Information regarding the study should be publicly available

- Ethical publications extend to publication of the results and consideration of any potential conflict of interest

- Experimental investigations should always be compared against the best methods, but under certain circumstances a placebo or no treatment group may be utilized

- The interests of the subject after the study is completed should be part of the overall ethical assessment, including assuring their access to the best proven care

Independent external review

- ***Independent Ethics Committee (IEC)***
- ***Institutional Review Board (IRB)***

An **independent** body constituted of medical, scientific, and non-scientific members, whose responsibility is to **ensure the protection of the rights, safety and well-being of human subjects involved in a trial** by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects

Good Clinical Practice (GCP) guidelines

GCP is an **international ethical and scientific quality standard** for designing, conducting, recording and reporting trials

Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected

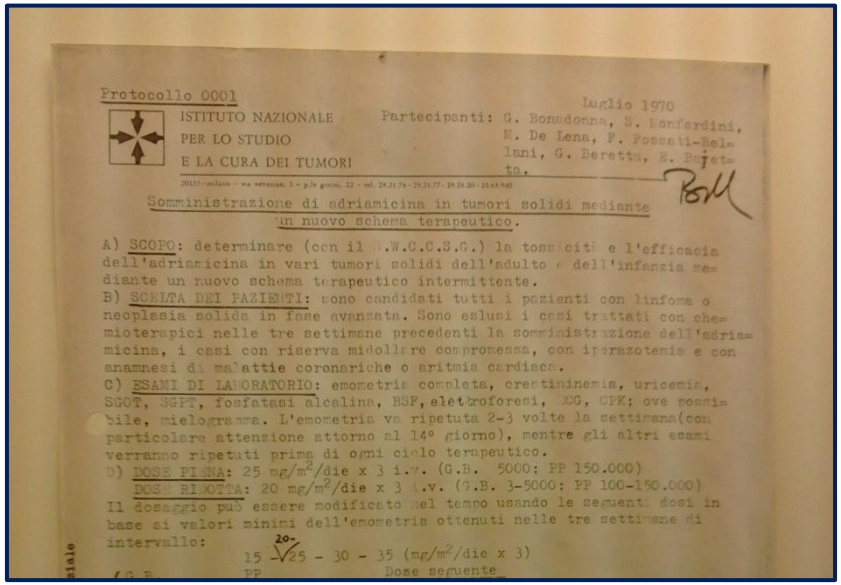
Quality assurance and inspections ensure that these standards are achieved.

GCP aims to ensure that the studies are scientifically authentic and that the clinical properties of the investigational product are properly documented

The objective is to provide a unified model to facilitate the acceptance of clinical data by the regulatory authorities in different jurisdictions

Evolution of research ethics

1970



Protocollo 0001

ISTITUTO NAZIONALE
PER LO STUDIO
E LA CURA DEI TUMORI

Luglio 1970

Partecipanti: G. Bonadonna, S. Bonfardini, M. De Lena, F. Fossati-Bellani, G. Beretta, E. Bajetta.

Somministrazione di adriamicina in tumori solidi mediante un nuovo schema terapeutico.

A) SCOPO: determinare (con il G.W.C.C.S.G.) la tossicità e l'efficacia dell'adriamicina in vari tumori solidi dell'adulto e dell'infanzia mediante un nuovo schema terapeutico intermittente.

B) SCELTA DEI PAZIENTI: sono candidati tutti i pazienti con linfoma o neoplasia solida in fase avanzata. Sono esclusi i casi trattati con chemioterapici nelle tre settimane precedenti la somministrazione dell'adriamicina, i casi con riserva midollare compromessa, con iperazotemia e con anamnesi di malattie coronariche o aritmia cardiaca.

C) ESAMI DI LABORATORIO: emometria completa, creatininemia, uricemia, SGOT, SGPT, fosfatasi alcalina, BSF, elettroforesi, EG, CPK; ove possibile, mielogramma. L'emometria va ripetuta 2-3 volte la settimana(con particolare attenzione attorno al 14° giorno), mentre gli altri esami verranno ripetuti prima di ogni ciclo terapeutico.

D) DOSE PIENA: 25 mg/m²/die x 3 i.v. (G.B. 5000; PP 150.000)
DOSE RIDOTTA: 20 mg/m²/die x 3 i.v. (G.B. 3-5000; PP 100-150.000)
Il dosaggio può essere modificato nel tempo usando le seguenti dosi in base ai valori minimi dell'emometria ottenuti nelle tre settimane di intervallo:

15 - 20 - 25 - 30 - 35 (mg/m²/die x 3)
PP Dose seguente

4 pages

2018

A multi-center, open-label, non-randomized, phase I dose escalation study of regorafenib (BAY 73-4506) in pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy.

Safety, tolerability and pharmacokinetics of regorafenib in pediatric subjects

Test drug:	BAY 73-4506/Regorafenib/STIVARGA®		
Study purpose:	Safety, dose finding, and pharmacokinetics		
Clinical study phase:	I	Date:	29 MAY 2017
EudraCT no:	2013-003579-36	Version no.:	4.0
Study no.:	BAY 73-4506/15906		
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany [1]		
Sponsor's medical expert:	Kaline Medeiros, MD, PhD [2] Phone: + 55 11 56944364 Fax: +55 11 5694 4075 Mobile: +55 11 98469 0431 e-mail: kaline.medeiros@bayer.com		

309 pages

Ethical aspects in early trials structure

- Inclusion and exclusion criteria
- Dose escalation / de-escalation
- Design: 3+3 / rolling 6 (phase I); two-stage (phase II)

PEDIATRIC SPECIFICITIES

- Previous experience in adults (known toxicities)
- Starting dose: 80% of adults MTD

- ***Minimize the number of patients exposed to a drug potentially harmful***
- ***Limit the number of patients treated with a drug without benefit***

Objectives of phase I trials

PRIMARY OBJECTIVES

- Safety and tolerability of a drug
- Dose limiting toxicities (DLT)
- Maximum tolerated dose (MTD)

SECONDARY OBJECTIVES

- Efficacy
- PK, PD, biomarkers,…

Fundamental difference

In phase I trials it is essential to differentiate between:

The **primary** **objective** of the study

(toxicity, MTD)

and

The **individual** **objective** for the patient/parents/MD

(the hope of tumor response and therapeutic benefit)

Informed consent

A **process** by which a subject voluntarily **confirms** his or her **willingness to participate** in a particular trial, after having been **informed of all aspects** of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Not only a signature, but a fundamental moment for the participation in a clinical trial

A process of:

- *COMMUNICATION*
- *RESPONSIBILITY*
- *AWARENESS*
- *COLLABORATION*

Informed consent

KEY ELEMENTS

- Purpose of the research
- Procedures required during the trial
- **Potential risks and benefits**
- **Alternatives to participation**
- Right to withdraw
- Confidentiality of the acquired data

be CLEAR and HONEST with your patients!

Assent

Assent is a child's affirmative agreement to participate in research

Various forms of assent (written / oral) defined by the different IRBs taking into account the ages, maturity and psycological state of the minor

- *Involvement of a child as active participant in the decision, not simply a passive bystander*
- *Respect for the mature role that adolescents play in decisions about their treatment*

CONTROVERSIES

- How objectively measure this affirmative agreement
- How seriously dissent should be taken
- At what developmental stage the child's wishes should take precedence over all else

Informed consent

VOLUME 30 · NUMBER 35 · DECEMBER 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Communicating and Understanding the Purpose of Pediatric Phase I Cancer Trials

Melissa K. Cousino, Stephen J. Zyzanski, Amy D. Yamokoski, Rebecca A. Hazen, Justin N. Baker, Robert B. Noll, Susan R. Rheingold, J. Russell Geyer, Stewart C. Alexander, Dennis Drotar, and Eric D. Kodish

- Debate about the quality of the consent given in phase I trials
- How to measure a subject's understanding
- How well the subject must understand the information provided to be considered truly "informed"

➢ Observation during informed consent communication and subsequent parents interview

Cousino M, et al. JCO 2012

Informed consent

Patient's understanding of the scientific purpose of the phase I trial:

- No understanding 35%
- Partial understanding 32%
- **Substantial understanding 32%**

Physician's explanation:

- Goal of the protocol 85%
- Dose cohorts 43%
- **Drug safety 23%**
- Dose finding 52%
- Dose escalation 53%

Physician-parent communication about the purpose of phase I trial have to be improved

Cousino M, et al. JCO 2012

Misunderstanding in clinical trials

Therapeutic misconception

Belief that an early clinical trial is designed only for the subject's benefit and deny that there may be disadvantages to participating

(misunderstanding about the objectives of the studies)

Therapeutic misestimation

Overestimation of the benefits that a study can grant and/or underestimation of the potential risks associated

Unrealistic optimism

Perception of personal outcome as more positive than those of other people in similar circumstances

Misunderstanding in clinical trials

Published in final edited form as:
Cancer. 2012 September 15; 118(18): 4571–4578. doi:10.1002/cncr.27397.

Therapeutic Misconception, Misestimation and Optimism in Subjects Enrolled in Phase I Trials

Rebecca D. Pentz, PhD[1], Margaret White, BA[2], R. Donald Harvey, PharmD[1], Zachary Luke Farmer, MDiv[3], Yuan Liu, PhD[4], Colleen Lewis, MSN, ANP-BC, AOCNP[5], Olga Dashevskaya, JD[1], Taofeek Owonikoko, MD[1], and Fadlo R. Khuri, MD[1]

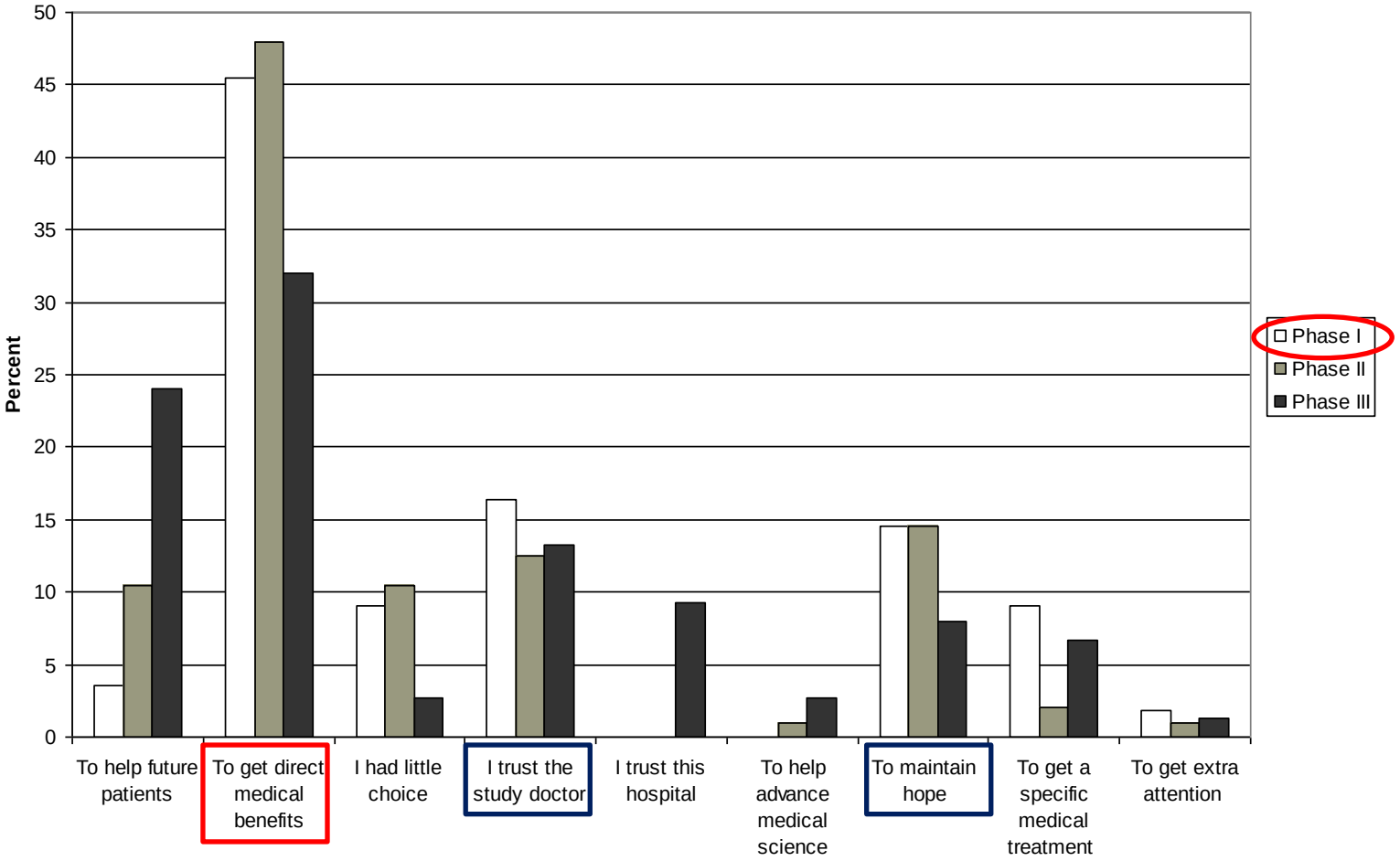
95 patients – interview during the first month of trial participation

- Therapeutic misconception: 68.4%
- Therapeutic misestimation: 94%
- Unrealistic optimism: 54.6%

Pentz R, et al. Cancer 2012

Motivation for cancer trial participation

N=252 adult trial participants and parents of paediatric trial participants



Response & toxic deaths rates in phase I

Citation	Ad/Ped	N	CR	CR+PR	TD
Estey ’86	Adult	6447	0.7%	2.9%	N/A
Decoster ’90	A&P	6639	0.3%	4.5%	0.5%
Roberts ‘05	A&P	6474	N/A	3.8%	0.5%
Horstmann ‘05	Adult	11935	3.1%	10.6%	0.5%
Furman ’89	Ped	577	1.9%	5.8%	0.5%
Shah ’98	Ped	1606	3.3%	7.4%	0.7%
Lee ’05	Ped	1973	2.8%	9.6%	0.5%

Response Rate: 3-10%

Toxic deaths: 0.5-0.7%

Response & toxic deaths rates in phase I

RESEARCH ARTICLE

Risk and surrogate benefit for pediatric Phase I trials in oncology: A systematic review with meta-analysis

<u>170 phase I pediatric trials</u> involving 4604 patients (2004-2015)

- ORR: 10.29% (solid tumors 3.17%, hematological 27.9%)
- Toxic deaths (AE grade 5): 2.09%
- Drug-related AEs grade 3-4: 1.32 per person
- ORR and AEs similar to those in adult phase I trials

Waligora M, et al. PLOS Med 2018

Clinical case 1

- male, 4 years old
- Long time to reach diagnosis

- ***Inflammatory Myofibroblastic Tumor (IMT)***
- ***Metastatic (bones, kidneys, lungs, liver, brain)***
- ***ALK gene rearrangement***

- Fever and worsening bone pain

- Parents want to start treatment immediately

Clinical case 1

Active phase I trial with LDK378 (ceritinib)…

…but 2 weeks waiting for the opening of new cohort

Protocol CLDK378X2103

A Phase I, open-label, dose escalation study of LDK378 in pediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)

Clinical case 1

What to do?

- Start chemotherapy
- Supportive care waiting for the phase I trial

Clinical case 1

What do you tell to the parents?

....

- Probable limited efficacy of chemotherapy
- Potential superior benefit expected from the experimental targeted therapy

Supportive care and wait for the cohort opening of the trial

Clinical case 1

- After 4 months complete remission achieved
- Treatment continued for more than 3 years, well tolerated
  - ***Transaminases increase (CTCAE G4) → dose de-escalation***
  - ***Nausea and diarrhea (CTCAE G1)***

- Onset of fever and cough, hematemesis
- Multiorgan failure and encephalitis
- nasal swab and sputum positive for H1N1 virus
- Complete recovery with supportive care

Clinical case 1

What to do?

- Restart administration of LDK378
- Permanently discontinue treatment

Clinical case 1

What do you tell to the parents?

....

- Long lasting complete remission
- Inability of absolutely exclude any role of LDK378 on the course of events → discussion with the sponsor
- Possibility of other treatments in case of relapse

Treatment permanently discontinued

Clinical case 2

- female, 16 years old
- Metastatic osteosarcoma *(lungs)*
- Relapsed 10 months after 1st line treatment
- Parents and patients heard that in our center was opened the phase I trial with Atezolizumab and they come asking to participate

Clinical case 2

What do you tell them?

.....

- Only first line treatment performed
- No clear benefit from the experimental drug
- Possible effective second line treatment

Avoid the idea of immunotherapy and phase I trial; Suggest second line treatment (chemotherapy +/- surgery could be a valuable option)

Comments

• Phase I trials are one of the possibilities, not the only possibility; particularly considering first or second line treatment

• Need to explain clearly the **alternatives** to avoid misunderstanding

• Accurate analysis of potential **benefits and risks** of the new treatment compared to the known data of the standard approaches

• Consider child's best interest first

• **Team review of the decision is advisable**

Clinical case 3

- female, 14 years old
- Metastatic rhabdomyosarcoma
  (lungs, pleura, pericardium, bones)
- Rapid progression after 2 lines of chemotherapy
- Bone pain, dyspnea
- Performance status (Karnofsky): 60%

- Parents know that in our center was opened the phase I trial with Vincristine + Irinotecan + Regorafenib and they ask insistently to participate
- Patient come to the hospital reluctantly because of symptoms

Clinical case 3

What do you tell to the parents?

…..

- Rapid sympthomatic progression
- Low PS
- Life expectancy < 3 months

The enrollment in a phase I trial doesn't seem to be the best option. Supportive care (+/- oral palliative chemotherapy) could be a more reasonable choice.

Comments

- Avoid **unrealistic optimism** of patients/parents but also of physician

- Understand when to stop antineoplastic treatment: also palliative care is an alternative

- Consider the **vulnerability** of terminally ill patients and families: stress related to relapse lead to cognitive and emotional biases that may interfere with their ability to comprehend risk and benefits

- Necessity of **selection criteria** to enroll patients in phase I trials

Selection of patients in phase I trials

- Necessity of specific eligibility criteria and prognostic factors to:

  - Maximize individual benefit

  - Ensure adequate assessment of study end points

Original Research

Prognostic factors of overall survival in children and adolescents enrolled in dose-finding trials in Europe: An Innovative Therapies for Children with Cancer study

Fernando Carceller [a,b,*], Francisco J. Bautista [c,1], Irene Jiménez [e], Raquel Hladun-Álvaro [c,2], Cécile Giraud [f,g], Luca Bergamaschi [h], Madhumita Dandapani [i], Isabelle Aerts [e], François Doz [e,j], Didier Frappaz [f,g], Michela Casanova [h], Bruce Morland [i], Darren R. Hargrave [k], Lynley V. Marshall [a,b], Gilles Vassal [l], Andrew D.J. Pearson [a,b,3], Birgit Geoerger [c], Lucas Moreno [d]

Carceller F, et al. EJC 2016

Selection of patients in phase I trials

Adult patients

Widely accepted eligibility criteria:

- *Adequate organ function*
- *Reasonable PS*
- *Life expectancy greater than 8-12 weeks*

RMH score

Albumin <35 g/L

LDH increased

>2 metastatic sites

MDACC score

Albumin <35 g/L

LDH increased

>2 metastatic sites

GI tumor type

ECOG PS ≥1

Carceller F, et al. EJC 2016

Selection of patients in phase I trials

Original Research

Prognostic factors of overall survival in children and adolescents enrolled in dose-finding trials in Europe: An Innovative Therapies for Children with Cancer study

- ***248 patients***
- 8 highest recruiting ITCC centres
- from 2000 to 2014
- 21 phase I or IB trials

Carceller F, et al. EJC 2016

Selection of patients in phase I trials

CONCLUSIONS

• **PS of 90-100%** and **school/work attendance** at enrolment are strong indicators of **long OS**

• RMH and MDACC scores correlated with survival in adolescents *(but not in children)*

• Basis for the development of a paediatric specific prognostic score

• Improve the efficiency of dose-finding studies

• Enhance the ethical aspects of recruitment

Carceller F, et al. EJC 2016

Difficulties of phase I trials in pediatrics

- Small number of pediatric patients with cancer involved in early phase trials

- Limited interest of the big pharma industries
  - *very narrow market*
  - *poor financial returns*
  - *slow recruitment*

- Few new agents studied in adults are offered for investigation in children

- Large temporal delay

Difficulties of phase I trials in pediatrics

PEDIATRIC vs ADULT

Pediatric phase I studies *(Lee et al., J Clin Oncol, 23, 8431, 2005)*	**Adult phase I studies** *(Horstmann E. et al., NEJM, 352, 892-904, 2005)*
Period: 1990-2004 **69 studies, 1.973 patients**	Period: 1991-2002 **460 studies, 11.935 patients**
55 single agent, 14 combinations	193 single agent, 267 combinations

TEMPORAL GAP

	Adult phase I	Pediatric phase I	Phase I "gap"	Adult approval	Pediatric approval
Nab-paclitaxel	2004	2013	9 years	2008	??
Atezolizumab	2010	2015	5 years	2016	??

Difficulties of phase I trials in pediatrics

OBJECTIVES

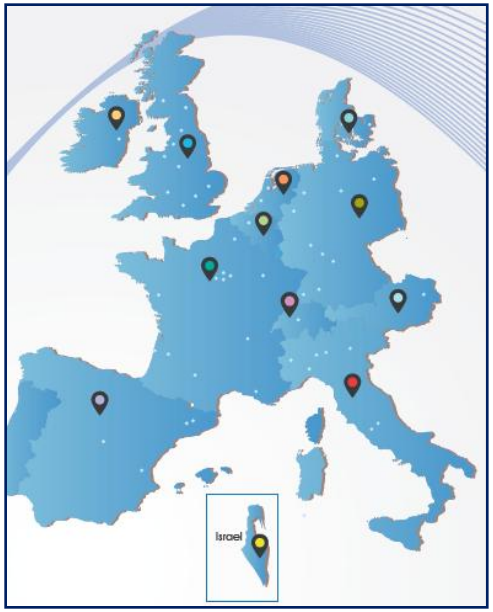
Collaboration with pharma industries and regulatory bodies in order to:

- Design a coherent and coordinated research and drug development plan
- Define prioritisation and selection of anticancer compounds to be used in pediatric cancers
- Identificate and validate new pediatric specific drug targets

Collaboration with parents / patients / representatives in order to:

- Improve access to information
- Develop ethical aspects of clinical research

Innovative Therapies for Children with Cancer
ITCC
European Consortium

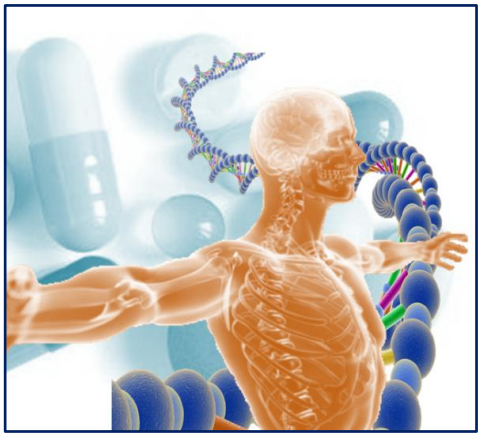


New ethical challenges: Personalized medicine

• Molecular analysis of a tumor in an individual patient to select specific targets and effective drugs

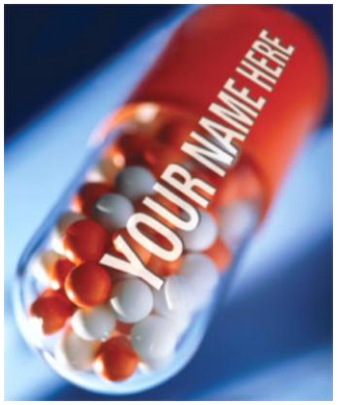
• Many cancer molecular profiling programs:

iCat (Usa)
INFORM (Germany)
iTHER (Netherlands)
COMETH (Great Britain)
MAPPYACTS (France, other EU countries)



• **Great amount of informations on diseases**

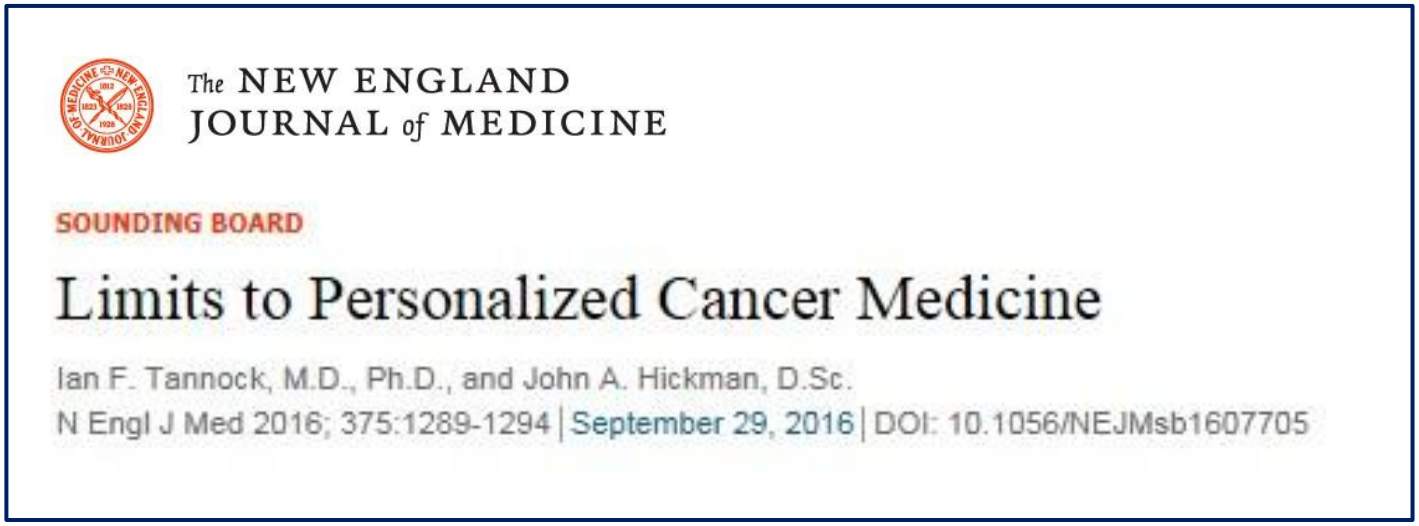
• **Prospective improvement for future patients**



• **Uncertain benefit for the individual patient involved in the trial**

• **Requirement of invasive procedures with some risks**

New ethical challenges: Personalized medicine



The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Limits to Personalized Cancer Medicine

Ian F. Tannock, M.D., Ph.D., and John A. Hickman, D.Sc.

N Engl J Med 2016; 375:1289-1294 | September 29, 2016 | DOI: 10.1056/NEJMsb1607705

- Discouraging outcome data
- 30-50% of patients with cancer driver mutations
- 3-13% of patients with treatment selected by individual molecular analysis
- *SHIVA trial:*
  - randomized trial of matched molecular targeted agent or physician's choice
  - no significant difference in PFS, HR for death or disease progression

New ethical challenges: Personalized medicine

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

Patient/parent perspectives on genomic tumor profiling of pediatric solid tumors: The Individualized Cancer Therapy (iCat) experience

Jonathan M. Marron[1,2,3,4] | Steven G. DuBois[1,2] | Julia Glade Bender[5] | AeRang Kim[6] | Brian D. Crompton[1,2] | Stephanie C. Meyer[1] | Katherine A. Janeway[1,2] | Jennifer W. Mack[1,2,3]

- 89% hoped participation would help find cures for future patients
- 59% hoped participation would increase their/their child's chance of cure

- Participants in pediatric molecular profiling studies perceive benefits for themselves and others, but ***expectations of personal benefit exceed actual positive impact***

Necessity to improve communication during consent discussion to increase patient's awareness about molecular research participation

Marron J, et al. PBC 2016

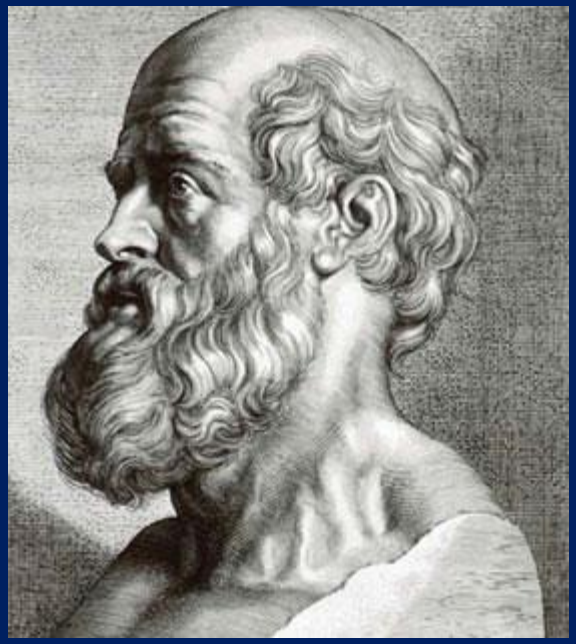
Conclusions

- Balance between our role as caregivers and researchers

- Importance of clear and honest communication in order to take a decision morally founded for all parties

- Patient's best interest above all

- ***No child should ever be considered only as a mean*** to know recommended dose and side effects of a new drug



“… I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being…”

(Hippocratic Oath, modern version, 1964)