DESIGN AND CONDUCT OF CLINICAL TRIALS

A. Zurlo

Medical Advisor, European Organisation for the Research and Treatment of Cancer (EORTC) Data Center

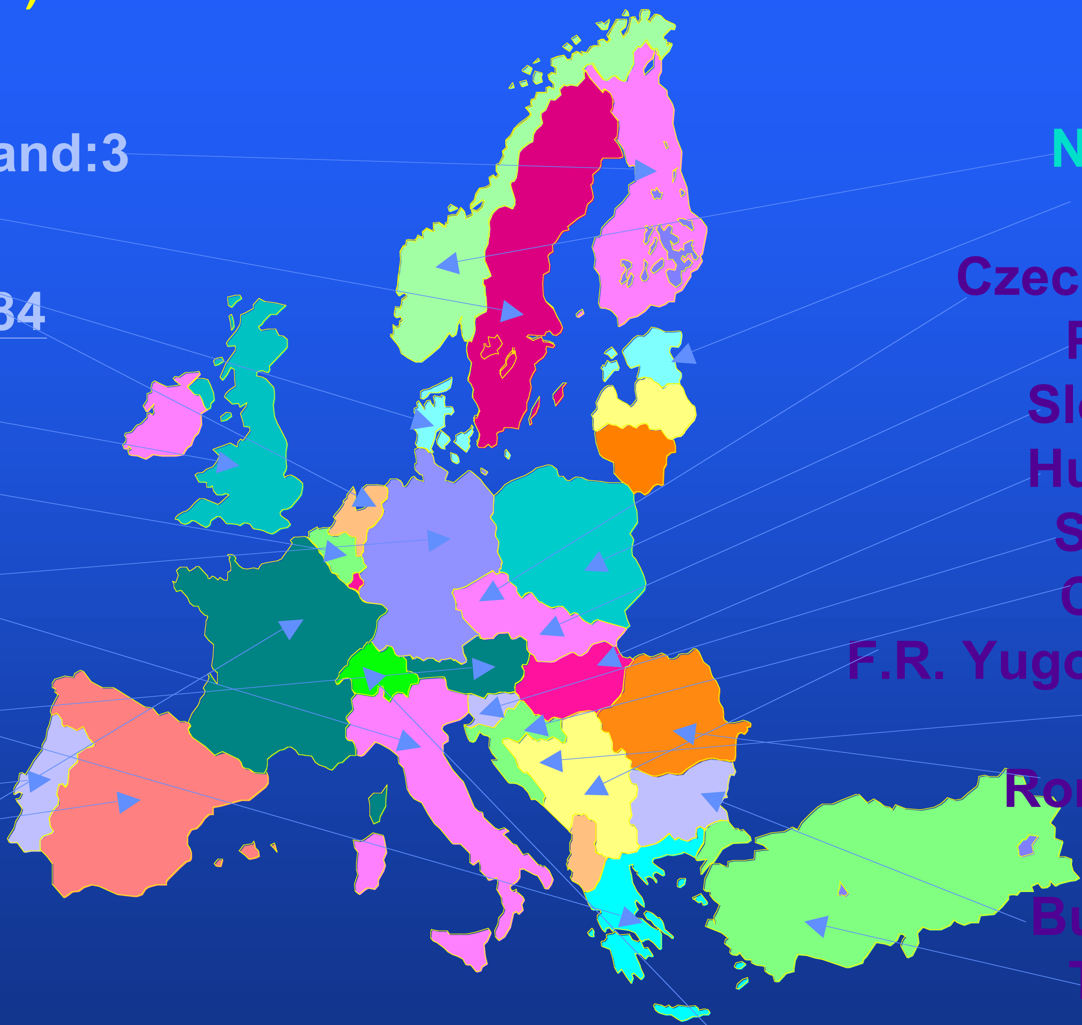
EORTC TODAY (I)

- Aims :
  - **Improvement of cancer treatment and related problems**
  - **Education to high quality clinical research**
- How ?
  - **Multicenter - multinational → intercontinental cancer clinical trials**
  - **Research projects on methods and practices for**
    - **cancer clinical trials**
    - **anti-cancer agents development**
    - **cancer management procedures**
  - **Dissemination of know-how : courses - symposia - workshops**

EORTC TODAY (II)

- Network of more than 350 institutions from 31 different countries
- +/- 2,000 collaborators (clinicians, pathologists, researchers,....)
- +/- 7,000 patients are entered each year in EORTC trials (database of more than 100,000 patients)
- +/- 30.000 patients in follow-up
- +/- 120 trials open to patients entry (Phase I -> Phase III)

PATIENT ACCRUAL IN EORTC CLINICAL STUDIES 2000 (6509 PTS)



EORTC

EORTC CLINICAL RESEARCH GROUPS

- Boron neutron Capture Therapy
- Brain Tumor
- Breast Cancer
- Children’s Leukemia
- Early Clinical Studies
- Gastro-Intestinal Tract Cancer
- Genito-Urinary Tract Cancer
- Gynecological Cancer
- Head and Neck Cancer
- International Antimicrobial Therapy
- Invasive Fungal Infections
- Leukemia
- Lung Cancer
- Lymphoma
- Melanoma
- Radiotherapy
- Soft Tissue and Bone Sarcoma
- Chronotherapy
- Biological Therapeutics Development
- Quality of Life
- Osteosarcoma
- Oncology Nurses / Data Management /

INTERGROUP COLLABORATION

Canada
- NCIC
- CGCRC

North America
- NCI
- SWOG
- ECOG
- RTOG

South America
- ABCG

Australia-N.Z.
- ANZBCG
- TROG

EORTC

Missions of the EORTC Data Center

- To provide an optimal infrastructure for carrying out multicenter cancer clinical trials
- To ensure independent, objective analysis
- To provide expertise in all related areas of clinical research
- Quality of life and health economics
- Appropriate computer facilities
- Education role:
  - Courses
  - Manuals

Advantages for Patients to Participate in Clinical Trials

- Better follow-up
- Better outcome
- Sure to benefit at least of the standard treatment in a randomized setting

Criteria to determine that protection for human research subjects is adequate

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Privacy of subjects and confidentiality of data are protected
- Monitoring of data (if appropriate) to ensure safety of subjects

Phase I Clinical Trials
Regulatory Aspects

- Potential therapeutic benefit
- Main objective : - Determine the Maximum Tolerated Dose (MTD)
- Other objectives : - Determine Dose Limiting Toxicity (DLT)
  - Determine pharmacokinetic / dynamic profile of the drug
  - Identify most frequent side effects
- Population :
  - Patients with advanced disease
  - No alternative of effective treatment
  - Adults only (new drug)

Phase I Clinical Trials
Regulatory Aspects

- Principles
  - Treat small group of patients with increasing dose level
  - Treat the smallest number of patients at each dose level
    - In general 3 patients / dose level if no major toxicity
    - Fewer patients if no / minimal toxicity
    - Within patients escalation if no / minimal toxicity

Phase I Clinical Trials
Regulatory Aspects

- Methodology commonly used : Modified Fibonacci schedule
  - First group treated with 0.1 $MELD_{10}$
  - Subsequent groups treated with incremental dose level (100%, 67%, 50%, 40%, 33%, 33%,...)
  - Decision rule based on % of DLT
  - MTD reached when DLT > 33%
  - Average of 40 patients and 5/6 steps
- Alternatives : Fixed intervals, doubling until toxicity, pharmacokinetically guided dose escalation

Phase I Clinical Trials
Common Pitfalls

- Definition of DLT
- Definition of MTD
- Recommended dose for phase II studies
- Response rate as an endpoint

Phase I Clinical Trials
New Concepts / Future Perspectives

- Improvement of preclinical models to adjust for starting dose
- New methodology to decrease number of patients exposed and accelerate the process
  - Accelerated titration
- New methodology for RT trials?

Phase II Clinical Trials
Regulatory Aspects

- Main objectives
  - Detect antitumor activity (single agent)
  - Identify tumor type sensibility and probability of response (single agent)
  - Quantify side effects (combination of agents)
- Other objectives
  - Further characterize pharmacokinetics, side effects and relation to dose and schedule, and the best route of administration

Phase II Clinical Trials
Regulatory Aspects

- **Population**
  - **Patients with advanced disease**
  - **No established form of therapy available**
  - **Children / elderly under specific conditions**
- **Principles**
  - **Treat small group of patients (14 - 40) with a multi-step procedure depending on RR**
  - **Document objective response according to predefined criteria (CR, PR, SD, PD)**
  - **Quantify acute toxicity and assess cumulative / subacute toxicity**

Phase II Clinical Trials
Regulatory Aspects

- Methodology
  - Many designs available - selected for specific endpoints
  - Most commonly used for early phase II : Gehan
  - Most commonly used for late phase II : Simon / Fleming
  - Most commonly used for feasibility studies : Bryant and Doy

Phase II Clinical Trials
Common Pitfalls

- Definition of response evaluation criteria
- Use of control group for comparative reasons
- Use of RR as a surrogate for therapeutic benefit
- Use feasibility studies to evaluate therapeutic benefit

Phase II Clinical Trials
New Concepts / Future Perspectives

- **Randomization with control group**
- **Modification of response evaluation criteria**
- **Phase II / III trials**

Phase III Clinical Trials
Regulatory Aspects

- Determinant to assess the **relative efficacy** of new treatment approaches
- Guided by the uncertainty principle
- Comparative by nature to control for
  - Systematic errors (biases)
  - Random errors (random variation)
- Both errors must be small in comparison to the size of the therapeutic effect

Phase III Clinical Trials
Regulatory Aspects

- Possible objectives
  - Determine the effectiveness of a new approach vs natural history of the disease
  - Determine if a new approach is more effective than the best current standard therapy
  - Determine if a new approach is as effective as the best current standard therapy but with less severe toxicity

Phase III Clinical Trials
Regulatory Aspects

- Randomization
  - Elimination of bias in the assignment of treatments
  - Balances treatment groups with respect to prognostic factors
  - Guarantees the validity of the statistical test of significance
  - Time trends affect all treatment groups in the same way

Phase III Clinical Trials
Regulatory Aspects

- Stratification
  - Reinforces the power of randomization to balance the treatment groups for
    - The number of patients assigned to each treatment
    - The distribution of prognostic factors
  - In general, stratification is considered for
    - The treating institution
    - The prognostic factors (max. 5) which are the most strongly correlated with patients' prognosis

- **Design**
  - **The parallel group design**
  - **The cross-over design**
  - **The factorial design**

Phase III Clinical Trials
Regulatory Aspects

- The parallel group design
  - Trials to show superiority
  - Trials to show equivalence of efficacy but with less toxicity, better QoL, lower costs
  - Trials with three or four treatment arms are generally inefficient and should not be recommended

Phase III Clinical Trials
Regulatory Aspects

- Endpoints
  - Primary treatment (M_0) - surgery / radiotherapy
    - Time to local recurrence
  - Adjuvant studies (M_0)
    1. Disease-free interval
       Local recurrence
       Distant metastases
    2. Duration of survival
    3. Duration of disease-free survival

Phase III Clinical Trials
Regulatory Aspects

- Endpoints
  - (Locally) Advanced disease
    1. Time to progression
       Duration of survival
       Symptoms control (QoL)
    2. Response rate
- Time to event is measured from the date of randomization

Phase III Clinical Trials
Common Pitfalls

- Inadequate sample size !!!
- Too many / unclear endpoints
- Subgroup analysis / data torture
  - Analysis according to “intent to treat principle”
- P-value and confidence interval

Phase III Clinical Trials
New Concepts and Future Perspectives

- Group sequential design
  - One or more interim analyses
  - Predefined early stopping rules
  - Independent Data Monitoring Committee
- Main objective : Terminate a trial early if
  - Unacceptable toxicity
  - Established superiority of treatment
  - Unlikely to demonstrate a relevant treatment difference

Phase III Clinical Trials
New Concepts and Future Perspectives

- Independent Data Monitoring Committee
  - For trials with large recruitment (> 500 pts)
  - For trials with a long recruitment period (> 4 years)
  - For intergroup trials
  - 1 statistician, 2 physicians all independent from the study
  - Evaluates all aspects of the trial (including recruitment) at regular (predefined) intervals
  - Major problem : Financing

Phase III Clinical Trials
New Concepts and Future Perspectives

- Intergroup studies
  - Mandatory to study rare tumors
  - Permit adjuvant trials with large sample size
- Problems
  - Find out common objectives
  - Agree on a common methodology
    - One protocol
    - One CRF
  - Quality control to be performed by one group

“It is also a question of politics”

Regulations of Clinical Trials

1. Declaration of Helsinki
2. European notes for guidance
   - Testing of new anticancer agents in human (March 1997)
   - Biostatistical methodology in clinical trials (June 1995)
   - Good Clinical Practice (GCP) - International Conference for Harmonization (ICH) (January 1997)
   - Pharmacovigilance - safety reporting (November 1996)
3. National regulations

Regulations of Clinical Trials
Declaration of Helsinki

- **Sets the ethical principles of any research on human subjects**
- **Research program should be reviewed and approved by an appropriate ethics committee**
- **Trial subjects should be informed about the study and should provide their consent**

Regulations of Clinical Trials
European Regulations

- **Notes for guidance are not regulations as such but deviations should be justified**
- **To be incorporated by national authorities in their legislation**
- **Relatively general by nature**

Regulations of Clinical Trials
European Regulations

- Testing new anticancer agents in human
- Tentative licensing based on RR after phase II trials may be considered provided that :
  - Benefits of the new treatment are unequivocally established
  - Further investigations (phase III) are foreseen

Regulations of Clinical trials
European Regulations

- **Good Clinical Practice (GCP)**
  - **Reinforces the protection of trial subjects and the consultation of ethics committees**
  - **Identifies relatively clearly the responsibilities of sponsors, monitors, investigators (research staff)**
  - **Defines how clinical data generated along the study should be handled**
  - **Defines the quality assurance system to be applied**

Regulations of Clinical Trials
National Legislations

- **Result from the incorporation of European recommendations and directives into existing legislations**

  "May be stronger but not weaker"

- **Major points to be considered :**
  - **Notification / approval of clinical trials to national health authorities**
  - **Insurance for trial subjects**
  - **Safety reporting to health authorities**

Regulations of Clinical Trials
Major Problems

- All regulations created for marketing authorization but cover all types of clinical trials
- Diversity and incompatibilities of national regulations considerably slow down the process
- Costs for performing trials independently from the pharmaceutical company are forbidding
- No real program to support clinical research at the European and national levels