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Commentary

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Integration of Translational Research in the European Organization for Research and Treatment of Cancer Research (EORTC) Clinical Trial Cooperative Group Mechanisms

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Abstract

The landscape for cancer research is profoundly different today from that only one decade ago. Basic science is moving rapidly and biotechnological revolutions in molecular targeting and immunology have completely modified the opportunities and concepts for cancer treatment. In contrast to the recent past where cytotoxic molecules were screened in the laboratory and then tested in early clinical studies with toxicity as endpoint instead of the often poorly defined mechanism for its potential anti-tumor effect, we now have entered the age of molecular therapeutics, rationally designed to target "strategic" checkpoints that underlie the malignant phenotype.

Translational research in early clinical trials (Phase I and II) is an integral aspect of the development of the new generation of cancer drugs as it is necessary to implement radically different early phase clinical trial design and to validate new biological end-points if the full potential of these new agents is to be realized. The "proof of principle with mechanistic analysis" strategy will allow optimisation of therapy from the beginning, and provide important feedback to pre-clinical drug developers. Translational research is also essential in late (phase III) clinical trials in defining different patient populations that may benefit to differing degrees from new treatments, and thus provide further insight and refine clinical practice in a more and more patient-tailored approach. In this editorial we will discuss the integration of Translational Research in the Organization for Research and Treatment of Cancer (EORTC).

Translational Research in Clinical Trials must take priority

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Complexity of Translational Research

Implementation of translational research as a key component of drug development and clinical research is complex and involves patients in various ways. Thereby it imposes some new ethical, legal, logistical and management constrains. Moreover translational research may require highly sophisticated machines, specific imaging techniques, biochemistry laboratories and imposes other infrastructural prerequisites, some of which should be in the direct vicinity of the clinical trial site. The usefulness of data generated during monitoring of such clinical trials with biologic/mechanistic endpoints is highly dependent on the quality of the assays and the availability of sufficient numbers of samples to conduct valid analyses.

Methodology Validation

Biological end-points require sufficient data on the reproducibility of the technique used to define statistically valid threshold of the biological "response". Assays used should be validated (specific and reproducible and also sufficiently sensitive to detect relevant "molecular signature") and appropriate controls are essentials to the interpretation of any outcome in laboratory monitoring of these trials. Early standardisation of methodology, reagents used and quality control in multicentric studies are so essential and mandate greater investment during preclinical development, and is important to realize that the tools required for translational research can take as long to develop as the drug itself.

Tissue Banking

Translational research may impose serial (tumor) tissue sampling during the investigational treatment. However, a balance has to be struck between what the laboratory researcher would prefer in terms of the size, frequency and number of samples taken; what the clinician feels is justified and technically feasible; and what an ethics committee will accept in terms of patients' interests and well-being, and of course what the patient can understand as being a reasonable request and can agree to. This tissue research needs to be supported by a specific centralized system of management that provides a reliable and fast toll for translational researchers and scientific exchanges that takes into account all legal and ethical aspects.

Translational research in (multicentric) clinical trials with will have to be conducted by multidisciplinary teams of clinicians and basic researchers (pharmacologists, molecular biologists, and biochemists), functional imaging specialists, "new-assay specialists", pathologists and statisticians and bioinformation scientists keen to relate biological findings to clinical outcome. These developments request that the premier laboratories are closely knitted into comprehensive clinical development programs of new anti-cancer drugs. In order to achieve this we need to establish a completely research minded integrated setting of laboratories, high quality patient-centered cancers services and a clinical-trial-research organization that can create, maintain and complete this circle of interactions as well to provide methodology, scientific and full logistic support.

The European Organization for Research and Treatment of Cancer Research (EORTC) has recognized and prioritized the organization and implementation of translational research as a mandatory and integral part of clinical cancer research and has developed a Translational Research Unit and a Central as well as a Virtual Tissue Bank system to organize, promote, coordinate and enhance the quality of translational research in association with its drug development program throughout the trajectory of phase I-II-III studies. This integrated program is described in the following paragraphs:

Role of the European Organization for Research and Treatment of Cancer Research (EORTC)

Need for Coordination and Centralization of Basic Science and Clinical Science Expertise

Translational research success depends on the creation of a high quality research environment in which close relationship between basic scientists and clinicians are fostered to avoid duplication of efforts and facilitate the sharing of key resources in order to decrease time between innovative agents discovery and its registration /availability in clinical practice. At this time, there is no mechanism to support and coordinate this centralized European translational research effort.

Core basic scientists and oncologists experts in Europe who are already funded to perform cancer basic laboratory and (early) clinical trials development should be brought together to:

• Establish better pre-clinical models to select rationally designed anticancer target-based compounds, and to further define mechanisms of anti-tumor response of these compounds in these models;

• Evaluate the incorporation of biological endpoints into novel early clinical trial designs that allow optimal evaluation of target-based new drugs ("proof of principle with mechanism analysis" strategy);

• Define current monitoring techniques and help to develop the tools, probes, biological and imaging assays suitable for *in vitro* assessment, in preclinical models;

• Conduct in a rapid coordinated manner highly specialised, complex, (early) clinical trials with rigorous standards to deliver complex, detailed data for licensing purposes (regulatory requests);

• Assure a high quality laboratory infrastructure and expertise with the capacity to provide biological readouts on clinical material in a timely manner.

A Common Structural Organization for Clinical Trials with Translational Research Coordination

The success of the integration of high quality basic research and clinical networks and translational research initiatives depends greatly on the coordination of a Pan European Clinical Trials Network.

This network should be articulated around a common structural Organization, which should a) coordinate and harmonize the development and submission of trial protocols to scientific and clinical independent peer reviewers, b) innovate new trial statistical design concepts, c) organize data management, study monitoring, and statistical analysis of the data and d) ensure that European regulatory requirements as well as all the other operational aspects to conduct appropriate translational work (from simple items as drug supply to complex aspects such as virtual tumor bank issues) are fulfilled.

It has been recognized by the EORTC that this type of support must be developed fully and provided by this organization. Priority for translational research in clinical cancer research prompted the EORTC to completely revisit its drug development pathway and operational structures these last 2 years as well to establish a method to fund the EORTC Groups research projects by creating a new grant system for translational research (EORTC Translational Research Fund).

The EORTC Drug Development Pathway with Translational Research

Since 1974 the EORTC has conducted clinical development studies through its Clinical Research Division (CRD). This has resulted in the establishment of a solid and dedicated network of medical doctors with focussed expertise in cancer drug development. Consistent with the changes in cancer clinical and laboratory research, the Laboratory Research Division (LRD) of the EORTC has refocused its activities in order to enhance translational research conducted as part of EORTC clinical trials. This EORTC LRD includes the Screening and Pharmacology Group, the Pharmacology and Molecular Mechanisms Group, the Receptor and Biomarker Study Group, the Functional Imaging Group and the Pathology Group. Through the LRD, the EORTC has access to the basic science expertise and experience needed for target-based drug discovery and clinical development.

The EORTC Data Center promotes and ensures an optimal flow of coordination and communication by creating translational procedures between the 2 EORTC Divisions, including the EORTC New Drug Development Program (NDDP), which allows for a swift continuation of scientific activities from pre-clinical testing to clinical research. In this respect, two new independent EORTC Committees of scientific and clinical experts have been implemented as of October 2002 to advice on the, relevance of translational and clinical research efforts, to be invested by the organization:

The EORTC New Drug Advisory Committee (NDAC)

This NDAC reviews all proposals for new drug development offered to the EORTC for further development. It ensures a coherent scientific strategy with regard to drug development and translational research. This committee may suggest, if necessary, additional pre-clinical studies for potential breach of pre-clinical data as well as propose potential laboratory/facilities support for additional work (pre-clinical models available within the EORTC LRD). NDAC thereby serves as a scientific committee for all the EORTC Early Clinical Trials. The NDAC comprises 10 permanent members.

The EORTC Translational Research Advisory Committee (TRAC)

The EORTC TRAC missions are (a) To stimulate and to provide expert scientific and practical advice on translational research projects conducted in the context of EORTC clinical trials. This activity includes the prioritising of projects; (b) To review and assess the EORTC Quality Assurance (QA) translational research program by prospectively reviewing the effectiveness of the translational research studies conducted by EORTC Groups, by supporting the EORTC Data Center in its QA assessment of laboratories performing EORTC projects and to make

sure that there is a Quality Control for each assay used. All disciplines of translational research in oncology are represented in the review panel.

The Operational Structure for Drug and Translational Research Development

Modernization of the mode of operation of the EORTC Data Center and acquisition of the expertise needed to conduct and support clinical research activities with translational research have been a necessary to proceed with the EORTC plans for translational research. This included the creation of a new unit and the adaptation of some tasks of existing specialised Units, which activities have to be coordinated during the life cycle of a clinical trial including contemporary translational research aspects:

The Translational Research Unit

In October 2002, the EORTC implemented a Translational Research Unit (TRU) to enhance and promote translational research projects conducted as part of EORTC clinical trials. This Unit is primarily responsible to generate high quality translational research trial data by: (a) Ensuring a constant EORTC forum between the Clinical and Laboratory Research Divisions of the EORTC, fostering interest in translational research within Clinical Groups and promoting clinical development of ideas/concepts emerging from Laboratory Groups; (b) Collaborating with member of the TRAC, clinicians located in their institutions and with other staff at the Data Center (statisticians, physicians, computer specialists, data manager) to guarantee close collaboration between all actors involved in clinical trials and translational research; (c) Collaborating with the Protocol Writing Committee to ensure adequacy of protocols and Case Report Forms (CRFs) for adequate translational data capture; (d) Prospectively supporting all the operational organisation aspects of specific TR Projects; (e) Ensuring that all EORTC translational research activities are performed according specific working procedures, in the general framework of EORTC policies and Standard Operating Procedures.

The EORTC Tumor Bank Unit

Since September 2000, the EORTC has set up a central Tissue Bank (centralised collection and storage of glass slides and paraffin blocks based at the EORTC Data Center, Brussels) and a Virtual Tumor Bank with tissues being stored at the clinical sites (with information on tissue samples available in the central database).

This EORTC project will supply a centralised system of management of material available from patients entered into EORTC clinical trials and will be able to: (a) Provide tools for efficient panel histology review (either by an individual expert of a panel of experts) improving the quality of the pathological diagnoses; (b) Provide a reliable and fast tool to allow translational research; and (c) Provide a web-interface to allow users to access (limited) data of the patients stored in the clinical database.

The EORTC Tumor Bank Unit develops and implements procedures for histology review and, in cooperation with the Regulatory Affairs Unit, solves the legal and ethical issues on this aspect.

Supportive Units

• The *Regulatory Affairs Unit* is implementing mechanisms not only to ensure compliance of clinical trials with European and national requirements, but also to allow a rapid adaptation to constantly evolving regulations and requirements from the competent National and European authorities and from international standards such as Good Clinical Practice and management of serious adverse events. The challenges to new methodology for clinical trials and evaluation of the outcome of new treatments should also integrate all translation research information. The Regulatory Affairs Unit is therefore involved in all the legal aspects related to the development of translational research project, which requires an appropriate ethical and legal framework (i.e. tissue research and tumor bank; property of the EORTC scientific translational discoveries; legal implications of the "biological characterization" of individual to provide appropriately tailored therapeutic approaches). This comes at the time where European regulatory framework will be completely reviewed due the implementation of the new clinical trials Directive.

• The *Safety Desk* and the *Monitoring Unit* ensure drug developers that EORTC trials are closely controlled for safety and accuracy. EORTC-Clinical Research Associates will be actively involved in the day-to-day monitoring of clinical trials, involving also the monitoring of translational research work at the hospital and the laboratory sites.

• The *Protocol Help Desk* provides logistic support to the members of the Writing Committee including the translational research study coordinator for assembling a study protocol according to standard procedures and ensures that the protocol is adequately developed in the shortest possible time and according the latest methodological, legal (e.g. SAE reporting issue) and ethical requirements (Informed Consent requirements for clinical and translational researches studies, latest version of the declaration of Helsinki, etc.).

The Information Technology Unit

The EORTC is one of Europe's leading players in the development of new technologies to facilitate and speed up cancer clinical research. Specific software is under devel-

opment following widely-accepted methodologies and validation procedures for remote translational research data entry (i.e. functional imaging, microarray data) to allow adequate analysis.

The EORTC Translational Research Fund

The EORTC promotes EORTC translational researches by establishing a method for better funding of EORTC groups translational research projects within clinical trials as well as through specific research projects. In that respect, a specific Translational Research Fund (TRF) has been created in order to fund selected high quality, innovative projects with clear objectives and methods.

Each year more than 30 projects proposal are submitted. Each project proposal is reviewed for its scientific, medical and ethical merit by the TRAC and approved by the EORTC Executive Committee. Intergroup TR projects within the EORTC (Laboratory and Clinical Groups) are always strongly encouraged in order to create an optimal flow of interaction between the two EORTC Divisions. This new granting system is running since 2001 and 12 projects have been already funded (5 in 2001 and 7 in 2002). These TRF grants function as "seed" money and will hopefully result in some larger translational research support from various sources.

EORTC Executive Committee, through the EORTC TR Unit, monitors progress and ensures that projects are operated within the budget. The Executive Committee and the chairmen of NDAC/TRAC are reviewing scientific progress twice a year.

Conclusions

Over the last five years, translational research has become an important aspect of cancer clinical research. This has been fostered by the development of new techniques of investigations of the tumor biology and the emergence of new families of potential anticancer agents. The EORTC has adapted its funding, advice and review mechanisms to stimulate the development of translational research within its clinical trial network. This evolution also encompasses some structural modifications of the EORTC central facility to address properly the demand from EORTC groups. The possible benefits of such initiative will not be evaluable before another decade or so.