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The EORTC and drug development

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Abstract

Early drug development at EORTC has always been subject to structural changes to adapt to the rapid changes that occur in oncological drug development. The expertise of early drug developers has always been cross-fertilised with disease-/tumour-oriented groups and also backwards to the laboratory research groups. This results in the establishment of a solid and dedicated network of medical oncologists with focused expertise in cancer drug development. The EORTC Data Center is fully equipped with all expertise to support clinical research activities and includes regulatory, safety, and quality assurance desks. The EORTC New Drug development Programme (NDDP) provides methodological expertise to early clinical trials and coordinates phase I and phase II studies addressing various approaches. Through NDDP, the early clinical groups and the disease-/tumour-oriented groups have created specific networks to address early drug development in specific tumour types. This results in very efficient networks which have the resources and the patients to address and conduct challenging clinical trials in a standardised fashion ensuring the highest standards in cancer treatment.

Keywords: Oncology drug development; Translational research

1. Drug development of EORTC: a constantly evolving field

Since 1976, the EORTC has conducted early clinical development studies through various of its co-operative groups. In particular, the groups dedicated to early drug development have always been subject to structural changes in order to adapt to the rapidly changing regulations related to oncology drug development. This has resulted in the establishment of a solid and dedicated network of medical oncologists with focussed expertise in cancer drug development. Through the EORTC network, this expertise has always been cross-fertilised with the disease-/tumour-oriented groups, and also backward to the laboratory research groups. Despite the fact that a number of clinical research features have been completely revisited at the EORTC, it is strongly believed that this essence of working is still valid nowadays and the EORTC has always built on such networking approaches and cross-fertilisation of scientific know-how.

Drug development in cancer strongly depends on the natural evolution of the disease and for conventional cytotoxic agents had to be tailor-made for each tumour type. The life-threatening character of cancer and the adverse drug reactions inherent to the molecules traditionally used in oncology, have modelled the approach of cancer patients from phase I to phase III alongside the discoveries of new targets and pathways which have helped in defining patient populations more suitable for a given approach. Therefore, drug development in oncology requires a perfect knowledge of this rapidly evolving field.

Results of EORTC studies have been important parts of the registration dossier of various agents. This was for example the case for docetaxel [1–3], CPT-11 [4,5]

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and topotecan [6] and is currently being considered for ET743 for soft-tissue sarcomas.

The role of the EORTC in drug development in Europe has greatly increased over the last 10 years. Drug development nowadays bears a number of new features due in particular to the better approach and insight on the mechanism of actions of the drugs used. This prompted the EORTC to again completely revisit its drug development pathway and operational structures in parallel.

1.1. The EORTC drug development pathway

The laboratory research and clinical research groups are now linked by translational procedures which allows for a swift continuation of scientific activities from preclinical testing to clinical research as indicated in Fig. 1. Conversely, clinical research projects may be implemented with relevant laboratory scientific endpoints such as pharmacokinetics or any laboratory project may be undertaken in close cooperation with the preclinical groups. This can also be extended to the Functional Imaging Group. Later in the development, phase III studies may be implemented with other objectives such as quality of life and health economic endpoints, also very relevant for drug development. The EORTC has also implemented and validated mechanisms to perform large phase III studies in cooperation with other European and/or American groups (intergroup studies). The

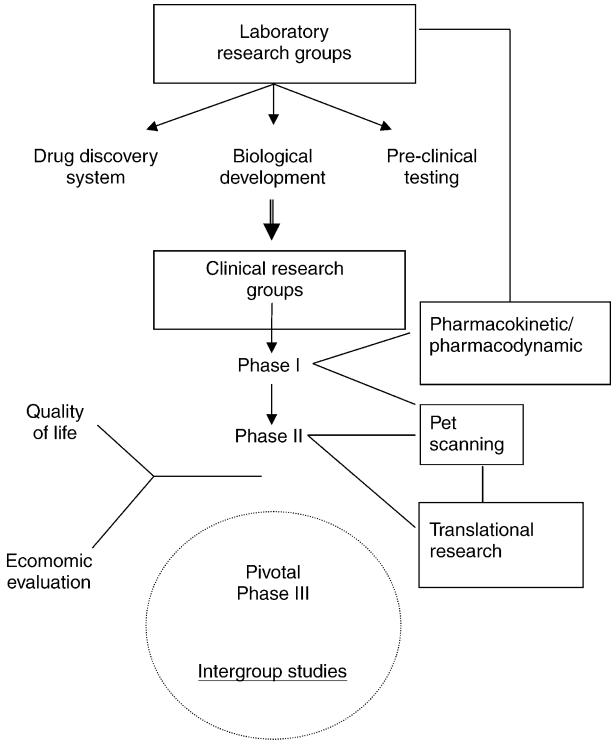

Fig. 1. EORTC drug development pathway. PET, positron emission tomography.

EORTC has therefore taken some compounds through phase I and II, such as E7070 and glufosfamide, up to phase III level for docetaxel, ensuring continuity in the development of these compounds.

1.2. The EORTC operational structure for drug development

Future developments are not possible without modernising the operations and the expertise needed to conduct and support clinical research activities. The EORTC Data Center, giving support to the clinician network, has therefore taken actions to adapt the implementation of new laws, directives and international standards such as good clinical practice and the management of serious adverse events. Over the past 10 years, the core teams of data managers and statisticians at the EORTC Data Center have seen a lot of changes. Gradually, medical doctors have joined such teams in order to further improve the specialised medical input in protocol designs, but also to facilitate the coordination of research protocol activities, while upgrading the working procedures to constantly evolving regulatory and international standards. This also required the creation of several specialised units, whose activities have to be coordinated during the life cycle of a clinical trial.

The Regulatory Affairs Desk now masters the laws of more than 35 countries and has established specific links with health authorities. Its activities are extended in cooperation with the Safety Desk, for expediting serious adverse drug reactions to the health authorities. The Safety Desk and the Monitoring Unit ensure that EORTC trials are closely controlled for safety and source data verification. Recently, the information technology unit has implemented and validated a system for remote data entry now piloted at phase I and II levels.

Last, but not least, all of these activities are now carefully monitored and controlled through the Quality Assurance Unit and the implementation of Standard Operating Procedures (SOPs) and policies, which have been filed at the Food and Drug Administration (FDA) (FDA Drug Master File 13059). The latter also further facilitates the possible use of EORTC data for drug registration purposes in the USA. In order to take the full drug development process into account, the EORTC has developed an International Cooperation Assurance Project (ICPA) with the United States National Cancer Institute (US NCI). The ICPA entitles the EORTC to perform transatlantic large phase III trials according to specific procedures, which take into account US federal requirements and US Office for Human Research Protection (OHRP). Altogether, these procedures guarantee a swift acceptation of such trials as being compliant with the major US requirements.

The EORTC has been successfully subject to FDA audits.

While the EORTC is fully equipped to perform high quality and GCP standard drug development clinical trials from phase I to phase III, and the procedures do guarantee that these generated data are suitable for drug filing purposes, the process by which the EORTC network conducts trials is a pragmatical approach and interpretation of international standards. This is the only way to ensure swift and efficient drug development, while adhering to the highest standards. There is no need to create counter-productive and redundant procedures, which in turn lead to too high development costs and too long development process. In the same spirit, there is a need to work towards common, simplified and relevant data elements when creating case report forms.

2. The EORTC novel approach for early drug development

Special attention has been given to early drug development by the creation a few years ago of the New Drug Development Program (NDDP). The NDDP supports activities to EORTC groups performing phase I and II studies, mainly those from the Early Clinical Studies Group (ECSG) and the Biological Development Therapeutic Group (BTDG). ECSG was successfully involved in the development of several new compounds which achieved market approval later on. These compounds include docetaxel, CPT-11 and topotecan. Presently, the most innovative compounds, like antisense molecules, farnesyl-transferase inhibitors and cdk2 inhibitors, are part of the drug portfolio of the Group. Various biological and antiangiogenesis compounds (Misletoe Lectin, collagenase type I inhibitors...) are also tested.

The EORTC Drug Development strategy is based on four basic policy principles: quality of the clinical work and documentation, speed of patient accrual, rapid communication within the Group and between the Group and external sponsors, and the effort to prioritise innovative treatment concepts. Due to the internal review process, the present number of centres is now 54 and includes representation 15 European countries. Of these, approximately 15 centres are available to perform demanding clinical phase I studies. Since 1996, almost 2000 patients have been enrolled in phase I and early phase II studies. Over the last 2 years, the ECSG and NDDP have initiated about 20 studies which have accrued nearly 400 patients. Phase II trials have so far addressed 11 different tumour types. The NDDP is now structured to give full support to early drug development activities from protocol preparation to final publication. NDDP is equipped with specific staff for GCP compliance and documentation handling and received support from the quality assurance unit for the day to day management and auditing procedures.

For phase II trials, specific working procedures have been created to cooperate with the disease-oriented groups according to the new drug development pathway. The example of the cooperation with the Brain Tumor Group (BTG) can best illustrate the potential of such networks. Specific criteria have been selected, both within the network of medical oncologists with specific expertise in drug development and brain tumour specialists with specific expertise to assess effects in brain tumours, to select those high quality centres that are capable of managing early drug development in brain tumours, requiring close cooperation on site between medical oncologists and neuro-oncologists and support by dedicated clinical research teams. This resulted in the creation of a network (Fig. 2) which has successfully conducted a series of three phase II studies with remarkable quality and within a very short time.

3. Future directions

The tremendous increase in our understanding of tumour cell division and tumour growth, coming from molecular research, creates the need to redesign study statistics, as well as study performance. With the increasing number of growth stimuli that are identified and are frequently independent of the histology of a disease, and the development of agents counteracting the effect of these stimuli, in models frequently without exerting major toxicity, we need new study templates.

The traditional approach of defining the maximum tolerated dose and dose-limiting toxicities may either still be valid or may not be the optimal approach to administer cytostatics given on a chronic basis. New endpoints have to be established and validated, on which decision criteria can be based. NDDP is currently exploring modified versions of the continuous reassessment method which allows a three-stage phase I design implementing at the same time an efficient dose-escalation process at the lower doses and a safe approach of the highest doses and the processing on the documentation of chronic doses. These methodologies are oriented to the clinic as safety observations feed the models, which subsequently allocate the next doses to patients. The role of clinical investigators in assessing the safety of the study drug is therefore of the highest importance for the performance of the study. The EORTC in parallel develops software where such algorithms are taken on board in order to have an efficient system that allows rapid dose assessments. In a similar approach, more appropriate designs and endpoints are being tested for phase II studies. Brain tumours are again a good example where tumour shrinkage does not necessarily indicate a

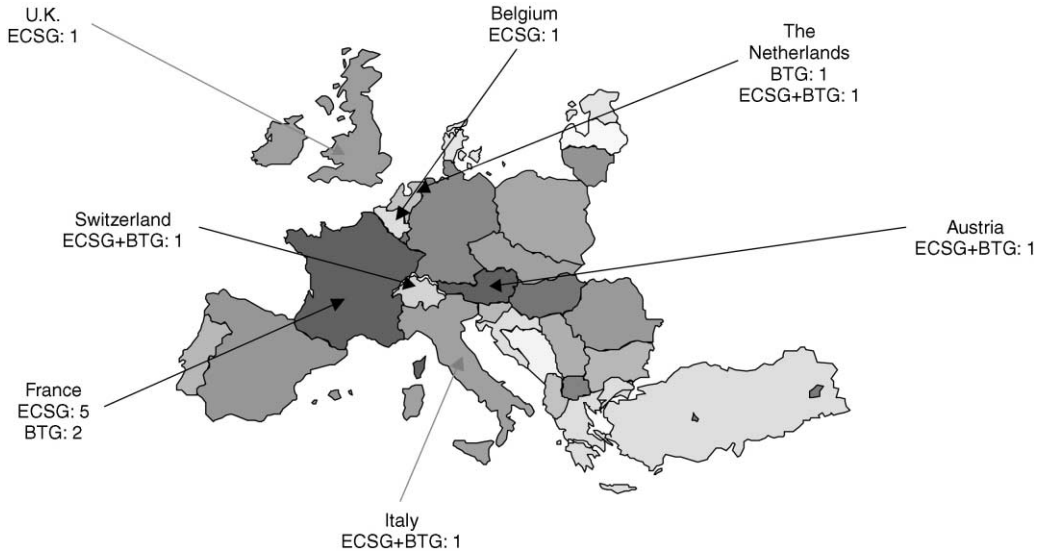

Fig. 2. EORTC high grade glioma drug development network.

drug with potential clinical interest. Indeed, in such aggressive tumours, stabilisation of tumour growth is of clinical interest. This leads to the revision of specific designs which not only challenge the definition of success/positive outcome in phase II studies, but also allow for one-stage instead of two-stage designs. Longer-term endpoints such as progression-free survival can therefore be taken into account.

The contacts and collaboration with study groups outside the EORTC like the NCI-C and US NCI should be further promoted. In the future, it is envisioned that these Groups work together towards a common approach of early drug development with, for instance, the implementation of common data elements and possibly conduct common studies stressing vertical clinical drug development programmes and translational clinical/preclinical research. Without doubt, this will result in faster approval of active agents in the future and will generate important research.

Finally, as part of its constantly evolving activities, the EORTC is a member of the European Drug Development Network (EDDN) where early drug development issues are discussed with the British Cancer Research Campaign and the Southern Europe New Drug Organisation.

4. Conclusion

New drugs coming to the clinic now and developed to interact with specific receptors or pathways are changing the face of drug development in oncology. Cytostatic drugs do address the methodological challenges of immunological approaches, while early drug development should be conducted according to the same principles regardless of the class of the therapeutic agent. The EORTC has taken steps to combine the expertise of its two Groups, namely the ECSG and BTDG, in one single early drug development group, the New Drug Development Group (NDDG) which will be officially launched as of March 2002. In the same spirit, NDDP is in the process of extending its expertise and support to all disease-oriented groups to ensure adequate early drug development from phase I to phase III studies. NDDG/NDDP constitute within the EORTC a unique organisation to investigate potential new drugs and methodological issues raised by the development of new molecular targets. These steps are taken while implementing an important quality assurance programme to guarantee that the EORTC drug development network produces a high quality output.

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