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ORIGINAL ARTICLE

Herbert M. Pinedo

European drug development and its impact on national activities: The Dutch example

Abstract The development of new anticancer agents is becoming an increasingly complex task which is often beyond the capabilities of a single institution or company. To ensure fast, efficient, high-quality drug development, good coordination and collaboration are essential prerequisites. In this paper, the Dutch national drug development program is described as an example and placed in the perspective of Europe-wide efforts. Since knowledge of new molecular targets and biological approaches by which the malignant growth of cells can be stopped or prevented is increasing, new guidelines for the development of noncytotoxic drugs are required. To avoid duplication and to make the results obtained using these new agents comparable so that patients will gain the maximum benefit of efforts in this field, further extension of international coordination will be of utmost importance in the coming years.

Key words Drug development · ECC · EORTC · NDDO

Organization of cancer research in the Netherlands

Comprehensive cancer centers

All hospitals in the Netherlands are assigned to one of the 9 Dutch Comprehensive Cancer Centres (CCCs), which together cover the whole country. The aims of the CCCs are to improve the treatment and care of cancer patients, to advance methods of cancer prevention and early cancer detection, and to stimulate clinical cancer research. The CCCs coordinate both local and national trials, in particular phase II and phase III trials, including data management and quality control activities.

Oncology working groups provide the basis for the functioning of the CCCs. Within these working groups, specialists from affiliated hospitals discuss the best treatment options and qualified consultants advise their colleagues in general hospitals. In addition, the CCCs develop regional and national guidelines and implement these in their regions. Clinical phase II and phase III protocols can be submitted for approval to the Commission for Clinical Comparative Research of the Dutch Cancer Society. In this way, the data management departments of the CCCs are partly supported by the Dutch Cancer Society. This approach has significantly improved the quality of data from phase II–III trials in the Netherlands. In Amsterdam and Rotterdam, the CCCs collaborate with the European Cancer Centre (ECC) and the South West Cancer Centre (SWCC), respectively.

The ECC and the SWCC

The ECC in Amsterdam was founded in 1991 as a collaborative effort between the Netherlands Cancer Institute, the Antoni van Leeuwenhoek Hospital, the University of Amsterdam Academic Medical Centre, and the Free University Hospital. The aim of the ECC is to improve scientific research on the borderline of fundamental cancer research and patient care. The ECC has performed a number of phase III trials, including extensive and elegant pharmacological studies, the results of which have been published in leading journals [3–5, 9]. For example, paclitaxel trials performed over the past few years are exemplary for ECC activities in the field of pharmacology. These studies, which were supported by Bristol Myers-Squibb, have led to the discovery and analysis of three paclitaxel metabolites: 6α-hydroxypaclitaxel; 3′A-p-hydroxypaclitaxel; and

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H. M. Pinedo (✉)
University Hospital, Vrije Universiteit, Department of Medical Oncology, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

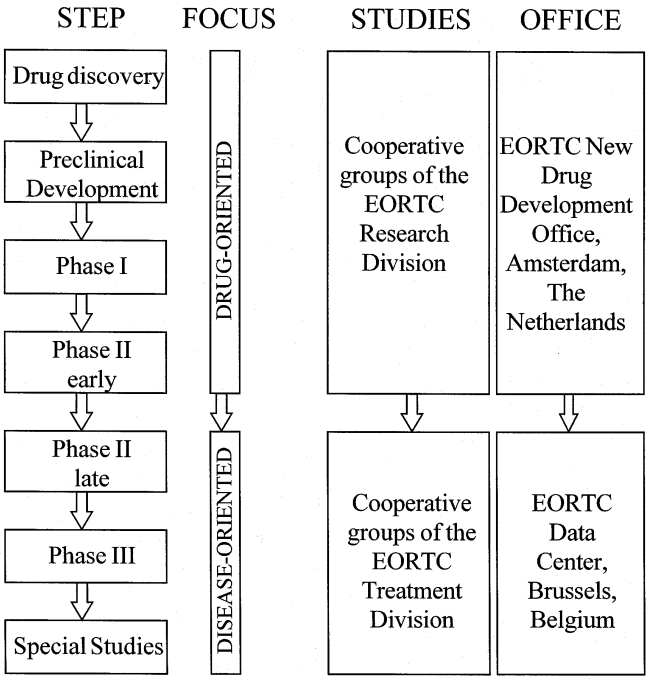

Fig. 1 EORTC New Drug Development Program

6α,3′A-p-dihydroxypaclitaxel [3, 4, 9]. In addition, important pharmacokinetic data were collected regarding the dosing of paclitaxel in patients with altered hepatic function [5].

The SWCC is a collaborative effort between the medical faculties, academic hospitals, and CCCs of Leiden and Rotterdam, and the Dr Daniel den Hoed Cancer Centre, which recently merged with the Academic Hospital of Rotterdam. The general objective of this organization, which was established in 1995, is to further progress in cancer research by combining the facilities and capabilities of the individual participants.

Many ECC and SWCC oncologists and researchers are involved in the activities of the European Organization for Research and Treatment of Cancer (EORTC) and the EORTC New Drug Development Program. More patients from the Netherlands than from any other European country participate in EORTC trials.

EORTC

The EORTC was founded in 1962 to perform large international multicenter phase II and phase III clinical trials. It is an independent scientific organization comprising about 40 collaborative groups in three divisions, with 3000 members from across Europe. The ultimate goal of the EORTC is to improve the standard of cancer treatment in Europe through the development of new drugs and testing new therapeutic regimens using drugs which are already commercially available, including combinations with surgery and radiotherapy.

EORTC New Drug Development Office

In 1984, the EORTC New Drug Development Office (NDDO) was established in Amsterdam to fill the gap between preclinical research and early clinical trials. There clearly was (and is) an urgent need to reduce the length of time between the discovery of new potential drugs and the start of the first clinical trials so that patients receive the benefits of the new treatment faster. Originally, the NDDO focused mainly on the screening and development of nonsponsored academic compounds, although several compounds identified by pharmaceutical companies were also investigated. In 1986, an agreement was signed between the US National Cancer Institute, the Cancer Research Campaign in the UK, and the EORTC to establish an intercontinental network for drug development. This agreement was updated in 1995, and due to the acceptance of the Standard Operating Procedures of the NDDO by the US Food and Drug Administration global regulatory affairs related to preclinical and clinical EORTC data have been greatly facilitated (Fig. 1). The Dutch Cancer Society supports the EORTC-NDDO with an annual grant for preclinical drug development; this grant is used only for drugs which are not being sponsored by the pharmaceutical industry.

During the past decade, pharmaceutical companies have discovered the NDDO as their gateway to European drug development. At present 35 compounds, including vaccines, signal transduction inhibitors, and antisense oligonucleotides, are in different stages of late preclinical and early clinical development by the NDDO. Two-thirds of these compounds originated from pharmaceutical companies. The NDDO is responsible for data management and monitoring of early clinical trials carried out within the Early Clinical Studies Group (ECSG) and the Biological Therapeutics Development Group (BTDG) of the EORTC.

ECSG

The ECSG, which originated from the Early Clinical Trials Group and the Clinical Screening Group, is an established group of 48 participating member institutes located in 14 European countries. The member institutes of this group have been performing multiinstitution phase II studies since the 1970s and have a substantial body of expertise. Examples of conventional drugs which are presently under investigation by the ECSG are carzelesin, topotecan, irinotecan, JM-216, and S-1. Members of the ECSG also perform phase I studies under the umbrella of the group. For example, the ECC has just completed a phase I study with S-1, a Taiho compound; this particular study reflects a recent tendency toward the development of oral anticancer agents.

S-1 is an oral formulation of tegafur, a prodrug of 5-fluorouracil (5-FU), combined with a dihydropyrimidine dehydrogenase inhibitor to prevent 5-FU breakdown, and oxonic acid, which inhibits 5-FU phosphorylation in the gastrointestinal tract (molar ratio 1:0.4:1) [8, 10]. The

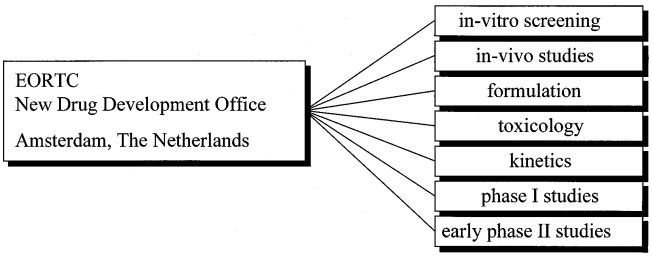

Fig. 2 EORTC NDDO

maximum tolerated dose (MTD), side effects, and pharmacokinetics of S-1 were determined in 28 patients with solid tumors (including seven colorectal and four gastric tumors) who received cycles consisting of oral S-1 administration for 4 weeks followed by a one-week rest period. Dosages of 25, 45, 35, and 40 mg/m^2 bid were successively studied in six, five, six, and 11 patients, respectively. The side effects were mild with S-1 25 mg/m^2, whereas at 40 and 45 mg/m^2 diarrhea was the dose-limiting toxicity (DLT) and several other severe types of toxicity were seen with S-1 45 mg/m^2. No severe toxicity was observed with S-1 35 mg/m^2. One confirmed partial response was observed in a patient with gastric cancer, and stable disease was observed in several patients. 5-FU levels reached a plateau of 0.3–2 μM after 1–2 h. It was concluded that 40 mg/m^2 bid is the MTD of S-1, with diarrhea being the most important DLT [12]. Phase II studies on the use of S-1 in colorectal and gastric cancer will be performed by the ECSG.

Oral administration of drugs is of interest not only due to its patient friendliness, but also because it is generally the most suitable formulation for studying biological, radiosensitizing, and antiangiogenic agents. Thus it is possible that a schedule developed by the ECSG will be used by both the EORTC Radiotherapy Group and the disease-oriented EORTC groups.

The ECSG also performs multinational phase I studies, such as that with the marine compound, ET-743, developed by the Spanish firm Pharmamar [2, 6, 7]. This drug has been studied at the Free University, Amsterdam, and at two institutions in Scotland (Edinburgh and Glasgow). ET-743 is a novel tetrahydroisoquinolone isolated from the Caribbean tunicate *Ecteinascidin turbinata.* It exerts antitumor activity as a DNA minor groove interacting agent and exhibits potent in vivo activity in human xenograft models. The DLTs in all species tested are hepatotoxicity and myelotoxicity. In an ongoing phase I trial, no DLT has been encountered (maximum dose 800 μg/m^2), while preliminary pharmacokinetic data show ng/mL concentrations at doses ≥100 μg/m^2. At the highest dose tested, some minor, transient changes in liver tests were observed [11].

BTDG

The BTDG of the EORTC, which was established only recently, will focus on preclinical and clinical research into anticancer therapy with biologically active agents such as cytokines and hematopoietic growth factors, as well as on new treatment strategies using antibodies, vaccines, and gene therapy approaches. The main aims of the BTDG are to examine the efficacy and safety of biological agents in clinical trials, to combine early clinical trials with ex vivo research to increase knowledge of the mechanism of action of anticancer agents, and to establish a network of preclinical and clinical researchers in the field of biological agents. Five phase I and II clinical trials with different vaccines and antibodies are in an advanced stage of preparation, some of which have already been activated.

New markers and endpoints for noncytotoxic agents

In the near future, the field of drug development will be faced with the need to introduce new guidelines for novel approaches to anticancer therapy alongside conventional cytotoxic agents. A few of these new approaches have already reached the clinic and include new radiosensitizing drugs, drugs stimulating cytokine production (DMXAA), small peptides affecting receptors and the cell cycle (SU 101, cyclin-dependent kinase-4, and flavoperidol), antisense compounds (anti-B-cell lymphoma-2 and anti-protein kinase C-a gene compounds), monoclonal antibodies (anti-CD20 and anti-EGF-R), antiangiogenic agents, antimetastatic agents (metalloproteinase inhibitors), gene therapy, and vaccines.

These novel approaches make the need to develop new guidelines for preclinical research and phase I/phase II studies an urgent one. The NDDO has previously devised many preclinical guidelines for screening and toxicology, including the development of a limited toxicology program that speeds up and reduces the costs of the drug development process significantly [1]. This limited toxicology package is now routinely used to establish a safe starting dose for phase I clinical trials and has been used successfully for the introduction of >50 new drugs in Europe. Likewise, the NDDO and the EORTC research groups are now trying to develop new criteria and guidelines for the development of new, noncytotoxic, anticancer therapies (Fig. 2).

Conclusions

It can be concluded that national and international drug development through the EORTC-NDDO mutually benefits by close collaboration. In the Dutch situation, it is apparent that the active participation of Dutch researchers and clinicians in EORTC trials has made a significant contribution to the development of a number of drugs, while the EORTC has stimulated them to improve the quality of their clinical research further; the same holds true for other European countries. Furthermore, it appears that the logistics for developing new anticancer agents are in place in Europe, but new guidelines for phase I and phase II studies

of the novel approaches which will enter clinical practice in the next 5 years need to be developed.

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