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Special Paper

EORTC-IDBBC (Investigational Drug Branch for Breast Cancer): 5 Years of European Collaboration in New Drug Development for Breast Cancer

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INTRODUCTION

THE SEARCH for new active agents or new combination regimens for the treatment of advanced breast cancer remains a high priority. Increasing demands for high-quality data and implementation of Good Clinical Practice standards have required the development of new efficient structures to enable optimal evaluation of such agents or combinations. For this reason, a phase II working subgroup named the IDBBC (Investigational Drug Branch for Breast Cancer) was created in 1990, within the large EORTC Breast Cancer Cooperative Group and in collaboration with the EORTC-New Drug Development Office (Amsterdam). This paper will deal with the framework and aims of the EORTC-IDBBC, the clinical research activity since its creation, as well as future directions.

FRAMEWORK AND AIMS OF THE EORTC-IDBBC

The central office of the IDBBC is located at the Jules Bordet Institute in Brussels. Its structure involves one secretary, one data manager, one statistician, one or two M.D. monitors (clinical research fellows), one clinical coordinator (part time) and the group chairman. These individuals are responsible for the preparation of the protocols, implementation and monitoring of the studies. The IDBBC has 12 active investigators in Belgium, France, U.K. and The Netherlands (Table 1), who are also members of the EORTC Breast Cancer Cooperative Group. The primary goal of this group is to perform, in a short period of time, phase II studies of high quality. The data generated by these studies are used to plan phase III trials for the EORTC Breast Cancer Cooperative Group as a whole. Emphasis is placed on new hormonal and chemotherapeutic agents as well as new multimodality treatments. High quality is ensured through protocol revision by the EORTC Protocol Review Committee, standard operating procedures at the central office, close contact between the principal investigators who meet every 3 months, optimal clinical and data management infrastructure at the participating

Table 1. Centres participating in the EORTC-IDBBC studies

Centre		Principal investigators
Amsterdam	Antoni van Leeuwenhoek Ziekenhuis	P.F. Bruning
Bordeaux	Fondation Bergonié	L. Mauriac
Brussels	Jules Bordet Institute	M.J. Piccart
Glasgow	Beatson Oncology Centre	C. Twelves
Leiden	Academisch Ziekenhuis Leiden	M. Nooij
Leuven	Universitair Ziekenhuis Gasthuisberg	R. Paridaens
London	Guy's Hospital	S. Houston
Nancy	Centre Alexis Vautrin	D. Spaeth
Nijmegen	Universitair Ziekenhuis Nijmegen	L. Beex
Rotterdam	Dr Daniel den Hoed Kliniek Dijkzigt	J. Klijn A. Van der Gaast
Sheffield	YCRC Weston Park Hospital	R. Coleman

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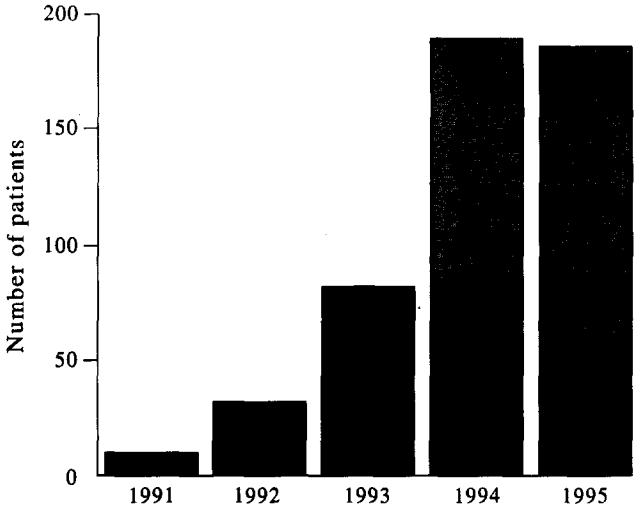

Figure 1. EORTC-IDBBC accrual.

centres and on-site data monitoring. The activity of the IDBBC has been steadily growing since 1991 (Figure 1).

CLINICAL RESEARCH ACTIVITIES OF THE IDBBC

The aims of the IDBBC are to accelerate the development of new anticancer agents or new strategies in patients with metastatic disease. Patients receiving first-line therapy, as well as patients with hormone or anthracycline-resistant tumours are the target for IDBBC protocols. Improving the therapeutic index of a drug or a combination is another goal of the IDBBC. The clinical trials run by the IDBBC from 1990 to 1996 are summarised in Table 2. Comments on the results of these studies (toxicity and antitumour activity) are summarised in Table 3.

Based on the results of the phase II studies performed by the IDBBC, two important randomised phase III studies were launched. Table 4 summarises the target patient population as well as the trial designs of these phase III studies. Tables 5 and 6 summarise IDBBC studies activated recently or expected to start later this year. Two out of five are randomised phase II studies with a possible extension into phase III trials.

TRANSLATIONAL RESEARCH PROJECTS

The IDBBC is generating an extensive database that can be used to create links between basic research and the clinic. Hopefully this will contribute to improve individualisation of patient treatment in the near future. The assessment of potential prognostic and/or predictive factors in patients with advanced breast cancer is also an ongoing project at the IDBBC. We are looking for the presence of biological markers such as HER-2/neu, p53 and MRP (MDR-related protein) on the primary tumour specimens of patients recruited for the paclitaxel versus doxorubicin trial and correlate their presence or absence with clinical out-

Table 2. EORTC-IDBBC experience since 1990

Drugs (year)	Mechanism of action	Study design	No. of patients expected/entered	Study status
Chemotherapy				
Zeniplatin (1990)	Platinum compound	Phase II	29	Closed
Epirubicin + CPA + G-CSF (1991)	Accelerated regimen	Feasibility study	33	Closed
Vinxaltine (1991)	Vinca alkaloid	Phase II	11	Closed
Paclitaxel versus doxorubicin (1993–1996)*	Tubulin interference / Anthracycline	Phase II → III (study with crossover)	331	Closed
Hormonal				
Vorozole (1992–1993)	Aromatase inhibitor (AI)	Phase II	27	Closed
Liarozole (1994–1996)	Retinoid metabolism interference + AI	Phase II + stratification according to prior therapy and HR status	116/99	Ongoing
Chemoprotector				
Docetaxel ± steroids (1992–1994)	Tubulin interference	Phase II + randomisation for steroids	83	Closed
MMC + VBL + amifostine (1995)	CT + Chemoprotector	Feasibility study	6	Closed

*In collaboration with EORTC Early Clinical Studies Group.

HR, hormone receptor; CPA, cyclophosphamide; MMC + VBL, mitomycin + vinblastine; CT, chemotherapy.

Table 3. EORTC-IDBBC studies: antitumour activity and toxicity

Study [Ref.]	Dose (mg/m^2)	Therapy for metastatic disease	Comments on activity and toxicity
Zeniplatin [1]	120–144	Second-line	RR 7% Main toxicities: Neutropenia and nausea/vomiting (no peripheral neuropathy)
Epirubicin + CPA [2] (+G-CSF)	120 + 830 (4μg/kg/d s.c.)	First-line	Feasible every 2 weeks RR (CR): 87% (28%)
Vinxaltine	0.32 (weekly)	First-line	Neutropenia (grade 3 or 4): 37% of patients No responses
Paclitaxel (P) [3] versus doxorubicin (D)	200 (3 h) 75	First-line	Haematological toxicity: D > P Clearcut antitumour activity was seen in second-line with both drugs. Final analysis: ASCO Meeting, 1997
Vorozole [4]	2.5 mg oral	Second-line†	Very well tolerated. RR: 29%
Liarozole [5]	150 mg bid → 300 mg bid if tolerated	*	Main toxicities: skin (retinoid-like) and gastrointestinal Antitumour activity seen in heavily pretreated patients
Docetaxel ± steroids [6]	50 d1 + d8	Second-line	Fluid retention significantly delayed in the steroid arm RR: 34%
MMC + vinblastine (+ amifostine) [7]	10 d1 + 5 d1 + d15 (910 d1)	Second- or third-line	Amifostine had no detectable chemoprotector effect in these heavily pretreated patients

*Stratification into four groups according to prior therapy and hormonal receptor status; †hormonotherapy; RR, response rate; bid, twice daily; CPA, cyclophosphamide; MMC, mitomycin.

come, taking into account the type of chemotherapy (anthracycline or taxane) administered.

QUALITY OF LIFE PROJECTS

To increase current knowledge about quality of life within clinical trials for metastatic breast cancer, the IDBBC has a close collaboration with the Quality of Life Unit of the EORTC Data Centre in Brussels. The docetaxel and paclitaxel versus doxorubicin studies are among the IDBBC protocols where quality of life analysis has been included.

FELLOWSHIP PROGRAMME

A fellowship programme has been set up by the IDBBC, with the financial support of the 'J.C. Heuson Fund'. Through this programme, the IDBBC attracts medical oncologists from abroad for extra training in new drug development and translational research projects. Since its creation, four visiting research fellows (from Canada, Brazil, Eastern Europe) have trained within the framework of the IDBBC. The new clinical research fellow for 1997 is from Australia.

CONCLUSIONS AND FUTURE DIRECTIONS

The EORTC-IDBBC provides an efficient framework to conduct and coordinate phase II studies with new agents (hormonal or chemotherapeutic) in metastatic breast cancer and to develop new multimodality treatments. Agents with potential activity in patients with visceral metastases or in tumours that are resistant to anthracyclines and taxanes have a high priority as targets for studies within the framework of the IDBBC. Moreover, the IDBBC is seeking to incorporate biological therapy, such as anti-angiogenesis and monoclonal antibodies in its clinical research programme. Finally, and in order to improve the outcome of patients

Table 4. Randomised trials based on the EORTC-IDBBC clinical research results in metastatic breast cancer

Previous phase II study	Target patient population	Phase III trial	Investigators
Accelerated epirubicin + CPA regimen + G-CSF	Locally advanced disease: T_4 N_X M_0 or Any N_2/N_3 M_0 or Inflammatory No prior therapy	CEF, D1 + 8, every 4 w (maximum treatment duration: 6 months) without G-CSF ↗ Randomisation ↘ EC + G-CSF every 2 w (maximum treatment duration: 3 months) doubling in dose-intensity as compared to CEF	EORTC + NCI-C + SAKK
Vorozole	Metastatic disease Second-line hormonal treatment ER+	Vorozole ↗ Randomisation ↘ Aminogluthetimide	Multicentric study (outside EORTC)

C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; ER, oestrogen receptor.

Table 5. Studies activated in 1996 for metastatic breast cancer

Drugs	Patient characteristics	Study design	Endpoints
Exemestane*	Receptor positive or unknown Postmenopausal First-line HT	Exemestane (E) ↗ †Randomisation ↘ Tamoxifen	Antitumour activity of E Analysis of the effects of E on the endometrium, lipid and coagulation profiles
Paclitaxel	First-line CT	Doxorubicin + paclitaxel ↗ ‡Randomisation ↘ Doxorubicin + cyclophosphamide	Time to progression Safety (stopping rule for congestive heart failure)
Docetaxel + Amifostine	One (or two) prior CT for MBC	Feasibility study	Haematological toxicity (Fluid retention, neurotoxicity) Pharmacokinetics

*Potent steroidal aromatose inhibitor; †phase II; ‡phase II → III.
HT, hormonotherapy; CT, chemotherapy; MBC, metastatic breast cancer.

Table 6. Studies expected to start soon

Drugs	Patient characteristics	Study design	Endpoints
Caelyx	Metastatic disease in patients with prior adjuvant anthracyclines* or older patients (> 70 years) who had never received anthracyclines	Phase II	Antitumour activity
Marimastat† + Docetaxel	One prior CT for MBC	Feasibility study	Toxicity, pharmacokinetics

*Chemotherapy-free interval ≥ 1 year; †metalloproteinase inhibitor.
CT, chemotherapy

with breast cancer and to improve individualisation of patient treatment, the IDBBC is developing translational research projects with the aim of creating links between basic research and the clinic.

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