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The EORTC Breast Cancer Group: 40 years of research contributing to improve breast cancer management

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Abstract

The EORTC Breast Cancer Group (EBCG) is a multidisciplinary international group created in 1962 in conjunction with the EORTC. This group has always focused its activities on the development of new cancer treatments and strategies for all categories of breast cancer. It has been active both in drug development, as well as in the development of new radiotherapy and surgical techniques to attempt to improve cure rates and loco-regional control. Over 40 years, the EBCG has performed dozens of clinical studies including several thousands of patients. Many of these studies have contributed to the clinical knowledge on the treatment of breast cancer and have influenced the standard management of this tumour. Beside its clinical research activities, the Group has also been very active in developing guidelines for breast cancer research, promoting high standards of care in conferences, as well as in fellowships and quality assurance programmes. EBCG is a founding member of the Breast InterGroup (BIG).

Keywords: EORTC; Breast; Research groups; Review

1. Introduction

The EORTC Breast Cancer Group (EBCG) previously called the Breast Cancer Cooperative Group (BCCG) is a multidisciplinary group involving oncologists mainly from European countries. Since its creation in 1962 (together with the creation of the EORTC), all disciplines involved in breast cancer treatment have been represented in the Group. Following the rapid expansion of the research perspective offered with new discoveries and emerging technology, pathologists, radiologists, biologists, and psychologists have been actively integrated into the activities of the Group.

The principal activity of the Group has been to carry out large clinical studies covering the entire spectrum of breast tumours from intraductal carcinoma to metastatic disease. These studies have focused on optimal local and systemic therapy of breast cancer and also consider quality of life and health economics. In the early 1990s, a special structure (the Investigational Drug Branch for Breast Cancer, IDDBC), was created to handle the early drug development trials and facilitate vertical phase II-III drug development. EBCG has also paved the way for intergroup collaboration, not only with other EORTC groups such as the Radiotherapy Group, the Quality of Life Group and the Receptor and Biomarker Group, but also with other groups outside the EORTC. Within recent decades, the EBCG has performed dozens of clinical studies including several thousands of patients. Many of these studies have contributed to the clinical knowledge on the treatment of breast cancer and have influenced the standard management of this tumour.

2. Structure and organisation

The structure and organisation of the EBCG are described in detail in the statutes of the Group (last revision 2000). The strategy of the Group is discussed within its Steering Committee including the officers (chairman, secretary, treasurer, quality assurance officer),

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representatives of the most active institutions and representatives of the EORTC Data Center. Like all EORTC groups, the officers are elected for a period of 3 years. Membership is open to every institution interested in participating in the clinical studies. New probationary members are elected for 2 years after having been approved by the Quality Assurance Committee of the Group. They then obtain the status of ordinary/active member, and maintain this provided they include at least 10 evaluable cases (ordinary members) or 15 evaluable cases (active members) into the Group's trials each year. At present, the Group comprises 17 active member-institutions, listed in Table 1, and 58 ordinary/probationary member institutions. Twice a year, the Group holds a meeting, during which important scientific and administrative matters are discussed, i.e. protocols, publications, special projects, membership, elections and finances.

3. Track record of the Clinical Research activities of the group

Between 1962 and 1973, the activities of the EBCG were almost exclusively restricted to endocrine therapy trials in advanced disease. The following drugs were tested: delta-1-testololactone (1962–1964), 6-aminochryséne (1967), estramustine phosphate (1969) and antiproclatin drugs (bromocryptin, CG603 and L-dopa) (1972). The Group was the first to demonstrate the antineoplastic activity of an anti-oestrogen, nafoxidine, which was found to be as effective as ethinyloestradiol in postmenopausal women. Nafoxidine, however, exhibited troublesome skin side-effects, explaining why it was rapidly supplanted by tamoxifen, a less toxic analogue. Already, in 1974, a combination of tamoxifen and two alternating regimens of chemotherapy, AV (doxorubicin + vincristine) and CMF (cyclophosphamide + methotrexate + fluorouracil) was tested by the Group [1]. The achievement of high response and complete remission rates stimulated the Group to pursue investigations in the field of hormonochemotherapy. Thereafter, many trials were initiated, covering all stages of disease and using all available therapeutic modalities, i.e. surgery, radiotherapy, hormonotherapy, chemotherapy and immunotherapy. To mention a few examples only: in operable breast cancer (tumours up to 5 cm), EBCG performed one of the largest studies comparing mastectomy versus breast-conserving therapy (BCT), showing that mastectomy provides a better local control without, however, any survival advantage over BCT (EORTC 10801) [2]. Another study (EORTC 10854) showed improved local control with perioperative chemotherapy, particularly in young women managed with BCT [3]. Recently, equivalent outcomes with preoperative and adjuvant postoperative chemotherapy have been demonstrated (EORTC 10902) [4]. In elderly operable patients, two studies showed inferior local control with tamoxifen alone (EORTC 10851) or with tamoxifen combined with local excision (EORTC 10850) compared with mastectomy [5]. In one of the largest clinical studies ever done in ductal carcinoma *in situ* of the breast (EORTC 10853), the EBCG demonstrated the beneficial effect of radiotherapy as a part of BCT [6]. In collaboration with the EORTC Radiotherapy Group (EORTC 22881–10882), more than 5000 patients with stage I/II breast cancer managed with BCT were recruited to demonstrate that an additional boost dose of radiation to the tumour bed reduces the risk of local recurrence [7].

In locally advanced disease, one study (EORTC 10972) demonstrated increased survival with adjuvant endocrine therapy, but not with chemotherapy following primary radiotherapy [8], whilst the other (EORTC 10921) showed no benefit of intensified induction chemotherapy with granulocyte colony stimulating factor (GCSF) support, compared with standard chemotherapy [9]. Finally, in metastatic disease, the EBCG has demonstrated that a 'classical' CMF was superior to a 3-weekly intravenous (i.v.) CMF schedule in postmenopausal patients (EORTC 10808) [10]. In another advanced disease study, a combination of tamoxifen and luteinising hormone-releasing hormone (LHRH) inhibitor was superior over either treatment alone in premenopausal patients (EORTC 10881) [11].

More recently, translational research evaluating correlations between clinical outcomes and biological tumour characteristics has become a high priority. Examples of such investigations include detection of micrometastasis in sentinel lymph nodes by polymerase chain reaction (PCR) (EORTC 10981) and evaluation of potential predictive value of *TP53* gene mutations in

Table 1
Active members of EBCG (2001)

U.Z. Gasthuisberg, Leuven	Belgium
Antoni Van Leeuwenhoekhuis, Amsterdam	The Netherlands
Institut Jules Bordet, Brussels	Belgium
The Institute of Oncology, Ljubljana	Slovenia
Weston Park Hospital, Sheffield	United Kingdom
Universita Degli Studi, Firenze	Italy
Leiden University Medical Center, Leiden	The Netherlands
Algemeen Ziekenhuis Middelheim, Antwerpen	Belgium
Algemeen Ziekenhuis Sint-Augustinus, Antwerpen	Belgium
Institut Bergonie, Bordeaux	France
Hopital Cantonal Universitaire, Genève	Switzerland
Western General Hospital, Edinburgh	United Kingdom
University Medical Center, Nijmegen	The Netherlands
Centre Henri Becquerel, Rouen	France
Medical University, Gdansk	Poland
Academic Medical Center, Amsterdam	The Netherlands
Centre René Huguenin, Paris	France

Active centres ordered by total number of patients recruited into the EBCG studies between 1998 and 2000.

primary tumours (EORTC 10994). A virtual tumour bank is being set up following the emergence of microarray technology.

In terms of drug development, the EBCG through the IDBBC has undertaken and completed several phase II trials to identify and quantify the potential anticancer activity of new anti-cancer agents either cytotoxic, such as zeniplatin, vinxaltine, oxaliplatin and liposomal doxorubicin, or hormonal, such as vorozole, liarozole and exemestane. The IDBBC also initiated two phase II-III studies comparing in metastatic disease anthracyclines versus taxanes (either alone or in combination) [12,13].

4. Special projects

4.1. Manual for clinical research in breast cancer

EBCG has prepared (first edition in 1991) and is continuously updating (four editions, recently also on CD-ROM), the Manual for Clinical Research in Breast Cancer, used as a reference for protocol elaboration, data collection and reporting of results. This manual summarises the major points in assessment, staging, treatment and follow-up of breast cancer patients. It enhances the uniformity of definitions and procedures in the different breast cancer protocols, and has also been used outside the EORTC.

4.2. Fellowships

In 1992, the EBCG was one of the first to initiate a fellowship programme by which young physicians were offered the opportunity to work at the Data Center, at the IDBBC or in the labs of some active institutions on projects from the group. Assistance in setting-up and conducting clinical trials, as well as in retrieving data and material for translational research, have been the main task of the fellows. Currently, five fellows are actively involved in the activities of the Group. Two of them act as quality control officers in the AMAROS study, one is involved in the hereditary breast cancer project, one is involved in the activities of the IDBBC and one conducts a translational research project in Leiden.

4.3. Quality assurance

In 1994, the EBCG was the first of the EORTC groups to officially set up a quality assurance committee with the following aims:

- improving the selection of new members,
- reviewing membership periodically and,
- providing assistance in terms of quality control for the studies of the Group (reviewing accuracy of the information reported on CRFs against hospital files whenever necessary).

Site visits have been organised for many new centres to check on local organisation and infrastructure. Furthermore, a programme of monitoring site visits performed by fellows of the Group has been organised to control the quality of selected studies.

A specific quality assurance procedure has been developed for surgery of the breast accompanied by a set of minimal information to be reported by the surgeon and pathologist to enable a correct retrospective evaluation of the quality of the surgery performed. Quality assurance programmes related to radiotherapy and chemotherapy administration have been conducted in parallel to larger projects run by the Quality Assurance Committee of EORTC.

5. The Breast Cancer Conference

The EBCG has a long tradition of organising breast cancer conferences. The first EORTC Breast Cancer Working Conference was held in Brussels in 1975. Because of its unexpected success, it became a regular event held every 4 years and subsequently every 2 years. From 1997, these conferences have been organised jointly, as European Breast Cancer Conferences, with the European Society of Mastology (EUSOMA) and Europa Donna (the European Breast Cancer Coalition). The aim of these meetings was to create a platform for closer cooperation between the three parties in order to stimulate both scientific progress and to provide a better standard care for this most common female malignancy. Each conference developed a consensus statement on breast cancer addressing several key issues on breast cancer research, treatment, prevention and advocacy. The three groups work towards these goals by lobbying European governments and the European Commission and by mobilising health-service providers, the scientific communities and the healthcare industry. Every other year, the European Breast Cancer Conference is attended by more than 3000 participants from all parts of the world.

6. The Breast InterGroup (BIG)

The EBCG is also a founding member of the Breast International Group (BIG), a consortium of 26 cooperative clinical groups from four continents (Europe, North America, South America and Australia), created in 1997. BIG was conceived as an international network to inspire and promote collaboration among independent cooperative groups; its aims are to facilitate the

initiation of large or difficult trials, mainly in adjuvant breast cancer clinical research, while maintaining scientific independence from the pharmaceutical industry.

7. Strategy for the future

The main focus of the EORTC Breast Cancer Group will remain the conduct of high quality clinical trials. In that perspective, the Group has recently developed a new series of large clinical trials addressing important clinical questions, such as for example:

- The role of radiotherapy in the adjuvant treatment of axillary sentinel node-positive breast cancer patients (EORTC 10981—intergroup—target accrual: 3500 patients)
- The role of taxane-based therapy and *TP53* mutation status in the neo-adjuvant treatment of locally advanced breast cancer (EORTC 10994—intergroup—target accrual: 1500 patients)
- The role of breast-conserving therapy in the management of locally advanced breast cancer (EORTC 10974—intergroup—target accrual: 1300 patients)
- The role of adjuvant trastuzumab treatment in HER2+ breast cancer patients (Intergroup HERA—target accrual 3200 patients)
- The role of trastuzumab in the treatment of metastatic breast cancer in combination with CMF (EORTC 10995—randomised phase II—135 patients)
- The place of capecitabine (single agent) in second- or third-line treatment of metastatic breast cancer (EORTC 10003—target accrual 220 patients)

The IDBBC remains active testing new agents such as ZD 1839 (Iressa), trastuzumab (as reversor of hormonal resistance) or multidrug resistance reversor. The collaboration initiated between the EBCG (IDBBC) and the Early Clinical Studies Group (ECSG) for several trials will be pursued with a progressive transfer of responsibilities from the IDBBC structure to the New Drug Development Programme (NDDP) at the EORTC Data Center over the next 3 years.

In the continuity of the good collaboration established with the Radiotherapy Group, EBCG is also participating in EORTC 22922 (EBCG 10925) a phase III randomised clinical trial investigating the role of internal mammary and medial supraclavicular (IM-MS) lymph node chain irradiation in stage I-III breast cancer.

Following the EORTC strategy, the Group also focuses its strategy on translational research with the incorporation of tissue banking. These studies aim to design optimal treatment strategies for individual breast cancer patients on the basis of prognostic factors (uPA/PAI1) or predictive factors (*P53*), and micro-array analysis profiles of the primary tumour.

According to the last two European Breast Cancer Conferences' statements, the following tasks will be undertaken or continued.

Recognising the importance of 'familial' breast cancer, the EBCG decided in 2000 to reinvest the benefit of the breast cancer conference in a research project addressing several aspects of hereditary breast cancer management. The project has three main objectives:

1. Identify mutation carriers from existing tumour material of patients entered into EORTC trials and investigate the possible relationship between these mutations and the clinical outcome of the patients (prognostic/predictive value).
2. Screen current procedures in various countries and institutions related to hereditary breast cancer management.
3. Set up a prospective registry for mutation carriers treated by prophylactic or therapeutic intervention.

EBCG will also collaborate with Europa Donna to establish the adequate legislation, protecting the patient from the possible deleterious consequences related to the expansion of genetic testing. With EUSOMA, EBCG will further ensure that findings from research, and specifically from clinical research, are rapidly translated into guidelines for 'state of the art treatment of breast cancer.

The quality assurance programmes, previously addressing radiotherapy and chemotherapy, will now be focused on other aspects of breast cancer management such as surgery, pathology and diagnostic radiology, all now also considered critical factors for the successful management of this disease.

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