LETTER TO THE EDITOR

Provision of data from the clinical database and of biological material from the tumor bank of the Danish Breast Cancer Cooperative Group 2008–2017

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Introduction

The capability to link health care information across various health care providers (institutions, clinics and professions) is increasingly recognized as an important source for clinical decision making and improved patient care [1]. A multi-institutional and -disciplinary records linkage system will potentially make information on treatments and events available to treating physicians and reduce repeat testing [2]. A comprehensive linkage of medical records also allows to access patient outcomes individually and for quality assurance and research if applied to a sufficiently large group over extended time. A clinical database becomes particularly informative if it is population-based, e.g., covers all residents in a well-defined area. The ability to improve quality of care will further increase when data in multiple databases can be coupled on an individual patient level, and in Denmark this is enabled by the unique civic registration number assigned to all inhabitants. Finally, the research opportunities will expand considerably by access to tumor tissue if linked to clinical data.

The clinical database of the Danish Breast Cancer Cooperative Group (DBCG) was established in 1977 in conjunction with the foundation of the multidisciplinary group [3]. Since then relevant data of diagnostic aspects, of loco-regional and systemic therapies and follow-up has been collected nationwide by the DBCG from all women newly diagnosed in Denmark with breast cancer [4]. The clinical database has collected data from about 130,000 breast cancer cases and the database has provided an instrument for monitoring community breast cancer standards and for the conduct of large series of randomized trials [5], and data from these trials have successively modified the current guidelines. These initiatives have significantly contributed to an improvement in the prognosis of breast cancer [6,7].

This paper will provide information on how data from the clinical database and of how biological material from the DBCG tumor bank has been utilized for correlative research studies.

The DBCG clinical database and access to the data

All Danish units involved in the diagnosis, treatment, and follow-up of breast cancer patients have contributed to the database in reporting data of histopathology, treatment, and follow-up [8]. Data from a total number of about 130,000 women have now been reported . A total of about 30,000 patients are currently in treatment or in follow-up, and 65,000 are still alive. Early on the data was reported by paper forms to the secretariat with subsequent transfer of data to the database, but from 2007 a web system was developed to enable on-line reporting from the departments.

From 2006 data concerning demographics, diagnostics, surgery, and oncologic treatment strategies, defined as quality data, have been extracted from the database to be used for the DBCG quality indicators [www.dbcg.dk/kvalitetsdatabase] according to the program of the Danish Clinical Registries (RKKP) [www.rkkp.dk].

The data of the database are unique. They are individual based, and longitudinal with successive dates of therapeutic interventions and events. And the database, following improvement over time, is now close to have a complete coverage of the Danish breast cancer population. This has been achieved by the development of an effective system of reminders, based partly on identification of gabs in the reporting and by linkage to the Danish Pathology Registry, which registers data from every pathology report performed by the Danish departments of pathology. Thus patients not registered from the departments can be identified and enquiries sent to the departments. And finally, the database is constructed to give advice to the clinicians, based on the reported data of the clinical, histopathological and genetic characteristics about the recommended oncological treatment according to current evidence based guidelines.

In addition link to other public registries by use of the unique 10-digit Danish Civil Registration Number (CPR), assigned to all Danish residents, offers an excellent possibility to run comparative research studies such as link to The Danish National Board of Health Registry (LPR) which

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registers all diagnoses from admission to hospital, such as other diseases, co-morbidity and long-term adverse events, link to the Danish National Prescription Registry which registers drugs prescribed, link to the Cancer Registry for other malignant diseases and link to the CPR for vital status.

Access of data from the database to be used for research by members of the DBCG-organization or by other groups or institutions with expertise in breast cancer research required an application sent to the DBCG secretariat and to be evaluated by members of the DBCG executive committee, possibly following advice from one of the relevant scientific committees [3]. The applications are approved provided certain scientific criteria, if necessary following correspondence with the applicant, and current legal requirements are met.

The DBCG tumor bank and access to biological material

The biological material from Danish breast cancer patients is stored at three locations. In the departments of pathology responsible for the diagnostic procedures as well as the molecular biological analyses required for allocation of the patient to the proper treatment. The material is stored as paraffin-embedded tissue, fresh frozen tissue and to a lesser extent extracted RNA/DNA. Since 2009 all Danish cancer patients have been asked for permission to collect biological material including paraffin embedded tissue and fresh frozen tissue, when available, as well as a blood sample to the Danish Cancer Biobank [www.cancerbiobank.dk]. Finally in the DBCG tumor bank, which was established in 1991, in connection with the initiation of the centralized biochemical ER analysis. Since then the DBCG tumor bank has stored biological material as paraffin-embedded tissue, fresh frozen tissue and extracted RNA/DNA, and excess TMA's collected in relation to translational research projects.

Access to biological material requires approval of the project by the DBCG executive committee as described for access to clinical data complemented by a Material Transfer Agreement signed by the medical leader of the DBCG secretariat and the chairman of the project in question. If the material is used to produce TMA's the residuals are to be returned to the DBCG tumor bank while residual RNA/DNA can be stored with the pathologist responsible for the specific study. The residual TMA's or RNA/DNA is registered for potential future studies.

Requests for access to data from the clinical database

Since the establishment of the database DBCG has received 350 requests for extracts from the database to be used in research studies. This analysis covers the time since January 2008 during that period DBCG received 167 requests. These are summarized in Supplementary Table 1. Applications concerning update of previously accepted studies are not included in the table. As it appears the topics cover almost all aspects of breast cancer: diagnostic aspects, including mammography, histopathology including potential prognostic and predictive factors, surgery, radiotherapy, systemic therapy, epidemiology, adverse events, importance of concomitant drug administration, genetics, and rehabilitation.

Since mid-2013, we prospectively recorded certain characteristics of the research projects ($n = 82$). During this period 16 of the studies was run as single institution studies but 64 (78%) were multicenter or nation-wide studies. In 24 of the cases the requested data included quality data only, but the majority of cases (70%) requested additional data from the database. Access to biological material, this was requested in 13 (=16%) of the applications.

Publications from these studies are included in the DBCG bibliography which as of ultimo 2016 counts 452 peer reviewed publications [www.dbcg.dk/publications].

Discussion

The data presented demonstrate how a well-organized clinical database in conjunction with a multidisciplinary organization can be efficiently utilized to answer a large variety of research questions related to the total course of the disease.

Several factors have probably been important in making the clinical database of the DBCG a major research resource. First, for 40 years DBCG has provided easily accessible application forms and guidelines for requesting data and the board of directors, the responsible authority, is appointed by the scientific societies. Second, the clinical database contains four decades of comprehensive and population-based data on breast cancer patients in Denmark. Third, linkage to information from a variety of other database has been possible on an individual patient basis. Finally, tumor-tissue has been available on around 80% of patients enabling biological research.

Disclosure statement

No potential conflict of interest was reported by the authors.

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LETTER TO THE EDITOR

Palliative treatment with carboplatin as late line therapy to patients with metastatic breast cancer

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Introduction

Among patients with breast cancer, 20–25% will develop metastatic disease, and the treatment will be palliative [1]. In this situation, the purpose of treatment will be to ease symptoms in order to maintain or improve quality of life and if possible, to prolong life [2,3].

When the disease no longer respond to standard treatment regimes, the patient is either treated symptomatic or with experimental chemotherapy. The optimal cytostatic treatment of heavily pretreated breast cancer patients is not standardized, often of low efficacy, and limited by comorbidity and performance status. As the treatment is palliative, the benefits of tumor response and improvement in disease-related symptoms as a result of chemotherapy must be weighed against treatment-induced toxicity and its impact on quality of life [4]. Still more patients are receiving chemotherapy near end of life [5]. This is due to constant improvement in breast cancer treatment and an increasing patient wish for further treatment [6]. For several patients, even the smallest possibility of benefit appears to be worth fighting for and they prefer to do something actively [6,7].

Carboplatin has been proved effective in the treatment of early-stage breast cancer, both as monotherapy [8,9] and as combination therapy [10–12]. The efficacy of carboplatin in the treatment of pretreated metastatic breast cancer is more equivocal [13–19]. Furthermore, the efficacy in treating heavily pretreated metastatic breast cancer is still debatable and only few studies exist [20,21]. Recent studies have indicated effect of platinum-containing regimes in treatment of triple negative breast cancer [14,20,22,23], and international guidelines have included platinum-containing regimes in the treatment of BRCA1/2 associated triple-negative metastatic breast cancer [2]. Most of the studies involving carboplatin, show an advantageous side effect profile [8,9,15–17], making the drug suitable for palliative care. The aim of the current study was to evaluate whether a carboplatin regime could be suitable for late line treatment of heavily pretreated patients with disseminated breast cancer, and to evaluate whether a carboplatin regime could be an option for those patients, who desire additional treatment, but with a reasonable balance between chance of effect and amount of side effects.

Patients and treatments

The study was performed at two oncological departments in Denmark, Aarhus (cohort 1) and Odense (cohort 2). The databases were searched to find all patients ever treated with a carboplatin regime. All files were accessible from October 1990, where the first patient, later treated with carboplatin, was diagnosed with breast cancer.

The patients included women with advanced breast cancer, treated with a carboplatin regime between July 2004 and February 2012. Inclusion criteria for this retrospective study were histological verified breast cancer, advanced disease proven by biopsy or radiological investigations, and a minimum of one treatment course with a carboplatin-regime. In addition, the patients should not have been exposed to carboplatin (cohorts 1 and 2) or gemcitabine (cohort 2) as part of prior treatment. As carboplatin was not a part of the standard treatment, the use of carboplatin was different in the two hospitals.

Treatments

In cohort 1, the treatment consisted of carboplatin AUC 5 monotherapy or carboplatin and trastuzumab 6 mg/kg (loading dose 8 mg/kg) in case of HER2-positive disease. Both treatments were given on day 1 in a 3 week cycle. In cohort

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