The Breast xxx (2015) 1–7

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Pregnancy after breast cancer: Are young patients willing to participate in clinical studies?

Olivia Pagani [a, o, *], Monica Ruggeri [o], Silvia Manunta [a], Christobel Saunders [b], Fedro Peccatori [c], Fatima Cardoso [d], Bella Kaufman [e], Shani Paluch-Shimon [e], Hanan Gewefel [f], Elisa Gallerani [g], OMalkahi Abulkhair [h], Barbara Pistilli [i], Ellen Warner [j], Emmanouil Saloustros [k], Lucien Perey [l], Khalil Zaman [m], Manuela Rabaglio [n], Shari Gelber [p], Richard D. Gelber [p], Aron Goldhirsch [o, q], Larissa Korde [r], Hatem A. Azim Jr. [s], Ann H. Partridge [t]

[a] Oncology Institute of Southern Switzerland (IOSI), 6500 Bellinzona, Switzerland
[b] School of Surgery, University of Western Australia, Perth, WA 6009, Australia
[c] Fertility & Procreation Unit, Division of Gynecologic Oncology, European Institute of Oncology (IEO), Via Ripamonti 435, 20141 Milan, Italy
[d] Breast Unit, Champalimaud Cancer Centre, Av. De Brasília, Doca de Pedrouços, 1400 - 038 Lisbon, Portugal
[e] Breast Cancer Service for Young Women, Oncology Institute, Sheba Medical Center, Tel Hashomer, 52621, Israel
[f] Woman and Fetal Imaging Clinic (WAFI), 2 Mohamed Farid Wagdy St., Suite41 Manial Al Roda Island, Cairo, Egypt
[g] Ospedale Multimedica, Viale Piemonte 70, Castellanza, VA, Italy
[h] Department of Oncology, King Abdul Aziz Medical City for National Guard, Riyadh, Saudi Arabia
[i] Oncology Department Macerata Hospital, Via S. Lucia 1, 62100 Macerata, Italy
[j] Sunnybrook Health Sciences Centre, Odette Cancer Centre, Medical Oncology, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada
[k] Hereditary Cancer Clinic, Dpt of Medical Oncology, University Hospital of Heraklion, Voutes, Box 1352, Heraklion 71110, Greece
[l] Greeceo Unité d'oncologie, Ensemble hospitalier de la Côte, Hôpital de Morges, Morges and Centre pluridisciplinaire d'oncologie (CePO), CHUV, Lausanne, Switzerland
[m] CHUV-Centre d'Oncologie, Rue du Bugnon 46, 1011 Lausanne, Switzerland
[n] Universitätsklinik und Poliklinik für Medizinische Onkologie/Brust-und Tumor Zentrum der Frauenklinik, Inselspital, Freiburgstrasse, 3010 Bern, Switzerland
[o] International Breast Cancer Study Group (IBCSG), Effingerstrasse 40, 3008 Bern, Switzerland
[p] IBCSG Statistical Center, Dana-Farber Cancer Institute, Frontier Science and Technology Research Foundation, Boston, MA, USA
[q] Program of Breast Health, European Institute of Oncology (IEO), Via Ripamonti, 435, 20141 Milano, Italy
[r] Division of Medical Oncology, University of Washington, Seattle, WA, USA
[s] Department of Medicine, BrEAST Data Centre, Institut Jules Bordet, Université Libre de, Bruxelles, Brussels, Belgium
[t] Dana-Farber Cancer Institute, 450 Brookline Avenue, Yawkey 12, Boston, MA 02215, USA

ARTICLE INFO

Article history:
Received 8 September 2014
Received in revised form
9 January 2015
Accepted 16 January 2015
Available online xxx

Keywords:
Breast cancer
Young patients
Pregnancy
Estrogen receptor
Endocrine treatment

ABSTRACT

Young patients with breast cancer (BC) are often concerned about treatment-induced infertility and express maternity desire. Conception after BC does not seem to affect outcome, but information in estrogen-receptor positive (ER+) disease is not definitive. From September 2012–March 2013, 212 evaluable patients with ER+ early BC, <37 years at diagnosis, from 5 regions (Europe/US/Canada/Middle-East/Australia) answered a survey about fertility concerns, maternity desire and interest in a study of endocrine therapy (ET) interruption to allow pregnancy. Overall, 37% of respondents were interested in the study; younger patients (≤30 years) reported higher interest (57%). Motivation in younger patients treated >30 months was higher (83%) than in older women (14%), interest was independent of age in patients treated for ≤30 months. A prospective study in this patient population seems relevant and feasible. The International-Breast-Cancer-Study-Group (IBCSG), within the Breast-International-Group (BIG) – North-American-Breast-Cancer-Groups (NABCG) collaboration, is launching a study (POSITIVE) addressing ET interruption to allow pregnancy.

* Corresponding author. International Breast Cancer Study Group (IBCSG), Effingerstrasse 40, 3008 Bern, Switzerland. Tel.: +41 91 811 8435; fax: +41 91 811 8436.
E-mail address: olivia.pagani@ibcsg.org (O. Pagani).

http://dx.doi.org/10.1016/j.breast.2015.01.005
0960-9776/

Introduction

Breast cancer (BC) is the most common female malignancy: in the developed world, approximately 7% of patients are diagnosed when <40 years, and BC accounts for more than 40% of all cancers in this age group [1]. A trend of increased incidence in younger Caucasian women has been reported in recent decades [2,3]. In the US, the cumulative risk in 2013 was anticipated to be 1:202 by the age of 40 and 1:26 by the age of 50 [4] with more than 12.000 women <40 years expected to be diagnosed with BC [5].

BC death rates among Caucasian women have consistently decreased since 1990, and this decline is more pronounced in younger women [6]. In a large prospective observational study conducted from 2000 to 2007 and including 2.956 BC patients <40 years at diagnosis, 50% had T1N0 disease: overall, women with estrogen receptor positive (ER+) disease had an 8-year distant disease free and overall survival of 68.3% and 67.5%, respectively [7].

Tamoxifen is the standard adjuvant endocrine therapy (ET) in premenopausal women with ER+ early BC. The substantial reduction (approximately 40%) in both the risk of BC recurrence and BC-related death with 5 years of treatment is independent of age or the use of chemotherapy, with 76% of women alive at 15 years [8]. Recent data from the ATLAS and aTTom studies suggest that continuing tamoxifen to 10 years gives a further significant reduction in recurrence and mortality [9,10]. The recently published results of the Suppression of Ovarian Function Trial (SOFT) showed, after a median follow-up of 67 months, no significant benefit by the addition of ovarian function suppression/ablation (OFS/OA) to tamoxifen in terms of disease-free-survival (DFS) in the overall study population. For women who received adjuvant chemotherapy and remained premenopausal after its completion, the addition of OFS significantly improved disease outcomes, especially if younger <35 years at BC diagnosis [11]. In addition, the results of the joint analysis of the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT) in 4.690 patients, showed a significantly improved disease-free survival (DFS) with exemestane plus the GnRH agonist triptorelin, as compared to tamoxifen plus ovarian suppression, with 96% of patients alive at 5 years in both groups [12].

In recent decades, there has been a trend toward delaying childbearing for a variety of reasons (e.g. cultural, educational, professional) so that the median age at first live birth in most developed countries is almost 30 years [13]. As a consequence, BC in young women often occurs before the completion of reproductive plans. Treatment-related infertility significantly impacts quality of life, resulting in substantial distress in young women with BC [14–16]. Fertility concerns influenced treatment decisions in 26% of patients in a large prospective observational study conducted in the US in 620 young women with BC (<40 years) [17]. Significant concern was associated with younger age and no children before BC diagnosis. Of note, only 9% of the respondents reported they did not want a future biologic child because they were afraid this would increase their risk of recurrence. The results of a survey conducted by the European Organization for Research and Treatment of Cancer (EORTC) and BIG in 389 women <35 years at diagnosis of early BC from several countries with different sociocultural attitudes, showed that 59% of participants wanted to have (more) children in the future. Interestingly, among those who did not, almost 40% were afraid of increasing the risk of tumor recurrence [18]. Fear of tumor recurrence might contribute to the low number (<10%) of women with previous BC who subsequently become pregnant [19]. In all reported series this is approximately half the pregnancy rate seen in both age-matched groups without BC and survivors from other cancers [20–22].

The best available retrospective evidence suggests that pregnancy after BC does not increase a woman's risk of disease recurrence [23–27]. In a recent multicenter, retrospective cohort study matching (1:3) patients who became pregnant any time after BC (n = 333) to patients with BC with similar ER and nodal status, adjuvant therapy, age and year of diagnosis (n = 874), after a median follow up of 4.7 years following conception, no difference in 5-year DFS was observed between pregnant and non-pregnant patients in the ER+ population [28]. In the same analysis, no difference in DFS was observed between patients who became pregnant <2 years following BC diagnosis and those who became pregnant afterwards.

Nevertheless, several questions remain unanswered regarding pregnancy in BC survivors, particularly those with ER+ disease. For women desiring children after BC, 5–10 years of ET may substantially reduce the ovarian reserve and the consequent chance of conception; however, a shorter duration of ET in this population has never been prospectively studied. It is therefore crucial to identify strategies allowing some women to become pregnant without waiting for the full standard duration of ET and without compromising their outcome.

Conducting a prospective clinical study of pregnancy after BC is challenging, given the relatively small numbers and the emotional and preference-laden issues involved. Results cannot be achieved without a global commitment by both patients and investigators. In 2009, the IBCSG, within the BIG – NABCG collaboration, committed to an ambitious program aimed to explore the safety of ET interruption in young women with ER+ early BC who wish to have children. A consortium of >50 dedicated investigators from 19 countries across the world was assembled to assess the feasibility of a clinical study in this setting and provide a global perspective of different cultural and social environments. Patients' selection was based on the following assumptions: 1) young BC patients (<40 years at BC diagnosis) face specific issues, including those related to fertility; 2) the rate of follicle loss accelerates around age 35 with an associated reduction in the ability to conceive afterwards; 3) ET for at least 2–3 years has a substantial impact on survival.

Patients' opinion was deemed crucial to successfully plan the development and sustainability of the whole plan. Before launching the project, the consortium decided to test the extent of patients' interest in the research question. A survey to explore young patients' interest in a study addressing pregnancy after BC was therefore launched and conducted worldwide from September 2012 to March 2013.

Patients and methods

Patients' selection included the eligible population for the trial: 1) ER+ early BC; 2) <37 years at BC diagnosis 3) ongoing adjuvant ET [selective estrogen receptor modulator (SERM) alone, LH-RH analog + SERM or aromatase inhibitor (AI)]. Patients could have received adjuvant chemotherapy prior to ET. No additional clinical-pathologic information was collected.

The survey included 8 multiple-choice questions about fertility concerns at BC diagnosis (3 questions), maternity desire (2 questions), current duration of ET (1 question), and willingness to participate in a study of ET interruption to allow pregnancy, if available (2 questions) (Appendix 1). The survey was submitted to patients during routine clinical consultations or by email.

Two-hundred-seventeen consecutive patients from 18 institutions in 5 different regions (Europe/US/Canada/Middle-East/Australia) answered the questionnaire (Table 1, Appendix 2). Most

Please cite this article in press as: Pagani O, et al., Pregnancy after breast cancer: Are young patients willing to participate in clinical studies?, The Breast (2015), http://dx.doi.org/10.1016/j.breast.2015.01.005