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Adjuvant therapy with GnRH agonists/tamoxifen in breast cancer should be a good council for patients with hormone receptor-positive tumours and wish to preserve fertility

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ABSTRACT

Infertility represents one of the main long-term consequences of the chemotherapy used for the adjuvant treatment of breast cancer. Approximately 60–65% of breast cancers express the nuclear hormone receptor in premenopausal women. Adjuvant endocrine therapy is an integral component of care for patients with hormone receptor-positive (HR+) tumours. The GnRH agonist (GnRHa) alone or in combination with tamoxifen produces results at least similar to those obtained with the different chemotherapy protocols in patients with HR+ breast cancer with respect to recurrence-free survival and overall survival. It is time to indicate adjuvant therapy with GnRHa associated with tamoxifen for patients with breast cancer (HR+ tumours) if they want to preserve their reproductive function. The evaluation of ovarian reserve tests: follicle stimulating hormone (FSH), anti-Mullerian hormone (AMH), inhibin B, antral follicle count (AFC) and ovarian volume 6 months, and 1 year after the end of therapy with GnRHa/tamoxifen must be realised. The recurrence-free survival and overall survival should be analysed. The major implication of this hypothesis will be to avoid adjuvant chemotherapy for patients with breast cancer (HR+ tumours) that request fertility preservation. It is expected that ovarian function should not be altered in almost all cases and subsequent pregnancy a real possibility.

Preservation of fertility

The increased incidence of breast cancer among young women under 40 years of age and the increasing age of women at the time of the birth of their first child emphasise the importance of providing counselling about fertility-preserving strategies in the management of breast cancer care [1]. Breast cancer is the most common malignant tumour in women. Women younger than 40 years comprise 25% of all women who are diagnosed with breast carcinoma.

Over half the women reported that the information received in the consultation about infertility was adequately addressed and as many as 30% reported that the information received in the consultation affected their treatment decisions [2]. Recent surveys of cancer survivors of childbearing age suggest that approximately one-half of these patients are not exposed to an appropriate discussion of infertility as a potential side effect of cancer treatment, but that a majority of patients have questions regarding delayed childbearing and its long-term effects on quality of life [2].

Generally local treatment in the form of surgery and radiation has no effect on the reproductive health of patients with breast cancer. However, the use of chemotherapy in the premenopausal breast cancer population requires attention with regard to the short-term and long-term effects on reproduction, both during and after treatment [2].

Infertility represents one of the main long-term consequences of combination chemotherapy used for the treatment of breast cancer. Even patients who do not lose their menses immediately due to chemotherapy may still experience infertility [3]. The incidence of chemotherapy-related amenorrhoea reportedly was 68% in patients who were treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)-like regimes, and it was higher for patients who were treated with anthracycline-based regimens [4]. The magnitude of the effect varies with the drug class, the total dose administered, and the age of the patient at the time of therapy. The drugs most frequently associated with ovarian failure are divided into three classes: drugs that are definitely associated with gonadal toxicity such as cyclophosphamide, drugs that are unlikely to cause gonadal toxicity such as methotrexate, 5-fluorouracyl, and 6-mercaptopurine, and drugs whose gonadal toxicity is unknown such as doxorubicin, bleomycin, vinca alkaloids

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(vincristine and vinblastin), cisplatin, nitrosoureas, cytosine, and arabinoside. The effects of early menopause may be more important at younger biological ages.

Clowse et al. [5] performed a systematic review and meta-analysis of studies examining whether a GnRH agonist (GnRHa) administered (preventive action) during chemotherapy is protective of ovarian function and fertility. Nine studies included 366 women. Three studies included women with autoimmune disease receiving cyclophosphamide and six included women with haematologic malignancy receiving combination chemotherapy. A total of 178 women were treated with a GnRHa during chemotherapy and 93% of them maintained ovarian function. Of the 188 women not treated with a GnRHa, 48% maintained ovarian function. The use of a GnRHa during chemotherapy was associated with a 68% increase in the rate of preserved ovarian function compared with women not receiving a GnRHa (RR = 1.68, 95% CI 1.34–2.1). Among the GnRHa-treated women, 22% achieved pregnancy following treatment compared with 14% of women who did not receive GnRHa therapy (RR = 1.65, CI 1.03–2.6). In conclusion, based on the available studies, GnRHa appear to improve ovarian function and the ability to achieve pregnancy following chemotherapy and, despite prolonged use, clearly have less negative effects on ovarian function.

In 2011, embryo and oocyte cryopreservation are the two fertility options most widely accessible to breast cancer patients. In 2008, the Society for Assisted Reproductive Technology/Center for Disease Control data indicated that the live birth rates from frozen embryo transfer were 35.5% in women less than 35 years of age, 29.3% in the 35–37 age group, 26.1% in the 38–40 age group, and 19.5% in the 41–42 age group [6].

According to the American Society for Reproductive Medicine, oocyte cryopreservation remains experimental; however, recent pregnancy rate data after oocyte cryopreservation have approached those obtained with frozen embryo transfer and even fresh transfer [7,8]. Pregnancies from cryopreserved oocytes have grown in recent years but embryo cryopreservation should remain the first choice. Cryopreservation of ovarian tissue has been performed for subsequent autotransplantation. There is concern that transplanted ovarian tissue could harbour malignant cells or undergo malignant transformation, although there are investigations that do not show evidence of malignant cells in ovarian tissue from breast cancer patients [9,10]. Therefore, ovarian tissue cryopreservation remains experimental and investigational.

The objective of the present report is to discuss the hypothesis of avoiding chemotherapy as adjuvant treatment of cancer of the breast (hormone receptor-positive tumours) in patients who desire to preserve reproductive function by using GnRHa (therapeutic action) more tamoxifen. This new strategy can avoid the loss of ovarian function and open possibilities for a future pregnancy.

GnRHa only versus chemotherapy for adjuvant breast cancer therapy

Approximately 60–65% of breast cancer tumours in premenopausal women are hormone receptor-positive. These patients may be suitable for hormonal treatment. The goal of hormonal therapy is to reduce the availability of oestrogen to the cancer cell.

Four studies were identified that compared a GnRHa versus chemotherapy, including a total of more than 4000 women [11–14]. All four trials used CMF: three as six cycles each of 28 days [11–13] and one as three cycles [14]. Two trials used classical CMF with cyclophosphamide given orally on each of the first 14 days of the cycle [11,12]. The ZEBRA trial allowed either classical CMF with oral cyclophosphamide or CMF with intravenous cyclophosphamide [13] and the GABG trial used intravenous cyclophosphamide [14]. There was also variability in the hormonal therapy used in these three trials. Goserelin (3.6 mg depot every 28 days) was used for 2 years in IBCSG VIII [11] in the absence of chemotherapy or for 18 months after 6 months of chemotherapy, and was used for 2 years in the GABG [14] and ZEBRA [13] trials. In the TABLE trial [12], the LHRH agonist was leuprorelin acetate (11.5 mg every 3 months) administered for 2 years.

The largest of these four trials was the ZEBRA trial (1614 patients; lymph node-positive breast cancer), in which three quarters of the women were oestrogen receptor-positive (ER+) (1189 of 1614, 73.7%), 304 (18.8%) were oestrogen receptor negative (ER−), and 121 (7.5%) had unknown ER status [13]. Overall, with a median follow up of 87 months, patients randomised to goserelin had significantly worse recurrence-free survival (49.8%) than those allocated to chemotherapy (56.2%) (RR 1.22, 95% CI 1.05–1.40, $P = 0.007$), and a non-significantly worse overall survival (RR 1.15, 95% CI 0.96–1.39, $P = 0.14$). However, a highly significant interaction was found between treatment and ER status ($P = 0.0016$) for recurrence-free survival. Patients who were ER+ had similar recurrence-free survival and overall survival in both treatment groups (RR for recurrence-free survival for goserelin versus CMF 1.05, 95% CI 0.88–1.24, $P = 0.60$; RR for overall survival 0.94, 95% CI 0.75–1.18, $P = 0.62$) with the worse outcome for goserelin-treated patients being due to the effect on ER− patients (RR for recurrence-free survival 1.64, 95% CI 1.13–2.39, $P = 0.0009$; RR for overall survival 1.83, 95% CI 1.33–2.52, $P = 0.001$) and ER-unknown patients (RR for recurrence-free survival 2.00, 95% CI 1.07–3.75, $P = 0.026$; RR for overall survival 1.81, 95% CI 0.81–4.05, $P = 0.14$). After 6 months of treatment in ZEBRA [13], amenorrhoea was more common in patients treated with goserelin (95%) than with chemotherapy (59%). However, after 3 years, 23% of patients who had received goserelin remained amenorrhoeic compared with 77% of patients treated with chemotherapy. The incidence of adverse reactions, including menopausal side effects, hot flushes, vaginal discharge and vaginal soreness, was similar in both groups (goserelin: 42.6%; chemotherapy: 48.0%). These side effects tended to resolve within a year after stopping goserelin but persisted in the chemotherapy group for the 30 months under investigation.

The IBCSG VIII trial randomised 1063 patients (lymph node-negative breast cancer) to CMF alone versus CMF followed by goserelin versus goserelin alone [11]. A fourth option of no adjuvant therapy was closed 2 years into the trial, when a total of 205 patients had been randomised to the trial as a whole. Two thirds of the women in the trial were ER+ (720 of 1111, 68%), 315 (30%) were ER−, and 28 (3%) had unknown ER status. Overall, with a median follow up of 84 months, there were no significant differences between treatment groups in disease-free survival or overall survival. However, differences between treatment groups were suggested for subpopulations defined according to ER status. The five-year disease-free survival (all patients) was 79% (95% CI 75–84%) for goserelin alone ($n = 346$) and 82% (95% CI 78–86%) for chemotherapy alone ($n = 360$). In the comparison of goserelin versus chemotherapy, the relative risk for disease-free survival was 1.13 (95% CI 0.83–1.53, $P = 0.44$). ER+ patients in both the goserelin group ($n = 229$) and the chemotherapy group ($n = 247$) had similar disease-free survival (5-year DFS 81%, 95% CI 76–87% in both groups; RR 0.97, 95% CI 0.66–1.42, $P = 0.86$). In contrast, ER− patients had a shorter but not significant disease-free interval in the goserelin group ($n = 106$) (73%, 95% CI 64–81%) compared to the chemotherapy group ($n = 105$) (84%, 95% CI 77–91%) (RR 1.52, 95% CI 0.89–2.58, $P = 0.12$). Toxicity of grade 3 or worse was experienced by 4.7% of the patients allocated to goserelin alone (mostly weight gain) and by 18.8% of patients during chemotherapy (mostly leucopenia, neutropenia, and nausea or vomiting). In younger women under the age of $\leqslant$39 years receiving chemotherapy, amenorrhoea occurred later, being observed in 50% of these

patients by the end of six cycles of CMF. On the other hand, 45% of the patients had amenorrhoea 35 months after randomisation. In women who received goserelin after chemotherapy, 90% became amenorrhoeic a few months after starting goserelin, but only 15% had amenorrhoea 35 months after randomization.

Quality of life has been reported in detail for 874 patients in the IBCSG VIII trial [11], based on an assessment at 36 months for 746 of these 874 patients [15]. Patients in the goserelin alone group showed a marked improvement or less deterioration in various quality of life indicators during the first 6 months compared to those receiving chemotherapy. However, there was no significant difference in quality of life at 36 months between the groups allocated to chemotherapy followed by goserelin versus goserelin alone.

The TABLE study [12] recruited 599 premenopausal patients (lymph node-positive/stage II or IIIA) with breast cancer who were not known to be ER−. The inclusion criteria were amended part way through the trial, so that only ER+ patients were randomised. Although 599 patients were recruited, 10 patients were excluded and the remaining 589 patients were assigned to leuprorelin acetate ($n = 294$) and chemotherapy with cyclophosphamide, methotrexate and fluorouracil ($n = 295$) with a median follow-up of 69 months. No significant differences in recurrence-free survival were found between groups (RR = 1.19; 95% CI, 0.94–1.51; $P = 0.15$). However, exploratory overall survival analysis favored leuprorelin acetate versus chemotherapy (RR = 1.50; 95% CI, 1.13–1.99; $P = 0.005$). The 5-year disease-free survival was 63.9% for women allocated to leuprorelin compared to 63.4% for women allocated to chemotherapy. Over 95% of women in the leuprorelin group became amenorrhoeic during treatment, compared to 62.1% of women treated with chemotherapy. Analysis by age showed that more than 90% of patients younger than 40 years at trial entry had normal menstrual function 1 year after the completion of therapy with the GnRHa. The most common adverse events were low-grade hot flushes, oedema, and fatigue among the leuprorelin patients; and alopecia, nausea and vomiting, and fatigue among the chemotherapy patients. The overall assessment of tolerability by patients was markedly better during the first 6 months of treatment in the leuprorelin group, but there was no significant difference between groups at 2 years.

The GABG study recruited 771 node-negative premenopausal patients with hormone receptor-positive breast cancer [14]. No significant differences in local recurrence, distant recurrence, event-free survival, or death without recurrence were found between treatments. The 5-year event-free survival was 85.0% for women allocated to goserelin ($n = 393$) compared to 81.0% for women allocated to chemotherapy ($n = 378$). The estimated hazard ratio or using an intention-to-treat analysis for goserelin versus CMF was 0.81 (95% CI 0.56–1.17, $P = 0.25$).

Most trials used goserelin as the GnRHa (88%) but the use of triptorelin or leuprorelin did not seem to lead to any difference in results [16].

GnRHa and tamoxifen versus chemotherapy for adjuvant breast cancer therapy

Three trials compared the effects of a combination of an LHRH agonist and tamoxifen versus chemotherapy [17–19], recruiting a total of 1611 women for this comparison. Two of these trials used CMF in six cycles of 28 days each [17,19], and the other used an anthracycline-containing regimen [18]. The ABSCG 05 [17] trial used intravenous cyclophosphamide on days 1 and 8, and goserelin (3.6 mg depot) every 28 days for 3 years plus tamoxifen (20 mg daily) for 5 years. In the FASG 06 trial [18], triptorelin (3.75 mg im every month) and tamoxifen (30 mg daily) were used for 3 years. The GROCTA 2 study [19] administered cyclophosphamide from day 1 to day 14 and 3.6 mg injections of goserelin monthly for 2 years.

The largest trial, ABCSG 5, randomised just over 1000 premenopausal women to goserelin (3.6 mg depot every 28 days) for 3 years combined with tamoxifen (20 mg daily) for 5 years versus CMF every 28 days for six cycles [17]. Most of the women were ER+. After a median follow up of 60 months, patients randomised to goserelin and tamoxifen had significantly better recurrence-free survival (81%) than those allocated to chemotherapy (76%) ($P = 0.037$). There was no statistically significant difference in overall survival between the hormonal therapy group (92%) and the chemotherapy group (90%) ($P = 0.195$). Hot flushes were the main side effect for patients in the goserelin and tamoxifen group, with 91% of patients experiencing at least one episode. Eventual decline in bone density consequent to the use of GnRH agonists may be prevented with bisphosphonates. Zoledronic acid was employed in breast cancer patients without significant collateral effects [20,21]. Moreover, bisphosphonates are supposed to have antitumor and antimetastatic properties [22]. The side effects of chemotherapy were typical of CMF: nausea (81%), alopecia (55%), and hot flushes (54%).

An anthracycline-containing regimen, rather than CMF, was used as the chemotherapy in the FASG 06 trial [18], in which 333 premenopausal women (one to three positive lymph nodes) with hormone-responsive breast cancer were randomised to triptorelin (3.75 mg im every month) and tamoxifen (30 mg daily) for 3 years versus FEC50 (cyclophosphamide, epirubicin, 5-fluorouracil). After a median follow-up of 83 months, recurrence-free survival was 76% in the hormonal therapy group and 72% in the chemotherapy group. This difference was non-significant ($P = 0.13$). There was also no significant difference in overall survival ($P = 0.20$), which was 91% and 88%, respectively. The GROCTA 2 [19] analysed 120 patients in the CMF group and 124 in the tamoxifen and goserelin group. At the time of analysis (median follow-up time, 76 months) no difference between groups had emerged with respect to either disease-free or overall survival.

There are fewer severe adverse effects amongst women treated with GnRHa in comparison to chemotherapy. The GnRHa for which there is most evidence is goserelin, given as a 3.6 mg depot subcutaneously every 28 days for 2 years [16,23].

Consequences of the hypothesis

The preservation of fertility in young women $\leqslant$40 years with endocrine-responsive (hormonal-receptor positive) tumours, especially those at low risk of recurrent disease, may not require chemotherapy provided they receive adequate endocrine therapy. However, it is important to reported that for hormone receptor-negative women chemotherapy is likely to lead to a reduction in the risk of recurrence and a delay in death compared to a GnRHa.

On the other hand, it is time to indicate adjuvant therapy with GnRHa associated with tamoxifen for patients with breast cancer (hormone receptor-positive tumours) if they want to preserve their reproductive function. For testing the hypothesis should be necessary to evaluate the ovarian reserve tests; follicle stimulating hormone (FSH), anti-Mullerian hormone (AMH), inhibin B, antral follicle count (AFC) and ovarian volume 6 months, and 1 year after the end of therapy with GnRHa/tamoxifen therapy. The recurrence-free survival and overall survival should be analysed.

The major implication will be to avoid adjuvant chemotherapy for patients with breast cancer (hormone receptor-positive tumours) that request fertility preservation. It is expected that ovarian function should not be altered in almost all cases and breast cancer prognostic will be at least similar to the use of adjuvant chemotherapy. Also, subsequent pregnancy will be a real possibility.

Conflicts of interest

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Sponsors: none.

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