Can We Keep the 'PROMISE'?

AGO Breast Commission: Commentary on Recent Evidence Regarding LHRH Analogues for the Preservation of Ovarian Function

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Keywords

LHRH · Ovarian function preservation · Fertility preservation · Chemotherapy · Breast cancer

Summary

Recently reported data from the German ZORO trial and the Italian PROMISE-GIM6 trial have come to different conclusions. The AGO Breast Commission does not recommend the general use of luteinizing hormone-releasing hormone (LHRH) analogues for the preservation of ovarian function. Instead, we distinguish between patients with hormone receptor-negative and hormone receptor-positive disease. This article reviews the AGO recommendations in light of the ZORO and PROMISE-GIM6 data. In conclusion, separate recommendations are needed for the prevention of ovarian failure and for fertility preservation because the trials did not investigate fertility rate as a primary outcome measure. The results from not yet published trials such as OPTION and POEM may shed new light on the role of LHRH analogues.

Schlüsselwörter

GnRH · Erhalt der Ovarfunktion · Erhalt der Fertilität · Chemotherapie · Mammakarzinom

Zusammenfassung

Kürzlich publizierte Daten der deutschen ZORO-Studie und der italienischen PROMISE-GIM6-Studie kommen zu unterschiedlichen Ergebnissen. In den aktuellen Leitlinien der AGO Kommission Mamma wird die generelle Gabe eines GnRH (gonadotropin-releasing hormone)-Analogons zum Erhalt der Ovarfunktion nicht empfohlen. Es wird aber unterschieden, ob die Patientin ein hormonrezeptorpositives oder -negatives Mammakarzinom hat. Der vorliegende Artikel beleuchtet die Empfehlungen noch einmal im Licht der aktuellen Daten. Zusammenfassend kann man sagen, dass der Erhalt der Ovarfunktion nicht mit dem Erhalt der Fertilität gleichgesetzt werden darf und es daher auch unterschiedliche Vorgehensweisen geben sollte. Daten aus anderen Studien wie OPTION und POEM werden sicherlich noch einmal die Rolle der GnRH-Analoga anders beurteilen.

Introduction

Breast cancer in young women is rare, with about 12% of early stage breast cancer patients being younger than 45 years [1]. Premature ovarian failure caused by chemotherapy may result in infertility and menopausal symptoms such as hot flashes, mood disorders, and cardiovascular symptoms. Many of these women have not yet completed family planning and wish to become pregnant after cancer treatment. However, fertility is only one aspect of ovarian function preservation. Whether resumption of menstruation can be used as a surrogate for fertility is questionable. Therefore, we need to distin-

guish between preservation of ovarian function to prevent premature menopause and menopausal symptoms on the one hand and fertility preservation on the other hand, because treatment options are different.

Ovarian function depression is common in women of child-bearing age receiving systemic anti-cancer therapy. The main factors influencing ovarian function are age and type of chemotherapy. The older the woman, the more likely it is that ovarian function will be irreversibly damaged by chemotherapy, and the higher the dose of cyclophosphamide and the number of chemotherapy cycles, the more likely it is for the patient to suffer from loss of ovarian function or premature

ovarian failure. Unfortunately, there is no unique definition of premature ovarian failure, and studies investigating these problem use different definitions. The recently published ZORO (Zoladex Rescue of Ovarian function) trial and PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients – Gruppo Italiano Mammella 6) trial have investigated the preventive effect of luteinizing hormone-releasing hormone analogues (LHRHa) on chemotherapy-induced menopause in breast cancer patients within prospective randomized studies. Both studies and a recent meta-analysis have added evidence. In the light of these new data, we need to reconsider our recommendations on ‘Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)’ as part of the 2011 AGO recommendations for endocrine therapy in premenopausal women.

Current Recommendation ‘Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)’

Currently, it is recommended to inform the patient of fertility preservation methods, since we need to provide information based on the current level of evidence even though the evidence supporting routine fertility counseling in young breast cancer patients is scarce. The AGO Breast Commission does not recommend the concurrent use of LHRHa with chemotherapy to preserve fertility in both hormone receptor-negative and hormone receptor-positive patients. These recommendations were based on the data available in January 2011.

LHRH Analogues

LHRHa have been suggested to provide ovarian protection under chemotherapy, although the exact mechanisms are still unclear. It has been hypothesized that reduction in gonadotropin levels places the ovaries in a quiescent or prepubescent state, although the potential protective value of this effect remains controversial [2].

Newly Available Trials

The randomized phase II ZORO trial investigated the effectiveness of goserelin in addition to modern-type anthracycline/taxane-containing chemotherapy to prevent chemotherapy-induced ovarian failure [3]. The primary objective was the incidence of regular menstruation defined as 2 consecutive menstruations between month 5 and 8 after the end of chemotherapy as reported by the patient in a menstruation log. 70.0% (95% confidence interval (CI) 53.6–86.4%) in the goserelin group compared to 56.7% (95% CI 39–74.4%) in

the control group remained without menstruation 6 months after the end of chemotherapy. The difference was 13.3% (95% CI –10.85 to 37.45; one-sided $p = 0.142$; two-sided $p = 0.284$). Thus, a 37% absolute increase in menstruation rate at 6 months with goserelin compared to the control group could not be ruled out. After adjusting for age, this difference became even smaller; 70.4% in the group with goserelin vs. 65.9% in the control group ($p = 0.708$) menstruated 6 months after the end of chemotherapy. Multivariate analysis revealed age to be the only independent predictor for menstruation at month 6 (odds ratio (OR) 1.15, 95%CI 1.01–1.29; $p = 0.028$); treatment group was not an independent predictor (OR 1.24, 95%CI 0.39–3.9; $p = 0.717$).

The PROMISE trial randomized 281 patients with primary hormone receptor-positive and -negative breast cancer to triptorelin from at least 1 week prior to chemotherapy vs. chemotherapy alone. The primary objective was incidence of early menopause at month 12 after the end of chemotherapy; the rate of early menopause was 8.9% in the LHRHa group compared to 25.9% in the control group, demonstrating an absolute difference of –17% (95%CI –27 to –8%; $p < 0.001$). Per-protocol analysis of the 260 evaluable patients gave similar results. The rate of early menopause was defined as no menstruation at month 12, plus estradiol and follicle-stimulating hormone (FSH) in the postmenopausal range. However, laboratory values were not available in about 30%. Administration of tamoxifen to hormone receptor-positive patients led, as expected, to a lower incidence of resumption of menses at month 12 compared to the hormone receptor-negative group not receiving tamoxifen. This is in line with previous data [4, 5]. Women with hormone receptor-positive breast cancer, who restarted menstruation, received an LHRHa parallel to tamoxifen.

In contrast to the ZORO trial, PROMISE did not differentiate between hormone receptor-positive and -negative patients in the main analyses. A post-hoc analysis according to hormone receptor status was done, resulting in 51 patients in the PROMISE trial being comparable to the 60 ZORO patients. In PROMISE, 27/29 (93%) patients in the LHRHa group menstruated 12 months after the end of chemotherapy compared to 24/30 (83%) in the ZORO trial. In the chemotherapy alone groups, 16/22 (74%) patients in the PROMISE trial and 24/30 (80%) in the ZORO trial menstruated 1 year after the end of chemotherapy. This result represents an absolute difference of 19% in the PROMISE trial and only 3% in the ZORO trial. Being not the primary objective in both PROMISE and ZORO, this demonstrates that the overall resumption of menstruation with modern-type chemotherapy is high. In fact, all but 1 patient menstruated 2 years after the end of chemotherapy in the ZORO trial. The PROMISE trial did not report any long-term data on ovarian function [6]. Both trials reported an almost identical time of restoration of menstruation of just over 6 months, with a non-significant difference favoring the use of LHRHa (table 1).

Table 1. Main differences between the ZORO and the PROMISE-GIM6 trials

	ZORO	PROMISE
Patients, n	60	281
Median age, years	38	39
Treatment	goserelin	triptorelin
Start of treatment	>2 weeks prior to chemotherapy	>1 week prior to chemotherapy
Hormone receptor status, n		
Positive	–	231
Negative	60	50
Primary endpoint	menstruation rate 6 months after chemotherapy	rate of early menopause 12 months after chemotherapy
Primary objective	30% absolute increase in menstruation rate	at least 20% absolute reduction in early menopause
Multivariable analysis	age as only independent predictive factor	treatment as only independent predictive factor
Resumption of menses at month 12 in HR– cohort, %		
With LHRHa	83	93
Without LHRHa	80	74
Median time to restoration of menstruation, months		
With LHRHa	6.1	not reached
Without LHRHa	6.8	6.7
p value	0.30	0.07
Cyclophosphamide dose, mg	4,600 vs. 4,700	4,080 vs. 4,008

HR– = Hormone receptor-negative; LHRHa = luteinizing hormone-releasing hormone analogue.

Both trials demonstrate the complexity of this question. In fact, it is very difficult to fully assess the impact of chemotherapy on ovarian function. Many factors influence the results, e.g. trial endpoints (amenorrhea vs. menstruation vs. laboratory values), time points for effect assessment, age of the population, type of chemotherapy applied, and methodologies. If the ZORO trial had chosen a different endpoint, results might have been different. It was decided to assess menstruation instead of amenorrhea because ‘no menstruation’ is not necessarily equivalent to ‘no ovarian function’. No difference in ovarian function would have been detected 1 year after the end of chemotherapy. 12 months after the end of chemotherapy, 25/30 (83%) women in the goserelin group had started regular menstruation compared to 24/30 (80%) in the control group ($p = 0.74$) without adjusting for age. Therefore, an assessment 6 months after the end of chemotherapy does not seem premature.

The rate of patients with recovery of menstruation seems high. Data by Ismail-Khan et al. [7] also showed a high menstruation recovery rate of > 85% in both groups at month 18, compared to 88% at month 18 in the ZORO trial. None of the ZORO patients received tamoxifen or a combination regimen of doxorubicin and docetaxel (AT) which are both associated with a significantly higher amenorrhea rate [8]. Ovarian function preservation is not only focused on fertility but also on preventing premature menopause with all its consequences. This is probably the reason why women over 40 were included in the studies if they wished to protect their ovarian function for whatever reason. The follow-up data of ZORO suggest that independent of the treatment group, ovarian reserve decreased rapidly. For women who desire a child after chemotherapy, other options should be considered such as oocyte or embryo freezing. The PROMISE trial did not provide data beyond 12 months.

The patient number in ZORO is probably somewhat low to detect a small difference between both study arms. Yet, in designing the trial, a difference of 30% in favor of the goserelin group had been considered clinically meaningful. The study by del Mastro et al. [6] with a higher patient number had the ability to detect a smaller difference. However, endpoint and time of evaluation were different, thus making an inter-trial comparison difficult.

If we really want to assess the effects of LHRHa on ovarian function, we need to concentrate on the hormone receptor-negative, over 40-year-old patients. Data from the hormone receptor-positive cohorts are influenced by resumption of LHRHa in those patients who restarted menstruation after the end of chemotherapy and by the use of tamoxifen which itself can lead to a higher amenorrhea rate not necessarily equivalent to early menopause [9].

The capacity of a chemotherapy regimen to induce premature ovarian failure is one of the key factors. The potential of current commonly used standard regimens to induce premature ovarian failure may not be high enough to show a meaningful difference between patients with and without LHRHa. The NSABP B-30 protocol [7] focused on the relationship between treatment amenorrhea and survival outcomes. In this trial, amenorrhea rates differed significantly by treatment arm. The group that received AT without tamoxifen had the lowest amenorrhea rate. Patients treated by longer chemotherapy duration (AT→T) had greater symptom severity and poorer quality of life only at 6 months; at month 12 there was no difference between the treatment groups regarding symptom severity and quality of life.

Other LHRHa trials which demonstrated a difference, such as that published by Badawy et al. [10], suffer from considerable methodological problems (e.g. different baseline hormone levels, unreported use of tamoxifen, comparably

high incidence of amenorrhea, short follow-up). A recent meta-analysis demonstrated an effect favoring LHRHa for the protection of premature ovarian failure. The results are mainly driven by the Badawy trial [10]. If the trial had been excluded from this meta-analysis, a benefit favoring the use of LHRH would no longer have been demonstrated (personal communication G. Griesinger). In another meta-analysis, an LHRHa effect was only seen if the non-randomized trials were included [11].

In our opinion, we should not draw final conclusions and promise patients that their ovarian function and fertility can be protected using an LHRHa until we have more reassuring data from the OPTION trial and the POEM trial. The OPTION trial from the UK reported in an abstract no difference with regard to premature menopause which measured 42.3% with and 36% without goserelin as ovarian protection [12]. The POEM trial is investigating the premature ovarian failure rate with or without LHRHa at 2 years in more than 350 patients [13]. With the available evidence, we can neither exclude a small benefit for patients receiving an LHRHa for reducing the risk of premature ovarian failure within 1–2 years nor can we guarantee the effect.

Very young women with modern type anthracycline/taxane-based standard treatments will have a very low chance of suffering from intermittent ovarian function loss. Current trials will investigate these issues in the light of chemotherapy in combination with modern biological treatments by measuring estradiol, FSH, anti-Müllerian hormone, and follicle count up to 2 years after finalizing chemotherapy [14].

Other data demonstrate that the majority of premenopausal patients undergoing chemotherapy will have premature menopause [15]. We cannot exclude this, as none of the current trials will have the ability to demonstrate long-term effects of the use of LHRHa. We also cannot recommend the use of LHRHa for fertility preservation as none of the trials had the primary aim to investigate this issue. Reported pregnancy rates were low in the ZORO and the PROMISE trial. As pointed out, other measures such as embryo freezing should be offered for fertility preservation [16].

In conclusion, we suggest adapting the recommendations as follows: We need separate recommendations for the prevention of ovarian failure and fertility preservation because the recent trials did not investigate fertility rate as primary outcome measure. Our patients need to be informed that the LHRHa effect on preventing early menopause is – at best – small. Whether LHRH analogues are really able to prevent early onset of menopause in breast cancer patients after chemotherapy, and whether they indeed preserve fertility, remains to be discussed, even after PROMISE. For further information visit the AGO recommendations on www.ago-online.org.

Disclosure Statement

The authors declare no conflict of interest.

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