GnRH Analogs for Fertility Preservation – Let’s Not Jump to Conclusions


Purpose: Chemotherapy-induced amenorrhea is a serious concern for women undergoing cancer therapy. This prospective randomized trial evaluated the use of gonadotropin-releasing hormone (GnRH) analog triptorelin to preserve ovarian function in women treated with chemotherapy for early-stage breast cancer.

Patients and Methods: Premenopausal women age 44 years or younger were randomly assigned to receive either triptorelin or no triptorelin during (neo)adjuvant chemotherapy and were further stratified by age (<35, 35 to 39, >39 years), estrogen receptor status, and chemotherapy regimen. Objectives included the resumption of menses and serial monitoring of follicle-stimulating hormone (FSH) and inhibin A and B levels.

Results: Targeted for 124 patients with a planned 5-year follow-up, the trial was stopped for futility after 49 patients were enrolled (median age, 39 years; range, 21 to 43 years); 47 patients were treated according to assigned groups with four cycles of adriamycin plus cyclophosphamide alone or followed by four cycles of paclitaxel or six cycles of fluorouracil, epirubicin, and cyclophosphamide. Menstruation resumed in 19 (90%) of 21 patients in the control group and in 23 (88%) of 26 in the triptorelin group (P = .36). Menses returned after a median of 5.8 months (range, 1 to 19 months) after completion of chemotherapy in the triptorelin versus 5.0 months (range, 0 to 28 months) in the control arm (P = .58). Two patients (age 26 and 35 years at random assignment) in the control group had spontaneous pregnancies with term deliveries. FSH and inhibin B levels correlated with menstrual status.

Conclusion: When stratified for age, estrogen receptor status, and treatment regimen, amenorrhea rates on triptorelin were comparable to those seen in the control group.

Commentary Frank Nawroth and Astrid Dangel, Hamburg

The ability of GnRH agonists to influence the gonadotoxic effect of chemotherapy has been controversially discussed for a long period of time. From a basic endocrinological point of view one would assume that using GnRH agonists as fertility protection method makes no sense: GnRH agonists lead to decreased gonadotropins and a reversible postmenopausal state that should result in ‘sleeping’ ovaries that could be protected against chemotherapy. However, we know that the activation of primordial follicles (which should be protected) is not gonadotropin dependent. GnRH agonists could directly act at the ovary but human primordial follicles do not have GnRH receptors [1]. We further know that various chemotherapeutic agents act directly on oocytes and indirectly on somatic cells surrounding them [2]. These considerations make GnRH agonists in that indication questionable.

What is the current knowledge, if we look at studies and meta-analyses dealing with GnRH agonist application during chemotherapy and the influence on gonadotoxicity? Problems of most studies are: they are not prospective, the patients...
studied are heterogenous (e.g., different age, different chemotherapy), or outcome parameters are inappropriate.

Concerning the last point, generally the outcome parameter is the recurrence of menstruation after therapy; however, that a patient has regular bleeding after chemotherapy does not mean that she is as fertile as before. If ovaries are only partly destroyed, the hypophysis can compensate. FSH levels increase and the woman has normal follicular maturation followed by regular cycles. But during the first months or even years of compensation FSH levels are not increased in the early follicular phase but only in the late luteal phase. Over time the ovaries react and FSH levels decrease to the reference range also during early follicular phase. During the first time only Anti-Müllerian hormone (AMH) levels decrease. AMH will be produced by the primary, secondary, and early antral follicles and levels correlate with the histological density of primordial follicles. Only this parameter is sensitive enough to detect whether chemotherapy has had an irreversible influence on the individual ovarian reserve. Therefore an appropriate study must be prospective, randomized, and must measure AMH levels before and during therapy and follow up.

One meta-analysis which included 7 randomized controlled studies stated: ‘Evidence from RCTs suggests a potential benefit of GnRH cotreatment with chemotherapy in premenopausal women, with higher rates of spontaneous resumption of menses and ovulation but not improvement in pregnancy rates’ [3]. The results were heterogenous, ranging from ‘no effect’ to ‘strong protective effect’. The main problem were again the outcome parameters. Only 1 study (stating ‘no effect’) [4] measured AMH but only in 17 of 60 patients. It is not possible to draw final conclusions from data with such a low number of patients included.

Another meta-analysis [5] also came to the conclusion that ‘The use of GnRH agonists should be considered in women of reproductive age receiving chemotherapy, ..., although no significant difference in pregnancy rate was seen.’ But again, the authors used the inappropriate outcome parameters ‘protecting menstruation and ovulation after chemotherapy’. ‘Fertility protection’ is not primarily the same as ‘pregnancy rate’. Fertility protection summarizes different aspects, which besides pregnancy include preserving ovarian function for hormone production, an aspect that is also important for patients. Therefore it is not understandable that some statements focus exclusively on the missing differences in pregnancy rates.

However, the criticism is the same for many later studies showing protective effects of GnRH agonists, as for example Del Mastro et al. [6]. They found a significantly higher rate of amenorrhoea in the chemotherapy only group. One can assume that there should be also an effect on AMH but it was not measured. This limits the importance of the study and also makes final conclusions questionable.

The quality of data published by Munster et al. [7] was higher, because not only FSH but also inhibin A and B were measured in a prospective randomized study. Inhibin B is a stronger parameter for ovarian reserve in comparison to FSH but does not have the diagnostic value of AMH. The authors found no beneficial effect of GnRH agonists regarding re-accumulation of menses and described a correlation of FSH and inhibin B with menstrual state.

In general, there is a trend to higher quality studies but until now every study has its weakness. For example, Marder et al. [8] measured significantly higher AMH levels in women with lupus treated with cyclophosphamide and GnRH agonists but the design was retrospective.

If we summarize the current knowledge, one must admit that it is too early to give a definitive answer regarding the protective effect of GnRH agonists during chemotherapy. At the moment the only possible conclusion from the available data must be ‘yes’ because there is a trend to a protective action of GnRH agonists. However, the quality and amount of data are not appropriate for final conclusions. We need more and better designed studies dealing with changes of AMH levels during and after chemotherapy as primary outcome parameter. It could be that the final answer in the future will be ‘no’ but up to now it is not justified to banish GnRH agonists from fertility protection in female patients.

If future meta-analyses could prove a benefit for GnRH agonists, we would urgently suggest to critically reanalyze the often recommended contraindication for GnRH agonists in hormone receptor-positive breast cancer patients during chemotherapy. The hypothesis that GnRH agonists decrease the efficacy of chemotherapy in such patients was never really proven. One must remember that we do not have many options for fertility preservation in these women. Therefore we should avoid jumping to conclusions before anything is proven.

References

MRI Screening in BRCA Mutation Carriers—The Best Alternative to Prophylactic Surgery?


**Background:** The addition of breast magnetic resonance imaging (MRI) to screening mammography for women with BRCA mutations significantly increases sensitivity, but there is little data on clinical outcomes. We report screening performance, cancer stage, distant recurrence rate, and breast cancer-specific mortality in our screening study. **Methods:** From 1997 to 2009, 496 women aged 25 to 65 years with a known BRCA1/2 mutation, of whom 380 had no previous cancer history, were enrolled in a prospective screening trial that included annual MRI and mammography. **Results:** In 1847 screening rounds, 57 cancers were identified (53 screen-detected, 1 interval, and 3 incidental at prophylactic mastectomy), of which 37 (65%) were invasive. Sensitivity of MRI vs mammography was 86% vs 19% over the entire study period (P<0.0001), but was 74% vs 35% from 1997 to 2002 (P=0.02) and 94% vs 9% from 2003 to 2009 (P<0.0001), respectively. The relative sensitivities of MRI and mammography did not differ by mutation, age, or invasive disease. Of the incident cancers, 97%, were Stage 0 or 1. Of 28 previously unaffected women diagnosed with invasive cancer, 1 BRCA1 mutation carrier died following relapse of a 3 cm, node-positive breast cancer diagnosed on her first screen at age 48 (annual breast cancer mortality rate=0.5%). Three patients died of other causes. None of the 24 survivors has had a distant recurrence at a median follow-up of 8.4 years since diagnosis. **Conclusion:** Magnetic resonance imaging surveillance of women with BRCA1/2 mutations will detect the majority of breast cancers at a very early stage. The absence of distant recurrences of incident cancers to date is encouraging. However, longer follow-up is needed to confirm the safety of breast surveillance.

Commentary by Dorothee Speiser, Berlin

Screening modalities for breast cancer are under constant evaluation. There still is no current consensus on the optimal screening strategy for women with BRCA mutations and women at high risk for breast cancer (declining genetic testing or strong family history but indeterminate mutation status). Their predicted life-time risk for breast cancer can reach up to 84% by the age of 70 [1, 2]. These mutation carriers often develop disease at a young age when dense breast tissue reduces the sensitivity of X-ray mammography (MG) [3]. There are numerous possible prophylactic interventions, such as prophylactic mastectomy, chemoprevention or risk-reducing salpingo-oophorectomy, which are all accompanied by adverse events. That is why these are not viable options for many very young BRCA mutation carriers [4]. Many of them opt for screening programs that require the power to detect breast cancer at the earliest stage possible to give the best chance of cure.

In the last decade enormous advances in early detection of breast cancer in these high-risk patients have been made, above all by introducing magnetic resonance imaging (MRI) screening to the surveillance programs. As early as 2005 a large study from the UK showed that MRI screening was more sensitive for cancer detection in BRCA1 carriers than MG [5]. This finding was replenished by a study of Warner et al. [6] that showed a significant reduction in the incidence of advanced stage breast cancer in women undergoing MRI screening. The differentiation between BRCA1 and BRCA2, which was not found in the study by Passaperuma, was supported by the findings of Shah et al. whose study hints at different outcomes of surveillance and prevention strategies in BRCA1 versus BRCA2 mutation carriers [7]. Lowry et al. [3] used a computer model to assess the benefit of yearly digital mammography starting from the age of 30 alternating with MRI starting from 25 years. This curriculum provided the highest life expectancy in mutation carriers.

Although the number of studies supporting MRI as an adequate screening modality grows, the question remains if MRI could fulfill all or most relevant prerequisites of an adequate screening modality. First of all, an adequate method has to detect cancer at the earliest possible state when cure is still possible. Warner et al. [6] tried to prove indirectly that mortality rates are decreasing by reasoning that breast tumors detected by MRI are at less advanced stages. This study also emphasized the ability of MRI to detect more interval cancers, which also contributes to the decrease of the mortality rate. Second, the method has to be safe and cost-effective. The last point has already been discussed in 2006 when Plevritis et al. [8] used a computer model to calculate the cost per quality adjusted life year. They found that MRI screening was more cost effective in high-risk patients than MG screening.
The commented study by Passaperuma et al. basically asks the question if mortality rates in the screened study collective are on par with the rates of patients who had prophylactic mastectomy. The methods used are largely based on indirect evidence like interval cancer rate, rate of tumors greater than stage I, and recurrence rate. While the study was set up and performed meticulously some minor limitations should be mentioned. First, the study population seems quite heterogeneous: From 1997 to 2003 patients who had breast cancer before could enter the study, while from 2004 to 2009 only unaffected women were eligible. Thus, there is a gap in data acquisition. Also the study protocol was changed during data acquisition from yearly screening with MG, contrast MRI, and ultrasound to MG and MRI only. Further, the classification of cancers in the study differs slightly from other definitions: DCIS was not discriminated as to presence of microinvasion and multicentric disease was not classified as prognostic feature, but only the largest component was reported [9]. As size and spread of breast cancer lesions are important not only for prognosis but also for therapy this could be assessed as a small imprecision even if it is common practice in MRI diagnostics.

The median age on first screen was 44 years. According to recent studies, MRI is a crucial screening tool especially in young high-risk consulters, so the median age in this study seems to be too high to be relevant for that age group. Also, the median age at the onset of cancer does not seem to be typical for BRCA mutation carriers. It was 48 years in this study (range 32–68). A recent study by Litton et al. showed that the age at onset of BRCA associated cancers becomes significantly lower in subsequent generations [10].

Despite these limitations the screening performance in this study was impressive and even showed an improvement over the years – 94% sensitivity for MRI versus only 9% sensitivity for MG between 2003 and 2009. This effect is partly accounted for by the excellent expertise in MRI diagnosis on the part of the doctors performing them, as well as the slightly neglected development in the field of MG. The sensitivity of MG was not correlated with higher patient age but only with greater tumor size. Nevertheless, in most cases MRI and MG offer complementary information and in BRCA mutation carriers this combination of screening modalities offers the greatest benefit so far [11]. Another recent study from Grann et al. [4] also showed that the combination of MRI and MG is the most effective strategy in reducing the risk of late detection of breast cancer.

In Germany, however, we follow a slightly different approach. The intensive screening program under the supervision of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) for young patients at high risk for breast cancer differs from the above study protocol (digital mammography only from 2008, ultrasound screening was discontinued in 2005, so currently only MRI and MG are performed). Since the annual risk of hereditary breast cancer is significant starting from the age of 25 [7] the program starts at this age or at least 5 years before the age at which the first cancer in the family was diagnosed. The program comprises yearly MRI, ultrasound and MG (from the age of 30), and another ultrasound screening after 6 months. MRI seems to be the most sensitive method in this collective of very young patients. Current data support the combination of ultrasound, MG and MRI as the best alternative to prophylactic surgery. Additional studies are needed to determine the optimal screening frequency and the possibility to abstain from yearly mammography in very young consulters.

References


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