Thursday, 22 March 2012 08:00–08:45

EUROPA DONNA TEACHING LECTURE

Managing/Monitoring Adverse Effects of Treatments

196 Invited

Managing adverse effects of treatment − Fertility

S. Loibl[1], B. Gerber[2]. [1]*German Breast Group, Neu-Isenburg, Germany;* [2]*Klinikum Südstadt, Universitätsfrauenklinik, Rostock, Germany*

Around 12% of all breast cancers are diagnosed in women with fertility potential. Adjuvant chemotherapy in premenopausal women with breast cancer may induce premature ovarian failure which results in permanent or intermittent amenorrhea and affects fertility.

Chemotherapy induced amenorrhea (CIA) is strongly related to patients' age, type and amount of cytotoxic agents and treatment duration. Cyclophosphamide is the agent with the highest incidence of amenorrhea. In the NSABP-B30 study the amenorrhea rate at 12 months after start of chemotherapy was significantly different a between the treatment arms 69.8% for AC-T, 57.7% for TAC, and 37.9% for AT (P 0.001). Women treated with tamoxifen had a higher risk of amenorrhea. However, the study also showed that women who experience CIA have a better disease free survival.

There are several options under discussion for fertility preservation for young women who wish to have a biologic child after breast cancer and are at increased risk for infertility. Options include cryopreservation of embryos, oocytes, ovarian tissue prior to treatment, and ovarian suppression with LHRH analogues starting prior to chemotherapy. The ability of LHRH analogues for prevention of CIA is still under discussion. The recently published prospectively randomised ZORO and PROMISE GIM-6 trials demonstrated at best a small effect of reducing CIA. But it has not been proven that reducing the rate of CIA will result in a higher fertility rate. Most of the other measures are considered experimental with the exception of cryopreservation of embryos/fertilized oocytes. There have been concerns that pregnancy after breast cancer may worsen prognosis in light of the endocrine manipulations used to treat breast cancer, particularly for women with hormone sensitive disease. However, a recent metaanalysis revealed a better survival for women who became pregnant after breast cancer.

Ovarian stimulation as prerequisite for embryo or oocyte preservation leads to an increased estradiol level. Letrozole in combination with FSH resulted in significant lower peak estradiol levels than anastrazole combined with FSH and standard stimulation protocols, but in a similar fertilization rate.

Conclusion: Today freezing of fertilized oocytes/embryos is considered to be the standard for fertility preservation for women at risk for CIA. However, patients need to be informed about the risk and benefits of the ovarian function preserving modalities.

197 Invited

Bone Fragility in Subjects Treated With Aromatase Inhibitors

M.L. Brandi[1]. [1]*University of Florence, Unit of Metabolic Bone Diseases, Florence, Italy*

Background: aromatase inhibitors (AIs) are now the standard treatment for hormone receptor-positive breast cancer. However, deleterious effects of AIs on bone health have been reported. An ESCEO working group proposes guidance for the management of post-menopausal women with breast cancer receiving AIs to prevent bone loss and fragility fractures.

Methods: a panel of experts addressed the issue of skeletal effects of AIs and effectiveness of antifracture therapies for the prevention of AI-induced bone loss and fractures. Recommendations by national and international organizations, and experts' opinions on this topic were evaluated.

Results: all aromatase inhibitors are associated with negative effects on the skeleton, resulting in bone loss and increased risk of fragility fractures. Current guidelines suggest approaches that differ both in terms of drugs proposed for fracture prevention, and duration of treatment.

Conclusion: The ESCEO working group recommends that all AIs-treated women should be evaluated for fracture risk. Besides general recommendations, zoledronic acid 4 mg i.v. every 6 months, denosumab s.c., or at least oral bisphosphonates should be administered for the entire period of AI treatment to all osteoporotic women (T-score hip/spine <−2.5 or ⩾1 prevalent fragility fracture), to women aged ⩾75 irrespective of BMD, and to patients with T-score <−1.5 + ⩾1 clinical risk factor or T-score <−1.0 + ⩾2 clinical risk factors. Alternatively, therapy could be considered in patients with a FRAX-determined 10-year hip fracture probability ⩾3%.

Thursday, 22 March 2012 10:30–11:15

PROFFERED PAPER

Implications of Adjuvant Therapy and Toxicity

198 Proffered paper oral

Specific Adverse Events Predict Survival Benefit in Early Breast Cancer Patients Treated with Exemestane in the Dutch/Belgian TEAM Trial

D. Fontein[1], D. Houtsma[2], E.T.M. Hille[1], W.M. Meershoek-Klein Kranenbarg[1], H. Putter[3], C. Seynaeve[4], L.Y. Dirix[5], R. Paridaens[6], C.J.H. van de Velde[1], J.W.R. Nortier[2]. [1]*Leiden University Medical Center, Surgery, Leiden, The Netherlands;* [2]*Leiden University Medical Center, Medical Oncology, Leiden, The Netherlands;* [3]*Leiden University Medical Center, Medical Statistics, Leiden, The Netherlands;* [4]*Erasmus MC Daniel Den Hoed, Medical Oncology, Rotterdam, The Netherlands;* [5]*Oncology Center St. Augustinus Hospital, Medical Oncology, Wilrijk, Belgium;* [6]*UZ Gasthuisberg, Medical Oncology, Leuven, Belgium*

Background: Many adverse events (AEs) begotten by aromatase inhibitors (AIs) involve symptoms related to the body's depletion of circulating estrogens, such as hot flashes (HFs) and musculoskeletal AE (MSAEs). These AEs may be a predictor of treatment efficacy. This study assesses the occurrence of MSAEs and HFs in relation to outcome in patients treated with exemestane (EXE) in the context of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study.

Material and Methods: Patients were selected from the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial and were treated with 5 years EXE (25 mg once-daily). Primary endpoint of the TEAM study was relapse-free survival (RFS), defined as the time from randomization to disease recurrence or death from breast cancer. AEs reported in the first 6 months of treatment were documented. MSAEs included arthralgia, arthritis, arthrosis, joint disorders and muscle pain, and HFs were any subjective, transient sensation of heat or sweats; all other reported AEs were classified as nonspecific AEs. A landmark analysis was performed and Cox proportional hazards models (95% CI) assessed survival differences. Analyses were adjusted for age at diagnosis, tumor size, nodal stage, histological grade, surgery, adjuvant radiotherapy and chemotherapy.

Results: Of the 1485 EXE patients included in this analysis, 175 patients (11.8%) reported HFs, 113 (7.6%) MSAEs, and 64 (4.3%) reported both HFs and MSAEs. At 5 years follow-up, multivariable analysis showed that patients with HFs had a better RFS than patients without HFs. The occurrence of MSAEs did not predict better RFS (table 1). Patients who reported MSAEs and/or HFs more frequently had been treated with adjuvant chemotherapy (20.4% vs 7.6%, $p < 0.001$ and 20.2% vs 14%, $p = 0.002$ respectively).

Conclusions: HFs predicted a better outcome to exemestane in terms of RFS than when no HFs were present. Patients with MSAEs did not show a superior treatment response than patients without MSAEs.

Table 1. Adverse events and relapse-free survival

	5 years survival (%)	Univariate HR (95% CI)	p value	Multivariable* HR (95% CI)	p value
Hot Flashes			**0.211**		**0.026**
No hot flashes	86.1	1 (ref)		1 (ref)	
Hot flashes	90.1	0.746 (0.472–1.180)		0.458 (0.23–0.911)	
Musculoskeletal AE			**0.258**		**0.14**
No MSAE	86.2	1 (ref)		1 (ref)	
MSAE	90.3	0.736 (0.433–1.252)		0.658 (0.377–1.147)	

*HR adjusted for age, histological grade, T stage, nodal stage, ER&PR, most extensive surgery, prior radiotherapy, and prior chemotherapy.