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P-463 Anti-Müllerian hormone levels in breast cancer patients receiving chemotherapy with or without concurrent luteinizing hormone-releasing hormone agonist: results from the PROMISE phase III trial

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Study question: How (neo)adjuvant chemotherapy and concurrent administration of luteinizing hormone-releasing hormone agonist (LHRHa) affect Anti-Mullerian hormone (AMH) and estradiol level dynamics in premenopausal breast cancer patients.

Summary answer: Breast cancer chemotherapy has a major negative impact on patients' ovarian function and reserve. Women receiving LHRHa showed higher probability of long-term ovarian function recovery.

What is known already: The risk of developing treatment-induced premature ovarian insufficiency (POI) and infertility following chemotherapy is among the most important concerns in premenopausal breast cancer patients. AMH is a promising biomarker for assessing treatment-induced gonadotoxicity in patients receiving anticancer therapies. Concurrent administration of LHRHa with chemotherapy is associated with a lower risk of treatment-induced ovarian failure and higher rates of menstrual function recovery. However, data on the impact of LHRHa during chemotherapy on patients' ovarian reserve are still insufficient.

Study design, size, duration: Between 2003 and 2008, the PROMISE-GIM6 trial randomized 281 premenopausal early breast cancer women to receive chemotherapy alone (control group) or chemotherapy plus triptorelin (LHRHa group). Primary endpoints were incidence of early menopause and long-term ovarian function. For exploratory purposes in a subset of patients, AMH and estradiol levels were measured at baseline, <3 months after last cycle of chemotherapy, 1 year after last cycle of chemotherapy, and at the end of adjuvant endocrine treatment.

Participants/materials, setting, methods: The main results of the trial showed that use of concurrent LHRHa significantly reduced the risk of early menopause, increased the chances of long-term ovarian function recovery and did not influence survival outcomes (JAMA 2011, JAMA 2015, JNCI 2022). The present exploratory analysis reports on dynamics of ovarian biomarkers (AMH and estradiol) at baseline and following (neo)adjuvant chemotherapy.

Main results and the role of chance: Out of 281 enrolled patients, 48 enrolled at the coordinating centers had at least one measurement of AMH and estradiol levels at baseline and after (neo)adjuvant chemotherapy. Baseline patient characteristics were similar between treatment arms, with median age being 41 and 39 years, and median AMH levels being 3.9 and 4.9 mcg/L in the control and LHRHa groups, respectively.

In the overall population, estradiol levels showed a significant decrease at the end of chemotherapy, a significant increase after one year, and a return to baseline values at the end of endocrine therapy. By contrast, AMH levels showed a constant decrease over time.

As compared to patients in the control group, those in the LHRHa group had a significant reduction in the risk of early menopause (p = 0.02) and significantly higher estradiol levels at the end of chemotherapy and 1 year after chemotherapy (p < 0.001), suggesting a higher probability of ovarian function recovery. By contrast, no significant differences were observed in the AMH level dynamics between patients receiving LHRHa and those who did not.

Limitations, reasons for caution: Relatively small number of included patients (n = 48) and small number of patients with AMH and estradiol levels determined at each timepoint.

Wider implications of the findings: This biomarker analysis within a phase III randomized trial confirmed that patients receiving LHRHa had a higher probability of ovarian function recovery also supported by estradiol dynamics. However, both patients in the LHRHa and control group showed a major decline in AMH levels after chemotherapy that persisted over time.

Trial registration number: NCT00311636