

5. Filippi AR, Botticella A, Bello M et al. Interim positron emission tomography and clinical outcome in patients with early stage Hodgkin lymphoma treated with combined modality therapy. *Leuk Lymphoma* 2013; 54(6): 1183–1187.

6. Rigacci L, Puccini B, Zinzani PL et al. The prognostic value of positron emission tomography performed after two courses (INTERIM-PET) of standard therapy on treatment outcome in early stage Hodgkin lymphoma: A multicentric study by the fondazione italiana linfomi (FIL). *Am J Hematol* 2015; 90(6): 499–503.

7. Simontacchi G, Filippi AR, Ciammella P et al. Interim PET after two ABVD cycles in early-stage Hodgkin lymphoma: outcomes following the continuation of chemotherapy plus radiotherapy. *Int J Radiat Oncol Biol Phys* 2015; 92(5): 1077–1083.

8. Zinzani PL, Rigacci L, Stefoni V et al. Early interim 18F-FDG PET in Hodgkin's lymphoma: evaluation on 304 patients. *Eur J Nucl Med Mol Imaging* 2012; 39(1): 4–12.

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### Goserelin does not preserve ovarian function against chemotherapy-induced damage

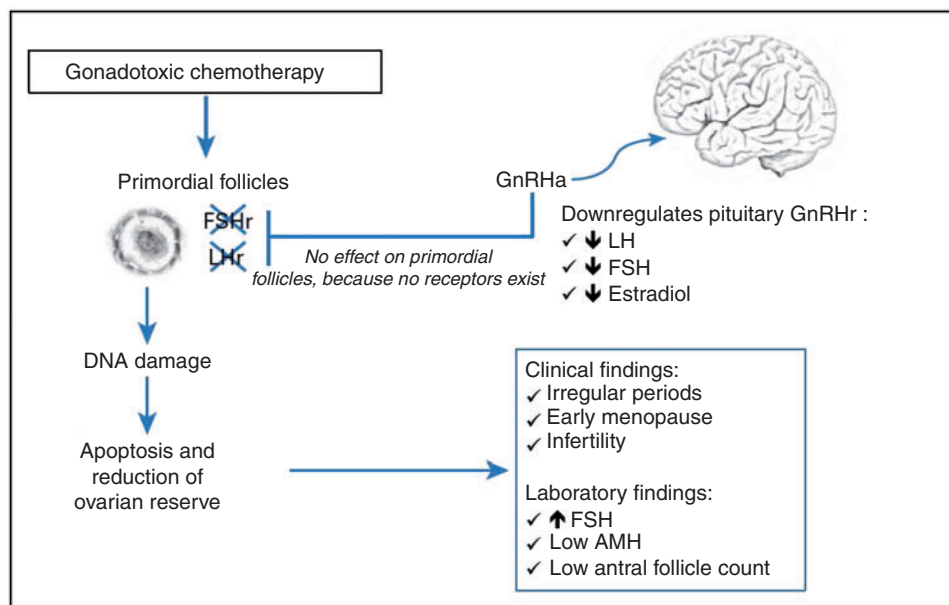
In this randomized trial of Goserelin for ovarian protection during adjuvant chemotherapy in women with breast cancer, Leonard et al. concluded that ovarian suppression may reduce likelihood of amenorrhea and Premature Ovarian Insufficiency (POI) in those aged <40 years [1]. However, we are concerned about the validity of these conclusions.

First of all, in this trial, both ER-negative and -positive women were included, and it appears that the data were not controlled for Tamoxifen use. Because Tamoxifen is an ovarian stimulant, it can cause menstrual abnormalities including amenorrhea and alter serum FSH and E2 levels [2].

Leonard et al. [1] cited STRAW guidelines as a reference to their POI criteria [3]. However, those guidelines only apply to healthy women and exclude cancer patients. Moreover, FSH

value of >25 IU is considered as a criterion for perimenopause, not for POI. The same guidelines also accept low AMH as a diagnostic criterion for perimenopause and indicate the variability of FSH levels in even later stages of menopausal transition. The correct criteria for POI/premature ovarian failure are, age <40 years with 3–4 months of amenorrhea and two serum FSH levels (at least a month apart) in the menopausal range (>30–40 IU/l, depending on the laboratory). The authors' figure 2 shows FSH levels >10 IU/l but <30–40 IU/l in both groups, indicating that the majority of the patients in this study, as expected, have diminished ovarian reserve, but not POI. This explains why there was no difference in serum AMH levels between two groups.

Another point of concern is that the best- and worst-case scenarios were not calculated for those under age 40 years. In addition, for both 12- and 24-month time points, FSH levels were evaluated without any reference to menstrual cycle day and E2 levels. In women with diminished ovarian reserve, E2 levels can be elevated in response to rising FSH levels, which in turn by a



**Figure 1.** Impact of gonadotoxic chemotherapy and gonadotropin-releasing hormone analog (GnRHa) on ovarian reserve and function. Gonadotoxic chemotherapy reduces ovarian reserve, which is made up of resting and hormone-insensitive primordial follicles, by induction of DNA damage and apoptotic death. While serum FSH can fluctuate and be an unreliable marker of ovarian reserve, serum AMH level is currently the most specific and sensitive biochemical surrogate of primordial follicle reserve. Ovarian antral follicle counts by transvaginal ultrasound examination have similar sensitivity to serum AMH. GnRHa reduces pituitary gonadotropin-releasing hormone (GnRH) production and, as a result, blocks the release of follicle-stimulating and luteinizing hormone (LH) from the pituitary, which in turn results in the cessation of late-stage follicle development. Because primordial follicles do not have FSH, LH or GnRH receptors, GnRHa cannot have a direct influence on ovarian reserve. AMH, anti-Müllerian hormone; FSHr, FSH receptor; LHr, LH receptor; GnRHr, GnRH receptor. (Modified from Oktay et al., *J Clin Oncol* 2016; 34: 2563–2565, used with permission.)

feed-back mechanism suppresses gonadotropin release and results in spuriously low FSH levels. In fact, at the 24-month evaluation, E2 levels appear to be higher in the Goserelin-treated group. Without controlling for cycle day (if menstruating) and serum E2 levels, authors' comparison of serum FSH levels will not be valid.

Leonard et al. [1] surmised that serum AMH levels are independent of the diagnosis of POI, which is not an accurate assessment. POI is the result of diminished primordial follicle reserve and AMH is currently the most sensitive biochemical marker of it. Hence given that ovarian suppression did not protect serum AMH levels, as also reported in previous randomized studies [4], it cannot be concluded that it reduces the incidence of POI. The more plausible explanation is that serum AMH measurements are less likely to be affected by the confounders cited above.

Given that there is no biological rationale [5] (Figure 1) and that neither ovarian reserve nor fertility is preserved by ovarian suppression, our interpretation is that ovarian suppression should not be recommended to any group of women for preservation of ovarian function, including fertility.

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## Disclosure

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## References

- Leonard RCF, Adamson DJA, Bertelli G et al. GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial. *Ann Oncol* 2017; 28(8): 1811–1816.
- Welt CK, Pagan YL, Smith PC et al. Control of follicle-stimulating hormone by estradiol and the inhibins: critical role of estradiol at the hypothalamus during the luteal-follicular transition. *J Clin Endocrinol Metab* 2003; 88(4): 1766–1771.
- Harlow SD, Gass M, Hall JE et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012; 97(4): 1159–1168.
- Demeestere I, Brice P, Peccatori FA et al. No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. *J Clin Oncol* 2016; 34: 2568–2574.
- Oktay K, Bedoschi G. Appraising the biological evidence for and against the utility of GnRHa for preservation of fertility in patients with cancer. *J Clin Oncol* 2016; 34(22): 2563–2565.

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## Nivolumab-associated bone marrow necrosis

Bone marrow necrosis (BMN) is an uncommon pathologic entity of unknown etiology. It is highly associated with metastatic tumor or hematolymphoid malignancies, typically in the setting of chemotherapy [1]. Common symptoms include bone pain and fever. The majority of patients have pancytopenia, as well as elevated lactate dehydrogenase (LDH) and alkaline phosphatase levels [2]. We describe a patient with diffuse large B cell lymphoma who was treated with nivolumab and developed BMN while on treatment. This is the first case in the literature reporting this potential adverse event.

A 52-year-old man with a history of high-grade non-Hodgkin's lymphoma diagnosed in January 2014 was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone for six cycles and achieved a complete response. He had evidence of disease relapse in the mediastinum in April 2015 on surveillance imaging. He was treated with rituximab, ifosfamide, carboplatin, and etoposide for three cycles. His bone marrow evaluation in June 2015 showed a normocellular marrow with no lymphoma, and he was able to undergo an uneventful stem cell harvest and autologous stem cell transplant. His disease

relapsed again in March 2016 with evidence of mediastinal and retroperitoneal lymphadenopathy; he received salvage chemotherapy with rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin for two cycles and had an inadequate response on positron emission tomography scan in June 2016. He received rituximab, gemcitabine, oxaliplatin for two cycles and again had an inadequate response with a hypermetabolic mass in the abdomen and progressive lymphadenopathy. At that point, his bone marrow evaluation again was normocellular marrow with no evidence of lymphoma or other malignancy (Figure 1A).

The patient was started on nivolumab in an attempt to achieve a response that would make him a candidate for an allogeneic stem cell transplant. He received 300 mg every 2 weeks for five cycles. Repeat imaging showed a complete response with no evidence of hypermetabolic disease. A repeat bone marrow biopsy in December 2016 showed extensive necrosis and regenerative-type fibrosis replacing 90% of the core biopsy (Figure 1B). No viable lymphoma was identified. His blood counts showed a hemoglobin level of 12 g/dl, platelet count of 171k/μl, WBC of 6 × 10(9)/l. Serum chemistries including liver enzymes were normal. LDH was 190 U/l. The patient went on to receive four more cycles of nivolumab and an allogeneic SCT in March 2017. He remains in remission as of July 2017 with evidence of chronic graft-versus-host disease of the skin.