GnRH agonist for gonadal protection during chemotherapy

Tommaso Falcone1,* and Halle C.F. Moore2

1 Cleveland Clinic Lerner College of Medicine and Obstetrics, Gynecology and Women’s Health Institute, Cleveland, Cleveland, OH, USA
2 Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA

*Correspondence address. E-mail: falcont@ccf.org

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Approximately 40,000 adolescent and young adult females between the ages of 15 and 39 years are diagnosed with cancer yearly. The high survival rate of many cancers has broadened the focus of what is considered an optimal clinical outcome to include preservation of ovarian function. Ovarian function has many implications for the cancer survivor including fertility, bone health, and psychosocial well-being. Preservation of ovarian function, fertility and prevention of premature menopause are important for how the ovary is exposed to, or responds, to parenteral gonadotoxic chemotherapy and options to prevent or decrease the devastating consequence is an important aspect of the consultation with the multidisciplinary team. Although alkylating agent-based chemotherapy and radiation therapy are often the agents most associated with ovarian failure, the complex nature of cancer treatments, and possible subsequent recurrence of disease with more treatment, makes the immediate recommendations even more challenging.

The use of gonadotrophin releasing hormone agonists (GnRHa) to protect ovarian function from the effects of chemotherapy is the subject of many controversial debates and conflicting clinical reports with no clear consensus. Several systematic reviews and meta-analyses have been published with different results depending on which studies were included or excluded (Bedaiwy et al., 2011; Elgindy et al., 2015). The lack of consistency between randomized clinical trials can be attributed to many factors such as heterogeneity across the studies and multiple different end-points, including surrogate markers for ovarian reserve or even ovarian failure with few studies assessing pregnancy rates. Furthermore, it is important to understand that premature ovarian failure is not universal after exposure to alkylating agents and a significant number of patients retain ovarian function and achieve pregnancy (Schmidt et al., 2013). This clinical observation exemplifies the complex nature of chemotherapy-induced gonadal damage.

Since primordial follicles are not hormone-sensitive, the biologic plausibility for the use of GnRH agonist has been called into question. This implies that we know the specific molecular events that lead to gonadal toxicity by a specific chemotherapeutic drug. In vitro data show a complex mechanism of damage that involves multiple components of ovarian tissue that includes the stromal cells, vascular structures, granulosa cells and the oocyte. The specific mechanism by which primordial follicle loss occurs is unclear and may only be part of the specific target of chemotherapeutic agents (Morgan et al., 2012).

In this issue of Human Reproduction, Bildik et al. report an in vitro model to explore if there is molecular evidence for-or-against the role of GnRHa in the prevention of chemotherapy-induced ovarian damage (Bildik et al., 2015). The authors investigated whether GnRHa co-administered with the active metabolite of cyclophosphamide preserves steroidogenic activity and follicle number and expression of anti-apoptotic genes. Overall, this excellent in vitro experiment shows that GnRHa does not affect these parameters.

The laboratory model used by Bildik et al. is not an established model for how the ovary is exposed to, or responds, to parenteral gonadotoxic chemotherapy in vivo so its clinical applicability is limited. In addition, the in vitro design investigates only one potential mechanism of how GnRHa may work to protect the ovary. GnRHa probably acts at multiple levels and may be protective because of altered vascular effects; the immune system could play a role in protection against chemotherapy-induced gonadotoxicity in vivo. The in vitro model is also limited by the temporal relationship of the administration of the agonist and chemotherapeutic agent. Typically GnRHa are administered 7–14 days before chemotherapy starts. In this in vitro study, both classes of drugs were administered concurrently or the GnRHa was administered 1–2 h before chemotherapy was given. This is quite a difference from 7 to 14 days in vivo.

The study used a mixed patient population for their study materials. Ovarian cortical tissues were obtained from 15 patients (mean age ± SD: 27.8 ± 2.7, range: 14–37) undergoing laparoscopic surgery for the removal of benign ovarian cysts between the years 2014 and 2015. Ovarian cortices embedded in the cyst wall were removed. The number of tissue samples was small (15) with a large age range and the ovarian samples were taken from cyst walls and only contained few follicles to begin with (control samples had a mean 2.5 primordial and 0.6 pre-antral/antral follicles). Most of these patients had endometriomas that can affect apoptosis. Can we extrapolate these in vitro observations to the in vivo clinical situation? The purpose of in vitro experiments is not to exclude a clinical option for patients but to ascertain if a specific
proposed mechanism of action of a therapeutic drug is responsible for its clinical effects. Isolated in vitro systems do not necessarily reflect the in vivo response. It is difficult to reproduce all the cellular structures that can be affected by chemotherapeutic agents especially the stromal, immune and vascular systems of ovarian tissue. Furthermore, the in vivo repair response that enables survival of these cells is not accounted for in in vitro models. It is therefore not clear if the effectiveness of a drug in a particular disease process requires a more complex in vitro model or solely an in vivo model to demonstrate its effectiveness. For example, the effectiveness of systemic antibiotic therapy for the treatment of acne is related to its anti-inflammatory effects rather than its antibacterial effects. In vitro models for the effectiveness of oral contraceptives on hyperandrogenism will also fail to show an effect. If you add chemotherapy and pegfilgrastin to bone marrow cells in vitro, you would not expect to prevent bone marrow cytotoxicity.

So, while the data support the conclusion that GnRHa does not appear to have a protective effect when given with chemotherapeutic agents, the major difference in the timing of GnRHa administration in vivo versus in vitro and the limitation of the in vitro (ovarian cells or ovarian tissue only) versus in vivo (intact ovary, intact hypothalamic-pituitary axis, ovarian perfusion, immune system) design cannot be used to exclude the use of GnRHa agonists for gonadal protection.

Ultimately, we need to consider the science of the drug therapy. In vitro data provide us concepts but cannot account for the tremendous variation in patient response that is attributed to drug distribution, delivery, metabolism and clearance, binding to its natural receptor, physiological variables and not just a single drug-receptor interaction. This applies to both GnRHa and chemotherapeutic drugs. Chemotherapeutic drug delivery to the ovary may be influenced by altered organ perfusion and local parameters that affect organ distribution.

Recent clinical data support a protective effect of GnRHa on ovarian function and fertility (Moore et al., 2015). The Prevention of Early Menopause Study (POEMS), a large RCT (N = 218) that included breast cancer patients from our center, observed that the administration of GnRHa was associated with a reduced incidence of ovarian failure, and higher rates of pregnancy and live births. While this study does not elucidate the mechanism of ovarian protection with GnRHa, it demonstrates that GnRHa protects ovarian function and fertility in women with ER-negative early-stage breast cancer. Demonstration that one of a variety of potential mechanisms does not explain the activity of GnRHa in this setting does not negate the clinical findings. Furthermore, the safety of this approach in women with ER-negative breast cancer was demonstrated by the improved survival observed in women randomized to the GnRHa in POEMS.

Standard fertility treatments such as oocyte and embryo cryopreservation before the start of a chemotherapy regimen are very successful but may not be possible for many patients because of the timing of the start of chemotherapy, depending on the underlying malignancy, financial challenges and even access to successful assisted reproductive technology programs. Ovarian tissue freezing is an experimental procedure with great promise but is offered in few centers with perhaps 50 live births reported worldwide since the publication of the first pregnancy in 2004 (Dittrich et al., 2015). It is important that the patient is offered options and that one treatment modality does not exclude another. The use of GnRHa does not exclude oocyte or embryo cryopreservation and can be easily used for breast cancer patients where there is flexibility in the timing of initiating treatment. In summary, these experiments rule out a specific molecular explanation for GnRH agonist efficacy but do not rule out its efficacy in some patient populations undergoing chemotherapy.

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References


