

Response to “Absence of Conclusive Evidence for the Safety and Efficacy of Gonadotropin-Releasing Hormone Analogue Treatment in Protecting Against Chemotherapy-Induced Gonadal Injury”

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We read with interest the article by Oktay et al. [1], which purports that gonadotropin-releasing hormone (GnRH) analogue treatment for protection against chemotherapy-induced ovarian damage is ineffective.

Though we firmly agree that randomized controlled trials are necessary to confirm GnRH analogue cotreatment efficacy, the preponderance of available evidence is very encouraging. A recent meta-analysis, inclusive of 320 patients from seven controlled studies, found GnRH agonist use during chemotherapy to be significantly associated with ovarian function preservation (relative risk, 1.7; 95% confidence interval, 1.4–2.2) [2].

We would like to specifically address several comments in the review by Oktay et al. [1] relevant to our published trial of leuprolide acetate in systemic lupus erythematosus (SLE) patients undergoing cyclophosphamide (CYC) therapy [3].

Oktay et al. [1] questioned our use of the absence of premature ovarian failure as our primary outcome (defined as menses in the preceding 12 months and a follicle-stimulating hormone level < 40 mIU/ml) because we did not assess fertility. We argue that the presence of menses is a valid indication of intact ovarian function, albeit without the ability

to assess gradations of ovarian reserve. Though fertility potential/fecundity are of interest, there are logistical and ethical constraints in using these as primary endpoints, because they restrict the eligible study population to women planning to attempt conception within a defined time frame post-chemotherapy.

Oktay et al. [1] were critical of our protocol's use of add-back estrogen in patients receiving GnRH analogues, although we view this as a strength in that our study was able to demonstrate, for the first time, that the potential protective effect of GnRH analogues did not result from a hypoestrogenic environment.

As we discussed, our controls had, on average, 1.5 years longer SLE duration and potentially greater lupus severity than patients in the GnRH analogue group. However, given the fact that all GnRH analogue-treated and control patients in our study had SLE activity warranting i.v. CYC therapy, and the lack of evidence or plausibility suggesting that the severity of lupus affects the development of CYC-induced ovarian damage, we do not believe that these issues impact the overall interpretation of our findings.

Finally, the authors were critical of our use of survival analysis, in part because of their post hoc calculation of

power. Post hoc power calculation is not only a controversial statistical practice [4], but is irrelevant when the null hypothesis has already been rejected, indicating the ability to detect a statistical difference between groups. Oktay et al. [1] further state that because there was only one case of premature ovarian failure in our GnRH analogue–treated group, it is hard to make a statistical argument. Clearly, statistical testing is designed to support or refute qualitative assessments.

The state of available evidence indicates that GnRH analogue therapy for the prevention of CYC-induced ovarian injury has strong potential as a safe, cost-effective, and eas-

ily administered method for ovarian preservation in women undergoing chemotherapy for various indications. With a range of comorbidities known to be associated with premature ovarian failure (e.g., cardiovascular disease, osteoporosis, depression), the ultimate therapeutic goal should be the preservation of normal ovarian function, not solely salvaging reproductive potential.

AUTHOR CONTRIBUTIONS

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REFERENCES

- Oktay K, Sönmezer M, Oktem O et al. Absence of conclusive evidence for the safety and efficacy of gonadotropin-releasing hormone analogue treatment in protecting against chemotherapy-induced gonadal injury. *The Oncologist* 2007;12:1055–1066.
- Clowse M, Behera M, Anders C et al. Ovarian preservation by GnRH-agonists during chemotherapy: A meta-analysis. *Arthritis Rheum* 2007;56(suppl 9):S736.
- Somers EC, Marder W, Christman GM et al. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 2005;52:2761–2767.
- Hoenig J, Heisey D. The abuse of power: The pervasive fallacy of power calculations for data analysis. *Am Stat* 2001;55:1–6.