Published in final edited form as:

Nat Clin Pract Neurol. 2009 January ; 5(1): 18–19. doi:10.1038/ncpneuro0951.

Do estroprogestinic hormones protect against chemotherapy-induced amenorrhea in multiple sclerosis?

Rhonda Voskuhl* and TC Jackson Wu

R Voskuhl is Professor of Neurology and Director of the Multiple Sclerosis Research and Treatment Program in the Department of Neurology at the University of California, Los Angeles (UCLA), and TCJ Wu is Medical Director of the Fertility Center in the Department of Obstetrics and Gynecology, UCLA, Los Angeles, CA, USA.

SUMMARY

This commentary discusses a paper by Cocco *et al.* that addresses the treatment of multiple sclerosis (MS) with the drug mitoxantrone in women of childbearing age. This is a very important issue, as mitoxantrone is thought to be associated with the development of chemotherapy-induced amenorrhea (CIA) in women with MS. CIA is a condition characterized by cessation of menstrual bleeding that can be associated with either temporary or permanent infertility. In the study, a clear cumulative dose effect of mitoxantrone on the development of CIA was demonstrated. The risk of CIA was also shown to increase with age. However, the incidence of CIA was lower in women who took estroprogestinic hormones concurrently with mitoxantrone. The authors concluded that mitoxantrone may markedly affect reproductive capacity in women with MS and that estroprogestinic drugs should be administered alongside mitoxantrone to guard against these possible effects. The potential for estroprogestinic drugs to guard against CIA is intriguing and warrants further investigation.

Keywords

chemotherapy-induced amenorrhea (CIA); estrogen; mitoxantrone; multiple sclerosis; progesterone

COMMENTARY

Mitoxantrone, a drug traditionally used to treat cancer, is now used as a treatment in patients with multiple sclerosis (MS) who have relatively aggressive disease—specifically, progressive relapsing disease that generally has responded sub-optimally to treatment with interferon β (IFN- β) or glatiramer acetate. Mitoxantrone is, however, thought to be associated with the development of chemotherapy-induced amenorrhea (CIA). This finding is worrying, as MS is not traditionally associated with CIA or early menopause, and the fertility of women with MS is thought to be normal.¹ Numerous autoimmune diseases, including MS,² predominantly affect women, and these women are often of childbearing age; therefore, finding a treatment that could prevent the development of CIA in these patients would be of major importance. Cocco *et al.*³ have demonstrated a cumulative dose effect of mitoxantrone on the development of CIA and that this risk increases with age. These findings were important to document but are not surprising. However, intriguing novel data were also presented in this paper that showed that those women who were taking estrogen or progesterone during treatment with

*Correspondence, Neuroscience Research, Building 1, Room 475D, 635 Charles Young Drive, South, Los Angeles, CA 90095, USA
E-mail: rvoskuhl@ucla.edu.

Competing interests

The authors declared no competing interests.

mitoxantrone had a decreased incidence of CIA and menopause compared with those not taking estroprogestinic drugs.

Cocco and colleagues investigated the incidence of CIA in 189 women with MS who were treated with mitoxantrone (for at least 3 treatment cycles) before the age of 45 years. As reported through an 'ad hoc' questionnaire, 48 (26%) of the patients subsequently developed CIA. The incidence of CIA rose with increases in mitoxantrone dose (by 2% per mg/m² of cumulative dose) and age (by 18% for each additional year of age) but was reduced in women who had taken estroprogestinic hormones concurrently with mitoxantrone. In this study, relative to the timing of mitoxantrone administration, 54% of the patients had been previously treated, 4% concurrently treated, and 44% subsequently treated with IFN- β . Treatment with IFN- β during pregnancy has been associated with menstrual abnormalities and poor pregnancy outcomes in MS⁴ (although persistence of these effects beyond discontinuation of this treatment has not been demonstrated). Absence of treatment with IFN- β in women who that took estroprogestinic drugs could, therefore, have confounded the findings with regard to estroprogestinic hormones. Thus, it would be useful to know whether the frequencies of IFN- β treatment were equally distributed between those who had and those who had not taken estroprogestinic hormones—data not reported by Cocco *et al.* Assuming that there was a random distribution of IFN- β treatment, and that this was not a confounding factor in the finding of protection from CIA with estroprogestinic hormones, this apparent protective effect of hormones clearly warrants further attention.

The authors hypothesized that the protective effect against CIA of estroprogestinic hormones taken concurrently with mitoxantrone could result from the hormones' inhibition of the ovarian cycle.³ They base their hypothesis on a paper that described a higher incidence of CIA when chemotherapeutic drugs were administered during the follicular phase of the cycle.⁵ The situation may, however, be more complex. Generally speaking, in relatively young women, approximately 20–30 primordial follicles become activated each month from the oocyte pool. Of these activated follicles, one will become dominant and mature during each cycle. Chemotherapy may act to reduce the oocyte pool before activation, interfere with the initial activation of follicles, or interfere with follicular maturation and development of the dominant follicle. These are not mutually exclusive events. Infertility during concurrent chemotherapy would support the theory of interference with either follicular activation or maturation. On the other hand, when menstrual cycles return after completion of chemotherapy, only to be followed by a reduced ability for subsequent conception and an increased risk of early menopause, this would suggest that chemotherapeutic agents lead to a reduced oocyte pool before follicular activation.

If treatment with estroprogestinic hormones is indeed protective in CIA, as described by Cocco *et al.*, it should be determined whether oocytes express estrogen receptors or progesterone receptors, either before or during follicular activation.⁶ Estrogens in particular have been shown to have potent antiapoptotic properties in the brain.⁷ Thus, it is possible that there are direct effects of estrogens in protecting against chemotherapy-induced apoptosis of oocytes. Alternatively, there may be indirect effects whereby estrogens act on estrogen receptors in ovarian stromal cells that support oocytes. These questions can now be answered in animal models through use of conditional cell-targeted knockouts of estrogen receptor alpha or beta. Determining the mechanism by which hormones exert their protective effect against CIA could lead to specific targeting of the ovarian cell of interest by treatments that use estrogen-receptor-specific ligands. The protective effects could, thereby, be maximized and the toxic effects in other cells and organ systems minimized.⁸

In conclusion, the finding that estroprogestinic hormones may be protective against chemotherapy-induced infertility warrants confirmation in further studies. If proven, then

investigation into the mechanisms of this protection would be important to discern, since this could lead to prevention of a major problem for women with MS or other autoimmune diseases who are treated with chemotherapeutic agents.

PRACTICE POINT

When deciding whether to use chemotherapeutic agents in women with MS, the patients' ability to have a successful pregnancy in the short or long term, accounting for cumulative dose and patient age, should be considered. Possible protective effects of estroprogestinic hormones should be assessed by capturing this information as a covariant in trials of chemotherapeutic agents.

References

1. Giesser BS. Gender issues in multiple sclerosis. *Neurologist* 2002;8:351–356. [PubMed: 12801436]
2. Whitacre CC, et al. A gender gap in autoimmunity. *Science* 1999;283:1277–1278. [PubMed: 10084932]
3. Cocco E, et al. Frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis: the FEMIMS study. *Mult Scler* 2008;14:1225–1233. [PubMed: 18701568]
4. Boskovic R, et al. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology* 2005;65:807–811. [PubMed: 16186517]
5. Di Cosimo S, et al. Incidence of chemotherapy-induced amenorrhea depending on the timing of treatment by menstrual cycle phase in women with early breast cancer. *Ann Oncol* 2004;15:1065–1071. [PubMed: 15205200]
6. Wu TC, et al. Detection of estrogen receptor messenger ribonucleic acid in human oocytes and cumulus-oocyte complexes using reverse transcriptase-polymerase chain reaction. *Fertil Steril* 1993;59:54–59. [PubMed: 7678235]
7. Rau SW, et al. Estradiol attenuates programmed cell death after stroke-like injury. *J Neurosci* 2003;23:11420–11426. [PubMed: 14673006]
8. Tiwari-Woodruff S, et al. Differential neuroprotective and antiinflammatory effects of estrogen receptor (ER)alpha and ERbeta ligand treatment. *Proc Natl Acad Sci USA* 2007;104:14813–14818. [PubMed: 17785421]