

## Late complications after allogeneic hematopoietic cell transplant

I read with interest the excellent article by Granat et al<sup>1</sup> on long-term management after allogeneic hematopoietic cell transplant. As the authors noted, most patients will experience premature ovarian insufficiency (POI) after treatment. Premature (before age 40) and early (before 45) loss of estrogen are associated with multiple negative consequences, including adverse cardiovascular, neurologic, mortality, bone, quality-of-life, and sexual-health outcomes.<sup>2</sup> There is agreement that POI management should include menopausal hormone therapy (MHT) at higher doses to correct the physiologic deficiency until at least the age of natural menopause (age 51 or 52).<sup>2</sup> The notable exceptions are the small percentage of women who would require antiestrogen therapies to treat their condition. Yet in clinical practice young individuals are frequently asked to discontinue MHT based on misinterpretation of risks that apply to women who start hormones in their 60s or later. Thus, clarification of MHT risks is critical to the care of young cancer survivors with POI.

The authors caution about endometrial cancer risk with MHT, but this is only a concern when estrogen is used unopposed (without adequate progestin) in individuals with a uterus. Appropriately dosed MHT has been associated with a neutral to decreased risk of endometrial cancer and hyperplasia.<sup>3–5</sup> To ensure endometrial safety, progestin should be offered for no less than 12 days of each month, at a dose to match the higher estrogen doses typically required to reach physiologic premenopausal ranges.

The authors also note the importance of assessing fracture risk and discuss treatment options such as bisphosphonates. MHT has been associated with preservation of bone density and fracture reduction at all sites (including the hip). In contrast to other osteoporosis therapies mentioned in the article, MHT has not been associated with risks of long-term suppression of bone turnover, such as osteonecrosis of the jaw or atypical femoral hip fractures. Given that women under age 50 have relatively lower fracture risk, MHT is an important option to postpone the need for other bone agents in those with POI, thereby limiting the duration of exposure and the rare risks of long-term bone suppression. Women who have undergone hematopoietic cell transplant and who suffer from POI should be reassured that MHT at physiologic dosing offers a favorable risk-benefit ratio, including protection from bone loss, without increased risk of endometrial cancer when correct formulations are chosen.

Pelin Batur, MD, FACP, MSCP  
Professor of Ob/Gyn and Reproductive Biology  
Cleveland Clinic, Cleveland, OH

### REFERENCES

1. Granat LM, Ondeck M, Osantowski B, et al. Late complications after allogeneic hematopoietic cell transplant: What primary care physicians can do. *Cleve Clin J Med* 2023; 90(8):499–508. doi:10.3949/ccjm.90a.23006
2. Kapoor E. Premature ovarian insufficiency. *Curr Opin Endocr Metab Res* 2023; 28:100435. doi:10.1016/j.coemr.2023.100435
3. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev* 2012; (8):CD000402. doi:10.1002/14651858.CD000402.pub4
4. Brinton LA, Felix AS. Menopausal hormone therapy and risk of endometrial cancer. *J Steroid Biochem Mol Biol* 2014; 142:83–89. doi:10.1016/j.jsbmb.2013.05.001
5. Tempfer CB, Hilal Z, Kern P, Juhasz-Boess I, Reznicek GA. Menopausal hormone therapy and risk of endometrial cancer: a systematic review. *Cancers (Basel)*. 2020; 12(8):2195. doi:10.3390/cancers12082195

doi:10.3949/ccjm.91c.01001