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Commentary

It Is Time to Talk About Fertility and Immunotherapy

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Fertility preservation is an important issue for a significant proportion of young women and men with cancer, as many may require systemic therapy, including gonadotoxic chemotherapy [1]. As women and men increasingly postpone childbearing for professional, cultural, and societal reasons, a growing number of patients diagnosed with cancer have not completed their families and have concerns about treatment-related infertility. The risk of infertility varies according to the patient's age at the time of treatment, complications from the primary cancer, and type of systemic treatment. Although the gonadal damage induced by chemotherapy agents is well known, the impact on patients' reproductive potential of the newer targeted treatments remains to be established [1].

Immune checkpoint inhibitors (ICIs) have changed the landscape of cancer treatment for many solid tumors in the advanced stage. In February 2019, based on the results of the KEYNOTE-054 trial [2], pembrolizumab received its first approval in the adjuvant setting in the U.S. for patients with resected, stage III melanoma. Following this approval, we queried clinicaltrials.gov and found more than 92 clinical trials studying anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), anti-programmed death protein 1 (PD-1), and anti-programmed death-ligand 1 (PD-L1) agents in the neoadjuvant and adjuvant settings, suggesting that their role will continue to gain value for patients with early-stage disease. One ongoing concern regarding the use of ICIs in the early-stage setting is the effect of these agents on fertility and subsequent pregnancies. CTLA-4 inhibitors, anti-PD-1, and anti-PD-L1 agents are overall new, and we lack long-term data in this regard. Many experts in the field are optimistic about the effects of these agents on conception, but concrete data are missing so far.

The National Comprehensive Cancer Network guidelines advise that patients of reproductive age use effective birth control during and for at least 5 months after immunotherapy. Most clinical trials also required patients of reproductive age to use at least two anticonception methods while receiving anti-PD-1 or anti-PD-L1 agents up to 6 months after the last dose. However, data supporting this recommendation are lacking.

Conception can be affected by these agents in several ways, including endocrine dysfunction due to immune-related adverse events and direct effects on reproductive organs. Adverse events with ICIs can occur to any organ, including the endocrine system [3]. Hypothyroidism (all grades) is a common complication of ICIs, 6% for PD-1 and PD-L1 inhibitors and 15% for CTLA-4 inhibitors [4, 5]. Also, reported rates of hypophysitis vary from <1% to 3% with anti-PD-1 and PD-L1 agents [3] and up to 11% with CTLA-4 therapy [6]. The pituitary gland plays a vital role in the regulation of the ovary and testes, and disruption of this pathway can have serious consequences like premature menopause and low testosterone with subsequent erectile dysfunction and decreased sperm production. In addition, higher rates of endocrine immune-related adverse events have been reported in premenopausal women, placing them at risk for infertility after receiving neoadjuvant or adjuvant anti-PD-1 and anti-PD-L1 agents [7].

Anti-CTLA 4, anti-PD-1, and anti-PD-L1 agents can potentially have direct effects on oogenesis and spermatogenesis. Preclinical studies of ipilimumab in monkeys showed bounding of the compound to the connective tissue of the ovary, although no histopathology changes in the ovarian morphology were observed. They also noticed decreased testicular weight in the male monkeys without sperm histopathology changes [8]. In the case of pembrolizumab, no studies have been performed to test its potential for carcinogenicity or genotoxicity [9]. Preclinical data at 1 month and 6 month in monkeys reported no notable effects in the female and male reproductive organs; however, most animals in these studies were not sexually mature [9]. Comparable data can be found for nivolumab and durvalumab [9]. In the case of atezolizumab, infertility in females was described in animal studies. Weekly administration of atezolizumab to female monkeys at the highest dose tested caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries. However, it should be mentioned that this effect occurred at six times the recommended atezolizumab dose in primate animal models and was reversible. There was no effect on the male monkey reproductive organs [10].

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Because of high target specificity, humanized monoclonal antibody therapeutics requires reproductive toxicity testing in nonhuman primates. Even though primates have more comparable reproductive physiologies to humans, such as menstrual cycle timing and duration of spermatogenesis [11], it is difficult to translate fertility risk from preclinical animal testing alone, particularly with most of the studies including animal models that have not reached sexual maturity.

Other factors affecting fertility should also be accounted for, including immune complications secondary to the primary malignancy, for example, lymphoma-induced antiphospholipid syndrome and the use of supportive therapies that have limited safety data in pregnant patients (e.g., pegfilgrastim). In addition, the receptor occupancy of immune checkpoint inhibitors ranges from 3 weeks to 30 months, suggesting that the effects on fertility may be long lasting and patients need to be followed for many months after completion of therapy [10, 12, 13].

Studying the effects of these agents in fertility brings unique challenges in patients with metastatic cancer. Many of these patients may have been exposed to cytotoxic therapy before immunotherapy, and because of the uncertainty of patients' response to therapy, finding the "best" time for testing and conception would be difficult or impossible to determine. The approvals of combination therapies including ICIs, in serial or with radiation therapy, will only further complicate the assessment of fertility risk, particularly in the context of malignancies such as melanoma and lymphoma that disproportionately afflict the young. The lack of fertility data points to the need for research in this area, including the effects on fertility after these agents have been discontinued in patients with prolonged complete responses and for those that have received them in the adjuvant setting. International and multi-institutional collaborations including multiple disease types will be needed to generate an adequate sample, owing to the limited number of women and men of reproductive age receiving ICIs. In order to understand the full effects of these agents, long-term follow-up will be necessary with the inclusion of additional surrogates for fertility such as subsequent pregnancies, miscarriages, live births, and birth defects.

Thanks to the advances in medically assisted reproductive technologies, options for fertility preservation are increasingly available. Therefore, it is crucial to perform a proper oncofertility counseling at the time of diagnosis with all patients diagnosed with cancer during their reproductive years so that they are informed on both the risk of treatment-related gonadotoxicity and the potential needs of accessing the fertility clinic before starting anticancer therapies. Patient education regarding known and unknown fertility data is essential. Immune checkpoint inhibitors have significantly improved survival in many patients and can potentially cure some patients with advanced disease. Further understanding of their effects on fertility will allow us to have a more honest conversation with our patients when considering these agents. Consideration of future fertility should become a critical component of cancer care in patients who will receive anti-PD-1 and anti-PD-L1 agents. It is our duty as physicians to give our patients the opportunity to decide their reproductive future. Cancer will change our patients' lives, and it should not be forgotten that fertility is an essential element of cancer survivorship.

Disclosures

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