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Female Fertility Following Immune Checkpoint Inhibitor Therapy

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ABSTRACT

Advancements in oncological therapeutics have engendered deeper elucidation into the protracted ramifications of interventions, notably the conspicuously pervasive gonadal insufficiency. The paramount objective of therapy has veered toward the preservation of reproductive potential, an objective conceivably attainable through the amelioration of ovarian toxicity. The burgeoning susceptibility of neoplastic affliction in the youthful demographic has concomitantly rendered a burgeoning cohort of childbearing-aged patients eligible for Immune Checkpoint Inhibitor (ICI) regimens. Among the panoply of Immune-Related Adverse Events (irAEs), endocrine derangements manifest with prodigious frequency; nevertheless, the dossier pertaining to the prospective consequences of ICIs upon female fecundity remains palpably incomplete. Antecedently documented evidence has sporadically alluded to secondary ovarian injury precipitated by hypophysitis, potentially imperiling fertility, whilst the corpus of information pertinent to primary female reproductive detriment remains conspicuously absent. Preclinical studies have shown that a pronounced escalation in abortion rates is demonstrable. Fundamental investigations probing these sequelae are imperative for the formulation of more substantiated practice guidelines.

Introduction

Immune Checkpoint Inhibitor (ICI) has significantly enhanced the therapeutic landscape for numerous malignancies that had previously been characterized by a bleak prognosis [1]. They have garnered attention within the realm of tumor management due to their holistic bioactivity across various histological neoplasms, the durability of their treatment response, and the effectiveness of their interventions, even in the context of metastatic and chemotherapy-resistant malignancies. Nearly all patients subjected to ICIs are liable to experience a minimum of one Immune-Related Adverse Event (irAE) [2,3]. These irAEs possess the capacity to impact any organ system and may manifest as severe complications, contingent upon the specific therapeutic regimen and the underlying health status of the patient. Of note, endocrine toxicities represent one of the most prevalent categories of irAEs, distinguished from their counterparts by their propensity for irreversibility and necessitating lifelong hormonal replacement [2,3]. It merits emphasis that a substantial proportion of cancer patients of reproductive age necessitate immunotherapeutic interventions. Nonetheless, our knowledge concerning the potential ramifications of ICIs on female gonadal function remains limited (Table 1). Our objective in this endeavor is to scrutinize the amassed body of literature pertaining to the reproductive toxicity of ICIs and proffer management guidelines.

Secondary Ovarian Damage Through ICI-Related Hypophysitis

Hypophysitis stands as one of the prevalent immune-related endocrine maladies. Ipilimumab, a monoclonal antibody targeting CTLA-4, exhibits a more pronounced association with this immune-related adverse event (irAE) [4-7]. In individuals subjected to ipilimumab therapy, the global prevalence of hypophysitis ranges between 10-15%, with its manifestation being a rarity in patients undergoing alternative ICI treatments, such as anti-PD-1/PD-L1 antibodies [8,9]. Hypophysitis may ensue in the early stages or several

months following the commencement of ICIs. ICI-induced hypophysitis typically manifests with non-specific symptoms, including fatigue, vertigo, headache, appetite loss, nausea, and emesis. The chief clinical consequence of ICI-related hypopphysitis is the depletion of one or more pituitary hormones, with the most frequently affected hormones being thyroid-stimulating hormone, adrenocorticotrophic hormone, follicle-stimulating hormone, and luteinizing hormone. Growth hormone deficiency and aberrant prolactin levels are less commonplace, and diabetes insipidus is exceptionally infrequent. The investigation conducted by (Kanie, et al. [10]) posited that the ectopic expression of ACTH in tumors may precipitate hypophysitis induced by anti-PD-1/PD-L1 antibody.

Table 1: Immune checkpoint inhibitors and female reproduction.

Drug	Species	Evidence	Ref
Ipilimumab (CTLA-4 antibody)	human	hypophysitis and secondary ovarian damage	[4,6,12]
Atezolizumab (PD-L1 antibody)	mouse	lack of new corpora lutea formation	[14]
Ipilimumab (CTLA-4 antibody)	mouse	reduced ovarian follicle reserve	[13]
Nivolumab (PD-1 antibody)	monkey, mouse	abortion or neonatal death when received during pregnancy	[17,18]

Primary Impacts of ICIs on Ovarian Function

The evaluation of gonadal function in reproductive-age women receiving ICIs must not be further delayed. ICIs are progressively employed in the curative context as adjuvant therapy, where the risk of ICI-induced hypogonadism, premature menopause, infertility, and their enduring repercussions necessitates a delicate equilibrium against the absolute risk reduction of disease recurrence. This complex discussion should be engaged with the patient, as it has the potential to influence the acceptance of such prophylactic therapies. The incidence of cancer in young adults is on the rise, with approximately 5% of all cancer diagnoses now occurring in women in 20s and 30s [11]. Hence, it is plausible that more reproductive-age women will be exposed to ICIs in the future, necessitating informed awareness regarding the potential for gonadal toxicity [12]. Clinical data and case studies concerning the direct effects of ICIs on female gonadal function are scarce, but several preclinical investigations rooted in animal experimentation have postulated that ICIs exert a direct influence on female gonadal function and have explored their mechanisms of action. For ipilimumab, preclinical trials in primates have demonstrated that the antibody exhibits specific binding to the ovarian connective tissue without histopathological alterations in oocyte morphology [13].

Repeated-dose toxicity assessments of atezolizumab, anti-PD-L1 antibody in female cynomolgus monkeys have resulted in irregular menstrual cycle patterns and a deficiency in the formation of new corpora lutea [14]. In (Xu, et al. [15]) study involving anti-mouse PD-1 antibodies, it was proposed that PD-1 immune checkpoint blockade impacts ovarian reserve through a mechanism involving the infiltration of CD3+ T cells. This marks the first study linking ICIs to inflammation-mediated follicle depletion in preclinical models of prepubertal pediatric patients.

ICIs During Pregnancy

Another pivotal concern revolves around the teratogenic potential of ICIs. The PD-1/PD-L1 and CTLA-4/CD80/CD86 pathways play a vital role in inducing maternal tolerance and preventing the rejection of the semi-allogeneic fetus [11,14,16]. In pregnant mice, treatment with anti-PD-L1 antibodies substantially elevates the abortion rate (18%) compared to spontaneous abortion (18%) by depleting regulatory T cells [17]. Pregnant cynomolgus monkeys that received PD-1 antibodies from the outset of organogenesis until delivery exhibited increased rates of abortion and premature neonatal death [17,18]. The Food and Drug Administration recommends that women of childbearing age avoid conception during treatment with ICIs, extending this caution for six months following the completion of treatment [13].

Conclusion

ICIs have substantially enhanced the treatment landscape for numerous cancer types. The heightened cancer risk among young individuals has rendered an increasing number of childbearing-age patients eligible for immunotherapy. Endocrine toxicities stand as among the most prevalent immune-related adverse events (irAEs), yet the potential ramifications of ICIs on female fertility remain insufficiently documented. Preclinical studies have uncovered an elevated risk of fetal demise. Systematic investigations on these outcomes are imperative to formulate more evidence-based clinical guidelines.

Conflict of Interest

The authors declare that they have no conflict of interest.

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