Measuring ovarian toxicity in clinical trials: an American Society of Clinical Oncology research statement

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Anticancer agents can impair ovarian function, resulting in premature menopause and associated long-term health effects. Ovarian toxicity is not usually adequately assessed in trials of anticancer agents, leaving an important information gap for patients facing therapy choices. This American Society of Clinical Oncology (ASCO) statement provides information about the incorporation of ovarian toxicity measures in trial design. ASCO recommends: (1) measurement of ovarian toxicity in relevant clinical trials of anticancer agents that enrol post-pubertal, premenopausal patients; (2) collection of ovarian function measures at baseline and at 12–24 months after anticancer agent cessation, as a minimum, and later in line with the trial schedule; and (3) assessment of both clinical measures and biomarkers of ovarian function. ASCO recognises that routine measurement of ovarian toxicity and function in cancer clinical trials will add additional complexity and burden to trial resources but asserts that this issue is of such importance to patients that it cannot continue to be overlooked.

Introduction

Globally, an estimated 9·2 million women are diagnosed with cancer per year; 1·4 million (15%) are younger than 45 years and are likely to be premenopausal.[1] The most common types of cancer in this age group are breast, gynaecological, thyroid, gastrointestinal, and haematological malignancies.[2] Curative-intent treatment with systemic therapy is common and survival rates are high.[2] Therefore, addressing the long-term effects of anticancer treatments should be prioritised.

Loss of ovarian function is a potentially irreversible toxicity from anticancer treatment.[3,4] It can lead to infertility and long-term morbidities resulting from early-onset menopause and oestrogen deficiency, including vasomotor symptoms, sexual and cognitive dysfunction, osteoporosis, and cardiovascular disease.[5,6] The adverse effect of anticancer therapies on ovarian function and fertility is concerning for patients making treatment decisions, and can contribute to non-adherence to treatment.[7,8] Non-randomised studies suggest pregnancy in breast cancer survivors is not likely to adversely affect disease outcomes, including among patients with hormone sensitive cancers who temporarily interrupt adjuvant endocrine therapy.[9–11] Guidelines[12–15] consistently recommend informing prepubertal and premenopausal patients with ovaries about the possibility of ovarian toxicity from anticancer therapies, as well as considering possible mitigation strategies such as fertility preservation procedures and the use of gonadotropin hormone-releasing (GnRH) agonists.

To counsel patients about the risk of treatment-induced ovarian toxicity, oncologists must know the likelihood of loss of ovarian function from the proposed anticancer regimen, and the effect that patient factors, such as age, could have on this risk. Many cytotoxic chemotherapy agents are known to have negative effects on ovarian function,[3,4] but there are minimal clinical data on the potential effects of newer anticancer therapies, including immune checkpoint inhibitors, poly ADP ribose polymerase (PARP) inhibitors, antibody–drug conjugates, tyrosine kinase inhibitors, and monoclonal antibodies.[16] Existing evidence regarding the effects of these agents on the ovaries (mostly derived from non-clinical studies) are either reported in published articles[17–19] or, when conducted in support of product development and marketing applications, included in prescription and patient labelling.

Although cancer clinical trials collect detailed information on a range of treatment adverse effects, ovarian toxicity is often not assessed, and data on ovarian toxicity, when collected, are usually inadequate to be of practical value in advising patients.[16] This is likely to be because the issue of ovarian toxicity from new anticancer agents is generally not considered when discussing proposed endpoints and data collection during the design phase of clinical trials; even when ovarian toxicity is considered as an endpoint, those involved in developing clinical trials report lack of knowledge about how and when to measure such data.[20]

Therefore, this American Society of Clinical Oncology (ASCO) research statement aims to: (1) guide clinical trial design by providing information to clinical trial stakeholders on how to incorporate the measurement of ovarian toxicity into trials enrolling post-pubertal patients; and (2) encourage data acquisition to ensure that patients and clinicians have information about the possible long-term effects of treatment on ovarian function to facilitate informed decision making regarding treatment options.

Current knowledge regarding the effects of systemic anticancer treatment on ovarian function

Cytotoxic chemotherapy

The finite primordial follicle pool (ie, the ovarian reserve) is established in utero and decreases over a woman's reproductive lifespan as follicles undergo recruitment,

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maturation, and atresia until menopause.[21] The primordial pool is the basis for long-term ovarian function, while oestrogen production (and its key consequences, ovulation and menstruation) reflects the presence of the later stages of follicle growth. The gonadotoxic effects of chemotherapy, particularly alkylating drugs, have been recognised for many decades and include rapid loss of growing follicles and thus, often, amenorrhea.[3,4] If the primordial follicle pool has not been depleted, growing follicles can be rapidly replaced in the post-treatment recovery period. Conversely, treatment-induced depletion of the primordial pool results in the clinically important later effects on fertility and reproductive lifespan. Direct measurement of the primordial follicle number requires histological analysis of harvested ovaries which is inappropriate; measurement of anti-Mullerian hormone in serum provides a clinically useful and meaningful indirect correlate of primordial follicle number.[22] The degree of depletion of the primordial pool varies depending on factors including the age of the patient (as an index of their pretreatment ovarian reserve) and the use of, and cumulative dose of, alkylating chemotherapy.[3,23,24] Several mechanisms have been proposed by which chemotherapy induces ovarian damage, including direct DNA damage with or without apoptosis of primordial follicles, disruption to the ovarian vasculature and stromal tissue, and atresia of growing follicles leading to accelerated primordial follicle recruitment.[25,26] GnRH agonists given during cytotoxic chemotherapy can decrease the risk of premature ovarian insufficiency.[27,28]

Immune checkpoint inhibitors

Immune checkpoint inhibitors are increasingly used across multiple cancer types.[29] Endocrinopathies associated with immune checkpoint inhibitors are common.[30] Hypophysitis occurs in approximately 6% of patients treated with combination immune checkpoint inhibitors, which can result in secondary hypogonadism and indirectly affect ovarian function (appendix pp 1–5). No data are currently available regarding the direct effect of immune checkpoint inhibitors on the human ovary.[31] Information on the potential ovarian toxicities related to immune checkpoint inhibitors from animal studies varies for the different checkpoint inhibitor drugs.[32–35] Studies that included sexually immature animals reported no notable findings in reproductive organs based on general toxicology studies.[32–34] However, a study of atezolizumab in sexually mature monkeys indicated irregular menstrual cycle patterns and a lack of newly formed corpora lutea.[35] On the basis of independent non-clinical studies, mice treated with PD-L1 inhibitors and CTLA-4 inhibitors had significantly reduced numbers of primordial follicles compared with control mice, and increased atresia of growing follicles and disruption of follicle maturation and ovulation.[18] In these mice, increased numbers of intra-ovarian T cells and elevated circulating and intra-ovarian inflammatory cytokine concentrations, particularly tumour necrosis factor-α, were observed,[18] suggesting the mechanism of ovarian damage from immune checkpoint inhibitors might be different to that from cytotoxic chemotherapy. There is an urgent need for clinical studies to understand if, and to what extent, these agents directly affect human ovarian function and how to overcome this potential toxicity.

See **Online** for appendix

Other targeted therapies

Some of the molecular targets important for cancer cell growth and survival are also important for normal ovarian function; therefore, targeted agents could create a high potential risk of ovarian toxicity (appendix pp 1–5).[36] There are limited data on the effects of targeted therapies on human ovarian function. For the 32 novel non-cytotoxic cancer agents approved by the Food and Drug Administration (FDA) from 2014 to 2018, there are no published human clinical data on fertility or ovarian function; animal reproductive toxicity data are available for 23 of the 32 agents.[37]

The ovarian toxicity of HER-2 targeted agents in patients remains unclear. Studies investigating ovarian toxicity of HER-2 targeted agents within clinical trials have had sub-optimal designs, including the use of amenorrhea as a surrogate marker for ovarian function, which can be unreliable. The single-arm phase 2 APT trial of adjuvant paclitaxel–trastuzumab[38] and the randomised phase 2 ATEMPT trial of adjuvant trastuzumab–emtansine versus paclitaxel–trastuzumab,[39] both showed a lower incidence of post-treatment amenorrhea than what is historically seen with regimens containing alkylating chemotherapy. However, weekly paclitaxel plus trastuzumab is associated with acute decline in anti-Mullerian hormone concentrations, suggesting that this regimen could cause ovarian damage.[40] The four-group phase 3 ALTTO trial of adjuvant monotherapy trastuzumab or lapatinib, or trastuzumab followed by, or concurrent with, lapatinib showed a high incidence of amenorrhea at 37 weeks in all groups, especially in premenopausal patients aged 46 years and older, those who received anthracycline-based and taxane-based chemotherapy, and those receiving endocrine therapy[41] (amenorrhea beyond 37 weeks was not reported).

2 years of adjuvant CDK4 inhibitors is the strategy used to treat high-risk hormone receptor-positive, HER2-negative early breast cancer based on the MonarchE trial results.[42] Few clinical data exist regarding the ovarian toxicity of CDK4/6 inhibitors, and animal fertility studies showed no adverse fertility findings.[43–46] The phase 3 PENELOPE-B trial, which randomly assigned patients with breast cancer to adjuvant endocrine therapy with or without palbociclib for 1 year after neoadjuvant cytotoxic chemotherapy, observed no difference in follicle-stimulating hormone, oestradiol, or anti-Mullerian

hormone concentrations between study groups during or at the end of treatment.[47] However, interpretation of these data is difficult as participants received endocrine therapy and 203 (33%) of 616 premenopausal women also received a GnRH agonist, which are known confounders of serum follicle-stimulating hormone, oestradiol, and anti-Mullerian hormone markers. Furthermore, longer follow-up after treatment cessation has not been reported.

Other novel targeted agents of interest are olaparib (a PARP inhibitor), and imatinib (a BCR-Abl kinase inhibitor). The product label for olaparib indicates no adverse fertility findings in female rats;[48] however, in a saline-controlled study of female mice, olaparib significantly depleted primordial follicles by 36% and increased DNA damage in surviving primordial follicles.[17] Another study showed dysfunction of granulosa cells (important for follicle growth and hormone production) in olaparib-exposed mice.[19] According to information on the product label for imatinib, fertility was not affected in female rats.[49] However, in a separate study, adult female mice receiving injections of imatinib for 4 weeks or 6 weeks had fewer primordial follicles and lower total follicle count than control mice, but increased numbers of growing follicles, suggesting an increase in primordial follicle activation and depletion over time.[50] There are no published peer-reviewed clinical or non-clinical data regarding the long-term ovarian toxicity of other antibody–drug conjugates, tyrosine kinase inhibitors, and monoclonal antibodies.

Measures of ovarian function

Toxicity in cancer clinical trials is routinely measured using the US Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE). Three current CTCAE terms potentially measure ovarian toxicity (premature menopause, amenorrhea, and irregular menstruation),[51] but they are not usually collected systematically or after treatment, making them insufficient to identify permanent ovarian toxicity (which requires continuing data collection after treatment cessation). Additionally, the term premature menopause in the CTCAE is defined by symptoms, including mood swings and decrease in sex drive[51] (which often have other causes) or laboratory findings of elevated luteinising hormone and follicle-stimulating hormone, but these are not routinely measured, and the term does not reflect current understanding or terminology in reproductive medicine.[6]

There are several markers of ovarian function that are routinely used in endocrinology and reproductive medicine including: (1) clinical measures, such as menstruation, pregnancy, and livebirth; (2) hormones produced by, or controlling, ovarian function, such as anti-Mullerian hormone, follicle-stimulating hormone, oestradiol, and inhibin B; and (3) imaging measures, such as the number of follicles visualised on ultrasound of the ovary (ie, antral follicle count). Advantages and disadvantages of each measure are summarised in table 1. Anti-Mullerian hormone is produced by the granulosa cells of growing pre-antral and small antral follicles and is an indirect marker of the ovarian reserve (the primordial follicle pool).[53] Unlike follicle-stimulating hormone and oestradiol, which primarily reflect the final stages of follicle growth preceding ovulation, anti-Mullerian hormone concentration remains relatively stable throughout the menstrual cycle, a point of clear practical value. Low concentrations of anti-Mullerian hormone have been shown to be a marker of ovarian toxicity and risk of premature ovarian insufficiency in patients with cancer.[22] Measurement of anti-Mullerian hormone allows detection and quantification of incomplete ovarian function loss (unlike amenorrhea, follicle-stimulating hormone, and oestradiol, which only reliably reflect total ovarian failure). The combination of anti-Mullerian hormone, follicle-stimulating hormone and oestradiol provides the most comprehensive biochemical information regarding the ovarian effects of exposure to anticancer therapies, and potential reversibility.

It is essential to recognise that profound changes in all these endocrine markers during anticancer treatment are common, but they do not indicate permanent ovarian damage: the key is whether these changes are reversible after treatment. In patients with cancer, menstruation can return many months to years after treatment completion,[54] but even patients with regular menstruation can have damaged fertility potential[55] and the risk for premature ovarian insufficiency or early menopause cannot be excluded in patients who maintain or resume menstruation after treatment.[56]

Similarly, concentrations of anti-Mullerian hormone, follicle-stimulating hormone, and oestradiol can become abnormal during systemic anticancer treatment and then normalise over the following months and years. Thus, measurement of these biomarkers only before, and immediately on completion of, anticancer therapy is inadequate to determine whether any effect on the ovary is temporary or permanent and does not indicate whether the primordial follicle pool (ie, the ovarian reserve) is depleted.[57] Measuring these biomarkers at 1–2 years after completion of systemic treatment, and preferably also at later timepoints, allows analysis of the change in these markers between the baseline pretreatment measure and at stable recovery, which is the most accurate index of long-term ovarian damage that is currently available. This is clearly demonstrated by the changes in anti-Mullerian hormone concentration during treatment of Hodgkin lymphoma with two regimens, both of which result in a similar decline in anti-Mullerian hormone concentration during treatment, with full recovery thereafter in one group, but 100-times lower concentrations in the other group 2 years later.[58] A period for potential recovery is necessary to distinguish whether only the growing follicles have been affected or whether the primordial follicle pool, the ovarian reserve, has also been affected. These complexities require

	Clinical		Biochemical			Imaging
	Menstruation	Pregnancy and livebirths	Anti-Mullerian hormone	Follicle-stimulating hormone or oestradiol	Inhibin B	Antral follicle count
Advantages						
Demonstrated to correlate with ovarian reserve in patients with cancer	No	No	Yes	No	Yes	Yes
Commonly used and accepted measure of ovarian function[7]	Yes, in combination with follicle-stimulating hormone or oestradiol	Yes, but must account for use of assisted reproductive technology	Yes, but must account for use of GnRH agonists, endocrine therapy, and hormonal contraception	Yes, but must account for use of GnRH agonists, endocrine therapy, and hormonal contraception	No	No
Allows detection and quantification of incomplete ovarian function loss	No	No	Yes	No	Yes	Yes
Direct measure of fertility	No	Yes, but must account for use of assisted reproductive technology	No	No	No	No
Performed by most laboratories	NA	NA	No	Yes	No	NA
Able to standardise between different laboratories and institutions	NA	NA	Yes	Yes	Yes	No
Disadvantages						
Need to time measurement to menstrual cycle	NA	NA	No	Yes	Yes	No
Additional data collection, assay or imaging cost	Yes	Yes	Yes	Yes	Yes	Yes
Requires long-term follow up (many years)	No	Yes	No	No	No	No
Confounded by intent and desire for pregnancy	No	Yes	No	No	No	No
Confounded by use of assisted reproductive technology	No	Yes	No	No	No	No
Confounded by concomitant use of hormonal contraception, endocrine therapy, or GnRH agonists	Yes	Yes	Yes	Yes	Yes	Yes

Anti-Mullerian hormone is produced by the granulosa cells of growing pre-antral and small antral follicles and is an indirect marker of the ovarian reserve (the primordial follicle pool). Follicle-stimulating hormone is a gonadotropin secreted by the pituitary gland. It regulates folliculogenesis, oocyte selection, and synthesis of sex hormones. It is elevated in ovarian failure due to negative feedback from reduced sex hormone concentrations. Oestradiol is a sex hormone mostly produced by the ovaries in premenopausal women. It is important for the regulation of the female menstrual and reproductive cycles as well as the development of secondary sexual characteristics, sexual function, bone health, cardiovascular health, and cognition. Concentrations are low in ovarian failure. Inhibin B is secreted by the granulosa cells of growing follicles and inhibits follicle-stimulating hormone production. It is an indirect marker of the ovarian reserve. Inhibin B does not add additional information beyond anti-Mullerian hormone and it is infrequently used in practice; its use is not recommended in this research statement. Antral follicle count is the measurement of the small growing antral follicles using ultrasound and, similar to Anti-Mullerian hormone, is an indirect marker of a person's ovarian reserve.[52] For reliable antral follicle count measurement, the count should be performed by a specialist reproductive medicine ultrasonographer; however, this is not always available at cancer centres and thus is not feasible in multicentre clinical trials. Inter-observer differences in ultrasound performance and sonographer technique[52] are also important limitations that reduce their value in multicentre trials. Because antral follicle count does not add additional information beyond anti-Mullerian hormone, its use is not recommended in this research statement. GnRH=gonadotropin releasing hormone. NA=not applicable.

Table 1: **The advantages and disadvantages of candidate measures of ovarian function**

due consideration when collecting and analysing data on the ovarian toxicity of anticancer agents.

Methods

In June, 2022, ASCO convened the Ovarian Toxicity Taskforce to develop a research statement regarding the measurement of ovarian toxicity in cancer clinical trials. Taskforce members included a patient advocate, ASCO Research Committee members, adult and paediatric medical oncologists, gynaecological oncologists, a reproductive endocrinologist, a reproductive biologist, FDA regulatory agency representatives, and a pharmaceutical company representative. Between June, 2022, and March, 2023, meetings occurred online (June 29, 2022, July 25, 2022, Aug 24, 2022, Sept 18, 2022, and March 15, 2023) with email correspondence between meetings. The taskforce reported draft recommendations, based on expert consensus, to the ASCO Research Committee, which approved the recommendations and directed the taskforce to develop a research statement for submission to the ASCO Board of Directors. The statement was approved by the ASCO Board Executive Committee on April 13, 2023.

Recommendations

Recommendation 1

Recommendation 1 is to include measurement of ovarian toxicity in relevant clinical trials of anticancer agents in

which premenopausal, post-pubertal patients with ovaries are enrolled.

Examples of possible exploratory endpoints regarding ovarian toxicity to include in such trials are listed in the appendix (p 6).

Recommendation 1a

Recommendation 1a is that ovarian toxicity assessment should be included in all new curative-intent or primary prevention cancer clinical trials which assess investigational agents, and should be considered for ongoing and completed trials.

Ovarian toxicity should be considered a safety endpoint in randomised trials of premenopausal, post-pubertal patients and non-randomised trials that are likely to change practice. Detailed assessment of ovarian toxicity (both short term and long term) should be a key part of the drug development plan. The number of premenopausal patients anticipated to be recruited to the trial will be a consideration when incorporating these endpoints in trials for which this number is anticipated to be very small, and meaningful assessment of ovarian toxicity might not be feasible. Ovarian toxicity assessment should also be considered for ongoing trials if these measures can be added to the existing follow-up schedule, acknowledging the regulatory and ethical requirements for protocol amendment. Ovarian toxicity biomarkers could also be retrospectively assessed for completed trials that have stored biospecimens collected at relevant timepoints, such as before and (preferably at least 12 months) after treatment cessation. Additional ethics approval and informed consent might be needed for these retrospective analyses.

Recommendation 1b

Recommendation 1b is that ovarian toxicity assessment may also be considered in clinical trials enrolling patients with advanced and metastatic cancer, especially trials enrolling treatment-naive patients.

This recommendation is important in an era during which treatment for metastatic disease might be potentially curative or lead to very long progression-free survival. Confounding factors to be considered in this setting include the effect of previous and subsequent lines of cancer treatment on ovarian function. For highly efficacious anticancer agents, long treatment durations in the metastatic setting could also make data collection of the post-treatment ovarian measures challenging. The decision to assess ovarian toxicity should be considered on an individual trial basis and consideration needs to weigh factors including the age of the enrolled population and expected overall survival.

Recommendation 2

Recommendation 2 is to collect ovarian function measures at baseline and at 12–24 months after cessation of the anticancer agent, as a minimum, and at later timepoints in line with the trial schedule. For trials of anticancer agents, for which the mechanism and extent of ovarian toxicity (if any), and the time to recovery are not known, additional data collection every 6–12 months during treatment, at the end of treatment, and after cessation of treatment is considered optimal.

Documentation of baseline ovarian function, ovarian reserve, and previous pregnancies and livebirths is essential in establishing whether exposure to a given therapy is associated with potential ovarian toxicity. Assessment of ovarian toxicity during treatment can aid in the evaluation of effects of the anticancer agent on the growing follicles of the ovary, but the limitations of current biomarkers to indicate changes in the primordial pool of follicles means that effects on the ovarian reserve only become apparent later. If ovarian function recovers, it is usually within 12 months after cytotoxic chemotherapy, especially for younger premenopausal patients.[22,24,57] In a small proportion of patients (especially older patients), ovarian function recovery can be delayed for months to years but if reversible usually recovers by 24 months after treatment completion,[22,24,57] and can occur while patients are being treated with endocrine therapy.[59] Therefore, 12–24 months after cessation of treatment with the agent under investigation is the optimum time for measurement of persistent ovarian toxicity in trials in which cytotoxic chemotherapy is used (table 2). Collection of pregnancy and livebirth data (in combination with attempt at pregnancy and use of assisted reproductive technology) and menstruation data (in combination with potential confounding factors) at later timepoints that fit the trial schedule is recommended to assess longer term ovarian toxicity and fertility. Given the confounding effects of adjuvant endocrine therapy, collection of these data after completion of endocrine therapy should be considered.

Although there are established data regarding the time to ovarian function recovery after cytotoxic chemotherapy, the time course for newer anticancer agents remains unknown; thus collection of clinical measures, such as pregnancy, livebirths, and menstruation beyond 24 months is recommended. The assessment of additional biomarkers beyond 24 months after completion of treatment is also encouraged.

Recommendation 3

Recommendation 3 is to assess both clinical measures and biomarkers of ovarian function.

Assessments of the clinical markers of menses, pregnancy and livebirth, and the combination of biomarkers including anti-Mullerian hormone, follicle-stimulating hormone, and oestradiol are recommended (table 2). Given that concomitant medications such as GnRH agonists, hormonal contraceptives, and endocrine therapy, and surgical procedures such as hysterectomy, endometrial ablation, tubal ligation or salpingectomy, and bilateral oophorectomy can affect the interpretation of these measures, these data should be collected.

	Clinical measures		Biomarkers*			Confounders			
	Menstruation	Pregnancy and livebirths	Anti-Mullerian hormone	Follicle-stimulating hormone	Oestradiol	Hysterectomy,† bilateral oophorectomy, salpingectomy, or tubal ligation	Attempt at pregnancy‡	Use of surrogate embryos or oocytes, or use of embryos or oocytes stored before cancer treatment	GnRH agonists, hormonal contraception, or endocrine therapy
All trials									
Baseline	Yes	Yes	Yes*	Yes*	Yes*	Yes	Yes	Yes	Yes
12–24 months post treatment cessation(fit to trial schedule)	Yes	Yes	Yes*	Yes*	Yes*	Yes	Yes	Yes	Yes
Later timepoints beyond 24 months (fit to trial schedule)§	Yes	Yes	Yes§	Yes§	Yes §	Yes	Yes	Yes	Yes
Trials of agents with sparse data on the mechanism and extent of ovarian toxicity									
Baseline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Every 6–12 months on treatment¶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
End of treatment within 30 days of the last dose of investigational agent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12–24 months post treatment cessation (fit to trial schedule)	Yes	Yes	Yes*	Yes*	Yes*	Yes	Yes	Yes	Yes
Later timepoints beyond 24 months (fit to trial schedule)§	Yes	Yes	Yes§	Yes§	Yes§	Yes	Yes	Yes	Yes

GnRH=gonadotropin releasing hormone. *Biomarkers are strongly recommended, but could be challenging in some (eg, low-resource) settings. Inclusion of biomarker data provides far superior data on ovarian toxicity than do strategies in which they have been omitted. †Endometrial ablation could also be a confounder. ‡Pregnancy should not be attempted while on anticancer treatment. §Data on pregnancy, livebirth and menses, and confounders, should be collected for all patients at later timepoints beyond 24 months from cessation of treatment. Measurement of biomarkers at these later timepoints should be strongly considered for trials of agents for which little is known about ovarian toxicity and might be necessary for trials planned for regulatory submission, depending on the guidance of the relevant regulatory agency. ¶Assessment of ovarian function every 6–12 months on treatment detects the loss of growing follicles but does not reflect whether there is loss of the ovarian reserve.

Table 2: **Recommended timepoints for collection of ovarian toxicity measures**

Similarly, desire for and attempt at pregnancy and use of assisted reproductive technology can alter the usefulness of pregnancy and livebirth as markers of post-treatment ovarian function, so they should also be documented. An example case report form with suggested datapoints is shown in the appendix (pp 7–8).

Recommendation 3a

Recommendation 3a is that if ovarian function biomarkers cannot be assessed, clinical measures (menstruation, pregnancy, and livebirth) and data on possible confounders (hysterectomy, bilateral oophorectomy, attempt at pregnancy, and use of hormonal contraceptives, endocrine therapy, GnRH agonists, and assisted reproductive technology) should be collected as a minimum.

Although it is recommended to collect data on both clinical markers and biomarkers (as outlined in table 2), this is not always possible. Cost and trial resources are important considerations when designing a clinical trial and selecting trial endpoints.[60] For biomarkers, the costs of any additional phlebotomy, biomarker assays, sample storage, and shipping need to be considered. Although these costs are often only a small proportion of total trial expenditure, it might not be possible for all trials to allow for this extra expense. In this scenario, the clinical measures of menses, pregnancy, and livebirth, as well as potential confounders (surgical procedures, concomitant medications, attempt at pregnancy, and use of assisted reproductive technology) should be collected at a minimum. Although these measures provide less informative data than assessment of clinical and biochemical measures, they still provide some information regarding the effects of the investigational agent on ovarian function.

Recommendation 3b

Recommendation 3b is that the type of assay used to measure anti-Mullerian hormone, follicle-stimulating hormone, and oestradiol should be considered during trial design.

The different assay techniques (eg, automated versus manual assays) require different laboratory expertise and equipment.[61] Different assays might also have different levels of detection and quantification. Use of an ultrasensitive anti-Mullerian hormone assay might be preferable, especially in trials with cytotoxic chemotherapy-containing treatment regimens, when a lower level of detection and quantification is desired.[62] If individual trial sites use their local laboratories there could be variation with regard to the assays used and the detection and reference ranges. To minimise the effect of this variation, all samples for one patient should be measured in the same laboratory, when possible, to allow assessment of change in ovarian function over time. Use of the same assay in a central laboratory for all trial samples is considered optimal.

Discussion

The data collected during a clinical trial determines the safety profile of investigational agents before marketing

and routine use. Clinical trials must collect and report information regarding the adverse effects of investigational drugs.[63,64] Although data regarding long-term adverse events, such as cardiotoxicity, are increasingly assessed,[64,65] ovarian toxicity has mostly been overlooked, despite its recognition many decades ago, and its huge importance to patients. For example, between 2008 and 2019 only 9% of phase 3 neoadjuvant breast cancer trials prespecified ovarian function as an endpoint, and only 20% collected preintervention and postintervention ovarian function data; most only collected data on menstrual status.[16] Although several regulatory guidance documents are available to address evaluation of reproductive toxicities to support product approval, specific recommendations for reproductive assessment in clinical studies are limited,[66–68] and there are no specific recommendations regarding systematic, standardised collection of ovarian toxicity data in the clinical trial setting. Inadequate knowledge about the long-term consequences of cancer treatments on ovarian function (particularly newer agents) is currently a crucial information gap for patients and clinicians, especially when deciding between treatments with potentially similar anticancer efficacy.

The first step in understanding ovarian toxicity is to collect these data routinely and systematically in clinical trials of anticancer agents, as recommended in this research statement. However, there are several future research questions that also require attention. As novel classes of cancer therapies are developed and enter clinical practice, identifying the presence or absence and nature of ovarian toxicities for each class and the timeline for ovarian function recovery, if any, is essential. Understanding the effect of other risk factors, such as age, and the utility of baseline biomarker concentrations to personalise the prediction of an individual's risk of ovarian toxicity to each drug regimen needs to be better studied. Knowledge regarding the mechanism of ovarian toxicity of novel classes of anticancer drugs will aid the future development of ovarian toxicity protection strategies; for example, currently recommended GnRH agonists in breast cancer might or might not be protective in the setting of new agents.

Although this research statement focuses on the assessment of ovarian toxicity in cancer clinical trials that enrol pre-menopausal, post-pubertal patients with ovaries, assessing the effects of cancer treatment on gonadal function in prepubertal children and post-pubertal patients with testes is also important. Ovarian toxicity related to non-surgical treatment is potentially devastating and is estimated to affect 9·1% of childhood cancer survivors.[69] Ovarian toxicity in children can affect pubertal development and growth[69,70] and can lead to infertility and other adverse health-related outcomes associated with early menopause. Monitoring for symptoms of premature ovarian insufficiency (such as amenorrhea), evaluating follicle-stimulating hormone and oestradiol concentrations, and tracking growth and pubertal development for at-risk prepubertal and peripubertal childhood cancer survivors is recommended.[71]

In conclusion, ASCO recognises that routine measurement of ovarian toxicity in cancer clinical trials is of such importance to our patients that it can no longer be overlooked. Although complexity and burden to trial resources might increase, in many cases this will be a relatively small addition. Previous trials in both breast cancer[47] and lymphoma[72] demonstrated that assessment of ovarian toxicity can be prospectively incorporated into oncology trials.

Search strategy and selection criteria

The literature on PubMed was searched using the terms ("premature ovarian failure" or "premature ovarian insufficiency" or "premature menopause" or "infertility") and ("cancer" or "antineoplastic" or "neoplasm"). The search was restricted to full text articles in English published from database inception until Dec 31, 2022. References were also identified through searches of the authors' own files. We selected references according to their relevance to the review.

Contributors

This manuscript was prepared by an Ovarian Toxicity Taskforce convened by the American Society of Clinical Oncology (ASCO) to develop a statement regarding measurement of ovarian toxicity in cancer clinical trials. The statement was approved by the ASCO Board Executive Committee to be published as an official ASCO Research Statement. WC, RPR, SSB, JG, CS, and K-AP were responsible for supervision. SSB and CS were responsible for project administration. WC, RPR, RT, RAA, SSB, JG, CS, and K-AP were responsible for conceptualisation. WC, RPR, RT, RAA, SSB, ND, JG, ML, KHL, TP, SW, CS, DS, and K-AP were responsible for methodology. WC, RPR, RT, RAA, SSB, ND, JG, ML, KHL, SM-M, TP, DS, SP, CS, and K-AP were responsible for writing the original draft. All authors were responsible for validation and writing, and reviewing and editing the manuscript. All authors accept responsibility for the decision to submit for publication.

Declaration of interests

WC reports honoraria from AstraZeneca, Pfizer, Merck Serono, and Eisai. RAA reports grants or contracts (research funding) and consulting fees from Roche Diagnostics. ND reports employment by AstraZeneca; grants or contracts (research funding) from Amgen, Novartis, Genentech, Lilly, Pfizer, Daiichi Sankyo, and Immunomedics; and travel, accommodations, expenses, and stock options from AstraZeneca. DS reports grants or contracts (research funding) from Janssen; consulting fees (advisory role) from Janssen Oncology, AstraZeneca, Boston Scientific, Bayer, Blue Earth, Varian Medical Systems, Pfizer, and Myovant Sciences; and honoraria from Varian Medical Systems. All other authors declare no competing interests.

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