RBMO

REVIEW

Targeted cancer treatment and fertility: effect of immunotherapy and small molecule inhibitors on female reproduction

BIOGRAPHY

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KEY MESSAGE

Targeted cancer therapy induces temporary and permanent changes to the female reproductive system, in both a class- and drug-specific manner. Additional characterization of its effect on fertility is needed given the rapid introduction of targeted therapy agents into clinical practice.

ABSTRACT

Targeted cancer therapy is rapidly evolving the landscape of personalized health care. Novel approaches to selectively impeding tumour growth carry significant potential to improve survival outcomes, particularly for reproductive-aged patients harbouring treatment refractory disease. Current agents fall within two classes: immunotherapy and small molecule inhibitors. These are collectively divided into the following subclasses: monoclonal antibodies; immunomodulators; adoptive cell therapy; treatment vaccines; kinase inhibitors; proteasome inhibitors; metalloproteinase and heat shock protein inhibitors; and promoters of apoptosis. The short- and long-term effects of these treatments on the female reproductive system are not well understood. As a result, clinicians are rendered unable to appropriately counsel women on downstream effects to their fertility. Data-driven consensus recommendations are desperately needed. This review aims to characterize the effect of targeted cancer therapy on the female hypothalamic–pituitary–ovary axis, direct ovarian function and conception.

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INTRODUCTION

The female reproductive system can be disrupted transiently or permanently by cancer treatment. Although the effect of conventional cancer treatments on the female reproductive system are relatively well understood, newer modalities may not be. Advances in tumour biology, cell signalling and genetic sequencing over the past few decades have revolutionized our treatment of human malignancy. More specifically, they have created a transition from traditional cytotoxic chemotherapy to targeted immunotherapy and small molecule cell signalling inhibitors (*Hoelder et al., 2012*; *Eno, 2017*). Indeed, these new treatment modalities are being used to manage cancer in nearly every organ system as of 2020 (Supplementary Table 1) (Cancer Research Institute 2021). The benefit of these targeted therapies lies not only in their application to individualized care and improved survival outcomes, but also in their reduced toxicity profiles and the subsequent satisfaction of patients receiving them (*Borghaei et al., 2015*; *Shaverdian et al., 2017*; *Ihrig et al., 2020*).

Targeted cancer therapy is collectively made up of two classes: immunotherapy and small molecule inhibitors. The first immunotherapy to obtain Federal Drug Administration (FDA) approval in 1986 was an antitumour cytokine known as interferon-alpha 2 (Cancer Research Institute, 2021). Since then, immunotherapy has primarily evolved into four major subclasses varying by mechanism of action: monoclonal antibodies; immunomodulators; adoptive cell therapy; and treatment vaccines. Development of new immunotherapy modalities, such as oncolytic virus therapy, is also under way (American Society of Clinical Oncology, 2020; *Nash et al., 2021*). Small molecule inhibitors are agents that modify cell signalling pathways essential for tumour growth and have similarly differentiated since 2001 with the approval of Gleevec (imatinib mesylate) into four unique subclasses: kinase inhibitors; proteasome inhibitors; metalloproteinases and heat shock protein inhibitors; and promoters of apoptosis (*Savage and Antman, 2002*; *Lavanya et al., 2014*). As with immunotherapy, additional approaches to small molecule inhibition are rapidly being developed (*Zhong et al., 2021*). A hierarchical breakdown of targeted treatments for human cancer in the USA is presented in FIGURE 1.

A necessary aspect of patient-centred oncologic care involves counselling the patient on the potential adverse effects of treatment (*Patel et al., 2020*). This includes referral to specialists for fertility preservation, as recommended by the American Society for Reproductive Medicine, the American Society of Clinical Oncology, the European Society of Clinical Oncology and the European Society of Human Reproduction and Embryology (*Peccatori et al., 2013*; *Ethics Committee of ASRM, 2018*; *Oktay et al., 2018*; Anderson *et al*., 2020). Counselling is particularly important for patients receiving targeted cancer therapy, as treatment duration is often 12–24 months and the risks of relapse may prohibit its discontinuation before ovarian stimulation (*Friedlaender, 2020*; *Pfisterer, 2021*). Fertility-desiring women who do not receive adequate counselling may ultimately face an increased risk of developing anxiety, depression and decreased quality of life after treatment (*Domar et al., 1993*; *Schweiger et al., 2012*; *Logan and Anazodo, 2019*). Despite the improved tolerance observed in patients receiving immunotherapy and small molecule inhibitors, little is known about the effect these medications have on the female reproductive system. Studies to date have examined their influence on the hypothalamic–pituitary–ovarian axis, gonadal function and

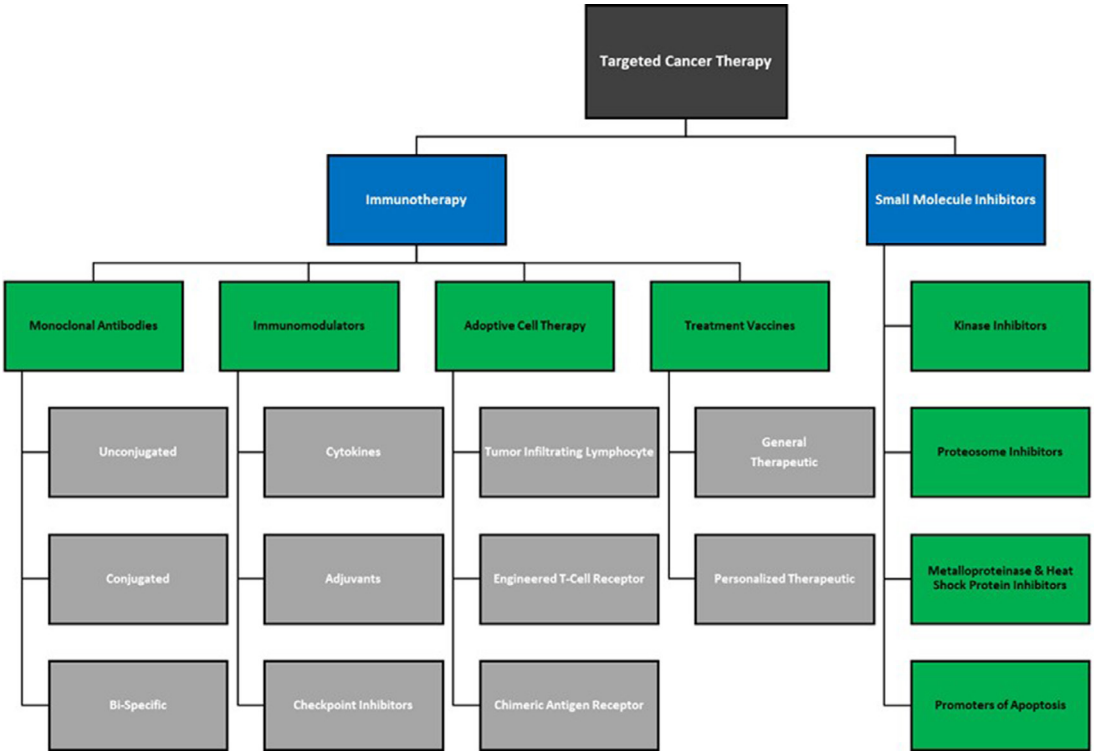

FIGURE 1 Breakdown of targeted cancer therapy by class, subclass and group.

ability to conceive, although data are limited and measured clinical end points vary widely. Data-driven, consensus recommendations are urgently needed so that clinicians can provide their pre-menopausal patients with appropriate guidance. This review aims to summarize, therefore, all available data describing the effect of cancer immunotherapy and small molecule inhibitors on the female reproductive system. It further highlights areas in need of additional study (TABLE 1).

IMMUNOTHERAPY

Cancer immunotherapy is grounded in its ability to alter the host immune system such that it is better equipped to recognize and clear malignant cells. This is achieved by, but not limited to, elevation of the host's pro-inflammatory state, normalization of aberrant cellular division, augmentation of the innate immune system's ability to recognize the tumour as non-self, and provision of pre-formed, tumour antigen-specific antibodies. Artificially heightening the host immune system, however, introduces an opportunity for inadvertent, off-target effects to normal tissue, both recurrently observed and theoretical.

Monoclonal antibodies

Monoclonal antibodies (MAb) are pre-formed, tumour antigen-specific antibodies. They are the most widely described immunotherapy subclass that interacts with female reproduction, per our review of the literature. This can likely be attributed to their homogeneity and single-target inhibition, which facilitate relatively straightforward study of 'knockout' models. Monoclonal antibodies are commonly subdivided into three groups. Unconjugated MAb are single-unit antibodies, which bind directly to receptor ligands and tumour cells to quiesce tumourigenic signalling pathways, whereas conjugate MAb facilitate direct administration of chemotherapeutics (*Kantarjian et al., 2016*) into cancer cells and bi-specific antibodies bind members of the innate immune system directly to cancer cells (*Kantarjian et al., 2017*; *Bayer, 2019*) (FIGURE 2). Although MAb are designed to bind tumour-specific receptors and ligands, their off-target binding to normal tissue (also known as 'on-target toxicity') places recipients at risk of unwanted effects (*Kizhedath et al., 2017*; *Sewell et al., 2017*). This is likely the case in female fertility (Imai *et al*., 2017). Additional damage may be caused through binding to targets on healthy tissue that share similar structure to their intended targets (also known as 'off-target toxicity'). Available data are limited to the effects of MAbs as a single entity and have not been broken down by MAb group.

Hypothalamic–pituitary–ovarian axis

Specific investigations of FDA-approved MAb on the hypothalamic–pituitary–ovarian (HPO) axis are scarce. Vascular endothelial growth factor (VEGF) and endothelial growth factor receptor (EGFR) are two common MAb targets that have been identified to promote pituitary cell survival and prolactin secretion, respectively (*Zatelli et al., 2014*). Those receiving anti-VEGF therapy may be especially prone to HPO dysregulation, as inhibition of VEGF induces a preferential reduction of fenestrated capillaries within endocrine organs (*Cao, 2014*).

Ovarian function

The effect of MAb on ovarian function seems to depend on the stage of female sexual development during which exposure to treatment occurs, as well as the target of interest. The Genotype-Tissue Expression Portal has identified many of the cell-surface receptors commonly targeted by monoclonal antibodies as receptors, which are also highly expressed in normal ovarian tissue (GTEX, 2021). VEGF receptor (VEGF-R) is one such receptor that has repeatedly been identified as essential for proper ovarian and follicular development (*Wulff et al., 2002*; *Tamanini and de Ambrogi, 2004*). For young women who have not yet undergone puberty, therefore, concern exists that inhibition of VEGF-R may permanently impede future ovarian function. Interestingly, studies in women whose ovaries have already completed normal development suggest the effect of MAb may be neutral and even beneficial. One cross-sectional study, for example, evaluated the serum anti-Müllerian hormone (AMH) level in premenopausal women (aged 25–50 years) who received chemotherapy for breast cancer (*Morarji et al., 2017*). The addition of trastuzumab (n = 25), an inhibitor of receptor tyrosine-protein kinase *HER2*, to treatment regimen had no effect on AMH level (n = 25, P = 0.307). In survivors who reported normal menstruation while undergoing treatment, trastuzumab exposure was even associated with an overall increase in AMH levels (P = 0.027). This potential protective effect of adjuvant trastuzumab on ovarian reserve is consistent with two previously published studies (*Ben–Aharon et al., 2015*; *Silva et al., 2019*). Data from the ALTTO trial further support the safety of trastuzumab on ovarian function, as its addition to a regimen of cytotoxic chemotherapy and lapatinib in patients with breast cancer was not associated with increased risk for developing treatment-related amenorrhoea (*Lambertini et al., 2019*). Future studies are needed to evaluate outcomes associated with single-agent treatment with MAb rather than their combined use with cytotoxic chemotherapies. Further, the safety profile of trastuzumab cannot be extrapolated to MAb targeting other receptors. Characterization of additional MAb is needed.

Conception

Standard clinical practice for women receiving MAb includes delaying conception to allow for a 'wash out' period (*Imai et al., 2017*). This is driven in part by the understanding that MAb are proteins that harbour a much longer half-life than traditional chemotherapeutic agents. Available data, however, suggest waiting for MAb concentrations to decrease is more of a safety measure than an absolute requirement to achieve pregnancy. One study evaluating the consequences of certolizumab-homologous antibody exposure in rats, for example, found no effect on female rat mating performance, fertility or uterine implantations of rat blastocysts (*Wakefield et al., 2011*). A second study found natalizumab to have no effect on female guinea pig pregnancy rates when administered at standard doses. Reduction in pregnancy rates (29.6% versus 63.3% in controls) were only observed in doses 36 times higher than that commonly used in humans (*Wehner et al., 2009*). Though sparse, observational data in humans also describe minimal interference of MAb on achieving pregnancy. One case report described successful conception after fertility treatment in a woman receiving denosumab (*Su et al., 2016*). Some studies have suggested the potential for MAb targeting tumour necrosis factor alpha to improve IVF outcomes in women with immune profiles characterized by T-helper cell cytokine elevation (*Winger et al., 2009*; *Clark, 2010*). Ongoing efforts

TABLE 1 KNOWN EFFECTS OF IMMUNOTHERAPIES AND SMALL MOLECULE INHIBITORS ON THE FEMALE REPRODUCTIVE SYSTEM OUTSIDE OF PREGNANCY

Class	Subclass	Indications	Mechanism of action	Effect on HPO axis	Effect on ovarian function	Effect on conception
Immunotherapy	Adoptive cell therapy	Approved for lymphomas, leukaemias and multiple myeloma if first-line therapies fail.	Artificial activation, enhancement and expansion of innate immune cells to attack cancer cells.	No specific studies. May cause indirect effects owing to certain toxicities, i.e. cytokine release syndrome, encephalopathy.	No specific studies.	No studies in cancer patients. May enhance fertility in patients with depleted T cells.
Immunotherapy	Immunomodulators	Approved for leukaemia, lymphoma, sarcoma, and cancer of the brain, breast, lung, head and neck, oesophagus, skin, stomach, kidney, liver, pancreas, colon/rectum, bladder, ovary, cervix and prostate.	Modulate key cell signalling pathways to intensify response of the innate and adaptive immune system and to improve the immune system's ability to recognize tumour as non-self.	Cytokine use may prolong menstrual cycle length by delay, inhibition of luteal phase lysis, or both. Prolonged cytokine use may cause hypothyroidism. No specific studies are available for adjuvant therapy. Checkpoint inhibitors can induce hypophysitis and hypothyroidism.	Cytokine use may blunt ovarian response to gonadotrophin stimulation, as well as stabilize the corpus luteum. No specific studies are available for adjuvant therapy. Checkpoint inhibitors may potentiate the DNA-damage induced by cytotoxic chemotherapy. Inhibition of PD-L1 may disrupt normal menstrual cycles and inhibit formation of corpora lutea.	Short-term use of cytokines may improve ovarian stimulation outcomes, particularly in women with essential thrombocytopaenia. Long-term cytokine use may decrease duration of luteal phase. No specific studies for adjuvant therapy or checkpoint inhibitors are available.
Immunotherapy	Monoclonal antibodies	Approved for leukaemia, lymphoma, sarcoma, multiple myeloma, and cancer of the brain, breast, lung, head and neck, oesophagus, skin, stomach, kidney, liver, colon/rectum, ovary, uterus and cervix.	Pre-formed, tumour antigen-specific antibodies that attenuate tumourigenic signalling pathways through binding of receptor ligands and tumour cell surfaces, induce apoptosis through binding of chemotherapeutics directly to tumour cells and induce apoptosis through binding of members of the innate immune system directly to tumour cells.	Inhibition of VEGF and EGFR may induce hypophysitis and disrupt prolactin secretion.	Inhibition of VEGF may disrupt ovarian and follicular development in pre-pubertal women. Monoclonal antibodies do not seem to alter menstruation in post-pubertal women, and they may protect ovarian reserve in those receiving cytotoxic chemotherapy.	Monoclonal antibodies, when administered at levels typically used in humans, have no effect on mating performance, fertility or pregnancy rates in animals. They do not inhibit conception altogether. Targeting TNFα might improve IVF outcomes in women with immune profiles characterized by T-helper cell cytokine elevation. Targeting IgE may improve pregnancy rates in asthmatic women seeking fertility treatment.
Immunotherapy	Treatment vaccines	Approved for skin, prostate and bladder cancer.	Concentrated antigen solutions that commonly increase the immune system's ability to recognize and mount response against such antigens present in the body.	No specific studies.	No specific studies.	No specific studies
Small molecular inhibitors	Kinase inhibitors	Approved for leukaemia, lymphoma, sarcoma, polycythemia vera and cancer of the brain, breast, lung, head and neck, skin, kidney, liver, pancreas, intestine, colon/rectum, bladder, and tenosynovium.	Inhibit kinases essential for tumour growth.	Imatinib, dasatinib, and nilotinib may induce hyper- or hypothyroidism, modify glucose metabolism and decrease growth hormone secretion. Chronic imatinib use may reduce serum gonadotrophins and induce oligo- or amenorrhoea.	Kinase inhibitors may disrupt oogenesis, follicular maturation, ovulation, ovarian cell apoptosis, ovarian release of progesterone and oestradiol, corpus luteum development and function, and granulosa response to LH. Kinase inhibitors targeting mTOR and BCR-ABL may protect ovarian reserve in those receiving cytotoxic chemotherapy.	Imatinib may reduce blastocyst development, embryo implantation rates and response to ovarian stimulation. They do not inhibit conception altogether.
Small molecular inhibitors	Matrix metalloproteinase and heat shock protein inhibitors.	–	Prevent breakdown of connective tissue. Inhibit stability of cancer proteins.	No specific studies.	No specific studies.	No specific studies.
Small molecular inhibitors	Promoters of apoptosis	–	Potentiate pro-apoptotic or inhibit anti-apoptotic pathways	No specific studies.	No specific studies.	No specific studies.
Small molecular inhibitors	Proteasome inhibitors	Approved for lymphoma and multiple myeloma.	Induce tumour cell damage by preventing proteasomes from digesting excess intracellular proteins.	No specific studies.	No specific studies.	No specific studies.

EGFR, endothelial growth factor receptor; HPO, hypothalamic–pituitary–ovarian; VEGF, vascular endothelial growth factor; –, Not currently FDA-approved for the treatment of cancer.

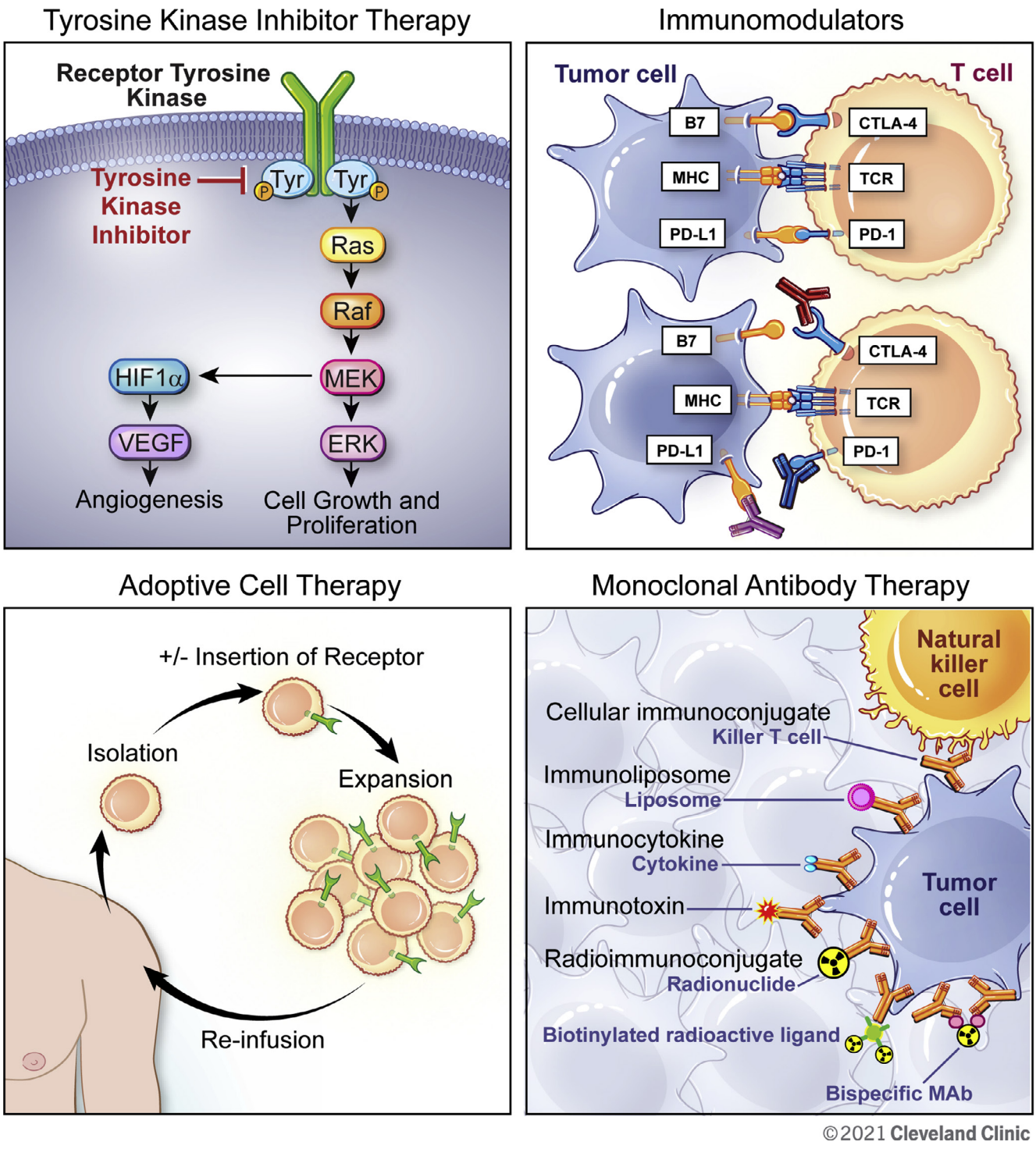

FIGURE 2 Examples of targeted cancer therapies under investigation. (A) Kinase inhibitor therapy, a class of the small molecular inhibitors, demonstrating some of the downstream pathways that are disrupted following treatment; (B) an overview of checkpoint inhibitors, a subclass of immunomodulators; (C) schematic highlighting how adoptive cell therapy is carried out; (D) schematic showing several strategies using conjugated monoclonal antibodies for drug treatment.

by the PRO-ART study are also being made to identify omalizumab, a MAb that targets immunoglobulin E, as a potential treatment for improving pregnancy rates in asthmatic women seeking fertility treatment (Tidemandsen *et al.*, 2020).

Immunomodulators

Immunomodulators are a subset of immunotherapy that modulate key cell signalling pathways to intensify response of the innate and adaptive immune system and to improve the immune system's ability to recognize tumour as non-self. These compounds can be divided into the following groups: cytokines, adjuvant therapies and checkpoint inhibitors. Cytokines are proteins that exploit autocrine

and paracrine signalling pathways to facilitate local growth and maturation of the immune system. Adjuvants further stimulate members of the innate and adaptive immune system, particularly dendritic cells, by activating cellular pattern recognition receptors and thus increasing transcription of important NF-κB and interferon signalling pathways (*Circelli et al., 2017*). Checkpoint inhibitors intercept the binding of checkpoint proteins on tumour cell surfaces with partner proteins on surrounding leukocytes (FIGURE 2). In doing so, they inhibit cell signalling pathways that tumour cells use to downregulate immune cell activation. Current FDA-approved agents are designed to target programmed death receptor 1 (PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), with development of additional targets under way (*Finn, 2012*).

Hypothalamic–pituitary–ovarian axis

Immunomodulators seem to transmit a group-specific effect, both direct and indirect, on the crosstalk between the brain and the ovaries.

The influence of cytokine therapy on the HPO axis is primarily derived from studies of Interferon-alpha (IFN–α), which includes both IFN–α2a and IFN–α2b protein recombinants. Short-term exposure to IFN–α in humans has not been shown to alter levels of FSH, LH, prolactin, insulin or thyroid-stimulating hormone (*Kauppila et al., 1982*). With prolonged use, however, these agents are associated with development of autoimmunity and resultant hypothyroidism (*Vitale et al., 2009*). A study of red deer suggests IFN–α suppresses the synchronous pulsatile secretion of oxytocin and prostaglandin F2 alpha from the pituitary gland, and thereby delays or inhibits luteal phase lysis (*Bainbridge and Jabbour, 1997*). If validated in humans, this could theoretically improve fertility outcomes in the subset of women with a short luteal phase at baseline.

Adjuvant therapies include imiquimod and polyinosinic-polycytidylic acid-poly-l-lysine carboxymethylcellulose, both of which are administered topically. No data were encountered on their influence on the HPO axis.

Of the three immunomodulator groups, checkpoint inhibitors are the most highly associated with detrimental effects to the endocrine system. The two most common manifestations are pituitary inflammation, or hypophysitis and hypothyroidism. Hypophysitis has been documented to occur in 1–3% of women receiving PD-1/PD-L1 inhibitors and up to 11% of CTLA-4 inhibitors, whereas hypothyroidism (all grades) is reported in 6% of women using PD–1/PD–L1 inhibitors and 15% for CTLA–4 inhibitors (*Caturegli et al., 2016*; *Postow et al., 2018*).

Ovarian function

The effect of immunomodulators on ovarian function remains largely unknown, with most conclusions supported by animal studies.

Cytokines do not seem to damage ovarian cells, in contrast to checkpoint inhibitors, but rather alter ovarian response to gonadotrophins and modify menstrual cycle length. In one study of five healthy human individuals, exposure to IFN–α had no effect on serum levels of LH or FSH. Exposure significantly decreased serum progesterone and oestradiol levels, however, suggesting IFN–α administration may blunt ovarian response to gonadotrophin stimulation (*Kauppila et al., 1982*). Review of ovarian function in animal models treated with cytokines found IFN–α2b to produce an overall lengthening of menstrual cycle (*Walter et al., 2016*). Mechanistic study in ewes concluded such menstrual cycle lengthening was caused by IFN–α2b's ability to stabilize the corpus luteum; however, orthogonal validation in humans is needed to confirm these findings (*Martinod et al., 1991*).

No studies investigating the role of adjuvant immunomodulators on ovarian function was obtained in our literature review.

Checkpoint inhibitors can directly impart molecular changes to ovarian tissue, which carry uncertain clinical significance. Evaluation of checkpoint inhibitors in mice suggests inhibition of checkpoint kinase 1, but not of checkpoint kinase 2, leads to granulosa cell apoptosis and subsequent follicle atresia at clinically relevant concentrations. Inhibition of checkpoint kinase 1 may additionally potentiate the DNA-damage induced by traditional agents such as gemcitabine and doxorubicin (*Xu et al., 2020*). Ipilimumab, which functions via inhibition of CTLA-4, has been found to bind connective tissue of the ovary, but such binding does not seem to result in histopathologic changes (*Duma et al., 2020*). As *Duma et al. (2020)* report, this is consistent with the absence of changes to female reproductive organs observed during preclinical studies of pembrolizumab, nivolumab and durvalumab. In contrast, inhibition of PD-L1 with supratherapeutic levels of atezolizumab in monkeys has been associated with temporary disruption of normal menstrual cycles as well as formation of corpora lutea.

Conception

The effect of immunomodulators on conception is dependent upon immunomodulator group.

Cytokines are the most common immunomodulator group to be studied in human conception. In certain cases of aggressive malignancies for which women may not survive a treatment holiday, temporary transition to IFN–α may allow for continued treatment as well as improved fertility preservation outcomes. In one woman with chronic myeloid leukaemia, for example, switching from imatinib to IFN–α led to a notable increase in oocytes retrieved (8 versus 43) in one cycle of ovarian stimulation (*Gazdaru et al., 2018*). Temporary administration of IFN–α has also been linked to improved success rates of natural conception as well as intrauterine insemination in women with essential thrombocytopaenia (*Iki et al., 1999*; *Leković et al., 2015*). Chronic exposure to cytokine therapy (up to 7 years in one case report) may decrease duration of the luteal phase, although it does not seem to definitively inhibit conception (*Lipton et al., 1996*).

No data were available for the role of adjuvant immunomodulator therapy on human conception.

As with MAb, it is recommended that checkpoint inhibitors are discontinued for a period of 4 to 5 months before attempting conception (*McGettigan and Rubin, 2017*). No reports of conception while receiving immunomodulator therapy were encountered in our review to support or disclaim the value of this practice.

Adoptive cell therapy

Adoptive cell therapy (ACT) is a rapidly evolving designer immunotherapy

that is engineered through artificial activation, enhancement and subsequent expansion of innate immune cells (FIGURE 2). Its application is currently approved for lymphoma, leukaemia or multiple myeloma that has failed multiple lines of traditional therapy (*Callahan et al., 2019*; *Raje et al., 2019*); however, ACT treatments are being developed for a broad spectrum of malignancies. The three primary ACT groups include tumour-infiltrating lymphocyte (TIL), engineered T cell receptor (TCR) and chimeric antigen receptor (CAR) T cell therapies (Cancer Research Institute, 2021; *Hoteit et al., 2021*). The TIL treatment overcomes inadequate T cell volume and activity level by isolating T cells that have successfully infiltrated tumour, followed by stimulation and expansion before re-introducing them into the host. Unlike the stimulation of tumour-infiltrating T cells used in TIL therapies, TCR introduces new receptors (typically via viral plasmids) into isolated T cells before their amplification and reintroduction into the host. This makes TCR valuable in cases in which host T cells that are unable to infiltrate tumours caused by an inability to recognize tumour antigens presented via major histocompatibility complex (MHC). CAR T further builds upon TCR therapy in that it equips T cells with chimeric antigen receptors able to recognize non-MHC bound antigens. This way, even tumour cells with downregulated MHC-bound antigens can be infiltrated. Efforts to augment additional immune cell types, most recently natural killer cells, are also under way.

Hypothalamic pituitary ovarian axis

Toxicity from ACT can be attributed to the treatment itself as well as the factors required for its administration. Toxicities directly related to ACT include cytokine release syndrome, encephalopathy, and on- and off-target toxicity. Additional consequences include organ dysfunction secondary to high doses of IL-2 (often administered alongside TIL therapy) and complications secondary to pre-conditioning lymphodepletion (*Maude et al., 2018*; *Jin et al., 2021*). Although severe encephalopathy may certainly lead to dysfunction of the HPO axis, no studies evaluating the specific effect on the HPO axis were encountered in this review.

Ovarian function

The effect of ACT on ovarian function has not been well studied. On- and off-target toxicity could theoretically damage healthy ovarian tissue, especially if ACT is developed to treat gynaecological malignancy, although no data are available to support this.

Conception

The leukaemias and lymphomas currently targeted by ACT commonly occur in children. Patients begin ACT after multiple lines of cytotoxic chemotherapy and are, therefore, already predisposed to neuroendocrinological abnormalities associated with decrease fertility. Understanding the long-term effect of ACT on conception, therefore, is an especially important consideration regardless of its severity (*Callahan et al., 2019*). No data were found in our review on conception while receiving ACT for treatment of cancer, highlighting the need for additional study. Studies of ACT treatment in participants without cancer suggest it may improve pregnancy rates in patients with dysregulation or depletion of their regulatory T cells. In this sub-population, ACT has been shown to improve embryo implantation (*Heitmann et al., 2017*) and to reduce frequency of spontaneous miscarriage (*Lamprianidou et al., 2020*).

Treatment vaccines ('reverse vaccinology')

Vaccines are concentrated antigen solutions that commonly increase the immune system's ability to recognize and mount response against such antigens present in the body. Historically, they have been used in the oncologic setting to prevent viral infections known to promote cancer (notably, the human papilloma and hepatitis B viruses). Newer vaccine types, highlighted in this review, are used as therapeutic interventions for cancer that has already developed. They can be separated into general therapeutic cancer vaccines, those that heighten the host's immune system through the introduction of known antigens or antigen-presenting cells and personalized therapeutic vaccines, those that heighten the host's immune system through the introduction of neoantigens expressed specifically by cancer cells.

The only two FDA-approved therapeutic vaccines include the Bacillus Calmette–Guerin vaccine and the Sipuleucel-T vaccine, which are used for bladder and prostate cancer, respectively. No FDA-approved personalized neoantigen vaccines are available, and no data have been reported on the effect of these new agents on the HPO-axis, ovarian function or conception.

SMALL MOLECULE INHIBITORS

Small molecule inhibitors (SMI) are low-molecular weight compounds that impair signal transduction pathways and biological processes essential to tumour cell survival. Their extremely small size, typically 500 Da or less, allows them to work at the cell surface and intracellularly. As of January 2021, 62 SMI have been approved by the FDA, 55 of which were designated for the treatment of cancer (*Roskoski, 2021*). Current subclasses include kinase inhibitors, proteasome inhibitors, metalloproteinase and heat shock protein inhibitors, and promoters of apoptosis. Kinase inhibitors work primarily by outcompeting adenosine triphosphate bindings sites on tyrosine-, serine- and threonine-kinase receptor proteins (FIGURE 2). This leads to a resultant quiescence of signal transduction pathways known to promote cancer development. Proteasome inhibitors, currently only used for haematologic malignancies, prevent proteasomes from digesting excess intracellular proteins (*Horton et al., 2019*). Given cancer cells are more reliant on proteasome function than healthy cells, the intra-cellular toxicity caused by protein accumulation leads to preferential death of malignant cells. The third subclass of small molecule inhibitors includes metalloproteinase and heat shock protein inhibitors. Downregulation of matrix metalloproteinases reduces tumourigenesis by preventing breakdown of connective tissue, and inhibition of heat shock proteins create instability of various proteins required for cancer cell survival. Lastly, promoters of apoptosis are small molecules that either potentiate pro-apoptotic or inhibit anti-apoptotic pathways.

Kinase inhibitors

Kinase inhibitors currently make up the largest majority of FDA-approved SMI. They are used to treat solid and non-solid tumours, most frequently through inhibition of BCR-ABL, epidermal growth factor receptor (EGFR), VEGF-R, v-raf murine sarcoma viral oncogene homolog B1 (B-raf), and anaplastic lymphoma kinase receptor proteins (*Roskoski, 2021*). Much like MAbs and ACT, kinase inhibitors have potential to damage healthy tissue through on- and off-target effects. In the case of MAbs, effects to

the female reproductive system identified through basic science research are often incongruent with observations in the clinical setting.

Hypothalamic–pituitary–ovarian axis

The effect of duration, magnitude and direction (positive or negative) of kinase inhibitors on the HPO axis depends largely on drug target. Despite their preferential use in solid tumours, clinical data have primarily been derived from treatment of leukaemia and lymphoma in children. Imatinib, dasatinib and nilotinib are three of the most widely examined agents and have collectively been associated with the dysfunction of most human endocrine pathways. Their associations with hyper- and hypothyroidism, unpredictable modification of glucose metabolism, and decreased growth hormone secretion, for example, may all indirectly alter female fertility (*Samis et al., 2016*). Direct measurement of HPO modulation in humans is limited to case reports of female menstruation. Imatinib, pazopanib and sirolimus have specifically been documented to induce oligomenorrhoea (*Christopoulos et al., 2008*; *Braun et al., 2012*; *de Sanctis et al., 2019*). One case of single-agent imatinib therapy for chronic myeloid leukaemia in an otherwise healthy 28-year-old woman described a development of oligomenorrhoea followed by amenorrhoea and primary ovarian insufficiency (*Christopoulos et al., 2008*). The investigators reference links between c-kit, a target of imatinib, and maintenance of mammalian oogenesis and folliculogenesis, although the actual mechanism underlying amenorrhoea is unclear and imatinib's reduction of serum LH and FSH levels may also be at play (*Hutt et al., 2006*; *Yaghmaei et al., 2009*). Pazopanib was also found to induce oligomenorrhoea; however, discontinuation of treatment led to a return of regular menses within 2 months. These differences highlight the importance of characterizing the common effect of kinase inhibitors as well as their effects on an individual basis.

Ovarian function

Studies aiming to characterize the effects of kinase inhibitors on ovarian function are relatively abundant. Available data suggest their effect ranges from harmful to beneficial and, similar to their effect on the HPO axis, depends on the drug target being inhibited. Common kinase inhibitor targets, such as tyrosine-protein kinase KIT (c-kit), phosphoinositide 3-kinase (PI3K), extracellular signal-regulated protein kinase 1 and 2 (ERK 1/2), VEGF and platelet derived growth factor (PDGF) protein have all been identified as essential regulators of granulosa cell response to LH, oogenesis, follicular maturation, ovulation, ovarian cell apoptosis and ovarian release of progesterone and oestradiol (*Stouffer et al., 2001*; *Fan et al., 2009*; *Sirotkin, 2011*; *Grosbois and Demeestere, 2018*). A recently published review by *Rambhatla et al. (2021)* further describes many of these associations. Possibly the most well described sequela of kinase inhibitor use is interference with corpus luteum development and function (*Ferrara et al., 1998*; *Stouffer et al., 2001*; *Fraser et al., 2005*; *Pan et al., 2014*). Interestingly, the ovary may be able to overcome kinase inhibitor-induced damage via compensatory upregulation of alternative cell cycle signalling pathways. Upregulation of the signal transducer and activator of transcription 3 (STAT3) pathway in mice has been found to counteract the inhibition of EGFR caused by lapatinib, as in the study by *Liao et al. (2020)*. This may explain the overall neutral effect on corpora lutea seen in animal models exposed to kinase inhibitor therapy (*Catlin et al., 2019*; *Zhang and Tian, 2020*).

Unlike the negative and neutral effects of kinase inhibitors on ovarian function, kinase inhibitors targeting mammalian target of rapamycin complex 1 (mTOR) may prove valuable in preserving fertility, specifically for women already receiving traditional cytotoxic chemotherapy. The addition of an mTOR inhibitor to mice receiving cisplatin or cyclophosphamide, compared with mice receiving cisplatin or cyclophosphamide alone, has demonstrated remarkable improvements in ovarian reserve, primordial follicle counts and serum AMH levels (*Goldman et al., 2017*; *Tanaka et al., 2018*). Inhibiting mTOR seems to induce a temporary arrest of ovarian cell activation such that cells are less receptive to surrounding chemotherapy (*Grosbois et al., 2019*). Imatinib, which targets the BCR-ABL tyrosine kinase protein, may provide a similar protection (*Kim et al., 2013*; *Morgan et al., 2013*). Additional research is needed to validate these findings.

Conception

Kinase inhibitors may reduce one's ability to conceive, but they do not prevent it together. Research to date has found that the effects of kinase inhibitors occur primarily at the levels of blastocyst development and embryo implantation. Imatinib exposure in mice had no effect on ovulation or fertilization rates in one study, i.e. it was associated with a reduced number of cells at the blastocyst stage. Also, blastocysts from imatinib-treated mice displayed a reduced ratio of inner cell mass to trophectoderm cells (*Salem et al., 2020*). Kinase inhibitors seem to modify implantation through regulation of endometrial receptivity. Inhibition of c-kit and BCR-ABL have been found to decrease embryo implantation rates (Park *et al*., 2018) and reduce embryo implantation site sizes (Salem *et al*., 2019), respectively. As observed in one case report, imatinib may also decrease ovarian response to gonadotrophin stimulation in those seeking fertility preservation (*Zamah et al., 2011*). Despite these negative effects, numerous case reports of healthy conception in women undergoing treatment with kinase inhibitors demonstrate they are not absolutely prohibitive of achieving pregnancy (*Kelly et al., 2006*; *Conchon et al., 2009*; *Kroll et al., 2010*; *Alizadeh et al., 2015*; *Abu-Tineh et al., 2020*). Also, not all kinase inhibitors impair implantation and it is important to consider each drug separately. Inhibition of Bruton's tyrosine kinase (BTK) in rats had no effect on implantation rates in one study (*Zhang and Tian, 2020*), for example, and inhibition of mTOR has even been found to improve implantation in women with T regulatory cell depletion (*Royster et al., 2019*).

Proteasome inhibitors, matrix metalloproteinase and heat shock protein inhibitors, and promoters of apoptosis

Proteasome inhibitors, matrix metalloproteinase and heat shock protein inhibitors, and promoters of apoptosis, are relatively new classes of small molecule inhibitors. The pathways they target are well characterized, but their application to clinical care has partially been limited by the challenges of developing compounds with adequate specificity for target tumours (*Fields, 2019*; *D'Aguanno and del Bufalo, 2020*). The effect these agents have on the female reproductive system is not described.

CONCLUSIONS

Targeted cancer therapy is rapidly evolving the landscape of personalized

health care. Although these novel approaches to selectively impeding tumour growth carry significant potential to improve survival outcomes, they can lead to off target effects, including collateral damage of the female reproductive system, both temporary and permanent. In select populations, certain classes of targeted cancer therapy may improve reproductive outcomes. Data to provide adequate characterization of these risks and potential benefits are extremely lacking, rendering physicians unable to appropriately counsel women on downstream effects to their fertility. This is an especially pertinent issue given targeted therapy is commonly used in young patients, a population who is most vulnerable to long-term sequelae to reproductive health. Further study of both class- and individual drug-specific effects is needed.

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