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Infertility risk and teratogenicity of molecularly targeted anticancer therapy: A challenging issue

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ABSTRACT

The growing population of young cancer survivors and a trend toward postponing pregnancy until later in life are shifting areas of focus toward understanding treatment induced sequelae, particularly the effects of cancer and/or treatment on fertility. Whereas the fertility risk of cytotoxic agents for both men and women is well-recognized, the fertility risks and teratogenic potential associated with molecular targeted therapies are not established. We summarize available preclinical and clinical data on the impact of new molecular targeted agents on fertility in both sexes, and their potential teratogenic effects, providing

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recommendations for clinicians, where possible. Agents were categorized by class and the potential relevance of their target signaling pathways to gonadal maturation discussed.

1. Introduction

In recent decades, the number of cancer survivors in western countries has dramatically increased; two-thirds of them are expected to survive at least five years from diagnosis (Valdivieso et al., 2012). Five percent of current cancer survivors were diagnosed before the age of 40 years (Siegel et al., 2012). The growing population of young cancer survivors represents a clear challenge to clinicians and researchers to look beyond the search for a cure and to address the multifaceted needs of those patients living with and beyond a cancer diagnosis. One of the common sequelae that disrupts psychosocial aspects of adult life after anticancer treatment is infertility. Understanding the effects of cancer and/or treatment on fertility has become increasingly important because women are having children later in life (Johnson and Tough, 2012). As with the other potential complications of cancer treatment, oncologists have a responsibility to inform patients about the risks of potential treatment-related infertility and about fertility preservation options prior to treatment. However, available data are poor and heterogeneous and the issue is complicated by the large number of patient factors that influence fertility. Considering the most commonly used, cytotoxic agents, the greatest risks for both men and women involve the alkylating agents (particularly cyclophosphamide, ifosfamide, nitrosoureas, chlorambucil, melphalan, busulfan, and procarbazine), while several other drugs as methotrexate, fluorouracil, vincristine, bleomycin, and dactinomycin are associated with a low or no risk of infertility (Lambertini et al., 2016).

However, the field of oncology has recently entered the era of molecular target therapies (MTT), with the development of numerous targeted agents that inhibit various pathways responsible for growth and survival of cancer cells. Despite their high selectivity, these agents also affect signal transduction in normal cells and tissues, causing a wide range of previously unknown on-target and off-target side effects.

Numerous studies sought to identify and manage these target-related adverse effects, whereas little effort have been made to investigate the impact of MTT on gonadal function. Few preclinical studies have assessed the impact of MTT on fertility, and no prospective clinical trials are available. Most data are from retrospective evaluations or case reports.

Another poorly investigated issue is the potential teratogenic effects of new molecular drugs when used in pregnant women. Cancer diagnosis during pregnancy is relatively rare, affecting approximately one out of 1000 pregnancies, with an estimated 6000 new cases diagnosed in the USA every year (Pentheroudakis and Pavlidis, 2006; Pavlidis, 2002). However, the incidence is expected to grow given the trend toward postponing pregnancy later in life. Breast and cervical cancers are the most commonly diagnosed tumors during pregnancy, followed by melanoma, lymphoma and leukemia (Pavlidis, 2002). Managing cancer during pregnancy forces oncologists, hematologists, obstetricians and neonatologists to make crucial decisions without strong supporting evidence. On the other hand, the relative rarity of this situation precludes prospective clinical trials and thus decisions continue to rely on very limited evidence. We know that some of the molecular targets of these new compounds have a central role in both gonadal maturation and embryonic development, potentially causing serious harm to the developing fetus.

This review will summarize preclinical and clinical data on the impact of new molecular targeted agents on fertility in both sexes, and their potential teratogenic effects. Our aim is to emphasize these two aspects, and to provide useful recommendations for clinicians where possible.

2. Analysis by drug class

For clarity, we have divided the existing literature into five categories according to the classes of molecular targeted drugs:

1) Bcr-Abl, SCF/c-kit, and Plated Derived Growth Factor Receptor (PDGFR) signaling inhibitors
2) angiogenesis inhibitors (A-I)
3) mTOR inhibitors (mTOR-I)
4) Epidermal Growth Factor Receptor (EGFR) inhibitors (EGFR-I)
5) Anaplastic Lymphoma Kinase (ALK) inhibitors (ALK-I).

For each category, we have discussed the role of the molecular pathway in gonadal maturation (Table 1), and reviewed pre-clinical and clinical studies that have addressed effects on fertility and/or teratogenicity (Tables 2 and 3).

2.1. BCR-ABL, SCF/c-kit, and PDGFR signaling inhibitors: imatinib, nilotinib, and dasatinib

The pivotal role of SCF/c-kit signaling in regulating both male and female gonadal development is widely described (Mauduit et al., 1999; Mariani et al., 2002; Carlsson et al., 2006; Hutt et al., 2006; Nilsson et al., 2006). SCF/c-kit regulates primordial germ cell migration, proliferation and apoptosis during fetal gonad development, and spermatogonia proliferation in the adult. Accordingly, genetic defects of SCF/c-kit lead to a decrease in primordial germ cell migration and spermatogonia proliferation and an increase in germ cell apoptosis in adult mice, causing oligo or azoospermia (Mauduit et al., 1999). Moreover, PDGF is a key regulator of Leydig cell development in the testis (Mariani et al., 2002). SCF/c-kit is also expressed in human ovaries during follicular development,

Table 1
The role of molecular pathways in gonadal maturation.

Pathway	Role (Female)	Role (Male)
c-Kit/SCF	Survival of human ovaries during early folliculogenesis; Primordial germ cell establishment, primordial follicle activation, granulosa cell proliferation, theca cell recruitment, meiotic maturation	Germ cell migration, proliferation and apoptosis during gonadal development in the fetus; Proliferation of spermatogonia in the adult
PDGF	Transition of primordial to primary follicles	Leydig cell
EGF	Ovarian follicular growth and differentiation	Testes development and spermatogenesis
VEGF	Oocyte migration	Spermatogonia stem cell homeostasis
ALK	Not studied	Not studied