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Hot Topic

Targeted agents for cancer treatment during pregnancy

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ABSTRACT

The last decade has witnessed important advances in the field of managing cancer during pregnancy. However, still limited data is available on the safety of administering targeted agents in pregnant cancer patients. Given the increasing use of targeted agents in clinical practice, it is becoming vital to properly understand how far they can be used in a pregnant patient without compromising the outcome of the fetus. Unlike chemotherapy, monoclonal antibodies are large molecules that require active transport via the placenta to reach the fetus. On the other hand, similarly to chemotherapy, small molecules like tyrosine kinase inhibitors (TKIs) can cross the placenta throughout the pregnancy period.

The majority of targeted agents have worrying preclinical data discouraging their use during pregnancy. Multi-TKIs are of particular concern given their potential interference with other vital physiological functions that could be necessary in fetal development. Yet this does not mean that all targeted agents should be avoided completely during pregnancy. The current review provides a critical evaluation on all targeted agents that are currently in clinical use and provides a guide in order to help clinicians counseling their pregnant cancer patients.

Introduction

The last decade has witnessed important advances in the field of managing cancer during pregnancy [1–3]. Several groups have published large prospective and retrospective studies looking into the safety of administering chemotherapy during pregnancy particularly doxorubicin/epirubicin-based regimens and to a lesser extent taxanes [4–6]. Available data suggest that chemotherapy is associated with an increased risk of congenital malformations when administered during the first trimester, reaching up to 20% [7]. Yet the risk of malformations appears to be comparable to that of the general population when chemotherapy is started from the 14th week of gestation onwards, albeit pregnancy-related complications are relatively higher compared to untreated patients [7]. Nevertheless, if patients are managed in referral centers with specific expertise in the field, neonatal outcome are usually satisfactory [3].

Conversely, limited data are available on the safety of administering targeted agents in pregnant cancer patients. Most of these compounds are labeled by the Food and Drug Administration (FDA) as class D, indicating that they are contraindicated during pregnancy. However, in the majority of cases, this is based on limited preclinical data. Given the increasing use of targeted agents in clinical practice, with some playing a pivotal role in improving patient survival, it is becoming increasingly important to properly understand whether these compounds can be used in pregnant patients without compromising fetal outcome. Adopting the rule of thumb of chemotherapy – avoiding first trimester exposure and starting therapy with second trimester – is not always valid for two folds. First, such "rule" has not even proven to apply for all chemotherapeutics, with some cytotoxics (e.g. idarubicin), showing increased fetal morbidity and pregnancy complications even with exposure during the second and third trimesters [8]. Second, targeted agents have different structure, metabolism and pharmacokinetics than chemotherapy and hence their pattern of adverse events and safety in the pregnancy setting could be completely different (Fig. 1).

Another important point is that targeted agents do not represent a homogenous group of drugs. On one hand, biological agents such as monoclonal antibodies are large molecules that require active transport via the placenta to reach the fetus [9]. It has been shown that this does not take place before the 14th week of gestation suggesting that exposure to monoclonal antibodies during the first trimester of pregnancy is unlikely to be associated with high

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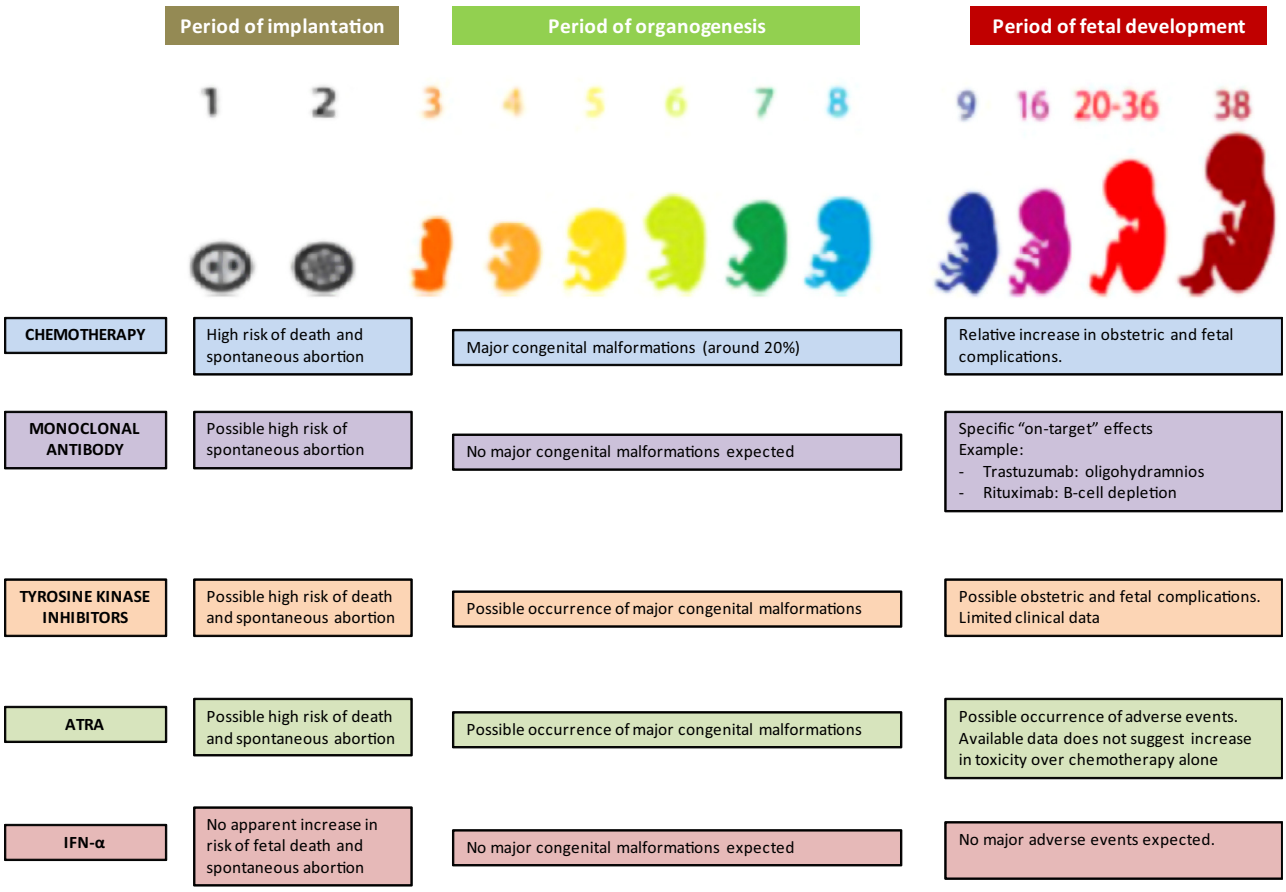

Fig. 1. Key differences between chemotherapy and different classes of targeted agents in terms of their expected toxicity during pregnancy.

fetal exposure [9]. This is not the case with small molecules like tyrosine kinase inhibitors (TKIs), which similar to chemotherapy can cross the placenta throughout the pregnancy period. On the other hand, targeted agents are by definition "targeted" against different tumor-related molecular aberrations, which in some instances could also have a physiological role in fetal development. Hence, each family of agents with specific "target" could have very specific pregnancy-related adverse events secondary to their on-target effect.

In this review, we provide a critical evaluation and discuss the available preclinical and clinical data dealing with the use of targeted agents in managing cancer during pregnancy. We will discuss how to counsel pregnant patients requiring treatment with targeted therapy and how to deal with patients who become accidentally pregnant while receiving any of these compounds.

Anti-HER2 agents

Trastuzumab

Trastuzumab is a humanized recombinant IgG1 monoclonal antibody that is approved in managing patients with human epidermal growth factor receptor 2 (HER2)-positive breast and gastric cancer [10]. It is considered one of the most important agents in the history of managing breast cancer, having resulted in significant improvement in survival both in the early and advanced settings when added to chemotherapy without considerably increasing chemotherapy-related toxicity [11–13]. Given the relative rarity of gastric cancer in women in the childbearing period, the focus here will be on women diagnosed with HER2-positive breast cancer during pregnancy and whether trastuzumab could be considered in these patients.

The HER2 pathway is involved in fetal organogenesis, as it plays a vital role in normal cardiac and neural development (Table 1) [14]. Moreover, HER2 seems to be involved in the early conception and implantation phases [15]. To date, no embryolethal or fetotoxic effects have been reported in laboratory animal studies with the use of trastuzumab [7].

In humans, around 34 breast cancer patients exposed to trastuzumab during pregnancy have been reported [16,17]. In only 5 cases, trastuzumab was "intentionally" started during the second or third trimester for pregnant patients with metastatic HER2-positive breast cancer [17]. Chemotherapy was given in all cases except one; two with paclitaxel, one with docetaxel and one with vinorelbine [17]. All cases were complicated with oligohydramnios resulting in preterm delivery. All babies were alive at the time of reporting but at least two had respiratory distress and renal failure at delivery [17]. All the remaining cases ($n = 29$) became accidentally pregnant on trastuzumab, thus being exposed during the first trimester [16,17]. The largest report came from the HERA trial in which 16 patients became pregnant while receiving adjuvant trastuzumab [16]. A total of 4 patients (25%) experienced spontaneous abortion. Of those who elected to continue pregnancy, trastuzumab was stopped once pregnancy was confirmed, and all delivered at term with no pregnancy complications or fetal malformations [16]. None of these cases developed oligohydramnios [16]. On the other hand, sporadic case reports on patients who elected to continue trastuzumab and pregnancy ($n = 8$) showed what appears to be a high risk of oligohydramnios ($n = 5$), preterm delivery ($n = 4$) and neonatal deaths ($n = 4$) [17]. Of note, no congenital