Drugs selection and dosing in pregnant cancer patients: insights from clinical pharmacokinetics

The co-occurrence of cancer and pregnancy is a rare clinical situation (1/1000 pregnancies), with breast cancer being the most frequent solid tumour in pregnant patients [1]. Recent clinical data indicate that systemic treatment in breast cancer patients during the second and third trimesters of pregnancy should be as close as possible to that used in non-pregnant patients (level of evidence 2b) [2–4], with the exception of trastuzumab that exhibits renal toxicity for the foetus, due to major transplacental transfer [4, 5].

Clinical experience indicates a good tolerability of anthracyclines and taxanes during the second and third trimesters of pregnancy [6–9], but the known physiological variations in drugs pharmacokinetics during pregnancy [10] raise important questions regarding the optimal drug dosage in pregnant patients. Indeed, the favourable toxicity profile of these agents during the late trimesters of pregnancy questions whether pregnant patients could achieve suboptimal plasma concentrations compared with that observed in non-pregnant patients, resulting in decreased anti-tumour efficacy.

Lessons from pharmacological literature in pregnant cancer patients could therefore be summarized as follows.

Firstly, most anti-cancer agents are prescribed according to body surface area (BSA), resulting in large inter-patient variability even outside the pregnancy setting. In the context of pregnancy, no data are available to date to support the use of alternative dosing methods, and dosing based on BSA, using the actual patient’s weight, remains a standard [11]. On the other hand, the use of target-area under the curve (AUC)-based dosing for carboplatin (in platinum-sensitive diseases such as triple-negative breast cancer, lung cancer and gynaecological malignancies) cannot be recommended in pregnant patients [11].

Secondly, an increase in the activity of major enzymes involved in the metabolism of taxanes and anthracyclines (such as cytochrome p450 isofrm CYP3A4) is observed during the late trimesters of pregnancy [12], potentially resulting in decreased drug exposure. In the present issue of Annals of Oncology, van Hasselt et al. [10] investigated the pharmacokinetics of doxorubicin, epirubicin, paclitaxel and docetaxel in pregnant and non-pregnant cancer patients. Whereas exposure to anthracyclines does not seem to be significantly influenced by pregnancy, exposure to taxanes was markedly decreased in pregnant patients. These data are in part supported by recent findings on doxorubicin pharmacokinetics in pregnant patients, pinpointing the lack of deleterious effects of pregnancy on doxorubicin AUC over 48 h [13].

As a consequence, current anthracyclines dosing methods should probably be remained unchanged, but clinicians should be aware of potential suboptimal exposure while using taxanes.

Thirdly, although maternal drug exposure is a concern in terms of treatment efficacy, the transplacental transfer of anti-cancer agents is critical for fetal safety. Data on transplacental transfer rates indicate similar and reassuring data on doxorubicin, epirubicin and taxanes [14–16], still with major inter-patient variability, particularly marked with docetaxel [16]. Consequently, from the fetal safety point of view, paclitaxel should probably be preferred to docetaxel in the setting of pregnancy. Further studies on placental transporters and their influence on drug disposition are ongoing and will probably help handling taxanes in pregnant patients. To date, whether paclitaxel dose increases could result in (i) improved anti-tumour efficacy and (ii) different fetal toxicity remains largely unknown.

Consequently, further clinico-pharmacological studies are needed before changing our practice on chemotherapy dosing during pregnancy. Although taxanes appear safe in the second and third trimesters of pregnancy, anthracycline-based chemotherapy should be preferred as initial treatment in breast cancer patients until concerns on paclitaxel exposure and efficacy are elucidated in pregnant patients.

Collaborative studies such as those proposed by the European Society of Gyneacological Oncology Cancer in Pregnancy Taskforce (http://www.cancerinpregnancy.org/) are mandatory to improve knowledge and patients care in such a complex clinical setting.

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