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SHORT COMMUNICATION

Paclitaxel and cisplatin chemotherapy for ovarian cancer during pregnancy: case report and review of the literature

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Abstract The safety of chemotherapy during pregnancy is debatable. We present a case of advanced ovarian cancer, diagnosed at week 28 of gestational age, treated with 2 cycles of paclitaxel/cisplatin (TC) chemotherapy during pregnancy, with no serious toxicity. At week 34, the patient underwent a caesarean section and delivered a healthy girl. Four additional cycles of TC were administered. Three months after completing chemotherapy, the patient developed abdominal progression and subsequently a huge metastatic cystic mass in the brain. Despite subsequent therapies, the patient died of progressive disease 35 months after the diagnosis. The infant had normal growth and development by 73 months of her age. This is another reported case of ovarian cancer diagnosed during the second trimester of the pregnancy treated with TC chemotherapy without apparent teratogenic effect.

Keywords Pregnancy · Ovarian carcinoma · Chemotherapy

Introduction

Diagnosis of cancer during pregnancy is uncommon, with breast and cervical cancer, lymphoma, and melanoma being the most frequent malignancies. Nevertheless, the incidence of cancer in pregnancy is increasing, probably due to routine use of sonography during prenatal care and the tendency to postpone childbirth to an older age. The standard therapy for advanced epithelial ovarian cancer (EOC) consists of cytoreductive surgery followed by chemotherapy, preferably including paclitaxel combined with cisplatin or carboplatin. We present here a case of a pregnant woman with advanced EOC, treated with paclitaxel/cisplatin (TC) chemotherapy, with preservation of the pregnancy.

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A case

A 24-year-old woman, gravida 1, presented with an asymptomatic polycystic adnexal mass diagnosed at week 28 of gestation at the routine ultrasound examination. The patient had no history of ovarian, colon or breast cancer in the family. She underwent a laparotomy with bilateral salpingo-oophorectomy, omentectomy and appendectomy. Intraoperative examination showed disseminated small multiple peritoneal nodules and a few superficial liver metastases up to 2 cm in size. The postoperative course was uneventful. The abdomen ultrasound performed postoperatively confirmed the presence of metastatic liver lesions sized 32–80 mm, located in both lobes. The final diagnosis was stage IV, grade 2 mucinous ovarian adenocarcinoma. After extensive discussion with the patient and her family, informed consent was obtained for postoperative chemotherapy, with attempted preservation of the pregnancy. Nineteen days after the surgery, chemotherapy consisting of paclitaxel 175 mg/m^2 over 3 h and cisplatin 75 mg/m^2, with standard premedication of steroids and anti-emetics (20 mg dexamethason twice a day, 8 mg ondansetrone) was initiated. The baseline serum liver and renal function tests were normal; the level of Ca 125 before starting chemotherapy was 71 IU/ml. After 3 weeks, the patient received a second chemotherapy cycle. Treatment was well tolerated.

At week 34, after administration of corticosteroids for foetal lung maturation, a caesarean section with staging laparotomy was performed. The exploration of the abdomen cavity showed multiple small persisted post-chemotherapy lesions located in the perimetrium, peritoneum of vesicouterine fold, Douglas sinus and the diaphragmatic dome, as well as metastatic lesions on the liver surface of 0.1–1 cm in diameter. The woman delivered a healthy girl (1,900 g, Apgar score 8 at 5 min, and normal laboratory tests). There were no peri- or postoperative complications. Four additional TC cycles were administered. Ca 125 level after completing the sixth cycle of chemotherapy was 39 IU/ml. Progressive disease in the liver (tumour lesions of 55 × 46 mm in size) and enlarged para-aortic lymph nodes were found on CT scans performed 3 months later. Subsequent 7 cycles of topotecan resulted in disease stabilization and Ca 125 level was 30 IU/ml. Topotecan administration was stopped after a huge cystic mass (55 × 45 × 50 mm) in the brain had been diagnosed, following headache complaints. Negative cytology was obtained after diagnostic biopsy. The patient received palliative whole brain irradiation of 20 Gy in 5 fractions followed by chemotherapy: subsequently single-agent carboplatin, cyclophosphamide/cisplatin and finally 2 cycles of liposomal doxorubicin. Despite therapy, 35 months after cancer diagnosis, the patient died of progressive abdominal lesions without central nervous system symptoms. The infant had normal growth and development at 73 months of her age.

Discussion

The development of malignant disease during pregnancy leads to an enormous emotional burden to the patient, her partner and the medical staff, accompanied by medical dilemmas. Surgery for malignant tumours seems to be safe, whereas the teratogenicity of cytotoxic agents depends on several factors, including their type, timing of exposure, dose and characteristics affecting placental transfer [1]. The use of chemotherapy during the first trimester increases the risk of spontaneous abortion, foetal death and major malformation and is generally contraindicated in this period. Accumulating data suggests that at the time organogenesis is completed, the risk of intrauterine growth restriction and low birth-weight is low. In consequence, chemotherapy is a viable option in selected pregnant women. However, only a few studies have evaluated the long-term consequences for children exposed to chemotherapy while in utero [1–5]. Owing to the limited clinical experience and the unique taxane antineoplastic mode of action, generally the use of taxanes in pregnancy is not recommended [1]. Until now, only a few cases of chemotherapy with taxanes, including paclitaxel alone or in combination with either cisplatin or carboplatin, applied during pregnancy, have been reported [1, 3, 4, 6–14]. In all cases but one, organogenesis had been completed by the time of treatment onset. Current experience includes five cases of EOC treated with 6, 5 (two cases), 4 and 3 cycles of paclitaxel-based chemotherapy, respectively, and one patient with FIGO III dysgerminoma administered 4 cycles of paclitaxel/carboplatin (Table 1) [6, 9–12, 14]. We presented another patient with advanced EOC, who received 2 cycles of TC chemotherapy during the second trimester of pregnancy. Therapy did not apparently affect the development of the infant during the first 6 years of observation. No teratogenic effects of 3 cycles of TC combination (with paclitaxel administered at 135 mg/m^2/24 h) for EOC during pregnancy were reported by Sood et al. [14] in 2001. Similarly to our case, the patient's outcome was fatal, whereas the growth and the development of the infant was normal at 29 months of age. No teratogenic effect was also shown within 20 months of the infant's life in the dysgerminoma patient administered paclitaxel/carboplatin chemotherapy [9]. In another case, the episode of respiratory insufficiency occurring immediately after the delivery in a newborn exposed to 3 cycles of TC chemotherapy due to mother's lung cancer was considered to be related to neonatal prematurity rather than chemotherapy toxicity [7].

Overall, there have been so far about 52 reports of pregnant women managed with platinum-based chemotherapy, including 19 women treated for EOC with 2–6 cycles of single-agent or cisplatin/carboplatin-containing multidrug chemotherapy, starting at the second or third trimester of gestation [3–6, 10–17].

Our patient was administered cisplatin as it is preferred over carboplatin owing to the higher risk of thrombocytopenia [1]. Additionally, in 2004 at the start of chemotherapy, the clinical experience on the use of carboplatin treatment in pregnant women was very limited.

The review of all studies (published in English from 1977 to March 2008) concerning platinum therapy showed 43 cases of pregnant women (cisplatin in 36, carboplatin in 6, and both agents in one patient) [5]. In this group two foetal malformations were recorded, in both cases after therapy with cisplatin. However, causality related to in utero cisplatin exposure could not be proven. Acute respiratory distress (in three premature newborns), cytopenia, elevation of serum creatinine and hearing impairment were also observed. No foetal malformations and normal neonatal examinations were reported after therapy with carboplatin. It is believed that the administration of both platinum salts is feasible during the second and third trimester of pregnancy; however owing to the transplacental transfer of these drugs in late pregnancy, collecting further data on teratogenic effects remains highly relevant.

Until now, the longest reported follow-up of the children exposed to intra-uterine chemotherapy with cisplatin or

Table 1 Case reports of the use of paclitaxel alone or with cisplatin/carboplatin chemotherapy during pregnancy for epithelial ovarian cancer

Ref.	Histological type/grade	FIGO staging	GA at diagnosis/ CHT starting (weeks)	Treatment during pregnancy	Treatment after caesarean delivery	GA at delivery	Foetal outcome	Maternal outcome
Doi et al. [6]	Mucinous cyst adenocarcinoma	Ic	15/24	USO, staging 5 cycles PXL 120 mg/m^2 C (AUC 3) Q 2 w	Omentectomy, staging, pelvic lymphadenectomy	36	Good at 40 months	Disease free at 40 months
Mantovani et al. [10]	Papillary serous cystadenocarcinoma	III	17/22	USO, lymph nodes sampling 5 cycles PXL 175 mg/m^2 Q 3 w	Hysterectomy, USO, omentectomy, appendectomy, staging, pelvic lymphadenectomy 6 cycles PXL 175 mg/m^2 C (AUC 5)	38	Good at 16 months	Disease free at 3 weeks after CHT completion
Mendez et al. [11]	Papillary serous adenocarcinoma	III	5/16–17	USO, omentectomy, lymph nodes sampling 6 cycles PXL 175 mg/m^2 C (AUC 5) Q 3 w	Hysterectomy, USO, staging, appendectomy, pelvic and PA lymphadenectomy	35.5	Good at 15 months	Disease free at 15 months
Modares Gilani et al. [12]	Papillary serous adenocarcinoma	III	20/22	USO, staging 4 cycles PXL/C	Hysterectomy, omentectomy, pelvic and PA lymphadenectomy	35	Good at 5 months	Disease free at 6 months
Sood et al. [14]	Papillary serous adenocarcinoma	III	27/27–28	USO, omentectomy. optimal cytoreduction 3 cycles PXL 135 mg/m^2/ 24 h CDDP 75 mg/m^2 Q 3 w	USO, hysterectomy, cytoreduction 3 cycles PXL/CDDP	37	Good at 30 months	Died at 29 months
Present case	Mucinous adenocarcinoma	IV	28/30	USO, omentectomy, appendectomy 2 cycles PXL 175 mg/m^2/3 h CDDP 75 mg/m^2 Q 3 w	4 cycles PXL 175 mg/m^2 CDDP 75 mg/m^2	34	Good at 73 months	Died at 35 months

GA gestational age, *CHT* chemotherapy, *C* carboplatin, *CDDP* cisplatin, *PXL* paclitaxel, *PA* para-aortic lymph nodes, *USO* unilateral salpingo-oophorectomy

paclitaxel, with no evidence of sequelae, has been 42 months and 40 months, respectively [6, 15]. We have reported another case of a child exposed to the TC combination with no evidence of sequelae after 73 months of follow-up.

The staging and treatment of cancer at pregnancy should preferentially follow the standard approach [2]. Due to increased levels of Ca 125 in pregnancy and puerperium, the diagnostic value of this assay is limited [18]. The typical management of ovarian carcinoma includes total hysterectomy. Pregnant women diagnosed with advanced EOC should undergo organ-saving surgery, with the removal of the reproductive organs only after the delivery [19]. In our case, the surgery was restricted to a mere staging and this might have worsened treatment efficacy.

The prognosis of maternal ovarian cancers is similar to those in non-pregnant women in the reproductive age [20]. Suboptimal therapy and initial advanced stage of disease as a result of delayed diagnosis in some pregnant women are associated with worse outcome. The presented case was diagnosed in an advanced stage, with no real chance for cure.

In conclusion, standard chemotherapy including paclitaxel for advanced EOC diagnosed during pregnancy seems to be safe; however, potential risks and benefits of this therapy still have to be cautiously weighted.

Conflict of interest None.

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