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ORIGINAL ARTICLE

Doxorubicin and ifosfamide for high-grade sarcoma during pregnancy

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Abstract
Purpose Doxorubicin and ifosfamide are highly active drugs for the treatment of high-grade sarcomas, but little is known on the optimal management of young patients who develop such malignancies during pregnancy.
Methods We report on a single-institution series of patients ($n = 9$) with high-grade sarcoma diagnosed during the third trimester of pregnancy. Neoadjuvant chemotherapy combining doxorubicin (50 mg/m^2 day 1) and ifosfamide (2.5 g/m^2 days 1–2) with standard mesna rescue every 3 weeks was administered during the third trimester of pregnancy in five patients.
Results We observed a favourable outcome for both the mother and the offspring in all cases. Maternal and neonatal pharmacokinetic data for ifosfamide were obtained from one patient and did not evidence a transplacental transfer of this drug. The use of other active drugs (cisplatin, etoposide, dactinomycin and cyclophosphamide) in sarcoma during pregnancy is discussed on the basis of a comprehensive review of the English literature.
Conclusions In view of this single-centre experience, we suggest that the treatment of high-grade sarcoma during the third trimester of pregnancy should include an adapted regimen tailored to the pharmacological specificities of the pregnant patients.

Keywords Chemotherapy · Osteosarcoma · Sarcoma · Pregnancy · Doxorubicin · Ifosfamide · Cisplatin · Cyclophosphamide · Etoposide · Dactinomycin

Introduction

Cancer is a rare complication of pregnancy that occurs in up to 1/1,000 pregnancies in Western countries [5, 40]. Although the incidence of osteosarcoma and Ewing's sarcoma is noteworthy high during the second and third decades (thus in potentially childbearing women), very limited data are available regarding the management of sarcoma during pregnancy. As an illustration, the largest series published more than 25 years ago [50] included 33 patients, amongst whom none received chemotherapy during pregnancy.

The treatment of malignancies during pregnancy requires a multidisciplinary approach. The main parameters that may influence therapeutic approaches are the stage of the malignant disease (i.e. curative vs. palliative situations), gestational age, the opinion of the parents on a potential therapeutic abortion and treatment-associated toxicity [40]. This latter factor is the least documented, and little information is available on the effects of anticancer agents during pregnancy, especially regarding drug delivery to the

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foetus. The collection of more information on the effects of anticancer drugs during pregnancy is an important issue, and the implementation of databases (as suggested by the European Society of Gynecological Oncology—ESGO—Cancer and Pregnancy Taskforce) is useful to generate new information and improve the guidelines.

Neoadjuvant chemotherapy is a cornerstone of the treatment of bone sarcomas [33, 46] and is an option that may improve resectability in locally advanced soft tissue sarcomas [10]. We report here on a series of patients diagnosed with sarcoma during pregnancy, including five cases successfully managed with neoadjuvant chemotherapy combining doxorubicin and ifosfamide.

Patients and methods

We retrospectively reviewed the electronic medical records of female patients diagnosed with high-grade sarcoma during pregnancy in our institution. During a 10-year period (1998–2008), 512 women aged 15–45 years were referred to the sarcoma unit of our tertiary cancer centre. We identified 9 women with newly diagnosed sarcoma during pregnancy. All cases were diagnosed during the third trimester of pregnancy. In 4 cases, the diagnosis of high-grade sarcoma was made during the late third trimester of pregnancy (after 34 weeks of gestation), and induction chemotherapy was postponed after induced delivery at 35–37 weeks. The remaining five patients were diagnosed earlier in the third trimester and were therefore considered eligible to receive *pre-partum* chemotherapy.

The chemotherapy regimen administered during pregnancy was designed with doses inferior to those used in non-pregnant patients (doxorubicin 50 mg/m^2 vs. 60 mg/m^2 and ifosfamide 5 g/m^2 vs. 6–9 g/m^2, respectively), as described in Table 1. Hence, this modified regimen administered every 3 weeks was expected to cause only mild haematological toxicity, making dispensable the use of G-CSF support. Indeed, the safety of G-CSF during pregnancy is not established to date. Regarding prevention of nausea and emesis, we used IV metoclopramide 10 mg tid and ondansetron 8 mg bid for 3 days, since the use of these drugs during pregnancy appears safe in view of the existing literature [23]. Corticosteroids, benzodiazepines and G-CSF were not administered. Foetal monitoring was standardized and included monthly United States and obstetrical examinations in a Department of Obstetrics specialized in the field of monitoring high-risk pregnancies.

Table 1 Chemotherapy regimen for sarcomas during the second and third trimesters of pregnancy

Drug	Schedule	Time
Doxorubicin 50 mg/m^2	IV bolus	Day 1
Ifosfamide 2.5 g/m^2/day	Continuous IV infusion over 48 h. (total dose: 5 g/m^2/cycle) + 3 litres of IV fluids/24 h. (NaCl 0.9%)	Days 1–2
Mesna	Continuous IV infusion, 100% of ifosfamide dose 15 min. before starting ifosfamide and 100% of ifosfamide dose for the 8 h. following the end of ifosfamide infusion	Days 1–2

Finally, post-partum chemotherapy was initiated 2–3 weeks after delivery, with specific attention paid to maternal risk factors for severe toxicity, given the pharmacological changes observed during the late pregnancy and the post-partum period [32]. Indeed, low albumin levels are common during this period and may alter protein binding and sensitivity to various cytotoxic agents [55].

In one patient, the pharmacokinetics of ifosfamide was studied before and after pregnancy. Eight blood samples were drawn, and plasma obtained after centrifugation was stored at −20°C until analysis. Ifosfamide plasma concentration levels were determined using a validated HPLC with UV detection method [8]. Pharmacokinetic parameters were estimated using Micropharm programme [53]. Cord blood and amniotic fluid samples were obtained at the time of delivery, and ifosfamide concentration levels were determined as well.

Results

The characteristics of the five patients who received pre-partum chemotherapy are summarized in Table 2. Median age was 30 years (range: 26–34), and the median gestational age at diagnosis was 27 weeks (range: 25–28). After imaging (MRI and thoracic CT scan were performed with abdominal shielding to decrease foetal irradiation), histology was obtained by surgical microbiopsy under local anaesthesia. Malignancies were Ewing's sarcoma/PNET (primitive peripheral neuro-ectodermal tumour) in 2 cases, grade 3 spindle-cell sarcoma in 2 cases and extraosseous osteosarcoma in 1 case. The search for *t*(11;22) translocation specific for Ewing's sarcoma was positive in cases 1 and 3.

One patient (case 4) underwent radical excision surgery during the 26th week of pregnancy. A total of 9 cycles of the above-mentioned chemotherapy regimen were administered during pregnancy (median per patient: 2). Pharmacokinetic data regarding ifosfamide were available in one case (Table 3, case 5). Importantly, ifosfamide could not be detected in maternal blood, amniotic fluid or cord blood (<5 μg/ml).

Table 2 Single-centre case series of pregnant patients diagnosed with high-grade sarcoma during pregnancy)

Case no.	Age (years)	Obstetrical history	GA at diagnosis (weeks)	Diagnostic workup	Pre-partum treatment	Post-partum treatment and follow-up
1	31	G1P0	27	CT scan: 76 × 53 mm mass on the right 7th rib SMB: PNET	AI50: 2 cycles	NEO-AI: 1 cycle Surgery (99% necrosis rate) Radiation therapy (50 Gy) Alive, NED at 20 months
2	30	G3P2	27	MRI: 90 × 82 mm mass of the right thigh SMB: high-grade extraosseous OS	AI50: 2 cycles	API: 2 cycles Surgery (85% necrosis rate) Ifo-VP16: 3 cycles Alive, NED at 6 years
3	27	G1P0	28	MRI: 120 × 50 mm para-spinal mass SMB: PNET	AI50: 2 cycles	NEO-AI: 5 cycles Surgery (80% necrosis rate) Ifo-VP16: 3 cycles Radiation therapy (50 Gy) Alive, NED at 4 years
4	26	G2P1	25	MRI: 120 × 60 mm mass of the right thigh SMB: grade III spindle-cell sarcoma	Surgery AI50: 2 cycles	AI75: 3 cycles Radiation therapy (50 Gy) Alive, NED at 6 years
5	34	G2P1	25	MRI: 90 × 80 mm mass of the left buttock SMB: grade III spindle-cell sarcoma	AI50: 1 cycle	AI50: 1 cycle, then NEO-AI: 3 cycles Surgery (80% necrosis rate) Radiation therapy (50 Gy) Alive, NED at 17 months

GA gestational age, *SMB* surgical microbiopsy, *OS* osteosarcoma, *API* doxorubicin 60 mg/m^2, ifosfamide 6 g/m^2 and cisplatin 100 mg/m^2 with G-CSF support, every 3 weeks, *AI50* doxorubicin 50 mg/m^2 and ifosfamide 5 g/m^2, every 3 weeks, *Ifo-VP16* ifosfamide 9 g/m^2 and etoposide 300 mg/m^2 with G-CSF support, every 3 weeks, *NEO-AI* doxorubicin 60 mg/m^2 and ifosfamide 9 g/m^2 with G-CSF support, every 3 weeks, *AI75* doxorubicin 75 mg/m^2 and ifosfamide 6 g/m^2 with G-CSF support, every 3 weeks, *NED* no evidence of disease

Table 3 Pharmacokinetics of ifosfamide (5 g/m^2 over 48 h) during pregnancy and after delivery (Case 5)

Time after starting ifosfamide infusion	Ifosfamide concentration (μg/ml) in maternal blood during pregnancy (cycle 1: 29 weeks)	Ifosfamide concentration (μg/ml) in maternal blood after delivery (cycle 2: day 10 *post-partum*)
0	<5	<5
24 h	24.7	23.4
48 h	20.3	19.6
48 h, 15 min	19.6	18.9
48 h, 30 min	19	18.3
49 h	16	15.2
51 h	13.1	10.1
54 h	6	7
60 h	2.8	<5
72 h	<5	NA

NA not assessed

Maternal toxicities and obstetrical outcomes are reported in Table 4. Grade 3 alopecia (5 cases) and grades 3–4 neutropenia (3 cases) were the most frequently observed toxicities. Nausea and emesis were not observed with the above-described antiemetic pre-medication. Prematurity was observed in all cases. Premature delivery was spontaneous in 1 patient and scheduled in another 3 patients. In the remaining patients (case 5), an obstetrical ultrasound at 29 weeks of pregnancy revealed oligoamnios. After multidisciplinary counselling, the patient received corticosteroids for foetal lung maturation, and elective caesarean section was performed at 29 weeks + 5 days (more than 3 weeks after chemotherapy). The newborn was a 1,080 g, healthy boy (Apgar scores 10 and 10 at 1 and 5 min). Neonatal blood tests including electrolytes, renal function, pH and lactates were normal. However, given prematurity, the baby was admitted to neonatal intensive care for close monitoring. His further development was normal, and he was discharged after 2 months. No pathological assessment of the placenta was performed. Long-term follow-up data on the babies are provided in Table 4.

Chemotherapy was reintroduced 10–15 days after delivery. In one patient (case 1), the first cycle of post-partum chemotherapy (doxorubicin 60 mg/m^2 and ifosfamide 9 g/m^2 with G-CSF support) was complicated by grade 4 febrile neutropenia. Another patient (case 5) received post-partum

Table 4 Use of ifosfamide during pregnancy ($n = 11$, including the present 5 cases)

Reference	Age (years)	Malignancy	Treatment received during pregnancy	Initiation of chemotherapy (weeks)	Toxicity during pregnancy	Delivery	Newborn: birthweight, gender and neonatal status	Follow-up of the offspring
[12]	20	RMS	Ifosfamide 5 g/day for 2 days, vincristine 2 mg/day (days 1 and 14), actinomycin D 1 mg/day for 2 days (2 cycles)	23	IUGR and anhydramnios at 27 weeks, maternal aplasia, foetal distress at 29 weeks	Emergency C-section, 29 weeks	720 g, female, Apgar 3, 7	Anuria, intraventricular hemorraghe, death at day 7
[27]	21	Ewing/PNET	Doxorubicin 50 mg/m^2, Ifosfamide 5 g/m^2 (3 cycles)	27	G3 neutropenia	C-section, 36 weeks	1,300 g, male	Normal at 30 months
[19]	21	Burkitt's lymphoma	CODOX-M, IVAC + G-CSF	26	0	C-section, 32 weeks	1,731 g, male, Apgar 8, 9	Normal at 14 months
[39]	28	Burkitt's lymphoma	CODOX, IVAC + rituximab + G-CSF	16	Severe emesis, erosive esophagitis, neutropenic fever, IUGR, oligoamnios	Vaginal, 26 weeks	NOS	Normal at 7 years
[33]	17	Ewing/PNET	Doxorubicin 50 mg/m^2, Ifosfamide 2 g/m^2 (3 cycles) + G-CSF	25	IUGR oligoamnios	Planned C-section, 32 weeks	1,245 g, female Apgar 7, 9	Normal at 8 months
[49]	28	Ewing/PNET	Doxorubicin 60 mg/m^2, vincristine 2 mg, cyclophosphamide 600 mg/m^2 (cycle 1), then Ifosfamide 9 g/m^2 over 5 days (cycle 2)	26	IUGR oligoamnios	C-section, 27 weeks (1 week after cycle 2)	Male, NIC, anaemia and thrombopenia at day 8	Normal at 12 weeks
Present report, case 1	31	Ewing/PNET	Doxorubicin 50 mg/m^2, Ifosfamide 5 g/m^2 (2 cycles)	29	G3 alopecia G3 neutropenia G2 infection	Vaginal, 34 weeks	1,400 g, female Apgar 8, 9	Normal at 8 months
Present report, case 2	30	Osteosarcoma	Doxorubicin 50 mg/m^2, Ifosfamide 5 g/m^2 (2 cycles)	30	G3 alopecia G4 neutropenia	Vaginal, 35 weeks	2,200 g, female Apgar 9, 9	Normal at 5 years
Present report, case 3	27	Ewing/PNET	Doxorubicin 50 mg/m^2, Ifosfamide 5 g/m^2 (2 cycles)	30	G3 alopecia G3 neutropenia	Vaginal, 36 weeks	2,200 g, female Apgar 8, 10	Normal at 3 years
Present report, case 4	26	High-grade sarcoma	Doxorubicin 50 mg/m^2, Ifosfamide 5 g/m^2 (2 cycles)	29	G1 nausea G3 alopecia	Vaginal, 35 weeks + 5 days	2,300 g, male Apgar 10, 10	Normal at 5 years
Present report, case 5	34	High-grade sarcoma	Doxorubicin 50 mg/m^2, Ifosfamide 5 g/m^2 (1 cycle)	26	G3 alopecia, oligoamnios at 29 weeks	C-section, 29 weeks + 5 days	1,180 g, male, Apgar 10, 10	Normal at 5 months

RMS rhabdomyosarcoma, *PNET* primitive peripheral neuro-ectodermal tumour; *CODOX-M* cyclophosphamide 800 mg/m^2, vincristine 1.5 mg/m^2, doxorubicin 40 mg/m^2, cytarabine 70 mg intrathecally, methotrexate 1,200 mg/m^2 then 240 mg/m^2/h over 23 h, leucovorin and G-CSF, *IVAC* etoposide 60 mg/m^2/day for 5 days, ifosfamide 1.5 mg/m^2/day for 5 days, mesna, cytarabine 4 g/m^2/day for 2 days, methotrexate 12 mg intrathecally, leucovorin, *C-section* caesarean section, *IUGR* intrauterine growth retardation, *NIC* neonatal intensive care, *NOS* not otherwise specified. Apgar scores are given at 1 and 5 min

chemotherapy using the same regimen given during pregnancy. Indeed, she had lymphopenia (680/µl) and low albuminemia (30 g/l) precluding the use of full-dose chemotherapy, given a high risk of haematological toxicity [1, 42]. In this patient, the pharmacokinetic parameters of ifosfamide (estimated clearance and AUC) were similar to those observed during pregnancy (Table 3). Maternal follow-up data are provided in Table 2.

Discussion

We describe a series of patients with high-grade sarcomas, including five women treated during the third trimester of pregnancy with doxorubicin and ifosfamide, resulting in a favourable outcome for both the mother and the foetus.

Diagnosis and imaging procedures

The diagnostic approach should be tailored specifically in every pregnant woman in whom sarcoma is suspected. Open biopsy, resection of small-size tumours and limb-sparing surgery may be relatively safe during pregnancy [27]. Ancillary tests should be chosen to minimize exposure to ionizing radiations. In our series, diagnostic work-up included MRI in 3 cases and a thoracic CT scan in the remaining cases. MRI is considered safe during pregnancy [36], although exposure to gadolinium during the first trimester has been shown to increase the risk of anomalies in animal models. Long-term effects of gadolinium-containing contrast media for the offspring are still unknown. Regarding CT scan, abdominal shielding may help decreasing foetal irradiation, and the use of enteric barium sulphate as an internal shield has been described to enhance foetal protection [39]. However, the use of X-rays and CT scan should be limited during pregnancy [2]. Indeed, performing CT scan of the chest during the third trimester is particularly risky given the high uterine level at this point in pregnancy, which makes the likelihood of unacceptable foetal exposure very high even in the presence of proper shielding.

Chemotherapy regimen and supportive care

Our aim in this series of patients was to obtain tumour control until delivery, with optimal obstetrical safety. Hence, the chemotherapy schedule used in our institution was designed to balance maternal and foetal safety with efficacy, in order to obtain a high tumour necrosis rate, a strong predictor of survival in advanced sarcomas receiving neoadjuvant chemotherapy [46, 48]. Although a low dose intensity might result in poorer histological response rates, we observed acceptable degrees of tumour necrosis in our case series (Table 2). Therefore, we would not recommend increasing chemotherapy doses with the use of G-CSF in all pregnant patients with high-grade sarcomas. However, pregnant patients treated with the above-described chemotherapy regimen should be informed that they will receive a regimen, which could be inferior to the standard given the lower doses used.

Overall, we consider that the therapeutic strategy in pregnant patients (third trimester) with non-metastatic sarcomas should be as close as possible to that offered to non-pregnant patients. Patients with bone sarcoma should receive 3–4 cycles of neoadjuvant chemotherapy followed by local treatment and adjuvant chemotherapy based on histological response rate. Patients with advanced soft tissue sarcoma should receive 4–6 cycles of neoadjuvant chemotherapy followed by local treatment [10]. The choice of chemotherapy agents and doses can be guided by the following overview of the literature on the topic.

Use of anticancer drugs active in sarcoma during pregnancy

The use of anthracyclines during pregnancy was described in 160 cases by Germann et al. [14], with a favourable toxicity profile when used during the second and third trimesters of pregnancy (83% of cases). Both maternal and foetal prognoses were significantly poorer under the following circumstances: administration during the first trimester of pregnancy, use of idarubicin, doxorubicin doses >70 mg/m^2 or in case of maternal acute leukaemia [14]. International recommendations stated that doxorubicin could be given to pregnant cancer patients during the second and third trimesters with minimal risk to the developing foetus [2]. In addition, we have reported that the use of epirubicin during pregnancy was associated with a risk similar to that observed with doxorubicin [31].

In contrast, the feasibility of other drugs active in sarcomas during pregnancy remains unclear, being documented only by single case reports. We aimed to collect data on the safety of these drugs in pregnant patients and therefore, carried out a systematic review of the English literature. Data were identified by search of Pubmed, Embase and Web of Knowledge, together with references from relevant articles, using the search terms '*drug name* AND pregnancy' (*drug name* being: ifosfamide, cisplatin, etoposide, methotrexate, actinomycin, vincristine and cyclophosphamide) and 'sarcoma AND pregnancy'. Only papers published in English from 1967 to 1 April 2011 were included.

We found only 6 reports documenting the use of ifosfamide during pregnancy [13, 20, 28, 35, 41, 51], summarized in Table 2. Toxicity profile was unacceptable in the first case ever reported [13]. However, the imputability of dismal foetal outcome remains unclear in this case. Indeed, maternal disseminated intravascular coagulation was

Table 5 Use of etoposide during pregnancy ($n = 25$)

Reference	Age (years)	Malignancy	Treatment received during pregnancy	Initiation of chemotherapy	Toxicity during pregnancy	Delivery	Newborn: birthweight, gender and neonatal status	Follow-up of the offspring
[19]	21	Burkitt's lymphoma	CODOX-M, IVAC + G-CSF	26 weeks	0	C-section, 32 weeks	1,731 g, male, Apgar 8, 9	Normal at 14 months
[39]	28	Burkitt's lymphoma	CODOX, IVAC + rituximab + G-CSF	16 weeks	Severe emesis, erosive esophagitis, neutropenic fever, IUGR, oligoamnios	Vaginal, 26 weeks	NOS	Normal at 7 years
[45]	24	Hodgkin's lymphoma	Etoposide 110 mg/m2 days 1–2, doxorubicin, vinblastine q. 28 days, 3 cycles	25 weeks	0	C-section, 36 weeks	2,190 g, female, Apgar 9, 10	Normal at 17 months
[47]	18	Alveolar RMS	Oral Etoposide 25 mg/m2 bid, days 1–10, trofosfamide, idarubicin	28 weeks	No grade 3–4 toxicity	Vaginal, 34 weeks	1,790 g, male, Apgar 9,9, normal CBC	Normal at 27 months
[5]	23	Ovarian endodermal sinus tumour	Etoposide, cisplatin, bleomycin (5 days), 4 cycles	15 weeks	No grade 3–4 toxicity, pre-eclampsia	C-section, 36 weeks	1,560 g, male, Apgar 9, 10	Normal at 21 months
[14]	25	Ovarian immature teratoma	Etoposide, cisplatin, bleomycin (5 days), 3 cycles + G-CSF	21 weeks	IUGR	C-section, 36 weeks	2,000 g, male, Apgar 9, 10	Normal at 8 months
[28] and references herein	18	Ovarian germ-cell tumour	Etoposide, cisplatin, bleomycin (3 days) every 28 days, 3 cycles	21 weeks	Mild pre-eclampsia	Induced vaginal delivery, 39 weeks	2,769 g, female, Apgar 4, 7	Normal, NOS
[28] and references herein	26	Ovarian endodermal sinus tumour	Etoposide, cisplatin, bleomycin (5 days), 1 cycle	25 weeks + 5 days	Ventriculomegaly at 26 weeks	C-section, 28 weeks	1,085 g, female, Apgar 7, 8	Normal at 2 months
[28] and references herein	26	Ovarian immature teratoma	Etoposide, cisplatin, bleomycin (5 days), 2 cycles	29 weeks	NOS	C-section, 39 weeks	3,100 g, female, Apgar 9, 10	Normal at 18 months
[28] and references herein	32	Ovarian endodermal sinus tumour	Etoposide, cisplatin, bleomycin (5 days), 3 cycles	18 weeks	NOS	C-section, 35 weeks	2,400 g, Apgar 7, 9	Normal at 12 months
[28] and references herein	NOS	Ovarian endodermal sinus tumour	Etoposide, cisplatin, bleomycin, 2 cycles	20 weeks	Pulmonary embolism, death	C-section, 31 weeks	–	–
[28] and references herein	27	Ovarian immature teratoma	Etoposide, cisplatin, bleomycin (5 days) every 28 days, 2 cycles	30 weeks	NOS	Induced vaginal delivery, 38 weeks	2,970 g, male, Apgar 9, 10	Normal at 26 months
[28] and references herein	21	Ovarian dysgerminoma	Etoposide, cisplatin (5 days), 4 cycles	27 weeks	IUGR, oligoamnios	Induced vaginal delivery, 38 weeks	2,320 g, female	Normal at 9 months

Table 5 continued

Reference	Age (years)	Malignancy	Treatment received during pregnancy	Initiation of chemotherapy	Toxicity during pregnancy	Delivery	Newborn: birthweight, gender and neonatal status	Follow-up of the offspring
[28] and references herein	25	Yolk sac tumour	Etoposide, cisplatin, bleomycin (5 days) every 28 days, 5 cycles	22 weeks	NOS	Vaginal delivery, 40 weeks	2,610 g, male, Apgar 9, 10	Normal at 72 months
[28] and references herein	32	Adenocarcinoma of unknown primitive	Etoposide, cisplatin, bleomycin (3 days)	26 weeks	Neutropenia NOS	Vaginal delivery, 27 weeks	1,190 g, female, Apgar 3, 8	Normal at 12 months, hear loss (received cisplatin and aminoglycosides)
[28] and references herein	22	Neuroblastoma	Etoposide, cisplatin + G-CSF	24 weeks	Neutropenia, nausea and emesis, foetal distress at 35 weeks	Emergency C-section, 35 weeks	1,825 g, male, Apgar 6, 8, NIC	Normal at 1 month
[3]	34	NHL	Etoposide 700 mg, cyclophosphamide, doxorubicin, vincristine, methotrexate	Third trimester	NOS	NOS, range 35–39 weeks	NOS	Normal, NOS
[3]	30	NHL	Etoposide 600 mg, cyclophosphamide, doxorubicin, vincristine, methotrexate	Third trimester	NOS	NOS, range 35–39 weeks	NOS	Normal, NOS
[3]	30	NHL	Etoposide 450 mg, cyclophosphamide, doxorubicin, vincristine, methotrexate, aracytine	Second trimester	NOS	NOS, range 35–39 weeks	NOS	Normal, NOS
[3]	26	NHL	Etoposide 650 mg, cyclophosphamide, bleomycin, vincristine, methotrexate	1st trimester	NOS	NOS, range 35–39 weeks	NOS	Normal, NOS
[43]	36	NHL	Etoposide 125 mg/m^2 (weeks 2, 4, 6, 8, 10, 12), cyclophosphamide, vincristine, bleomycin, prednisone	22 weeks	G3 neutropenia	Vaginal, 37 weeks	3,200 g, male	Normal at 21 months
[18]	39	SCLC	Etoposide 100 mg/m^2 days 1-3, cisplatin 80 mg/m^2 (4 cycles)	27 weeks	NOS	C-section, 34 weeks,	Male, Apgar 9, 9	NOS
[32]	36	AML	Etoposide 400 mg/m^2 days 8–10, cytosine arabinoside, daunorubicin (2 cycles)	25 weeks	IUGR from 30 to 32 weeks, foetal distress at 32 weeks	Emergency C-section, 32 weeks (11 days after the second cycle)	1,460 g, female, leukopenia and anaemia, fever and sepsis at day 2	Normal at 1 month

Table 5 continued

Reference	Age (years)	Malignancy	Treatment received during pregnancy	Initiation of chemotherapy	Toxicity during pregnancy	Delivery	Newborn: birthweight, gender and neonatal status	Follow-up of the offspring
[41]	29	AML	Etoposide 100 mg/m^2/day for 4 days, cytosine arabinoside, thioguanine, daunorubicin, mitoxantrone (1 course)	25 weeks	Pre-term rupture of the membranes, clear amniotic fluid	C-section after failed induction, 34 weeks	2,220 g, male, Apgar 3, 6, respiratory distress, NIC, normal blood tests	NOS
[41]	28	AML	Etoposide 100 mg/m^2/day for 4 days, cytosine arabinoside, thioguanine, daunorubicin, mitoxantrone (3 courses)	20 weeks	0	C-section after failed induction, 34 weeks	2,100 g, female, Apgar 6, 7, normal blood tests	NOS

CODOX-M cyclophosphamide 800 mg/m^2, vincristine 1.5 mg/m^2, doxorubicin 40 mg/m^2, cytarabine 70 mg intrathecally, methotrexate 1,200 mg/m^2 then 240 mg/m^2/h over 23 h, leucovorin, *IVAC* etoposide 60 mg/m^2/day for 5 days, ifosfamide 1.5 mg/m^2/day for 5 days, mesna, cytarabine 4 g/m^2/day for 2 days, methotrexate 12 mg intrathecally, leucovorin, G-CSF, *DAC* Dactinomycin, *C-section* caesarean section, *RMS* rhabdomyosarcoma, *SCLC* small-cell lung cancer, *AML* acute myeloid leukaemia, *NHL* Non-Hodgkin lymphoma, *IUGR* intrauterine growth retardation, *NIC* neonatal intensive care, *NOS* not otherwise specified. Apgar scores are given at 1 and 5 min

diagnosed before the introduction of pre-partum chemotherapy, resulting in premature birth. A lethal intraventricular haemorrhage occurred in the newborn, which could likely result from prematurity. Importantly, oligoamnios was diagnosed in 5 of the 11 cases with ifosfamide being given at various doses, suggesting a potential toxicity of ifosfamide on the developing kidney. These findings deserve confirmation in further reports, especially in patients treated at a dose of 5 g/m^2/cycle.

Amongst other active drugs in osteosarcoma, cisplatin displayed a favourable short-term toxicity profile [29] in 36 cases. However, asymptomatic transplacental transfer is well documented [7, 21, 24], with unknown long-term consequences. Maternal death due to pulmonary embolism was observed in one case, but the imputability of cisplatin in this fatal event remains speculative.

The use of etoposide was documented in 25 cases (Table 5) with a constant favourable outcome for the offspring [3, 6, 15, 19, 20, 29, 34, 41, 43, 45, 47, 49].

To our knowledge, high-dose methotrexate use during pregnancy was not reported to date.

Dactinomycin (Table 6) was successfully administered in another 8 cases [12, 18, 25, 26, 55]. Mitotic spindle poisons vincristine and vinblastine were administered in more than 110 cases [9], resulting in 1 malformation and 4 deaths (2 foetal and 2 neonatal) when given early during pregnancy. Overall, vinca alkaloids exhibit a favourable toxicity profile when given during the second and third trimesters of pregnancy [9, 30]. Regarding the transplacental transfer of vinblastine, the foetal concentration of the drug was 18% of that of the mother in a recent animal model in baboons. As a comparison, that of IV cyclophosphamide was close to 25% [54].

Intravenous cyclophosphamide (CPM) was found safe in large series of breast cancer patients treated during the second and the third trimesters [2]. Conversely, oral CPM was administered in 10 patients [4, 11, 16, 22, 37, 38, 44] with a median duration of treatment of 16 weeks (range: 7.5–36 weeks) and resulted in 4 foetal deaths and 2 malformations. Interestingly, the C_{max} after oral administration of CPM is almost as high as that measured at the end of a short infusion. More importantly, the concentration of CPM neurotoxic metabolite chloroacetaldehyde is approximately twice higher than that measured when the drug is given intravenously [52]. Despite a well-known relationship between the dose of CPM and its pharmacodynamic effects, we therefore postulate that toxic effects for the offspring may be observed even using very low doses. Hence, we suggest using IV route instead of continuous or repeated oral administrations. As a consequence, the use of oral CPM in sarcoma patients as described in the St-Jude protocol [17] should be avoided in pregnant patients.

Table 6 Use of dactinomycin during pregnancy ($n = 8$)

Reference	Age (years)	Malignancy	Treatment received during pregnancy	Initiation of chemotherapy (weeks)	Toxicity during pregnancy	Delivery	Newborn : birthweight, gender and neonatal status	Follow-up of the offspring
[12]	20	RMS	Ifosfamide 5 g/day for 2 days, vincristine 2 mg/day (days 1 and 14), DAC 1 mg/day for 2 days (2 cycles)	23	IUGR and anhydramnios at 27 weeks, maternal aplasia, foetal distress at 29 weeks	Emergency C-section, 29 weeks	720 g, female, Apgar 3, 7	Anuria, intraventricular hemorraghe, death at day 7.
[25]	15	Alveolar RMS	Weekly cyclophosphamide 500 mg/m^2 with doxorubicin 40 mg/m^2 and DAC 1 mg/m^2	24	Oligoanhydramnios	C-section, 29 weeks	2,800 g, female, Apgar 9, normal blood tests	NOS
[24]	18	RMS	Vincristine 1.5 mg/m^2, cyclophosphamide 2.2 g/m^2 plus mesna, DAC 0.5 mg/day for 5 days, q 21 days (3 cycles) + G-CSF	29	G4 Neutropenia G2 Anaemia G3 Thrombopenia, febrile neutropenia at each cycle; oligoanhydramnios	Vaginal, 36.5 weeks	2,443 g, female, Apgar 8, 9, normal blood tests	NOS
[17]	25	Ovarian endodermal sinus tumour	DAC 0.5 mg/day for 5 days, vincristine, cyclophosphamide	16	NOS	Vaginal, 37 weeks	2,850 g, male	Normal, NOS
[11]	19	Wilms tumour	Vincristine, DAC (doses NOS)	26	NOS	C-section, 28 weeks	1,150 g, female, NIC for 2 months	Normal at 10 months
[52] and references herein	21	Ewing/PNET	DAC, cyclophosphamide, doxorubicin, vincristine, bleomycin	25	NOS	C-section, 34 weeks	1,750 g, female, Apgar 7, 9, NIC	Normal at 1 month
[52] and references herein	25	Endodermal tumour of the ovary	Cyclophosphamide, vincristine, DAC 0.5 mg every 4 weeks	16	NOS	Vaginal, 37 weeks	2,850 g, male	NOS
[52] and references herein	NOS	Choriocarcinoma	Methotrexate, chlorambucil, DAC	15	NOS	NOS	Twins	Normal

RMS rhabdomyosarcoma, *DAC* Dactinomycin, *PNET* primitive peripheral neuro-ectodermal tumour, *C-section* caesarean section, *IUGR* intrauterine growth retardation, *NIC* neonatal intensive care, *NOS* not otherwise specified, Apgar scores are given at 1 and 5 min

Finally, prematurity and hypotrophy were frequent with almost all drugs (Tables 2, 4, 5). Neonatal cytopenia was observed when delivery occurred within 2 weeks following the last cycle of chemotherapy, as previously described [2, 29]. As a consequence, we suggest avoiding chemotherapy during 3 weeks before the theoretical term of delivery.

Conclusion

We documented the feasibility of chemotherapy combining doxorubicin and ifosfamide in pregnant patients with high-grade sarcoma. We consider that the management of such malignancies during the third trimester of pregnancy should include an adapted chemotherapy regimen tailored to the pharmacological specificities of pregnant patients. Keeping a multimodal therapeutic management close to that used in non-pregnant patients is critical to obtain malignant disease control in this setting. However, in view of the limited number of reports available, further pre-clinical and clinical studies on the transplacental transfer of anticancer drugs, as well as additional clinical reports, are warranted to better handle chemotherapy in pregnant sarcoma patients.

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Conflict of interest None.

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