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REVIEW ARTICLE

Neoadjuvant chemotherapy in locally advanced cervical cancer in pregnancy-Review of the literature

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Summary

Cervical cancer is the third most common malignancy in pregnancy. Pregnancy does not have a detrimental effect on the survival of patients with cervical carcinoma. Management of cervical carcinoma in pregnancy depends on the stage of the disease, tumor size, nodal status, pathohistological characteristics of the tumor, the gestation of pregnancy, age and parity of patient and her motivation to preserve the pregnancy.

In pregnant patients with the locally advanced cervical carcinoma (LACC) and strong desire to continue the pregnancy, the neoadjuvant chemotherapy (NACT) could be the option to preserve pregnancy while having cancer under the control. The goal of NACT in treatment of LACC in pregnancy is:

1. *To treat, stabilize and prevent further dissemination of the disease until the term*
2. *To decrease the volume and extent of the tumor, making it more operable or radiosensitive after delivery*
3. *To effect on lymph node metastasis and distant micrometastasis during pregnancy*

Chemotherapy should not be applied during the organogenesis, before 10th, preferably 14th week of gestation. Administration of chemotherapy after the first trimester is not related tothe increased number of congenital malformations. If applied in the second or third trimester, chemotherapy is connected withfetal growth restriction, low birth weight, and preterm labor.

Since data on safety and efficacy of NACT in LACC in pregnancy are still limited and based on a low level of evidence from 37 cases known so far, this treatment modality should remain experimental and reserved to highly motivated patients wishing to preserve the pregnancy.

Key words: *uterine cervical neoplasms, pregnancy, chemotherapy*

Introduction

Cervical cancer diagnosed in pregnancy remains a great challenge for clinicians dealing with this pathology. Relatively small incidence, ethical issues in conducting randomized trials, underreporting of unsuccessful cases and differences in management on a case-by-case basis are all the reasons why our knowledge of this topic is still limited. Providing the best possible oncological outcome, while preserving the pregnancy and delivering a healthy newborn should be our goal whenever possible.

Cervical cancer is the third most common malignancy in pregnancy, with an estimated incidence of 8 to 15 cases per 100,000 births [1,2]. The incidence is probably slightly higher due to the fact that the women who were not regularly controlled by a gynecologist before, seek medical care in the period of pregnancy. Regular gynecological examinations in pregnancy might be responsible for the more frequent diagnosis of early cervical cancer in pregnant than in non-pregnant women [3].Pregnancy does not have a detrimental effect

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on the survival of patients with cervical carcinoma [3-6]. Management of cervical carcinoma in pregnancy depends on the stage of disease, tumor size, nodal status, histopathological characteristics of the tumor,the gestation of pregnancy, age and parity of patient and the motivation to preserve the pregnancy.

Cervical cancer diagnosed in advanced stages is related to less favorable outcome for a patient. While an early stage cervical cancer diagnosed in pregnancy has a better prognosis and smaller tumor size which allows surgical procedures with preservation of pregnancy (lymphadenectomy for lymph node evaluation, conization or trachelectomy) or delay of treatment until term, such management is not an option in advanced stages [7-9]. According to the recent recommendations, radical trachelectomy should no longer be considered in pregnancy, especially in locally advanced disease, due to preterm delivery rate up to 60% [7-10].

Termination of pregnancy associated with the locally advanced cervical cancer (LACC) and subsequent standard treatment might be the easy way out. With the increasing success of oncological treatments, it is now even more crucial to implement procedures aimed at preserving fertility and pregnancy. Emerging new data about the use of neoadjuvant chemotherapy (NACT) in cervical cancer and safety of chemotherapy in pregnancy poses the question if pregnancies complicated with locally advanced cervical cancer should be terminated in every case. In pregnant patients with the locally advanced cervical carcinoma and strong desire to continue the pregnancy, NACT might be the safe way to continue the pregnancy until fetal maturity while having cancer under control.

Neoadjuvant chemotherapy in cervical cancer

The standard of care for the treatment of advanced-stage cervical cancer at the moment is concomitant chemoradiation [9]. Besides, almost 20 years of research in this field, the role of NACT in the treatment of the advanced-stage cervical cancer is still debatable and the focus of ongoing research.

Most of the studies conducted over these years were to seek for the efficacy of NACT followed by standard treatment (radiotherapy or surgery) and its possible benefit over standard treatment alone. A meta-analysis compared NACT followed by radiotherapy with radiotherapy alone in locally advanced cervical cancer and showed that NACT benefited on survival only in the group of patients where a higher dose of cisplatin was given and in the group with a shorter period between cycles [11]. The same study demonstrated better survival of patients treated with NACT+surgery than with radiotherapy alone (HR 0.65, absolute gain of 14% in 5-year survival) [11]. In their randomized trial Gupta et al compared the survival of patients with LACC, where patients in chemoradiation arm had better disease-free survival (DFS) than those in NACT+surgery arm, but with a notice that in patients with bulky tumors (IB2/IIA) NACT might have an advantage, yet, because of the limited number of patients in that group the results did not reach significantly better DFS. Also, Gupta et al point to the group of patients without response or progression that had the poorest outcome [12]. The role of NACT plus surgery versus surgery alone for early and locally advanced cervical cancer was assessed in a Cochrane review and showed better PFS, lower recurrence rate, fewer lymph node metastasis, less parametrial invasion and better resection rate in the NACT group, but without benefit on OS [13]. Zhao et al have not demonstrated relationship between NACT and longer DFS and PFS but in subgroup analysis of 8 studies involving 1.544 patients with locally advanced cervical cancer (FIGO stage IB2-IIB), the authors showed that NACT plus radical surgery significantly improved OS, decreased local and distant recurrence rates, lymph node metastasis rate, and the level of parametrial infiltration compared to radical surgery alone [14]. Also, NACT followed by surgery significantly reduced the need for adjuvant radiotherapy compared to surgery alone in early-stage bulky cervical cancer by decreasing the tumor size, decreasing the ratio of lymphovascular invasion, deep stromal invasion, lymph node and distant metastasis [15,16]. Responsiveness to NACT is an independent prognostic factor and can provide important information about tumor aggressiveness and resistance soon after the beginning of treatment [15,16].

Based on currently available data NACT followed by surgery is certainly not detrimental to patient outcome over surgery alone [11,13-17]. The one of the most awaited results was from the EORTC55994 study. The trial ran between May 2002 and June 2014. Chemotherapy followed by hysterectomy was given to 311 patients, and 309 received concomitant radiotherapy and chemotherapy without surgery. Analysis of the 12-year period, with a median follow-up time of 8 years, showed that overall survival was the same between the two groups. Also there was a trend for a better outcome after neoadjuvant chemotherapy (NACTS) for Stage IB2, and after concomitant chemoradiotherapy (CCRT) for Stage IIB and patients aged over 50. The authors concluded that treatment-related morbidity and quality of life need further analy-

ses, because the data presently available showed a higher short-term toxicity for NACTS option, while toxicity was higher in the long-term for the RTCT group [18].

NACT and pregnancy

Unclear benefits in pregnancy of NACT in locally advanced cervical cancer seem to make its use even more experimental. But, NACT in pregnancy has a more extensive role than when used out of pregnancy, which justifies even more its use in pregnancy.

The goals of NACT in the treatment of locally advanced cervical cancer in pregnancy are:

1. To treat, stabilize and prevent further dissemination of the disease until the term.
2. To decrease the volume and extent of the tumor, making it more operable or radiosensitive after delivery.
3. To limit lymph node metastasis and distant micrometastasis during pregnancy [13].

Safety of chemotherapy in pregnancy

Since 1948, when the first chemotherapeutic agent was applied during pregnancy [19] a significant number of patients received chemotherapy in pregnancy. Still, the effect on fetal outcome remains our biggest concern. It is known that organogenesis, which occurs between the 6th and 10th week of gestation, is the most vulnerable part of pregnancy for external agents, including cytotoxic medications, which can cause congenital malformations and abortion if applied during this period. The estimated teratogenic risk for a fetus in the first semester ranges from 7.5 to 17% with a single chemotherapeutic agent, compared with 25% with two or more chemotherapeutic drugs [20]. According to the general recommendations, chemotherapy should not be applied before the 10th, preferably the 14th week of gestation. Administration of chemotherapy after the first trimester is not related to an increased number of congenital malformations or some specific malformations [21]. If applied in the second or third trimester, chemotherapy is connected with fetal growth restriction, low birth weight, and preterm labor [21,22]. Having this in mind, regular obstetrical follow up during pregnancy with special attention on fetal development, intrauterine growth restriction and premature labor are recommended. Since brain and gonads are still under development in later gestation, late effect on cognitive function, carcinogenesis, fertility, and next generation effect in children exposed to chemotherapy *in utero* is questionable. Few studies investigated the effect on later development, cognitive and cardiac function and general outcome in children exposed to chemotherapy *in utero*. All of these studies showed that these children had as good outcome as the general population [22-24]. In one of those, Amant F et al. showed a high percentage of prematurity in a sample of 70 children exposed to chemotherapy *in utero* was observed. In 22 months follow up period premature children had significantly more altered cognitive function compared with children born at term [23]. Chardonick et al also reported significantly higher percent of prematurity in a group of children exposed to chemotherapy *in utero*, but it seemed to be without an impact on further cognitive development [22]. Iatrogenic preterm delivery should be avoided, since prematurity, and not chemotherapy, was linked with impaired cognitive function. Delivery should be planned at least 3 weeks after the last cycle of chemotherapy in order to allow the bone marrow to recover and minimize the risk of hematopoietic suppression (bleeding, infection, anemia) in the mother and the baby [25]. Due to the liver and renal immaturity, the fetal capacity to metabolize and eliminate drugs is reduced and this chemotherapy-free period will give time to drugs to be eliminated through the placenta. The last cycle should not be given after 35 weeks, in regard to a greater proportion of spontaneous delivery in that gestational period, which would increase the risk of hematopoietic suppression in a newborn [25].

Issues such as pharmacokinetics and transplacental passage of chemotherapeutic drugs during pregnancy were also part of our interest. Transplacental transfer of cytotoxics is mostly by passive diffusion. Placental transport depends on drug characteristics, such as lipid solubility, ionization, molecular weight and protein transfer [26]. The most widely used chemotherapeutic agents in the neoadjuvant setting for cervical cancer treatment are platinum derivates together with ifosfamide and taxanes. Kohler et al [27] conducted *in vivo* measurement of the platinum in amniotic fluid and umbilical cord blood and observed concentrations that were 11-42% and 23-65% of the maternal blood, respectively. Research conducted on a mouse model observed the same concentrations of carboplatin in fetal and maternal blood (117.0 ± 38.9%), while fetal blood concentrations of carboplatin were 57.5 ± 14.2% of the maternal blood in a baboon model [28,29]. Results on a mouse model showed no presence of taxanes in fetal blood, whereas in a baboon model the concentration of paclitaxel in fetal plasma was 1.4 ± 0.8% of maternal concentrations [28,29]. Still, taxanes are thought to

Table 1. Studies presenting pregnant patients with LACC treated with NACT

First author/year	*FIGO stage*	*Gestation at the time of diagnosis*	*NACT protocol*	*Response to NACT*	*Mode of delivery and treatments*	*Follow up in months*	*Outcome*	*Baby*
Lai 1997 [32]	Ib2	NA	Cisplatin Vincristine Bleomycin	SD	CS, RH, XTR	52	DOD	Well
Lai 1997 [32]	Ib2	12	Cisplatin Vincristine Bleomycin	PR	CS, RH	59	DOD	Well
Tewari 1998 [33]	IB2	21	Cisplatin Vincristine	PR	CS,RH, PLND	24	NED	Well
Marana 2001 [34]	IIb	14	Cisplatin Bleomycin	NA	CS, decline further Tx	13	DOD	Well
Traen 2006 [35]	IIa	19	Cisplatin Vincristine	NA	CS, RH, CT	80	NED	Well
Bader 2007 [36]	IIa	19	Cisplatin Vincristine	PR	CS,RH, PLND, CT	80	NED	Well
Palaia 2007 [37]	IIb	19	Cisplatin Paclitaxel	PR	CS,RH, PLND	10	NED	Well
Karam 2007 [38]	Ib2	23	Cisplatin	SD	CS, RH, PLND, PALND, XRT	14	NED	Well
Benhaim 2008 [39]	IIIb	22	Cisplatin	PD	CS, CT-XRT	10	DOD	Well
Boyd 2009 [40]	IIb	21	Cisplatin	NA	CS, XRT	15	NED	Well
Seamon 2009 [41]	IIIb	23	Cisplatin Vincristine	PR	CS, CT-XTR	48	NED	Well
Smyth 2010 [42]	Ib2	23	Doxorubicin Cyclophosphamide	PR	CS, CT-XTR	NA	NED	Well
Rabaiotti 2010 [43]	Ib2	15	Cisplatin	SD	CS, XTR	24	DOD	Well
Chun KC 2010 [44]	IIA	29	Cisplatin Paclitaxel	PR	CS, RH, PLND PALND	32	AWD	Well
Chun KC 2010 [44]	Ib2	29	Cisplatin Paclitaxel	PR	CS,RH,PLND, PALND, CT	60	NED	Well
Li J 2011 [45]	IB2	27	Cisplatin Paclitaxel	PR	CS,RH, CT-XRT	21	NED	Well
Lanowska 2011 [46]	Ib2	14	Cisplatin	NA	CS, RH, PLND, PALND, CT-XRT	1	NED	Well
Da Fonseca 2011 [47]	IIb	24	Cisplatin Vincristine	CR	CS, RH, PLND, PALND	12	NED	Well

Continued on the next page

First author/year	*FIGO stage*	*Gestation at the time of diagnosis*	*NACT protocol*	*Response to NACT*	*Mode of delivery and treatments*	*Follow up in months*	*Outcome*	*Baby*
Fruscio R 2012 [48]	Ib2	13	Cisplatin Vincristine	SD	CS, RH, PLND, XRT	27	DOD	Well
Fruscio R 2012 [48]	Ib2	18	Cisplatin	SD	CS, RH, PLND	153	NED	Well
Fruscio R 2012 [48]	Ib2	16	Cisplatin Paclitaxel	PR	CS, RH, PLND	113	NED	Well
Fruscio R 2012 [48]	Ib2	16	Cisplatin Paclitaxel	PR	CS, RH, PLND	115	NED	Well
Fruscio R 2012 [48]	Ib2	20	Cisplatin	SD	CS, RH, PLND, CT-XRT	27	DOD	Well
Geijteman 2014 [49]	IIB	25	Cisplatin Paclitaxel	NA	CS, XRT	NA	NED	Well*
Kong 2014 [50]	Ib2	13	Cisplatin Paclitaxel	PR	CS, RH, CT	36	NED	Well
Peculis 2015 [51]	Ib2	19	Cisplatin Doxorubicin	PR	CS, RH, PLND	20	NED	Well
Ricci C 2016 [52]	IIa	15	Cisplatin	PR	CS,RH,PLND, CT-XRT, BT	31	DOD	Well
Ricci C 2016 [52]	IIb	13	Cisplatin Paclitaxel	PR	CS, RH, PLND	36	NED	Well
Ricci C 2016 [52]	Ib2	18	Cisplatin Paclitaxel	CR	CS, RH, PLND, XRT	31	NED	Well
Ricci C 2016 [52]	Ib2	28	Cisplatin Paclitaxel	PR	CS,RH,PLND,CT-XRT	19	NED	Well
De Vincenzo 2018 [53]	Ib2	27	Cisplatin Paclitaxel	PR	CS, RH, PLND, PALND, CT-XRT	22	NED	Well**
Gil-Ibanez 2018 [54]	IIa1	21	Cisplatin Etoposide	SD	CS, RH, PLND, PALND, CT-XRT	38	NED	Well
Kayahashi 2018 [55]	Ib2	16	Cisplatin Paclitaxel	CR	CS, RH, PLND, CT-XRT	34	ND	Well***
Perrone 2019 [56]	Ib2	10	Cisplatin Paclitaxel	PR	CS, cone, PLND	18	NED	Well
Perrone 2019 [56]	IIa2	30	Cisplatin Paclitaxel	PR	CS,RH,PLND,CT	21	DOD	Well
Perrone 2019 [56]	IIb	18	Cisplatin Paclitaxel	PR	CS, CT-XRT	32	DOD	Well

NACT: neoadjuvant chemotherapy; PR: partial response; CR: complete response; SD: stable disease; CS: caesarean section; RH: radical hysterectomy; PLND: pelvic lymph node dissection; PALND: para-aortic lymph node dissection; NED: no evidence of disease; DOD: dead of disease; AWD: alive with disease; XRT: external-beam radiotherapy; CT: chemotherapy; BT: brachytherapy; *Child was diagnosed with a bilateral hearing loss; ** Acute myeloid leukemia at 22 months of age; ***Neonatal erythroderma

be deposited in fetal tissues more than the other agents thanks to their physicochemical properties [28,29]. Ifosfamide should be avoided in pregnancy, knowing its toxicity profile, limited information on its safety in pregnancy and suspected nephrotoxic and gonadotoxic effect [30]. Lower concentrations of certain cytotoxics in a fetus, due to placental barrier, reassure in the more secure use of chemotherapy in pregnancy.

Physiological changes in pregnancy such as the expansion of plasma and extracellular fluid volume, changes in serum protein concentration and binding capacities, increased glomerular filtration rate and altered liver function, can have a substantial influence on the pharmacokinetics of cytotoxic drugs. Since most of the cytotoxics have a small window between their toxic and therapeutic effect, these changes in pharmacokinetics can alter drug efficacy and safety. Van Carlsten et al reported decreased maximum plasma concentrations and area under the curve of all tested cytotoxic drugs in maternal blood in pregnancy, which was mainly due to the increased clearance and distribution volume of drugs that were also observed [28,31]. Considering this, it is questionable if standard treatment protocols are as effective in pregnant as non-pregnant women.

Results

We searched publications written in English from 1990-2019 and found 37 cases of locally advanced cervical cancer in pregnancy treated with NACT published in 25 articles (Table 1).

Discussion and conclusions

Within the trend of increasing average age at which women have their first pregnancy, the risk that the pregnancy will be overlapped with cancer is growing. This emphasizes the importance of widening medical knowledge of cancer in pregnancy since as physicians, we will progressively deal more with this problem. Decisions are often not easy and should be made while having in mind the sensitive balance between mothers' oncological safety, her right and wish to preserve pregnancy and fetal safety.

In the management of locally advanced cervical cancer in pregnancy, options are limited. Decision-making is even harder than in non-gynecological cancers in pregnancy, having in mind that the fetus develops in the same organ occupied with locally advanced neoplastic disease. Also, in the case of pregnancy termination, the subsequent standard treatment for locally advanced cervical cancer will make the next pregnancies impossible, since the patient will be surgically or radiologically sterile. This "now or never" situation can make patients even more motivated into pregnancy preservation.

What are the options in pregnancy preservation in LACC? As already mentioned, radical surgery and radiotherapy with a fetus *in utero* have an obvious bad outcome on fetal well being and fertility. Delay of treatment until term and delivery without treatment during pregnancy carries a great oncological risk. On the other hand, inducing early delivery, in order to start with treatment on time without fetus *in utero*, leads to iatrogenic fetal prematurity and its consequences on fetal well being. Less radical surgical procedures with the aim to preserve pregnancy such as conization or trachelectomy are not an option in the management of locally LACC.

If we decide to think about pregnancy preservation in LACC, the first thing to have in mind is to have an appropriate oncological candidate for that, despite our wishes for preservation. As many authors suggest, the main triage for preservation approach has to be the detection of lymph node status in a group of patients with LACC, even in non-pregnant women [8,57].

Sentinel lymph node (SLN) detection is still debatable in pregnancy; radiotracer is questionable, and methyl blue is linked with increased rate of allergic reactions. There are some promising results using SLN detection in breast cancer, but for cervical cancer in pregnancy representative publications are lacking. There are promising good results in the detection rate of SLN according to the authors experimenting with the new technology using indocyanine green as a detection tracer, but so far just in non-pregnant patients according to our knowledge [58].

In patients with LACC diagnosed during pregnancy NACT could be the option. Since data on safety and efficacy of NACT in LACC during pregnancy are still limited and based on a low level of evidence, this treatment modality should remain experimental and reserved to highly motivated patients wishing to preserve the pregnancy. Further studies with longer follow-up will be needed to draw definite conclusions about oncological and fetal safety of NACT in pregnancy.

Conflict of interests

The authors declare no conflict of interests.

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