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Evaluation of Efficacy and Safety of Neoadjuvant Chemotherapy in Pregnancy Complicated with Cervical Cancer

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Abstract: This study focused on the special clinical context of pregnancy with cervical cancer to comprehensively evaluate the efficacy and safety of neoadjuvant chemotherapy. Through the analysis of relevant cases and comprehensive studies, the role of neoadjuvant chemotherapy in controlling tumor progression and improving the survival rate of patients during pregnancy was discussed, and the adverse effects of chemotherapy on mothers and infants were closely paid attention to, including potential risks to fetal development, physical conditions of pregnant women and pregnancy outcomes. Comprehensive indicators and data to provide scientific basis and reference for clinical treatment decision-making, in order to achieve the best treatment effect and maternal and child safety protection.

Keywords: Pregnancy; Cervical Cancer; Neoadjuvant Chemotherapy; Efficacy and Safety.

1. Introduction

Cervical cancer is one of the most common malignancies in women, ranking fourth among female malignancies. There are about 110,000 new cases of cervical cancer in China each year, with about 34,000 deaths [1]. Gestational cervical cancer refers to patients diagnosed during pregnancy to 6-12 months postpartum, and is one of the most common malignant tumors during pregnancy, with an incidence of 1.5-12 cases / 100,000 pregnancies [2]. The treatment of cervical cancer includes surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy. The treatment of cervical cancer in pregnancy should consider the clinical stage, pathological type, gestational week, fetal condition and the wishes of patients and their families. When the patient wishes to continue the pregnancy, the gestational week should be extended as far as possible without affecting the prognosis to improve the newborn survival rate. According to the guidelines for the treatment of cervical cancer in pregnancy, postpartum management or cervical conectomy before 20 weeks of pregnancy can be considered if LVSI at stage IA1 is negative. If LVSI is positive in stage IA1, stage IA2, and stage IB1-2 are less than 22 weeks, laparoscopic pelvic lymph node dissection can be selected. If LVSI is positive, pregnancy should be terminated. In stage 2 of IB2, neoadjuvant chemotherapy can be followed by laparoscopic pelvic lymph node dissection, but the operation is easy to induce abortion. If IB3 or above is less than 20 weeks, it is recommended to terminate pregnancy and treat as soon as possible; Neoadjuvant chemotherapy is feasible at 20 weeks and above to extend the gestational age [4]. Neoadjuvant chemotherapy (NACT) is an innovative option for patients with stage IB2 and IB3 cervical cancer prior to cesarean section and radical hysterectomy, and a variety of chemotherapy agents are available. The cisplatin plus paclitaxel regimen performed well in maternal and fetal outcomes [5], but there were also problems such as disease progression, fetal malformation, developmental problems, and chemotherapy side effects in patients. This article will discuss the efficacy and safety of neoadjuvant chemotherapy in the treatment of pregnancy complicated with cervical cancer, and provide a new theoretical basis for clinical treatment.

2. Overview of Neoadjuvant Chemotherapy

Neoadjuvant therapy refers to 2-3 courses of chemotherapy for patients with cervical cancer before surgery or radiotherapy, and is applicable to patients with stage IB3-IV [3]. Neoadjuvant chemotherapy can not only reduce tumor volume and create conditions for surgery, but also reduce cancer cell activity and improve radiotherapy sensitivity [5,6]. Using NACT in the second and third trimester of pregnancy is also relatively safe for mother and child. Studies have shown that chemotherapy during pregnancy will increase the risk of mother and child, which may lead to myelosuppression, neurotoxicity, gastrointestinal reactions and serious obstetric complications for the mother, and spontaneous abortion, malformation, growth restriction, intrauterine death, premature delivery, low birth weight and myelotoxicity for the fetus [7]. These risks are closely related to the gestational age, drug type, dose, course of treatment and the ability of drugs to cross the placenta when receiving chemotherapy, especially the teratogenic effects are most obvious when chemotherapy drugs are used during 2-8 weeks of pregnancy [8]. Literature research has found that platinum single-drug chemotherapy, platinum combined with paclitaxel, platinum combined with vincristine, platinum combined with bleomycin, cisplatin + etoposide, doxorubicin + cyclophosphamide, vincristine + remycin + cyclophosphamide and other chemotherapy regimen have been applied, but there is no standard drug regimen at present. According to literature research, platinum monotherapy, platinum combined with paclitaxel, and platinum combined with vincristine are the most commonly used protocols [9-11]. Platinum drugs can induce apoptosis mainly by interfering with DNA replication and transcription, and loplatin can also

play an anti-tumor role by regulating cellular immunity and affecting cell cycle. Paclitaxel reduces the reproduction rate of cancer cells by inhibiting microtubule decomposition and affecting cell mitosis, which is fatal to chicken, rat and rabbit embryos, but does not cause human organ malformation [12,13]. Retrospective studies have found that ototoxicity, hematological tumors, hypospadias and retroperitoneal embryonal rhabdomyosarcoma were very rare in neonates delivered from patients treated with platinum-single drug chemotherapy [7], but the results were not convincing due to the small sample size. Due to the rarity of cervical cancer in pregnancy, doctors face the challenge of insufficient sample size in clinical practice, and the application of neoadjuvant chemotherapy in cervical cancer in pregnancy is a complex and sensitive issue, so it becomes particularly difficult to accurately evaluate the effectiveness and safety of neoadjuvant chemotherapy regimen. Therefore, it is particularly important to carry out a large sample randomized clinical trial to help fully understand the actual effect of neoadjuvant chemotherapy in cervical cancer in pregnancy. At the same time, doctors should fully consider the patient's gestational age, individual differences, tumor stage and type, as well as the potential impact of chemotherapy drugs on the fetus, and choose relatively safe and effective drugs to maximize the protection of fetal health. To sum up, the application of neoadjuvant chemotherapy in cervical cancer in pregnancy should be carefully and comprehensively considered. In the future, with the development of more clinical trials and the accumulation of data, it is expected to provide patients with more personalized and effective treatment plans.

3. Evaluation of Curative Effect

For stage IA2-IB1 tumors less than 2 cm in diameter with negative lymph nodes, cervical conectomy or cervical excision may be selected. For higher grades of cervical cancer, NACT is the only treatment that can maintain the fetus to maturity, but its safety is one of the issues to be considered. BERNARDINI [7] studied the effects of chemotherapy in 13 pregnant women with cervical cancer, and the results showed that most patients had a partial or complete response to NACT, only 2 patients had tumor recurrence, and 1 patient (7.7%) died of the disease. A 36-year-old woman was diagnosed with cervical adenocarcinoma stage IB1 at 19 weeks of pregnancy. She was treated with paclitaxel and carboplatin, and underwent cesarean section and radical hysterectomy combined with pelvic lymph node dissection at 32 weeks of pregnancy. No tumor recurrence was observed during postoperative follow-up [11]. A study of 48 patients with late-stage cervical cancer during pregnancy with paclitaxel combined with cisplatin showed that the complete response rate was 10%, the partial response rate was 63.4%, the mean disease-free survival was 48.5 months, and 67.4% of the patients gave birth to healthy newborns [14]. Two pregnant women were diagnosed with stage IB3 cervical cancer in the second trimester and were given intravenous chemotherapy with paclitaxel (albumin type) combined with cisplatin. Mri showed that the disease was stable and the tumors were smaller than before chemotherapy [15,16]. Most experts believe that platinum combined with paclitaxel chemotherapy can get a good response, and the treatment effect can be understood by color ultrasound and magnetic resonance. Combined with case reports, it can be seen that NACT is safe and effective in controlling the tumor load during pregnancy, and its impact on the fetus is relatively small, and it is feasible to perform radical surgery after the fetus is mature. In the course of chemotherapy, it is necessary to closely monitor the blood routine, liver and kidney function and other biochemical indicators of pregnant women to ensure the safe use of chemotherapy drugs. At the same time, regular color ultrasound and magnetic resonance examination can monitor the changes of tumor in real time, and provide basis for the adjustment of chemotherapy regimen. In addition, psychological support during chemotherapy is also crucial to help pregnant women ease anxiety and fear and improve treatment compliance.

4. Safety Assessment and Pregnancy Outcomes

Neoadjuvant chemotherapy can effectively treat the tumor of pregnant cervical cancer patients, but it also has a certain impact on mother and child. The effects on the fetus depend mainly on the gestational age, dose and type of drug at the time of administration. The main effects include intrauterine growth delay, intrauterine death, low birth weight and preterm birth. In addition, adverse reactions such as hematopoietic inhibition, infertility, growth retardation, canceration and second-generation teratogenesis have also been found [12], but studies on nervous system, cardiotoxicity and cognitive ability have not been clear. In order to reduce the impact on the fetus, Chinese guidelines do not recommend chemotherapy before 15 weeks, and neoadjuvant therapy in the third trimester is relatively safe. A number of studies have found that patients with cervical cancer in pregnancy were treated with paclitaxel combined with platinum and platinum combined with vincrimetin for 48-60 months, and the newborns were healthy with no evidence of abnormalities in metabolism, hematology, nephrology or nervous system [12,14]. However, other studies have found that the same chemotherapy regimen was used. During the follow-up, 2 neonates were diagnosed with bilateral sensory hearing loss and retroperitoneal embryonic rhabdomyosarcoma [4]. In this report, the average birth weight of 53 neonates was about 2,163.2 grams, and it was calculated that fetal growth restriction, premature birth and low birth weight were as high as 50%. For the patients, the side effects of chemotherapy are similar to those of non-pregnant cervical cancer patients, mainly gastrointestinal reactions, bone marrow suppression, liver function injury and oral ulcers. These adverse results suggest that the use of neoadjuvant chemotherapy must be weighed against its potential risks and benefits for the mother and child. Therefore, for pregnant women receiving neoadjuvant chemotherapy, strict prenatal monitoring and follow-up should be carried out to ensure that possible complications are detected and managed in time. In addition, the selection and adjustment of chemotherapy regimen also need to be comprehensively evaluated by professional doctors according to the specific conditions of pregnant women.

5. Conclusion

Persistent infection with high-risk human papillomavirus is the most important pathogenic factor of cervical cancer. More than 70% of people have been infected with HPV virus in their lifetime [17], but only a small number of people will turn into high-grade cervical intraepithelial lesions, which will develop into cervical cancer if not detected and treated in time. The combination of cervical cancer and pregnancy presents

clinical and ethical challenges for clinicians. With the change of the national fertility policy, the incidence of cervical cancer during pregnancy has increased year by year, ranking the second among tumors during pregnancy [18]. The main symptoms of cervical cancer in pregnancy are abnormal vaginal bleeding and fluid flow, and there may be changes in urine and feces in the late stage, which should be distinguished from threatened abortion in obstetrics, decidual polyps, placental abnormalities, premature rupture of membranes and other diseases. When pregnant women are suspected to have cervical cancer, "three-step screening" is required. Studies have found that "three-step screening" during pregnancy will not increase the risk of miscarriage or premature delivery [19], but temporary spotting may occur, so it is necessary to pay close attention to the bleeding situation and timely treatment. If the colposcopic biopsy is not satisfactory, diagnostic cervical conectomy can be performed at 14-20 weeks of pregnancy, avoiding cervical scratching and using "flat cone" can reduce the occurrence of miscarriage. When the diagnosis of cervical cancer in pregnancy is made, it is necessary to formulate an individualized treatment plan according to the clinical stage, pathological type, gestational age, and the pregnancy wishes of the patient and her family. If the pregnancy is not required to continue, the treatment principle is the same as non-pregnant cervical cancer. Before stage IIA2, radical hysterectomy and pelvic lymph node dissection can be performed directly at < 25 weeks of gestation, and radical hysterectomy and pelvic lymph node dissection should be performed directly at > 25 weeks of gestation, and it is necessary to confirm with patients and their families whether to rescue premature infants. When the clinical stage is higher than stage IIB, radiation therapy after abortion, induction of labor or hysterectomy is recommended. If the pregnancy is required to continue, the diagnosis of IA1 before 20 weeks of pregnancy and negative incisional margin can be delayed until postpartum treatment, and laparoscopic pelvic lymph node resection is feasible in stage IA2-IB2. If the lymph node is negative, the pregnancy can continue. Termination of pregnancy before 20 weeks of pregnancy with IB3 and above, and termination of pregnancy after 20 weeks of pregnancy with neoadjuvant chemotherapy until 34 weeks of pregnancy. NACT is the only way to extend the gestational period during pregnancy so that the fetus reaches maturity [20]. [21] Studies have compared the effects of the three treatment modalities of NACT group, direct surgery group, synchronous radiotherapy group and chemotherapy group on the survival of patients with cervical cancer during pregnancy IB2-IIB, and the results show that the 5-year progression-free survival of the three treatment schemes is 85.0%, 77.4%, 52.9%, and the 5-year overall survival rate is 88.7%, respectively. 80.2% and 64.4%, indicating that NACT can prolong the survival time of patients with cervical cancer during pregnancy, and the prognosis and survival rate of cervical cancer are not affected by pregnancy [22].

NACT in the first trimester increases the incidence of malformation by 10%-20%, while it is relatively safe in the second and third trimester [23], but is associated with fetal growth restriction, low birth weight and preterm birth [24]. Studies have found that preterm birth of newborns born to mothers with cancer during pregnancy may lead to increased neonatal mortality [25], and neonatal deaths due to NACT are rare. Of course, this could also be due to the fact that there are fewer cases of the disease and the problem is not detected. For NACT of cervical cancer in pregnancy, there is no standard chemotherapy regimen at present, and platinum drugs are recommended for the third trimester with high safety. The potential advantages of using platinum-based drugs for NACT during the second and third trimester of pregnancy are reducing tumor size, extending gestational age and improving neonatal survival, controlling micrometastases and enhancing radiosensitivity [26-27], but when used in patients who are not sensitive to platinum-based drugs, it may accelerate disease progression. Studies have shown that Akt plays a key role in regulating cell growth, proliferation, energy metabolism, and chemotherapy resistance, and is also associated with angiogenesis [28], but clinical data are lacking for verification. Due to the special nature of pregnancy, clinicians need to consider carefully when making plans. Traditional chemotherapy drugs, although they may show advantages in some cases, their potential risks cannot be ignored. Although biotherapy and immunotherapy, as new therapeutic means, have certain efficacy in non-pregnant patients, their application in pregnancy still needs to be cautious. Future studies should pay more attention to exploring the safety and effectiveness of these novel therapies in pregnant patients with malignant tumors, with a view to providing more appropriate treatment programs for patients. At the same time, interdisciplinary cooperation is also essential, including the participation of multidisciplinary experts in obstetrics, oncology, pediatrics, etc., to ensure the comprehensiveness and accuracy of the efficacy assessment.

For pregnant patients with malignant tumors, the evaluation of efficacy should take into account the safety of the mother and the fetus. In the evaluation of efficacy, we should not only pay attention to the changes of the tumor, but also comprehensively consider the safety of the mother and child. For example, when the mother has serious side effects of chemotherapy, how to choose drugs for targeted treatment is worth considering. Studies have proved that TCM can alleviate the toxic and side effects of chemotherapy [29], but the effectiveness of TCM in alleviating the side effects of chemotherapy during pregnancy is still unknown. Therefore, it is of great clinical significance to explore the application of traditional Chinese medicine in neoadjuvant chemotherapy during pregnancy. Future studies can further explore the specific mechanism of action of traditional Chinese medicine in neoadjuvant chemotherapy during pregnancy, and optimize the treatment plan of traditional Chinese medicine, so as to improve the efficacy of neoadjuvant chemotherapy on the premise of ensuring the safety of mother and child. At the same time, it is also necessary to pay attention to the long-term effects of TCM treatment and the potential impact on maternal and child health to provide a more comprehensive basis for clinical decision-making.

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