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LITERATURE REVIEW

Neoadjuvant Chemotherapy In Stadium Ib3, Iia2 And Iib Cervical Cancer

I Gde Sastra Winata[1]

Affiliations: *1. Obstetrics and Gynecology Department of Udayana University/Sanglah General Hospital Bali*

Correspondece: *I Gde Sastra Winata,, Email : sastra@unud.ac.id ; HP:*

Abstract

Aim: *This study aimed to describe Paclitaxel-Carboplatin chemotherapy as neoadjuvant chemotherapy in stage IB3, IIA2 and IIB cervical cancer.*

Materials and Methods: *The review was conducted by collecting journals from previous studies discussing neoadjuvant chemotherapy in cervical cancer stages IB3, IIA2, and IIB and in this case specifically discussing Paclitaxel-Carboplatin chemotherapy.*

Results: *Neoadjuvan chemotherapy refers to systemic therapy intended to reduce the size of the tumor before the definitive operation. Several studies have shown that neoadjuvant chemotherapy has greater advantages than surgery alone for early stage cancers (IB3, IIA2, and IIB). Paclitaxel and Carboplatin are known chemotherapeutic agents that can be used as neoadjuvant chemotherapy.*

Conclusions: *Neoadjuvant Chemotherapy regimen Paclitaxel Carboplatin is one of the options in performing therapy for early stage cervical cancer which can be very helpful in healing and cancer-free patient condition. Neoadjuvant chemotherapy followed by radical surgery has significant benefits that have been described in several previous studies.*

Clinical Significance: *Neoadjuvant Chemotherapy regimen Paclitaxel Carboplatin may be used as therapy regimen for early stage cervical cancer with all advantage compared to only surgery. Thus, this type of regimen can be used to decrease mortality and morbidity in patient with stadium IB3, IIA2 and IIB cervical cancer.*

Keywords: *Neoadjuvant Chemotherapy, Paclitaxel, Carboplatin, stadium IB3, IIA2 and IIB cervical cancer.*

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INTRODUCTION

Cervical cancer is a malignant tumor in the cervix caused by the infection of human papilloma virus (HPV). Cervical cancer is the most commonly found gynecological cancer and is the main cause of pain and death in women, especially in developing countries. Until now, the handling of cervical cancer is still very developing and in some early stages there are still many controversies, one of which is an IB3, IIA2 and IIB stage. [1-2]

Cervical cancer is ranked fourth most often found in women after breast cancer, colorectal and lung. The incidence of cervical cancer has increased since the last two decades. The incidence of cervical cancer globally is 13.1 cases per 100,000 women, which vary in each country. The incidence of cervical cancer in the world based on the International Agency for Research On Cancer (IARC) in 2015 is 17 cases per 100,000 women (hackers and vermoken, 2015; WHO, 2016). Bulky cervical cancer or cervical cancer with a mass size of ≥ 4 cm, i.e. IB3, IIA2 and IIB stadium are specialized problems related to the controversy of handling and the patient's prognosis. The prognosis of IB3 Stadium Cervical Cancer, IIA2 and IIB is worse than the initial stage to IB2 regarding the incidence of local recurrence and higher lymph node metastases.

Until now the IB3 stage cervical cancer management strategy, IIA2 and IIB is still controversy, where chemoradiation, operations radical hysterectomy or neoadjuvan chemotherapy which is then continued with radical hysterectomy can be done. The National Comprehensive Cancer Network (NCCN) recommends therapeutic modalities in cervical cancer this type is direct radical hysterectomy, radical hysterectomy after neouadjuvan chemotherapy or concurrent chemoradiotherapy (Shen, 2012; Wang, 2014).. The neoadjuvan chemotherapy regimens are often used include Cisplatin, Paclitaxel, Topotecan, Vinorelbine, Gemcitabine and iFosfamide (Berek and Hackers, 2015). In research by Mori et al. (2010),[1] the provision of Paclitaxel regimens and carboplatin per week continued with radical operations in Locally Advanced Cervical Cancer (LACC) patients is a promising therapy with a better prognosis. Neoadjuvan chemotherapy is able to reduce the risk of lymph node metastasis, parametrial infiltration and tumor size so that it can increase the survival rate, the quality of life of the patient and reduce the need for post-operating radiation therapy.[5]

METHODS

The review was conducted by collecting journals from previous studies discussing neoadjuvant chemotherapy in cervical cancer stages IB3, IIA2, and IIB and in this case specifically discussing Paclitaxel-Carboplatin chemotherapy. Pharmacokinetics and pharmacodynamics of Paclitaxel and Carboplatin were searched and compared and explored how the effects of these chemotherapy on angiogenesis, mitosis and tumor genetic instability. After that, it was described about the specific effect of this chemotherapy on cervical cancer stages IB3, IIA2, and IIB.

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RESULT

Neoadjuvan chemotherapy in IB3, IIA2 and IIB Stadium Cervical Cancer

Neoadjuvan chemotherapy refers to systemic therapy intended to reduce the size of the tumor before the definitive operation.[2] The provision of neoadjuvan chemotherapy is estimated to provide a better life expectancy than adjuvant chemotherapy, this is due to neoadjuvan chemotherapy can reduce genetic heterogeneity. Neoadjuvan chemotherapy followed by operations reportedly increasing the progression free survival (PFS) and diseases free survival (DFS) of 88.1% and 60.5% In addition, neoadjuvan chemotherapy can also be used to optimize the operative approach, and monitor response and adjust the use of chemotherapy regimens. This can be used at the beginning of the regiment, or if it fails to achieve the optimal response, and to choose chemotherapy or other additional therapies.

Historically, Cisplatin, Paclitaxel, and iFosfamide are considered as the most active platinum agent drug with a response rate of 20% in cervical cancer. The use of Cisplatin 100 mg / mg shows a higher level of response compared to 50 mg / m2, but in research by DKK bonomi. In 1985 reported the existence of nephrotoxicity and myelosuppression on the use of high-dose cisplatin. Besides Cisplatin, ifosfamide derived from alkylation agents also shows the level the combination of Paclitaxel Carboplatin's combination every 3 weeks shows an effect similar to the combination of Cisplatin Paclitaxel every 3 weeks in recurrent cervical cancer.[1] In addition, the side effects of nausea, neurotoxicity, muscoxicity, and nephrotoxicity from carboplatin are relatively lower than Cisplatin. Research [4] Using the Neoadjuvan Chemotherapy regimen Paclitaxel Carboplatin obtained a 67.8% of patients giving a good response to neoadjuvan chemotherapy, where the complete response was 7.1% and partial of 60.7%. [5] conducted a prospective study and reported that the combination of Paclitaxel Carboplatin provides a clinical response rate to reach 89% lower the size of the tumor so that it is very good in patients who are then operated. Research by (Mori et al., 2010) also reported a good chemotherapy response of Paclitaxel Carboplatin combination, where 84% was obtained complete and partial response. In Sanglah General Hospital, based on the Clinical Practice Guide Number YM.01.02 / ppk.xiv.6.1 / 35842/2018, Paxus Carboplatin is a choice of neoadjuvan chemotherapy in cervical cancer. Neoadjuvant chemotherapy will be given as many as 3 series before evaluation of operation and followed by radical acts of hysterectomy and removal of lymph nodes in the pelvis area.

Paclitaxel-Carboplatin Chemotheraphy

A. Paclitaxel

Paclitaxel is a metabolite of the isoprenoid group, more precisely it is pseudoalkaloids of expenses consisting of a Taxane ring and a group of n-benzoylphenylisoserine, with molecular formula C47H51NO14. Paclitaxel shows the unique pharmacological properties in inhibiting mitosis, in contrast to Vinka alkaloids and derivates of colchicine which inhibits the formation of microtubules, paclitaxel increases the polymerization of microtubules during cell division

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which will lead to multipolar division causing cell death. Paclitaxel is a chemotherapy agent commonly used as cervical, breast, ovarian and lung cancer therapy.

In adequate concentrations, paclitaxel works to induce multipolar cell division by binding to microtubule subunits, namely -tubulin. Paclitaxel and other microtubule-stabilizing agents bind to microtubules causing dynamic suppression and microtubular stabilization. A study states that the impact of microtubule-stabilizing agents inhibits the process of cell division and affects cell signaling pathways such as apoptosis. The process of cell mitosis then stops which will cause cell death during the mitosis process or the cell will continue to the next process called mitotic slippage. In mitotic slippage, a cell can enter the G1 phase of the cell cycle without going through anaphase or cytokinesis to produce a single cell that is tetraploid. These cells have the possibility to stop proliferating, die after mitotic slippage, or enter the next cycle. The factors that determine the outcome of this mitotic slippage process are still not clearly understood, but it is known that drug concentration and time of cell exposure influence cell death.

Another study states that this bond will lead to the formation of abnormal spindle fibers during the mitotic process and due to the presence of these spindle threads, additional spindle poles are formed during the mitotic process. Cells that enter anaphase, there will be separation of chromosomes in various directions (multipolar cleavage), which will have an impact on random chromosome segregation, then result in partial cytokinesis failure. The result of this partial cytokinesis failure is the presence of aneuploid cells resulting from division. These cells will then die (Figure 2.5). prevents the breakdown of microtubules so that aberrant clusters of microtubules and microtubule structures are found in the mitotic phase. This prevents mitosis and is followed by apoptosis.

The cause of apoptosis by paclitaxel is not clearly known, but it is suspected that apoptosis occurs due to the activation of the transcription factor p53 (Figure 2.6), in addition to recent research that paclitaxel increases the production of Reactive Oxygen Species (ROS) and overexpression of genes and proteins associated with damage. on the endoplasmic reticulum (ER). Damage to the ER can lead to the release of Ca2+ and cause mitochondrial damage due to excess Ca2+. This will lead to an increase in ROS production. In a study conducted on dogs, it was shown that there was a decrease in the expression of the anti-apoptotic protein B-cell Leukemia 2 (Bcl-2) in tumor cells, as well as over-expression of the pro-apoptotic protein Bcl-2-associated X (BAX). These changes lead to mitochondrial apoptosis through disruption of the Mitochondrial Membrane Potential (MMP) and the release of cytochrome C from the mitochondria into the cytoplasm, as well as the cleavage of the protein caspase-3. However, the possibility of mitochondrial apoptosis due to increased ROS is not completely clear. [6]

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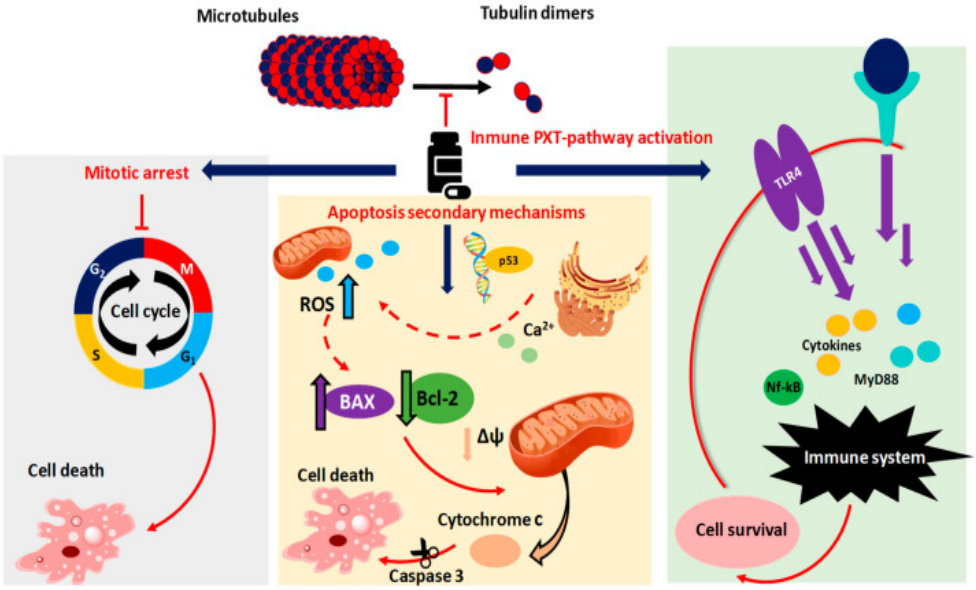

Figure 1 Mechanism of action of paclitaxel on cancer cells [6]

In the immune system, paclitaxel causes macrophage stimulation resulting in the secretion of TNF- or IL-2 cytokines that trigger the activation of NK cells, dendritic cells, and cytotoxic T lymphocytes that cause tumor cell eradication. In addition, paclitaxel acts directly by binding to Toll-like receptors on the surface of dendritic cells, resulting in antigen-presenting cell (APC) maturation. Paclitaxel has also been shown to decrease VEGF and Ang-1 expression in cervical cancer cells, and increase TSP-1 secretion in the tumor microenvironment. [7]

B. Carboplatin

Carboplatin is an agent of the platinum coordination complex group. Platinum coordination complexes covalently bind to nucleophilic sites on DNA and have many of the same pharmacological attributes as alkylating agents, but platinum coordination complexes do not form carbonium ion intermediates like alkylating agents as adjuvant therapy or salvage therapy for epithelial ovarian cancer. [8]

Carboplatin works by penetrating cell membranes, carboplatin will undergo hydrolysis so that it becomes positively charged, then binds covalently at the location of N7 purine bases forming monoadducts or intra and inter diadduct chains (Figure 2.6). This process gives rise to interactions between DNA or DNA-proteins. This binding between DNA and carboplatin can cause lesions on DNA so that it causes crosslinking between DNA (interstrand cross-linking) which is the most cytotoxic effect because it interferes with cell replication (G2/M growth stops) causing apoptosis or necrosis of cancer cells (Figure 2.10). [6]

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Paclitaxel Carboplatin Chemotherapy Relationship to Angiogenesis, Mitosis and Tumor Genetic Instability

Paclitaxel causes autophagy by increasing levels of protein 5 and Beclin-1. Protein 5 and Beclin-1 are proteins required for the formation of autophagosomes. This leads to increased expression of p53 and LC3B thereby regulating the initiation of autophagy. Paclitaxel also significantly reduces the density of microvessels in tumors, and reduces the synthesis of Vascular Endothelial Growth Factor (VEGF) in vivo. The antiangiogenic effect of paclitaxel is thought to be caused by the accumulation of paclitaxel in endothelial cells and carboplatin can increase p53 expression through DNA damage, resulting in acetylation of lysine associated with proapoptotic genes and preventing cells from entering the G2-M phase. Carboplatin induces ERK activation, which is a factor that increases the p53 response to DNA damage caused by carboplatin thereby preventing the development of cancer cells.

VEGF-C expression in bulky cervical cancer is triggered by cell hypoxia, resulting in an increase in Hypoxia Inducible Factors-1α (HIF-1α) and upregulation of VEGF gene expression levels, as well as an increase in transcriptional activity in the VEGF signal transduction pathway. VEGF-C is a VEGF derivative that plays a role in vasculogenesis and lymphangiogenesis, while HIF-1α is a transcription factor that plays a role in the regulation of neovascularization. HIF-1α levels are always increased by cancer cells to maintain oxidative metabolism and promote the growth and metastasis of cancer cells under hypoxic conditions. [9]Neoadjuvant chemotherapy is given with the aim of causing more neoplastic cell death thereby reducing tumor size in the cervix, improving irregular vascularization and oxygen imbalance resulting in high oxygenation and an indirect decrease in HIF-1α expression followed by a decrease in VEGF-C gene transcription.[8]In a study by Kartikasari et al (2019), 25 patients were given Paclitaxel-Carboplatin, and the expression of VEGF-C decreased significantly from an average of 6.16 to 4.20.]

Ki-67 protein is significantly associated with cell proliferation and acts in the mitotic phase, namely G1, S, G2, and M, and maintains DNA structure. (Pan et al., 2015). High levels of Ki-67 indicate that tumor cells have a fast cell cycle. Prevention of depolymerization by paclitaxel led to the cessation of late G2/M phase cell cycle progression followed by apoptosis. Under normal conditions, the phosphorylation of Ki-67 by CDK-1 occurs in the M phase so that the cell can pass through the mitotic state. Decreased tumor cell proliferation as indicated by a decrease in Ki-67 after paclitaxel administration, then along with tumor cell apoptosis and tumor cell necrosis due to VEGF inhibition increased the response to neoadjuvant chemotherapy for the better. The mechanism of regulation of Ki-67 levels is thought to be controlled by p53. In HeLa cell studies, it was found that p53 interacts with Sp-1 thereby suppressing the transcription of Ki-67.

Effectiveness of Paclitaxel-Carboplatin Neoadjuvant Chemotherapy in Stage IB3, IIA2 and IIB Cervical Cancer

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Neoadjuvant chemotherapy followed by radical surgery has significant benefit in early-stage cervical cancer. Research conducted in Thailand by Prueksaritanon, et al. (2012)[11], compared neoadjuvant chemotherapy followed by radical hysterectomy versus radical hysterectomy alone in patients with stage IB3, IIA2, and IIB cervical cancer. A total of 80 patients were included in the study, with the result that the need for postoperative adjuvant chemoradiation was reduced in patients receiving neoadjuvant chemotherapy compared to radical hysterectomy alone (27.5% versus 57.5%, p = 0.0007). The systematic review by Rydzewska et al. (2012)[12] involving six clinical trials reported an increase in DFS and PFS in patients receiving preoperative neoadjuvant chemotherapy. In addition, there was also a significant reduction in the incidence of pelvic and parametrial lymph node infiltration in patients receiving preoperative neoadjuvant chemotherapy compared to those undergoing radical hysterectomy alone.

A randomized clinical study conducted by Gupta et al. (2018),[13] on 633 patients with cervical cancer stages IB3, IIA2, and IIB to determine the effectiveness of neoadjuvant chemotherapy and surgery compared to chemoradiation. The study was conducted for 12 years, with an average duration of following patients for 58.5 months. A total of 316 patients were in the neoadjuvant chemotherapy group with surgery and 317 patients in the chemoradiation group. The five-year survival rate in the neoadjuvant chemotherapy and surgery group was 69.3% compared with 76.7% in the chemoradiation group (hazard ratio, 1.38; 95% CI, 1.02 to 1.87; P = 0.038) . The corresponding five-year survival rates were 75.4% and 74.7%, respectively (hazard ratio, 1.025; 95% CI, 0.752 to 1.398; P = 0.87). When compared between the neoadjuvan chemotherapy group with surgery and the chemoradiation group, the level of toxicity to surrounding organs such as the rectum, bladder and vagina in neoadjuvan chemotherapy followed by surgery was lower than chemoradiation.

In a study conducted by (Liu et al., 2018)[14] comparing the efficacy between neoadjuvant chemotherapy followed by radical hysterectomy surgery with primary surgical therapy for cervical cancer stages IB3, IIA2, and IIB. In 303 patients, it was found that patients who received neoadjuvant chemotherapy before surgery had less bleeding, shorter operation duration and better tumor efficacy with neoadjuvant chemotherapy.

In the systematic review and meta-analysis conducted by Ye et al. (2020),[15] to assess the efficacy and safety between neoadjuvant chemotherapy followed by radical hysterectomy with chemoradiation for cervical cancer stages IB3, IIA2, and IIB. This study found that patients who were given neoadjuvant chemotherapy before surgery had better OS and PFS and lower organ toxicity compared to chemoradiation.

Predictors of Neoadjuvant Chemotherapy Success in Stage IB3, IIA2 and IIB Cervical Cancer

Age

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Age has a significant influence on the incidence of cervical cancer. Therefore, age is an important factor to consider in predicting the success of neoadjuvant chemotherapy therapy accompanied by radical surgery in cases of cervical cancer. The study conducted by Jin Zhou et al. (2016),[9] showed that the overall response rate in younger patients, aged <35 years, was higher than in older patients. It was concluded that young patients with cervical cancer at stages IB3 and IIA2 had a better clinical response than older patients.

Parity

Not many studies have discussed the relationship between parity and response to neoadjuvant chemotherapy. Analysis of research conducted by (Khatimah and Muhammad, 2019) [14] showed that there was no significant relationship between parity and response to neoadjuvant chemotherapy in early-stage cervical cancer.

Tumor size

The study by Sardi et al, showed that in stage IB2 tumors measuring more than 4 cm, the response to neoadjuvant chemotherapy was 83.6%. Meanwhile, tumor size 6 cm gave a better therapeutic response than tumor size > 6 cm with a ratio of 50%: 74.3%. However, the analysis conducted by (Khatimah and Muhammad, 2019)[16] stated that there was no significant relationship between tumor size and neoadjuvant chemotherapy response.

Degree of differentiation

Differentiation is the process of maturation of immature cells into mature cells that have specific functions. In cancer, this process describes how much the tumor tissue looks like the normal tissue of origin. Well-differentiated cancer cells look like normal cells and tend to grow and metastasize more slowly than poorly differentiated or undifferentiated cancer cells (National Cancer Institute, 2011). In cervical cancer, the degree of differentiation can be a predictor of prognosis. Not many studies have discussed the relationship between the degree of differentiation and the success of neoadjuvant chemotherapy, but the research conducted by Matsuo et al. (2018)[17] stated that there was no significant relationship between the degree of differentiation and the response to neoadjuvant chemotherapy.

Histopathological type

Squamous cell carcinoma is the main histologic type that accounts for three-quarters of all cervical cancers. Adenocarcinoma and adenosquamous cell carcinoma represent 10–15% and other histology represents the remaining 10–15%. In general, histologic type did not significantly affect chemotherapy response. However, the squamous cell type has a better response to neoadjuvant chemotherapy, which is 84% versus 70%.[18]There are differences of opinion regarding the effect of histological type on the prognosis of cervical cancer. Some studies have found that adenocarcinoma has a poor prognosis, whereas other studies have found no evidence of histopathological type as a prognostic factor.[19] Another study concluded that cervical cancer with histopathological types of small cell carcinoma and adenocarcinoma correlated with poorer survival. [20]

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CONCLUSION

Neoadjuvant Chemotherapy regimen Paclitaxel Carboplatin is one of the options in performing therapy for early stage cervical cancer which can be very helpful in healing and cancer-free patient condition. Neoadjuvant chemotherapy followed by radical surgery has significant benefits that have been described in several previous studies. Neoadjuvant chemotherapy can help reduce the need for postoperative adjuvant chemoradiation in patients compared to radical hysterectomy alone, improve five-year survival and reduce toxicity to surrounding organs such as the rectum, bladder and vagina

CLINICAL SIGNIFICANCE

Neoadjuvant Chemotherapy regimen Paclitaxel Carboplatin may be used as therapy regimen for early stage cervical cancer with all advantage compared to only surgery. Thus, this type of regimen can be used to decrease mortality and morbidity in patient with stadium IB3, IIA2 and IIB cervical cancer

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