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Review Article

Comparison of Cisplatin Monotherapy and Cisplatin-Containing Combination Therapy in Term of Survival Rate in Recurrent Cervical Cancer

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Abstract

Cervical cancer is one of the primary cause of death in young female and globally, it is the second most common cancer in female population. Recurrent cervical cancer is the cervical cancer that comes back after the resolving the previous cervical cancer. This review discussed about the comparison of different chemotherapy for recurrent cervical cancer. We have performed a literature search in all available databases for almost all relevant articles regarding chemotherapy of recurrent cervical cancer. The data for this review is mainly composed of studies and articles from 1999 years onwards, inclusive of systematic review, phase III clinical trial and literature review. Cisplatin monotherapy and the cisplatin-containing combinations were evaluated in terms of overall survival, progression-free survival, response rate and toxicity. Based on these factors, the best approach is determined. Cisplatin single therapy has shown greater toxicity of 70% compared to 1.4% in the Cisplatin and Paclitaxel combination (PT) therapy. Cisplatin plus topotecan combination (PO) therapy exhibits hematologic toxicity, which is more frequent and severe compared to cisplatin alone. Neutropenia and leukopenia mostly occur in patients receiving cisplatin and vinorelbine combination (PV) and cisplatin and gemcitabine combination (PG) therapy. Hence, PT therapy is least toxic to the patients. In terms of response rate, progression-free survival, overall survival and degree of toxicity, cisplatin-containing combination therapy is more preferred than cisplatin monotherapy in treating recurrent cervical cancer. In addition to minimal overall survival benefit, PT therapy showed the best response rate, progression-free survival and least toxic among other available combinations.

Keywords: Cervical Cancer; Recurrent Cervical Cancer; Chemotherapy; Cisplatin Monotherapy; Cisplatin/Paclitaxel Combination Therapy

Introduction

Cervical cancer is a type of cancer that develops in the cells lining the woman's cervix, which is the lower part of the uterus (womb) from the vagina [1-3]. Cervical cancer is often asymptomatic in its early stage. The normal cells of the cervix gradually undergo pre-cancerous changes and overtime these pre-cancerous cells can become cancerous [4-7]. However, only some women with pre-cancerous cells will develop cancer and if these changes are detected early, treatment can reduce the risk of developing cervical cancer [8-11].

According to WHO classification, cervical epithelial carcinoma are classified into squamous cell carcinoma, adenocarcinoma, and others known as undifferentiated carcinoma and neuroendocrine tumors [8]. In fact, squamous cell carcinoma and adenocarcinoma are dominant in types for cervical cancer [12-14]. Squamous cell carcinoma accounts for 85% of cervical cancer and adenocarcinomas for 10% [12].

Squamous carcinomas are cells that are squamous-like but vary in their growth pattern or morphological characteristics [8]. They were further categorised into keratinizing, non-keratinizing, and small-cell squamous carcinomas. In the latest WHO classification, neuroendocrine tumours are termed as small-cell carcinoma. In keratinizing squamous cell carcinomas, there are keratin pearls which made of squamous cells in circular whorls with central keratin nests [8,15]. Intercellular bridges and cytoplasmic keratinization are commonly seen in these carcinomas. On the other hand, Nonkeratinizing squamous cell carcinomas are generally recognizable polygonal squamous cells and do not manifest keratin pearls theoretically, but some may still exhibit individual cell keratinization and intercellular bridges [13].

Adenocarcinoma is a type of carcinoma that originated from glandular epithelium that produce mucus [12,13]. These gland cells are called adenomatous cells which scattered along endocervical canal which is a passageway that runs from the cervix to the womb [13]. It shows highly varied differentiation [8,15]. Thus, most cervical adenocarcinomas are of endocervical type. They are not visibly mucinous and characterised by presence of eosinophilic cytoplasm [8]. In approximately half of all adenocarcinomas, the masses are exophytic, polypoid or papillary. Some masses are nodular with ulceration or diffuse enlargement in the cervix and barrel-shaped cervix is produced by infiltrate deeply into cervical wall [15]. Immunohistochemistry may be important to distinguish the condition, subtypes of the cervix and sometimes differentiate primary endocervical tumours from primary endometrial tumours [15].

Cervical cancer is clinically staged using the FIGO criteria (International Federation of Gynaecology and Obstetrics) in Scottish Intercollegiate Guidelines Network (SIGN guidelines) and Clinical Practice Guidelines Malaysia [16,17]. FIGO stages consist of I (subdivided into IA, IA1, IA2, IB, IB1, IB2), stage II (subdivided into IIA1, IIA2, IIB), stage III, (divided into IIIA, IIIB) and stage IV (categorized into IVA and IVB) [16,17]. The details of the cancer stages have been discussed in figure 1.

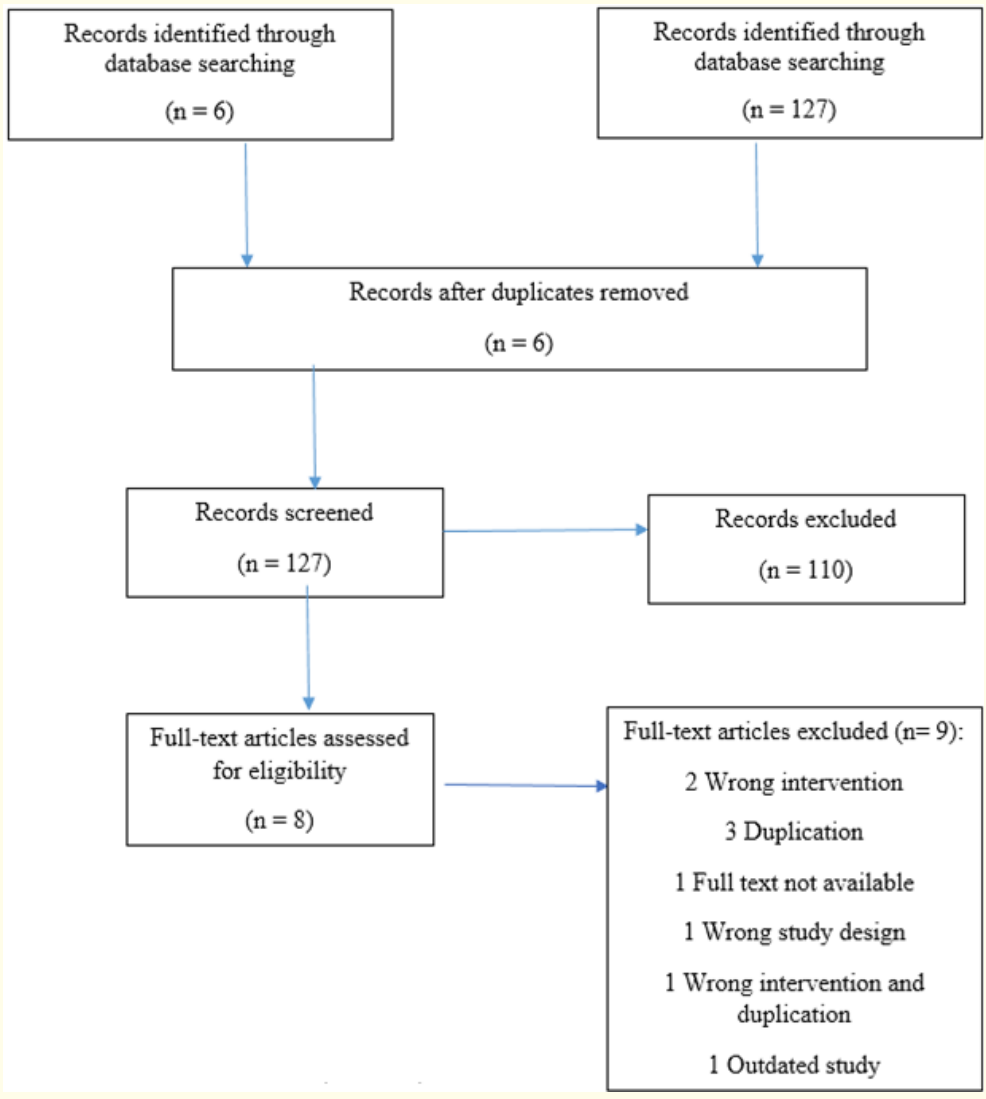

Figure 1: Flow chart showing the study characteristics.

Preventive measure

Cancer prevention is an action taken to lower the possibility of getting unwanted cancer, and in turn lowering the number of the deaths caused by cancer. So, to prevent the development of new cancers, decreasing risk factors like quit smoking, alcohol drinking, fats consumption, having sedentary lifestyle contribute to the increment of chances of developing cancer. By far, HPV vaccination has been proven to have a crucial role as prevention tool for cervical cancer over the past few years. Its efficacy has been proven to work specifically to women who are found to be in difficulty to reach any possible health intervention program. HPV vaccine is commonly known as the first vaccine developed in any cancer prevention and is currently available in two major forms which are bivalent vaccine (Cervarix™, GlaxoSmithKline Biologicals) and the quadrivalent vaccine (Gardasil™, Merck) [18]. The secretions and exudations of serum immunoglobulin G antibody against respective HPV types are from cervico-vaginal as well as micro-abrasions in the epithelium, respectively [19,20]. Hence, with the presence of antibodies, neutralization of the particular virus is secured before it gets an opportunity to bind and infect the basal keratinocytes. Teenage in the age range of 9 to 14 years old appear to be most susceptible to HPV infection so they should be highly recommended to be vaccinated with a series of HPV vaccines starting at the earliest age of 9 [21]. Meanwhile, it is well-known as the most cost-effective strategy for potential cervical cancer prevention in one combining HPV vaccination at 12 years old associated with triennial conventional cytologic screening starting from the age of 25 years onwards [21,22].

Recurrent Cervical Cancer

In this review, recurrent cervical cancer would be the main focus. Recurrence is defined as local tumor regrowth or the development of distant metastasis discovered within 6 months or more after complete regression of the treated lesion [23]. Although advancement of various treatment modalities have shown improved survival rates, the prognosis of recurrent event remains poor [23]. Among women who diagnosed with recurrent cervical cancer, approximately 30% of them died [23].

In a large retrospective North American study done in 564 patients who are initially treated for cervical cancer, it is reported that most of the recurrent cases occur within 18 - 24 months, 31% of them recurred, and among these, 58% of them recurred within 1 year and 76% within 2 years [4]. From the study, it has been estimated that about 40 - 45 years old is the average age of patients to get diagnosed with recurrent cervical cancer [4]. Recurrence rate by stage (based on FIGO staging) has been reported as follows: 10% for stage IB, 17% for stage IIA, 23% for stage IIB, 42% and 74% for stage III and IVA, respectively [4].

Recurrent cervical cancer can present as a local recurrence or as metastatic disease [24]. The predominant site of recurrence is mainly local (example: vaginal apex) or regional (example: pelvic sidewall) for women who received curative-intent therapy for previous cervical cancer [24]. Other retrospective studies also have reported the distribution of anatomic sites of recurrence predominantly involve in 22 - 56% of central site (example: vaginal apex or pelvis without side wall involvement), 28 - 37% for pelvic sidewall, 15 - 61% for distant metastases or multiple recurrence sites [24].

It has been reported that the incident of recurrence at distant site increases as the stages advances, which are 0 - 3% in stage IA, 13 - 16% in stage IB, 21 - 31% in stage IIA, 22 - 26% in stage IIB, 32 - 39% in stage III and 75% in stage IVA. The most common distant sites are the para-aortic lymph nodes (81%), lungs (21%) and supraclavear lymph nodes (7%) [4]. In the retrospective univariate analysis done in 284 patients have revealed that patient age, tumor appearance and tumor size were significantly associated with early recurrence of the disease ($P < 0.05$) [25]. Furthermore, the multivariate analysis also demonstrated these risk factors as independent risk factors for the early recurrence of cervical cancer ($P < 0.05$). However, clinical stage, tumor histology, pathological stage, grade of cervical lesion and prior treatment reportedly do not associate with early recurrence of cervical cancer ($P > 0.05$) [15].

Immunodeficiency, cigarette smoking, high serum hormone levels, cervical erosions, HPV16 infection, and high levels of survivin, cyclooxygenase 2, matrix metalloproteinase and CD44 expression are often exhibited by younger patients compared to older patients [25]. Younger patients with cervical cancer also exhibit poor tumor differentiation and lymph node metastasis [25]. These presentations may altogether lead to early recurrence of cervical cancer in younger patient population [25].

Studies also revealed that a cervical cancer lesion with a diameter > 4 cm is more difficult to control compared to smaller lesions [25]. In addition, another study also reported that estimated recurrence risk for tumors ≤ 2 cm is 1.2% while for the tumors which are ≥ 2cm, the recurrence rate is higher than former, as high as 21% [4]. This could be explained that large tumor lesions are more frequently associated with an earlier onset of distant metastasis [4]. As large cervical cancer lesions with a cauliflower-like and ulcerative tumor appearance often lack sufficient blood supply in their lesion centre. they consequently recruit hypoxic cells and are more resistant to anticancer therapy [25].

Methods

Study selection

Randomized controlled trials (RCTs) that include female with recurrent cervical cancer regardless of ethnicities and age were considered eligible. Intervention criteria included treatment with single agent and combined agents such as Cisplatin, Cisplatin and Paclitaxel, Cisplatin and Topotecan, Cisplatin and Ifosfamide, Cisplatin and Vinorelbine, as well as Cisplatin and Gemcitabine. Studies that include survival rate as outcome were selected.

Literature search strategy

The literature search of the electronic databases in PubMed and TRIP database was done since 9th January 2017 by using combined disease-specific terms and combined intervention-specific terms as following: “Randomized Controlled Trial”, “Cervical Cancer”, “Recurrent Cervical Cancer”, “Chemotherapy”, “Cisplatin monotherapy”, “Cisplatin/Paclitaxel combination therapy”, “Squamous Cell Carcinoma”, “Adenocarcinoma”, “Malignant”, “FIGO (International Federation of Gynecology and Obstetrics)”, “Cisplatin/Topotecan combination therapy”, “Cisplatin/Ifosfamide combination therapy”, “Cisplatin/Vinorelbine combination therapy”, Cisplatin/Gemcitabine combination therapy”, “Survival rate”, “Adverse effects”, “Neutropenia”, “Leukopenia”, “Toxicity”, “Peripheral Neuropathy”, “Hepatotoxicity”, “Anaemia”.

Results

Study characteristics

The treatment of recurrent cervical cancer is depending on previous treatment, disease-free interval, site or extent of recurrence, and performance status of patient. The carcinoma of the cervix has limited sensitivity to cytotoxic agent, especially in patient that have received irradiated pelvis before [5]. Based on our literature findings, there are several combinations therapies being compared with monotherapy of cisplatin. The list of drugs and drug combinations used in recurrent cervical cancer are shown in table 1. The details of clinical trial studies performed on cisplatin and its combination drugs is summarised in table 2 and the clinical outputs of these studies are summarised in table 3.

Therapy	Drug
Single/ Monotherapy	Cisplatin (P)
Combination	Cisplatin (P) and Paclitaxel (T) (PT)
	Cisplatin (P) and Topotecan (O) (PO)
	Cisplatin (P) and Ifosfamide (I) (PI)
	Cisplatin (P) and Vinorelbine (V) (PV)
	Cisplatin (P) and Gemcitabine (G) (PG)

Table 1: List of drugs used in the treatment of recurrent cervical cancer.

Year of Study	Clinical trial phase	Number of patients	Drugs	Dose and Duration	Reference
2002	Phase II	32	P+O	Cisplatin 50 mg/m^2 IV over 1 hour on day 1 and topotecan 0.75 mg/m^2 IV over 30 min on day 1, 2, and 3.	[14]
2002	Phase II	60	I+T+P	Ifosfamide 1500 mg/m^2 iv over 1 h on day 1-3, paclitaxel 175 mg/m^2 as a 3-h iv infusion on day 1 and cisplatin 75 mg/m^2 iv over 2 h on day 2	[15]
2006	Phase II	53	I+T+P	Ifosfamide 1500 mg/m^2 iv over 3 h on day 1-3, paclitaxel 135 mg/m^2 as a 24-h iv infusion and cisplatin 50 mg/m^2 iv over 30 min on day 1	[16]
1999	Phase II	47	P+T	Paclitaxel 135 mg/m^2 as a 24-h iv infusion followed immediately by cisplatin 75 mg/m^2 iv at a rate of 1 mg/min	[17]
2005	Phase III	293	P	Cisplatin 50 mg/m^2 every 3 weeks	[18]
			P+O	Cisplatin 50 mg/m^2 day 1 plus toptoecan 0.75 mg/m^2 day 1 to 3 for every 3 weeks	
			P+M+V+D	Methotrexate 30 mg/m^2 day 1, 15 and 22; vinblastine 3 mg/m^2 day 2, 15 and 22; doxorubicin 30 mg/m^2 day 2, and cisplatin 70 mg/m^2 day 2 every 4 weeks	
			P+O	Topotecan 0.75 mg/m^2 day 1, 2, and 3 plus cisplatin 50 mg/m^2 day 1 every 3 weeks	
2005	Phase III	293	P+T	Paclitaxel 135 mg/m^2 over 24 hours a day 1 and cisplatin 50 mg/m^2 on day 2, repeated every 3 weeks	[19]
			T+C	Paclitaxel 175 mg/m^2 over 3 hours and carboplatin 5 mg/ml/min on day 1, repeated every 3 weeks	

Table 2: Details and study characteristics of clinical trials.

P: Cisplatin; T: Paclitaxel; C: Carboplatin; O: Topotecan; I: Ifosfamide; V: Vinorelbine; G: Gemcitabine; M: Methotrexate; D: Doxorubicin.

Study	Targeted drug	Complete response (%)	Partial response (%)	Overall response rate (%)	Progression free Survival (months)	Overall survival (months)
(14)	P + O	9.4	18.7	28.0	5.00	10.00
(15)	I + T + P	19.0	27.0	46.0	8.30	18.60
(16)	I + T + P	4.4	42.2	46.7	8.00	19.00
(17)	P + T	12.2	34.1	46.3	5.40+	10.00+
(18)	P P + O	3.0 10.0	10.0 16.0	13.0 27.0	4.60 2.90	9.40 6.50
(20)	P P + T	6.0 15.0	13.0 21.0	19.0 36.0	2.80 4.80	8.80 9.70
(21)	P + T P + V P + G P + O	2.9 7.4 0.9 1.8	26.2 18.5 21.4 21.6	29.1 25.9 22.3 23.4	5.82 3.98 4.70 4.57	12.87 9.99 10.28 10.25
(19)	P + T T + C	3.9 7.1	- -	58.8 62.6	6.90 6.20	18.30 17.50

Table 3: Observed clinical outcomes from clinical trial studies

P: Cisplatin; T: Paclitaxel; C: Carboplatin; O: Topotecan; I: Ifosfamide; V: Vinorelbine; G: Gemcitabine.

However, this review is mainly focus on comparison of cisplatin monotherapy with cisplatin/paclitaxel combination therapy and cisplatin/topotecan combination therapy. The outline of chemotherapy of advanced, persistent or recurrent cervical cancer discussed in this review are based on the literature search of almost all relevant articles regarding chemotherapy of recurrent cervical cancer in available databases.

Cisplatin monotherapy

Many single-agents of chemotherapy have been tested for recurrent cervical cancer, but none of it supersede cisplatin, in terms of final primary and secondary endpoints which indicate overall survival of the patient, progression-free survival, adverse events, severe adverse events, rate of response, and the size of non-hospitalization periods in comparison with the planned treatment periods [5,26]. Cisplatin has a response rate of 17 - 21% in cervical cancer at a dose ranging from 50 to 100 mg/m^2 [5]. In addition, by administering cisplatin every 3 weeks, a response rate of 20 - 30% and overall survival of 7 months were observed [5].

In a study conducted by Potter., *et al.* with 68 eligible patients, an overall response rate of 40.2% were reported. However, patient with isolated lung metastases is more responsive to cisplatin monotherapy, which showed complete response rate of 6.3% and overall response rate of 73%. Meanwhile, complete responses were not observed in patient with recurrent cervical cancer

but 21% of partial responses instead [5]. According to GOG criteria, complete response is defined as the eradication of all gross evidence of disease for at least 4 weeks and partial response is a more than one half (50%) reduction in the 0product of bidimensional measurements of each lesion maintained for at least 4 weeks [27].

Besides, platinum analogues such as iproplatin and carboplatin have also been studied as the monotherapy to lower the toxicity of chemotherapy [5]. In a study conducted by Gynecologic Oncology Group with 394 recurrent cervical cancer patients, the result revealed a response rate of 15% for carboplatin and 11% for iproplatin. The patients in this study did not receive prior chemotherapy and they were randomized to treatment of either carboplatin (340 - 400 mg/m^2) or iproplatin (230 - 270 mg/m^2), which are equivalent to 75 - 100 mg/m^2 of cisplatin. Apart from response rate, grade 3 or 4 neurotoxicity were observed in a third of patients. Both of these platinum analogues seems to be secondary to those with the parent compound, cisplatin by having lower response rate than cisplatin [3,5]. Thus, single-agent cisplatin still remain as the current therapy of choice for cervical cancer [3,5]. However, as compared with combination therapy, the result of single-agent therapy has shown a significant higher toxicity with 70% versus 1.4% in Grade 3 or 4 neutropenia [26].

Cisplatin and Paclitaxel (PT) combination

Combination chemotherapy normally includes drugs with its own activity, non-overlapping toxicity and synergistic activity without further increment of toxicity [5]. In squamous cell carcinoma of cervix, Cisplatin has been frequently used to study and is the most active single agent. Paclitaxel is a new anticancer drug, which involved mitotic spindle's microtubular polymer complex stabilization [28]. Paclitaxel consists of a response rate of 21% to 33% in managing the lung, neck and head's squamous cell carcinoma. The toxicity of neutropenia was prevalent but neutropenic sepsis is less common. Paclitaxel and cisplatin's study was based on the basis of the modest activity of paclitaxel seen in cervix's squamous cell carcinoma and the addictive activity of the combination of paclitaxel and cisplatin [28].

Gynaecologic Oncology Group (GOG) has conducted a phase II study of paclitaxel and cisplatin as first line therapy in recurrent cervical cancer [28]. The starting dose administered was 135 mg/m^2 of paclitaxel infused over one day followed by cisplatin 75mg/m^2 every three weeks. On the basic of toxicity, paclitaxel's dose is increased to a maximum dose of 170 mg/m^2/d. Forty-four patients were assessed for toxicity. Forty patients had received prior pelvic radiation therapy, of which 14 had received para-aortic and extended pelvic field radiation therapy. The most frequent severe adverse effect is neutropenia grade 3 and 4. It was found out that the chance of suffering from grade 3 or 4 neutropenia is higher in the patients who had received extended-field radiation therapy compared to patients who had pelvic radiation. The study has found out an overall response rate of 46.3%. The response rate of 46.3% seems favourable compared with the result of previous studies of single-agent cisplatin [28]. As well as the toxicity was found to be significantly higher in single-agent cisplatin which is 70% as compared to 1.4% in TP combination [26].

Besides, GOG also conducted randomized phase III trial of cisplatin (P) versus cisplatin/paclitaxel (PT) which revealed a greater overall response and progression free survival in combination therapy compared to cisplatin alone. 134 patients were receiving cisplatin at an intravenous (IV) dose of 50 mg/m^2 at the rate of 1 mg/min every 3 weeks for six cycles. Another 130 patients were receiving paclitaxel at an IV dose of 135 mg/m^2 as a 24-hour infusion followed immediately by cisplatin at a dose of 50 mg/m^2 every 3 weeks for six cycles [29]. Lowering of cisplatin dose level to 37.5 mg/m^2 was needed if the patient experienced grade 4 nausea and vomiting, and lowering of cisplatin dose level to 25 mg/m^2 was needed if the patient experienced grade 2 neurotoxicity (peripheral neuropathy or ototoxicity). Cisplatin was discontinued in the event of grade 3 to 4 neurotoxicity. Lowering of paclitaxel dose level to 110 mg/m^2 was required for grade 3 to 4 neutropenic fever or grade 4 thrombocytopenia and lowering of paclitaxel dose level to 90 mg/m^2 was required if the patient experienced grade 2 peripheral neuropathy. Treatment with paclitaxel was discontinued for grade 3 to 4 peripheral neuropathy or hepatotoxicity. 92% of patients receiving cisplatin and 91% of patients receiving PT had prior radiation therapy. Among patients receiving PT, grade 3 anemia, grade 4 anemia and grade 4 neutropenia were more commonly seen. There were 6% complete response and 13% partial response from an overall response of 19% among patients receiving 0cisplatin alone [29]. There were 15% complete response and 21% partial response from an overall response of 36% among patients receiving PT [29]. Complete response was defined as disappearance of all gross evidence of disease for at least 4 weeks. Partial response was defined as a greater than 50% reduction in the product of perpendicular diameters obtained from measurement of each lesion, sustained for at least 4 weeks. The median progression free survival for patients receiving cisplatin was 2.8 months while the median progression free survival for patients receiving PT was 4.8 months. There were minimal difference in median survival observed among patients with cisplatin (8.8 months) and patients with PT (9.7 months) [23].

Cisplatin and Topotecan combination

In a randomised phase III trial by Long., *et al.* there were 146 patients randomly allocated to receive cisplatin 50 mg/m^2 intravenously (IV) on day 1 for every 21 days while 147 were randomly allocated to receive topotecan 0.75 mg/m^2 IV for 30 minutes in days 1, 2, and 3 plus cisplatin 50 mg/m^2 IV on day 1, repeated for every 21 days [27]. Nearly 60% of patients in both treatment arms had received prior cisplatin as part of a chemoradiotherapy regimen [27]. In terms of response rate, benefits were reported for patients receiving cisplatin plus topotecan when compared with patients receiving cisplatin alone. The combination of cisplatin and topotecan had shown 10% complete response and 16% partial response. 3% complete response and 10% partial response were shown in the treatment involving cisplatin alone [27]. By comparing both cisplatin plus topotecan and cisplatin treatment, results showed overall response rate of 27% vs 13% respectively (P = 0.004) [27]. A superior outcomes were also reported in those receiving cisplatin plus topotecan therapy when compared with patients receiving single-agent cisplatin, with median survival for 9.4 vs 6.5 months (P = 0.017), and median PFS of 4.6 and 2.9 months (P = 0.014) [27]. The drawback of this regimen is increased hematologic toxicity, which was more frequent and more severe in the cisplatin plus topotecan therapy compared with the cisplatin alone [27]. Grade 3 and 4 neutropenia occurred in 70% of patients who received cisplatin plus topotecan therapy and in only 1.4% of those who received cisplatin [27]. Overall, the combination of cisplatin and topotecan is advantageous for patients who have been or have not been treated with cisplatin as part of chemoradiotherapy [27]. In another phase III trial done by Monk., *et al.* the eligible patients who receive this combination therapy could not have the prior treatment of chemotherapy and 111 patients

out of total 434 patients were randomly allocated to cisplatin plus topotecan. Results showed 21.6% partial response 1.8% complete response [30]. Whereas, the therapy has median overall survival of 10.25 months (95% CI, 8.61 to 11.66 months) and the median PFS of 4.57 months (95% CI, 3.71 to 5.75 months) [30].

Cisplatin and Vinorelbine (PV) combination

There is a phase III clinical trial conducted by Monk., *et al.* Gynecologic Oncology Group (GOG), in University of California, a total of 434 eligible patients involved in this trial which comparing 4 different types of combination therapy. The patients will be ineligible to participate in this trial if they received prior chemotherapy. Subsequently, 108 patients were assigned randomly to receive PV therapy, the patients were administered with vinorelbine 30 mg/m^2 on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks. The duration of administering this therapy was maximum of six cycles for non-responders, including those with stable disease. While patients who achieved partial response with an acceptable level of toxicity were permitted to continue treatment with their assigned regimen beyond six cycles after discussion with the study chair. This therapy has the response rate of 25.9%. In term of the overall survival, this combination therapy has the median value of 9.99 months 0 (95% CI, 8.25 to 12.25 months). Whereas, it has the median value of 3.98 months (95% CI, 3.19 to 5.16 months) in the aspect of the progression-free survival. Meanwhile, the severe adverse effect which mostly occur in patients are neutropenia and leukopenia [30].

Cisplatin and Gemcitabine (PG) combination

A phase III trial that done by Monk., *et al.* conducted on the combination therapy of cisplatin and gemcitabine. In this combination therapy, 112 eligible patients were participated in this clinical trial. Initially, gemcitabine 1,000 mg/m^2 on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks has been administered. The duration of administering also same as the previous therapy. The response rate of this therapy is 22.3% and the median overall survival is 10.28 months (95% CI, 7.62 to 11.60 months) for this therapy. Whereas, this regimen has the median progression-free survival of 4.70 months 0 (95% CI, 3.58 to 5.59 months). Same as the previous combination therapy, the most frequent severe adverse effects are neutropenia and leukopenia [30].

Discussion

This review shows that even the cisplatin monotherapy is widely used in recurrent cervical cancer due to notable overall response rate and survival, cisplatin-containing combinations emerge to be more effective and present less toxicity for the patients. Among these combinations, cisplatin plus paclitaxel and cisplatin plus topotecan appear to give a greater response rate and survival.

Cisplatin-containing combination achieve a favorable overall response rate than that of cisplatin alone. According to table 3, all combinations recorded response rate above 20% whereas various trials of cisplatin monotherapy do not exceed 20% and shows an average of 16% response rate. Combination of cisplatin plus paclitaxel (PT) manage to achieve as high as 42.55% response rate on average. Highest recorded response is 46.3% from Rose., *et al*. trial. Both Dimopoulos., *et al*. and Choi., *et al.* clinical trials introduce an addition of ifosfamide to this combination, known as TIP and received high response rate, both at 46.0% and 46.7% respectively. Despite its high response rate, TIP still requires further investigation on optimal dose and schedule. In Cisplatin plus topotecan combination (PO), response rates from Friorica., *et al*, Long., *et al*, Monk., *et al*. are 28%, 27% and 23.4% respectively which then contribute to average of 26.13%. Cisplatin plus Vinorelbine combination (PV) receives 25.9% and cisplatin plus Gemcitabine (PG) at 22.3%. In these multiple trials, however, prevalence of partial response dominates complete response by a large margin. With the data given, the combinations are dominant over cisplatin single agent. Among the combinations, PT is the best available drug combination for treatment of recurrent cervical cancer because it is well responded. Another suitable alternative would be PO combination.

The overall survival rate of patient using Cisplatin monotherapy is 7 months. However, PO and PT showed an increased survival rate to 9.4 months and 9.7 months respectively compared to cisplatin monotherapy. Additionally, the combination of either PT or PO showed an improved median progression free survival rate of 4.8 months and 4.57 months respectively. Other combination therapies including PV or PG also showed significant increase in overall survival which is approximately 10 months. In contrast, the median progression free survival of PG is 4.7 months which is higher compared to PV which is only about 4 months. In general, combination therapy showed better survival rate compared to cisplatin monotherapy. Among all the combination therapies, PG combination showed highest survival rate while PT showed highest progression free survival.

Overall, cisplatin single therapy has shown greater toxicity of 70% compared to 1.4% in the PT therapy. Cisplatin single agent exhibits grade 3 and 4 neutropenia. For PT therapy, grade 3 and grade 4 anemia and grade 4 neutropenia are commonly seen. Neutropenia can be observed in both cisplatin and PT which is the common side effect. On the other hand, 70% of patients receiving PO therapy exhibit grade 3 and 4 neutropenia compared to 1.4% in cisplatin alone. Furthermore, PO therapy also exhibits hematologic toxicity, which is more frequent and severe compared to cisplatin alone. Neutropenia and leukopenia mostly occur in patients receiving PV and PG therapy. Hence, PT therapy is least toxic to the patients.

Conclusions

To summarize, in terms of response rate, progression-free survival, overall survival and degree of toxicity, cisplatin-containing combination therapy is more preferred than cisplatin monotherapy in treating recurrent cervical cancer. In addition to minimal overall survival benefit, PT therapy showed the best response rate, progression-free survival and least toxic among other available combinations.

Conflicts of Interest

The authors have no conflict of interest relevant to this article.

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