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Review Article

Role of cisplatin in oral squamous cell carcinoma – A review

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ABSTRACT

Oral cancer is one of the most common malignancies worldwide. The treatment options remain to be surgery, radiation, and/or chemotherapy. In spite of all modern technologies and advances in research, the survival rate of patients with oral cancer has not improved. Among the various chemotherapeutic agents, cisplatin is a commonly used drug for oral squamous cell carcinoma as induction, adjuvant, neoadjuvant, or palliative chemotherapy. This article reviews on the clinical trials done with cisplatin for oral cancer. Based on the review, it is suggestive that cisplatin is superior to other chemotherapy agent, but there is no advantage of cisplatin when used as an adjuvant or neoadjuvant therapy to surgery.

Keywords: Cisplatin, chemotherapy, oral squamous cell carcinoma

Introduction

Oral squamous cell carcinoma (OSCC) is one of the most aggressive malignancies worldwide. Despite continuous efforts to develop efficient treatments, the overall survival and prognosis of OSCC patients remain poor. Surgery, radiation, and chemotherapy still continue to be the mainstay management modalities. Patients who are ineligible for surgery mainly because of advanced local tumor growth, distant metastasis, or severe medical comorbidities are most commonly advised chemotherapy as induction, adjuvant, neoadjuvant, or palliative therapy. Chemotherapy is the use of anticancer drugs designed to slow or stop the growth of rapidly dividing cancer cells in the body. Among the various chemotherapeutic drugs, cisplatin, carboplatin, 5-fluorouracil (5-FU), paclitaxel, and docetaxel are most commonly used against OSCC.

Cisplatin, or *cis*-diamminedichloroplatinum (II) (CDDP), a high-potency anticancer agent was the first platinum based anticancer drug developed for clinical purposes. The discovery of cisplatin dates back to as early as 1845, with approval for clinical use as anticancer agent in 1978.[1] This platinum-based compound *cis*-[Pt(II)(NH(3))(2) Cl(2)] ([PtCl2(NH3)2] or CDDP), has been used to treat sarcomas, cancers of soft tissue, bones, muscles, and blood vessels.[2,3] However, the efficacy of cisplatin in OSCC in still controversial. This review elaborates the studies that included cisplatin in clinical trials.

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Materials and Methods

Relevant articles were obtained through PUBMED literature search. The databases were searched for published clinical trials examining the use of cisplatin as therapy, adjuvant, or palliative therapy. Limits for clinical trials and English language were used, but no limit was placed on the publication years. The search was made to include articles that had done clinical trials to compare the efficacy of chemotherapy with cisplatin over other treatment modalities. A total of 21 articles were finally selected after reading the title and abstract. Among these, omitting the other language articles and those with use of other agents were excluded. There were 11 relevant articles. Among the 11 studies, only three of them had a control group and were finally included in this review.

Results

Ye *et al.*, 2016[4] - In this study, intraarterial cisplatin with fluorouracil was found to be more effective and less toxic when compared to intramuscular Pingyanmycin.

Iyer *et al.*, 2015[5] - The authors favor surgery with radiation over combined chemotherapy with cisplatin and radiation. They did not find any significant difference in outcomes.

Umeda *et al.*, 2004[6] - This study also states that neoadjuvant chemotherapy (NAC) was of no advantage over surgical treatment.

A summary of the discussed studies are tabulated (Table 1).

Table 1: Summary of the reviewed articles

Author	Variables	Control group (C)	Experimental group (E)	Result	
Ye *et al.*, 2016[4]	n	43	47	ORR - 53.49% versus 72.34% CRT - 36.17% versus 11.63% $P<0.05$	CDDP + 5-FU effective with less toxicities
	Treatment	Pingyangmycin	CDDP + 5-FU		
	Drug Route	i.m	Intraarterial		
	Dosage	8 mg QD	100 mg/m^2 (24 h)+1000 mg/m^2 (72 h)		
	Duration	3 cycles 21 days/cycle	3 cycles 21 days/cycle		
Iyer *et al.*, 2015[5]	n	60	59	5 year DSS - 68% versus 12% $P=0.038$	No outcome difference. Advantage - Surgery + RT better than CCRT
	Treatment	Surgery+adjuvant RT	CCRT CDDP +5FU+RT		
	Route		Intravenous		
	Dosage	2 Gy/5 days/week 60Gy in 30 fractions over 6 weeks	20 mg/m^2 (96 h) +1000 mg/m^2 (96 h) +66Gy in 33 fractions over 6.5 weeks		
	Duration		Day 1 and Day 28		
Umeda *et al.*, 2004[6]	n	18	9	OS C - 81.5% E - 29.6% ($P<0.05$)	NAC of no advantage
	Treatment	Surgery	Neoadjuvant chemo TPF -(docetaxel+ CDDP+5FU) then surgery		
	Route		Intra venous		
	Dosage		60 mg/m^2+10 mg/m^2+500 mg/body		
	Duration		5 days		

CDDP: Cisplatin, FU: Fluorouracil, ORR: Objective response rate, CRT: Clinical response rate, DSS: Disease specific survival, OS: Overall survival, RT: Radiotherapy

Discussion

The treatment of oral cancer depends on various factors such as the stage of oral cancer, tumor site, patient's age, physician and patient's preference, and patient's status. Early stage patients treated with surgery have a relatively better prognosis, than patients with advanced stage lesions. In addition such advanced oral cancer often requires NAC.

Cisplatin, a platinum compound based drug has revolutionized the field of oncology and mainly chemotherapy due to its wide usage and versatility.[7] In general, it exerts its anticancer activity by introducing toxic DNA interstrand crosslinks into proliferating cells and inducing apoptosis (programed cell death) with different binding sites like Guanine-N7 by causing both cytostatic and cytotoxic effects. Cisplatin has become the main drug for the treatment of malignancies including testicular cancer,[8] medulloblastoma,[9] osteogenic sarcoma,[10] ovarian cancer,[11] and so on.

Ye *et al*.[4] investigated the clinical efficacy of a combination of cisplatin and 5-FU as an intra-arterial chemotherapeutic agent for oral cancer patients. They concluded that after arterial administration, there was a high concentration of cisplatin directly reaching the tumor site and also showed that the combination of 5-FU enhanced the efficacy of cisplatin, exhibiting a synergistic effect. Furthermore, regional arterial infusion of cisplatin had been effective in treating oral cancer with lower incidence of adverse effects.

Iyer *et al*.[5] compared the efficacy of concurrent chemotherapy and radiotherapy with surgery and adjuvant radiotherapy in patients with stage III/IV non-metastatic head and neck cancer. This long-term clinical trial concluded that surgery remained the main stay of treatment for patients with cancer involving the oral cavity and maxillary sinus. However, concurrent chemotherapy is an acceptable treatment modality for selected patients with oropharyngeal, laryngeal, and hypopharyngeal cancer with respect to organ preservation without compromising on the survival.

More recent studies have shown that cisplatin is capable of inducing caspase-3 activation and apoptosis by activation of ASK1 and the stress-induced protein kinase pathway.[12] Furthermore, another report by Yang *et al*. have showed that cisplatin binding to nuclear DNA is not necessary for induction of apoptosis in squamous cell carcinoma of the head and neck, which can instead result from the direct action of cisplatin on mitochondria.[13] They have also showed that cisplatin binds preferentially to mitochondrial membrane proteins, particularly the voltage-dependent anion channel and release of cytochrome C was observed after cisplatin treatment. It has also been reported that cisplatin is capable of stimulating apoptosis by inhibiting XIAP, a direct inhibitor of caspase-3, -6, and -7.[14]

Chemotherapy along with radiotherapy can be used in therapies such as neoadjuvant and concurrent, or adjuvant. As a neoadjuvant therapy it can be used to reduce tumor size before radiotherapy and as an adjuvant therapy it can be used to treat micrometastatic disease after the primary has been treated with radiotherapy. Concurrent chemoradiotherapy involves treating patients with chemotherapy agents at the time of radiotherapy administration. This method has been reported in a randomized trials on the analysis of chemotherapy, where concurrent administration of chemotherapy (5-FU with or without cisplatin) and radiotherapy improved overall survival and

loco regional control as compared with radiotherapy alone.[15] This method provides the greatest survival benefit but it is associated with increased side effects too, so can be performed only in fit patients.[16] In another study of 501 patients by Posner and crew, significant increase in survival rates in patients with stage III or IV HNSCC disease using the TPF regimen (docetaxel, cisplatin, and 5-FU) compared to the PF regimen (cisplatin and 5-FU) combined with radiotherapy was observed.[17]

Umeda *et al*.[6] studied the efficacy of cisplatin based NAC in stage III-IV squamous cell carcinoma of the oral cavity. The prognosis of the patients who underwent NAC was evaluated and they suggested that cisplatin based neoadjuvant therapy with cisplatin, docetaxel, and 5-FU offered no advantage over standard surgical treatment in advanced cancer treatments.

Kolja *et al*. evaluated the results of concurrent radiotherapy with 40Gy and low-dose cisplatin-based chemotherapy followed by major surgery in 207 patients with an OSCC of stage III or IV. The overall survival for all patients analyzed was 49.5% and 37% after 60 and 120 months, respectively. The study showed encouraging overall and disease-free survival rates for therapy responders.[18] In yet another study, a total of 407 patients received pre-operative low-dose radiotherapy of 20 Gy given in 10 fractions with concurrent low-dose chemotherapy with cisplatin (12.5 mg/m^2) as part of a pre-existing protocol. This was compared with 519 patients receiving surgery alone. Low-dose pre-operative radiotherapy combined with low-dose chemotherapy with cisplatin significantly improved overall survival for patients with resectable OSCC compared with surgery alone.[19]

Another study on radiotherapy alone versus radiotherapy with cisplatin (20 mg/m^2) in 371 patients demonstrated a significant improvement in overall response rate with chemotherapy but no change in complete response rate.[20] Based on the clinical trials in National Cancer Institute on patients with oral cavity SCC screened between 2001 and 2007, improved survival and lower recurrence was observed in patients who were treated with surgical ablation and adjuvant radiotherapy, when compared to standard radiotherapy in combination with platinum-based chemoradiotherapy.[21]

Conventional treatment for advanced head and neck cancer has included radical surgery and adjuvant radiotherapy or radiotherapy alone. Recently, induction chemotherapy has been used widely for management of oral cancer. Kohno *et al*. and Basu *et al*. reported that NAC was useful for increasing survival rate of patients with oral SCC,[22,23] while other authors have stated that NAC would be of benefit to preservation of organ function in those with locally advanced oral SCC.[24,25] Yet others have concluded that there was no advantage of NAC for head and neck SCC from their randomized clinical trials.[26,27] Thus, the role of cisplatin based chemotherapy in the management of head and neck cancer and OSCC has shown controversial results. From the above literature review it has been evident that cisplatin based chemotherapy has been effective in treating oral cancer with minimal adverse effects, however surgical management still remains the mainstay of treatment for advanced stage III and IV OSCC patients.

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