RESEARCH ARTICLE

Concurrent Weekly Cisplatin Versus Triweekly Cisplatin with Radiotherapy in the Treatment of Cervical Cancer: A Meta-analysis Result

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Abstract

Aims: To evaluate the adverse effect and survival outcome of weekly and triweekly cisplatin with radiotherapy in treatment of cervical cancer. Methods: After an extensive literature search between 1995-2011,we analyzed 7 studies to compare weekly cisplatin and triweekly cisplatin combined radiotherapy. Results: Our analysis established that weekly cisplatin has a lower risk of hematologic toxicity than triweekly cisplatin with concurrent radiotherapy in the treatment of cervical cancer. However, there were no differences in progression free survival and overall survival between weekly cisplatin and triweekly cisplatin (p>0.05). Conclusions: Weekly cisplatin combined with concurrent radiation has lower risk in hematologic toxicity than triweekly cisplatin, but does not improve survival. Triweekly cisplatin treatment has longer intervals and is therefore more convenient. Clinicians and patients can choose either weekly cisplatin or triweekly cisplatin combined radiotherapy for cervical cancer.

Keywords: Cisplatin - cervical cancer - weekly - triweekly - chemoradiation

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Introduction

Cervical cancer is a major world health problem for women. Cervical cancer rates are decreasing among women in the United States, although incidence remains high among Hispanic/Latino, Black, and Asian women (Barnholtz-Sloan et al., 2009). Radiotherapy is the primary modality for curative treatment of locally advanced cervical cancer (Klopp et al., 2011). Several randomized trials revealed that treatment regimens combining radiotherapy with platinum-based chemotherapy improve rates of overall survival and progress-free survival in women with Stage IIIB through IVA cervical cancer (Rose et al., 1999; Eifel et al., 2004; Kim et al., 2005).

In 1999, the University of Texas M. D. Anderson Cancer Center adopted the use of concurrent cisplatin and 5-fluorouracil (5-FU) with RT because of the positive results with the regimen seen in Radiation Therapy Oncology Group (RTOG) protocol 90-01. Beginning in 2002, they gradually replaced cisplatin and 5-FU with weekly cisplatin. The reason was weekly cisplatin chemotherapy had less toxicity (Rose et al., 2007). Platinum-based chemotherapy includes cisplatin, carboplatin and nedaplatin. Cisplatin is the standard agent for the chemoradiotherapy. Katanyoo (Katanyoo et al., 2011) reported that concurrent weekly carboplatin with radiation therapy yielded high response rate with modest progression-free and overall survivals in locally advanced cervical cancer. In Japan, weekly intravenous administration of cisplatin usually required heavy hydration and hospitalization, which reduced the compliance of this treatment (Niibe et al., 2007). Nedaplatin, another platinum agent, has been shown to have similar anti-tumor activity to cisplatin with lower renal toxicity (Idei et al., 2003). In summary, concurrent chemoradiation has become the accepted standard of care in the treatment of cervical cancer.

Ryu (Ryu et al., 2011) reported that triweekly cisplatin 75 mg/m^2 chemotherapy concurrent with radiotherapy was more effective and feasible than the conventional weekly cisplatin 40 mg/m^2 regimen and may be a strong candidate for the optimal cisplatin dose and dosing schedule in the treatment of locally advanced cervical cancer. So which prescription is better, weekly cisplatin or triweekly cisplatin? We felt a meta-analysis to better characterize the differences between weekly and triweekly cisplatin would be beneficial to clinicians and patients. Our analysis is a comparison of the adverse effect and survival between the dosing schedules.

Materials and Methods

Search strategy

A literature search was carried out for comparing weekly cisplatin versus triweekly cisplatin puls radiotherapy for cervical cancer treatment, published between 1995-2011, were identified through a search of the following computerized database: PubMed, Embase, The Cochrane Library, Gynecologic Oncology Group Publications with the key words with all the possible combinations: "weekly" "cisplatin" "cervical cancer" "triweekly". References of the identified articles were

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Table 1. The Characteristics of Enrolled Clinical Studies

Author Year	Methods	Stage	N(QW/Q3W)	Concurrent Chemotherapy
Ryu 2011	RCT	IIIB-IVa	51/53	QW: Cisplatin 40mg/m^2, 6 cycles; Q3W: Cisplatin 75mg/m^2, 3 cycles
Lee 2010	Retrospective Study	IB-IIB	71/130	QW: Cisplatin 40mg/m^2, 6 cycles; Q3W: Cisplatin 75mg/m^2, 3 cycles Combined FU, Paclitaxel, etc
Kim 2007	RCT	IIB-IVa	77/78	QW: Cisplatin 30mg/m^2,6 cycles; Q3W: Cisplatin 20mg/m^2/d, 5d, 3 cycles combined FU 1gm/m^2/d, 5d
Rose 2007	RCT	IIB-IVa	176/173	QW: Cisplatin 30mg/m^2, 6 cycles; Q3W: Cisplatin 50mg/m^2, 2 cycles combined FU 4gm/m^2/96h, Hydroyurea 2gm/m^2,twice per week
Torres 2007	RCT	I-IV	27/55	QW: Cisplatin 40mg/m^2, 6 cycles; Q3W: Cisplatin 75mg/m^2, 3 cycles combined FU 4gm/m^2/96h
Kim 2005	RCT	IIB-IVa	27/34	QW: Cisplatin 30mg/m^2, 6 cycles; Q4W: Cisplatin 20mg/m^2/d, 5d, 3 cycles combined FU 1gm/m^2/d, 5d, 3 cycles
Rose 1999	RCT	IIB-IVa	176/173	QW: Cisplatin 30mg/m^2, 6 cycles; Q3W: Cisplatin 50mg/m^2, 2 cycles combined FU 4gm/m^2/96h, Hydroyurea 2gm/m^2, twice per week

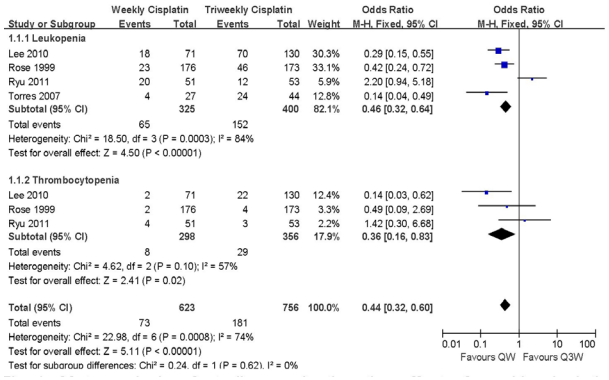

Figure 1. Meta-analysis of Studies Evaluating the Effect of Weekly Cisplatin or Triweekly Cisplatin Combined Radiotherapy in Grade3-4 Chemoradiation-related Hematologic Toxicity. CI=confidence interval, I^2=index of heterogeneity

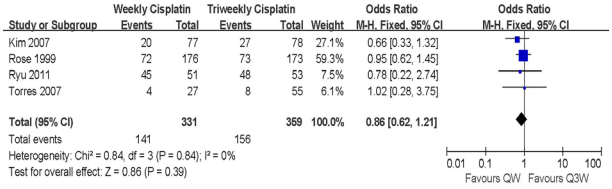

Figure 2. Meta-analysis of Studies Evaluating the Effect of Weekly Cisplatin or Triweekly Cisplatin Combined Radiotherapy in Grade3-4 Neuropathy Toxicity. CI=confidence interval, I^2=index of heterogeneity

also checked.

Data collection and anaysis

All eligible studies were retrieved and evaluated by 2 reviewers. When disagreements occurred, a third reviewer was consulted. The name of the first author and the year of publication of the article were used for identification purposes. The outcomes of interest were: adverse effect, the overall survival (OS), progression-free survival (PFS). All resulting citation abstracts were reviewed for potential eligibility, and the full article texts were obtained for further evaluation in cases in which abstracts did not provide enough details for the determination of eligibility. After we reviewed the research, 2 studies were excluded because of the absence of full length articles and one study was non-English literature because of lack of accessibility and reading. Finally 7 studies eligible for meta-analysis were conducted. The main characteristics of the 7 studies are listed in Table 1.

Statistical methods

We used the RevMan 5.1 software (Cochrane Collaboration's Information Management System) to perform this meta-analysis. The results of adverse effect were calculated as odds ratio and are presented with the correspondent 95% confidence interval (CI).But if we wanted to compare OS and DFS between patients treated with weekly cisplatin and those treated with triweekly cisplatin plus radiotherapy treatment, it is often problematic because the most appropriate summary statistics were typically not presented. The summary information from eligible studies were estimated from Kaplan-Meier curves to calculate hazard ratio(HR) and 95% confidence interval (CI) (Tierney et al., 2007).

Results

Adverse Effect

Four studies reported the adverse effect of the concurrent chemoradiation treatment including leucopenia or neutorpenia, neuropathy and gastrointestinal toxicity.

Hematologic Toxicity

Four studies reported the event number of grade 3 and 4 leukopenia or neutorpenia and were included in the meta-analysis. Weekly cisplatin significantly reduced the odds Grade 3-4 leukopenia (OR, 0.46;95% CI, 0.32-0.64, p<0.00001).There three studies were evaluable for grade 3 and 4 thrombocytopenia. The incidence of Grade 3-4 thrombocytopenia was lower for patients using weekly cisplatin compared with triweekly cisplatin (OR,0.36;95% CI, 0.16-0.83; p=0.02). Figure 1 shows the forest plot for grade 3 and 4 leukopenia and thrombocytopenia rate.

Neuropathy and Gastrointestinal toxicity

Data on neuropathy were extracted from four of the seven included studies. There was no different between weekly cisplatin and triweekly cisplatin in neuropathy (OR, 0.86; 95% CI, 0.62-1.21; p=0.39). Gastrointestinal toxicities included vomiting,nausea.et al. Weekly cisplatin didn't show reduce the risk of gastrointestinal toxicity compared to triweekly cisplatin (OR, 1.07; 95% CI, 0.61-1.90; p=0.81).

Survival

Only 4 studies showed the data of the overall survival caculated by the Kaplan-Meier method. We excluded the

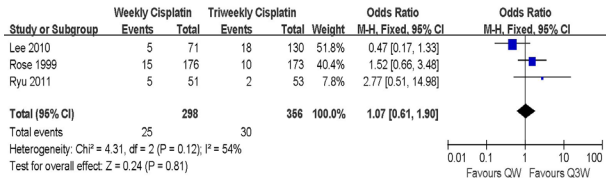

Figure 3. Meta-analysis of Studies Evaluating the Effect of Weekly Cisplatin or Triweekly Cisplatin Combined Radiotherapy in Grade3-4 Gastrointestinal Toxicity. CI=confidence interval, I^2=index of heterogeneity

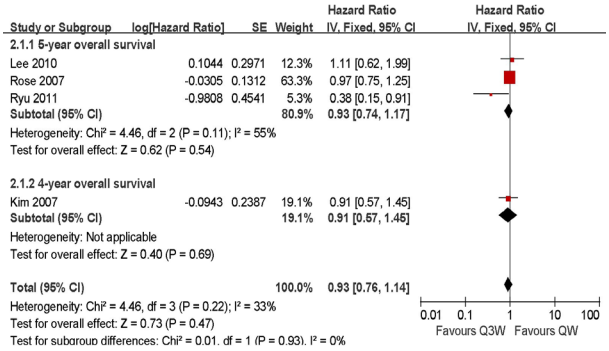

Figure 4. Meta-analysis of Studies Evaluating the Effect of Weekly Cisplatin or Triweekly Cisplatin Combined Radiotherapy in OS. CI=confidence interval, I^2=index of heterogeneity

Kim2005 study which data was updated by Kim2007. Three studies reported the 5-year OS and Kim2005 showed 4-year OS. The pooled analysis for OS could be performed on data from 4 studies and no difference with a HR of 0.93 (95%CI 0.73-1.10; p=0.29). Figure 4 showed the forest plot of OS.

The hazard ration (HR) for progression-free survival was estimated from 3 studies. Kim also showed the 4-year PFS and others showed the 5-year PFS. There was no differentiation between weekly cisplatin and triweekly cisplatin in PFS (HR, 0.89; 95% CI, 0.73-1.10; p=0.29).

Discussion

Cervical cancer is the leading cause of cancer incidence and mortality in women worldwide. Concurrent cisplatin-containing chemotherapy with pelvic irradiation has become a standard of care for the management of patients with advanced cervical cancer (Thomas et al., 1999). Chemotherapy prescription included cisplatin alone, platinum combined paclitaxel, fluorouracil, etc.

The aim of our analysis was to evaluate the efficacy of weekly cisplatin versus triweekly cisplatin plus radiotherapy in cervical cancer. Six studies were randomized controlled clinical trials with a parallel design in locally advanced cervical cancer, while Lee's (Lee et al., 2011) study was a retrospective study in postoperative cervical cancer. We knew that concurrent chemoradiation treatment would have more toxicities than radiotherapy alone. The result revealed that there was lower leukopenia toxicity in weekly cisplatin than triweekly cisplatin. The single dose of cisplatin was 30-40 mg/m^2, while combining dose was 75 mg/m^2. Fluorouracil maybe increases the risk of hematologic toxicity, although there had three weeks

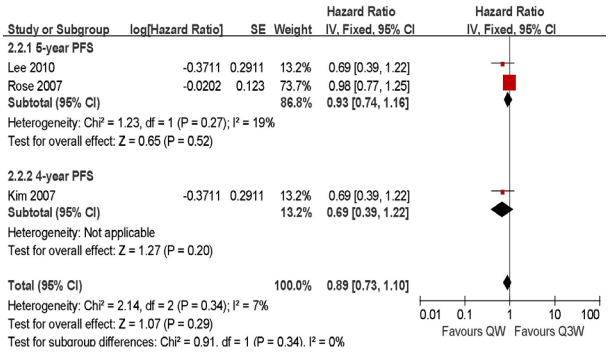

Figure 5. Meta-analysis of Studies Evaluating the Effect of Weekly Cisplatin or Triweekly Cisplatin Combined Radiotherapy in PFS. CI=confidence interval, I^2=index of heterogeneity

intervals.

Hernandez (Hernandez et al., 2000) reported that thrombocytosis is a frequent finding among patients with advanced cervical carcinoma and seems to be related to tumor burden. Rose (Rose et al., 1999) analyzed the data on 256 women with locally advanced cervical cancer; the proportion of patients developing thrombocytopenia was higher in the two groups of patients that received cisplatin than the group that only received hydroxyurea. Our meta-analysis showed that thrombocytopenia was lower in weekly cisplatin than triweekly cisplatin. It needs more studies to verify if thrombocytosis or thrombocytopenia is related to the poor survival.

Six randomized controlled clinical trials ignored index of anaemia. Tumor hypoxia may contribute to radioresistance and chemoresistance by inducing proteomic and genomic changes that lead ultimately to malignant progression, with reduced local control and metastatic spread, and ultimately, increased resistance and decreased survival time (Harrison et al., 2004). Hemoglobin levels during combined radiotherapy and cisplatin were independent predictors of treatment outcome in advanced cervical carcinoma (Winter et al., 2004). The use of growth factors or transfusion was not reported by participating institutions over the treatment period. There is no doubt that anemia and tumour hypoxia remain valid specific therapeutic targets in the treatment of cervical.

In other adverse effect there are no differentiation in neuropathy and gastrointestinal toxicity. It shows that the prescription of cisplatin combined with fluorouracil does not increase the risk of neuropathy and gastrointestinal toxicities compared with cisplatin alone.

Although patients prefer to receive chemotherapy every 3 weeks intervals, it was flexible and convenient, but weekly cispatin shows lower risk hematologic toxicity with concurrent chemoradiation in cervical cancer. There is no differentiation in PFS and OS between two groups. Lee et al. (2011) reported that the weekly cisplatin chemotherapy group experienced the same therapeutic effect as the triweekly combination chemotherapy group but with less toxicity. Therefore, weekly cisplatin chemotherapy is considered the more useful concurrent adjuvant chemoradiation regimen after radical surgery. So we look forward to further clinical trials to confirm

if weekly cisplatin is better not only in locally advanced cervical cancer, but also in neoadjuvant and adjuvant therapy. It requires more relevant studies for investigating on the anemia and different stages in cervical cancer.

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The author(s) declare that they have no competing interests.

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