RESEARCH ARTICLE

Nedaplatin Salvage Chemotherapy for Cervical Cancer

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Abstract

Purpose: This systematic analysis was conducted to evaluate the efficacy and safety of nedaplatin based salvage chemotherapy for treatment of patients with advanced cervical cancer. Methods: Clinical studies evaluating the efficacy and safety of nedaplatin based regimens on response and safety for patients with cervical cancer were identified using a predefined search strategy. Pooled response rates (RRs) were calculated. Results: For nedaplatin based regimens, 5 clinical studies including 264 patients with advanced cervical cancer were considered eligible for inclusion. The analysis showed that, in all patients, pooled RR was 74.6% (197/264). Major adverse effects were leukopenia, thrombocytopenia and nausea/vomiting. No treatment related death occurred with nedaplatin based treatment. Conclusion: This systematic analysis suggests that nedaplatin based regimens are associated with good activity with acceptable tolerability in treating patients with advanced cervical cancer.

Keywords: Cervical cancer - nedaplatin - response rate

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Introduction

Cervical cancer is one of the most common cancer among Chinese women (Du et al., 2014; Wang et al., 2014). In the USA, approximately 13000 patients developed cervical cancer in 2000 (Robert et al., 2001). Cervical cancer is usually radio sensitive and highly curable in early stage. The 5-years survival rate for patients with cervical cancer in 2002-2007 was reported to be 95.1% in the screened patients and 83.4% in the non-screened. For patients with stage IV disease or with recurrence after chemo- radio-therapy, however, the prognosis is still dismal. In such patients, most of the active chemotherapy agents achieve overall response rates of 20-35% when given a monotherapy, with a median response duration of 3-6 month and a survival time of 5-9 months (Thigpe et al., 1981; McGuire et al., 1996). Cisplatin-based concurrent chemoradiotherapy is a standard treatment for locally advanced cervical cancer. And a set of combinations of cisplatin-based chemotherapy were tested and reported in randomized trials (Lanciano et al., 2005; Vale et al., 2008), weekly cisplatin (40 mg/m^2) remains the standard treatment in daily practice and current clinical trials in the USA. However, gastrointestinal and renal toxicities were the main concern. Therefore, less toxic platinum agents with a similar effectiveness to that of cisplatin should be established for patients with cervical cancer.

Nedaplatin, a derivative of cisplatin, was developed with the aim of producing a treatment with a similar effectiveness to cisplatin, but with decreased renal and gastrointestinal toxicities (Sasaki et al., 1991; Kanzawa et al., 1998; Monk et al., 1998; Kawai et al., 2005; Uehara et al., 2005). A previous Phase II study conducted in Japan suggested that nedaplatin had a favorable clinical efficacy, comparable with that of cisplatin (Yokoyama et al., 2008). Many combination chemotherapy regimens have also been explored during the last two decades. High response rates have been obtained in some studies, but it is difficult to assess the relative merits of the various regimens because of differences in patient selection (Buxton et al., 1989; Papadimitriou et al., 1999).

According to this background, we hypothesize that nadaplatin originated chemo radiotherapy could be established as an optimal schedule for treating patients with locally advanced or metastatic cervical cancer.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (cervical cancer) and (nedaplatin). All clinical studies evaluating the impact of nedaplatin on cervical cancer. Published in English prior to December 1st of 2014 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with paclitaxel or gemcitabine; (2) The study was performed in

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accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified metastatic and/or locally advanced cervical cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) 2, age 18 years. Studies were excluded if one of the following existed: (1) duplicate data; (2) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

Results

There were 4 papers relevant to the search words by the end of December, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Watanabe et al., 2004; Yokoyama et al., 2008; Takekuma et al., 2012; Yamaguchi et al., 2012; Yin et al., 2012) when nadaplatin was used in chemo radiotherapy. These studies had been carried out in China, and Japan. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities.

Characteristics of nadaplatin as chemotherapy, studies included in this study are presented as short-term outcomes: the response rate of Takekuma et al. (2012) was 44.4%, of Yamaguchi et al. (2012) was 75.8%, of Yin et al. (2012) was 80.8%, of Watanabe et al. (2004) was 40.0%, of Yokoyama et al. (2008) was 100%. Totally, 197 patients were enrolled and 264 patients achieved CR or PR, the pooled response rate thus was 197/264 (74.6%).

Observation on major adverse effects included leukopenia, thrombocytopenia and nausea/vomiting. No treatment related death occurred with nedaplatin based treatment.

Discussion

Main treatment for cervical cancer includes surgery, radiao, and/or a combination with chemotherapy, however, the outcome is generally unsatisfactory. In the past two decades, many treatments were tried to improve the prognosis of advanced cervical cancer with a combination of radio- and/or chemotherapy. Therefore, it was suggested that a combination of radio- and chemotherapy could be effective for patients with advanced cervical cancer and is associated with a decreased risk of death from cervical cancer (Keys et al., 1999; Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999; Peter et al., 2000). Chemo-radiotherapy thus is considered a standard treatment for patients with cervical cancer.However, the adverse events of current treatment are associated with unusual toxicities. Nedaplatin is a new medication with acceptable toxicity. It is considered with better treatment effects than cisplatin and with less adverse reactions, especially renal and gastrointestinal toxicities.

In a previous study published in 2012, patients with measurable disease and histologic confirmation of the primary diagnosis as cervical cancer were treated with paclitaxel 175 mg/m^2 over 3 hours and nedaplatin 80 mg/m^2 intravenously over 1 hour on day 1 every 28 days until progressive disease or adverse effects prohibited further therapy. Fifty patients were enrolled into this study protocol. Their results demonstrated that 45 patients (90%) were eligible for assessment of response (RECIST version 1.0) to treatment; 31 patients (62%) received prior radiotherapy and 23 patients (46%) received prior chemotherapy (Takekuma et al., 2012). The overall response rate was 44.4% (11 complete responses and 8 partial responses) with 22.2% of patients having stable disease. Grades 3 or 4 adverse events (NCI-CTCAE) included neutropenia, febrile neutropenia, and anemia. But there was no significant thrombocytopenia (Takekuma et al., 2012). They concluded from this study that nedaplatin 80 mg/m^2 and paclitaxel 175 mg/m^2 intravenously on day 1 every 28 days for patients with advanced/recurrence cervical cancer was easily to be administered, with favorable antitumor activity, and the toxicity of this combination would be decreased compared with cisplatin-containing combinations (Takekuma et al., 2012).

In another study on neoadjuvant chemotherapy, 68 eligible patients were treated with nedaplatin (80 mg/m^2) on day 1 and irinotecan (60 mg/m^2) on days 1 and 8 of a 21-day cycle (Yamaguchi et al., 2012). Sixty-six patients were included in a full analysis set. The response rate was 75.8% (CR in 2 patients, PR in 48, SD in 12, PD in 0, and NE in 4). The mean number of treatment courses required for a response was 1.42 (1 course in 30 patients, 2 courses in 19, and 3 courses in 1). The incidences of grade 3 or 4 hematological toxicities were: neutropenia 72.2%, leukopenia 16.7%, anemia 13.6%, thrombocytopenia 7.6%, febrile neutropenia 1.5%, and elevations of alanine aminotransferase and aspartate aminotransferase 1.5% (Yamaguchi et al., 2012). Grade 3 or 4 non-hematologic toxicities included diarrhea 6.1%, nausea 3%, anorexia 1.5%, vomiting 1.5%, fever 1.5%, allergic reactions 1.5%, ileus 1.5% and vesicovaginal fistula 1.5% (Yamaguchi et al., 2012). The conclusion of this study was that neoadjuvant chemotherapy with nedaplatin and irinotecan could be considered as an effective and well-tolerated treatment for patients with squamous cell cervical cancer (Yamaguchi et al., 2012).

In an Osaka research, Watanabe treated 20 consecutive patients with nedaplatin and docitaxel (80 mg/m^2 and 60 mg/m^2), every 4 weeks for at least three courses and the dose was escalated to 70 mg/m^2 and 100 mg/m^2 (Watanabe et al., 2008). As a result, dose-limiting toxicity was granulocytopenia and the maximum tolerated dose was determined as 100 mg/m^2 and 70 mg/m^2, and a partial response was achieved in 8 patients (40.0%) (Watanabe et al., 2008). Thus they concluded that nedaplatin and docitaxel combination was a tolerable regimen for treating

patients with cervical squamous cell cancer (Watanabe et al., 2008).

With a purpose to evaluate the effectiveness and safety of concurrent chemoradiotherapy, Yokoyama treated 45 patients with locally advanced squamous cell cervical cancer with weekly nedaplatin (Yokoyama et al., 2008). Nedaplatin at 30 mg/m^2 was administered weekly 6 times with a concurrent external beam and intracavity radiotherapy. External beam radiation was delivered with a fraction dose of 2 Gy per day for 5 days a week during a 5-week period and intracavitary brachytherapy, of which the fraction size is 6 Gy to point A, was given once a week for a total of 4 times using a remote after-loading system (Yokoyama et al., 2008). Of the 45 patients, 40 (88.9%) completed the scheduled treatment and were evaluated for efficacy and safety. Of these, 4 were stage Ib2, 12 were stage IIb, 18 were stage IIIb and 6 were stage IVa. The age distribution ranged from 27 to 79 years with a median age of 58. The 40 patients achieved an objective response, 36 (90%) a complete response and 4 (10%) a partial response. At a median follow -up of 29 months (range, 8-52), the 3-year progression-free and overall survival were 58.7% (95% confidence interval, 42-75%) and 78.0% (95% confidence interval, 56-90.0%), respectively (Yokoyama et al., 2008). Three patients (6.7%) reported grade 4 leukopenia and neutropenia, respectively. Grade 3 diarrhea and nausea/ vomiting were observed in 2 (4.4%) and 1 (2.2%) cases. These results indicate that weekly nedaplatin of 30 mg/m^2 with concurrent radiotherapy is an effective and well-tolerated regimen for treating patients with advanced squamous cell cervical cancer (Yokoyama et al., 2008).

Our current study evaluated the efficacy and safety of nedaplatin based regimens on response and safety for patients with cervical cancer using a predefined search strategy. Pooled response rates (RRs) were calculated. Our results suggested that in all patients, pooled RR was 74.6% (197/264). Major adverse effects were leukopenia, thrombocytopenia and nausea/vomiting. No treatment related death occurred with nedaplatin based treatment. Thus we concluded that nedaplatin based regimens are associated with good activity with acceptable tolerability in treating patients with advanced cervical cancer.

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