

## RESEARCH ARTICLE

# A Pooled Study on Combination of Gemcitabine and Nedaplatin for Treating Patients with Non-small Cell Lung Cancer

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## Abstract

**Background:** This analysis was conducted to evaluate the efficacy and safety of a combination of gemcitabine and nedaplatin in treating patients with non-small cell lung cancer. **Methods:** Clinical studies evaluating the efficacy and safety of a combination of gemcitabine and nedaplatin with attention to response and safety for patients with non-small cell lung cancer were identified using a predefined search strategy. Pooled response rates for gemcitabine and nedaplatin were calculated. **Results:** In gemcitabine and nedaplatin based regimens, 4 clinical studies including 112 patients with non-small cell lung cancer were considered eligible for inclusion. The pooled analysis suggested that the pooled response rate was 40.2% (45/112). Main side effects included grade 3-4 neutropenia, thrombocytopenia, and anemia. Grade 3-4 nonhematological toxicity included nausea and vomiting, diarrhea, and hepatic dysfunction. There were no treatment-related deaths. **Conclusion:** This evidence based analysis suggests that the combination of gemcitabine and nedaplatin is associated with good response rate and accepted toxicity for treating patients with non-small cell lung cancer.

**Keywords:** Gemcitabine and nedaplatin - non-small cell lung cancer

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## Introduction

It is reported that the incidence of lung cancer demonstrated a decline trend in some Western countries (Jemal et al., 2011). However, for people lived in other area, ie., some developing countries, the incidence rate of lung cancer is not decreased (Jemal et al., 2011). It is estimated that 85% of all lung cancer patients will be diagnosed with non-small cell lung cancer (NSCLC) (Govindan et al., 2006), and approximately 40% of these patients are confirmed with an advanced disease (Ramalingam et al., 2008). But, very effective therapies for patients with advanced NSCLC and extremely those with poor PS (particularly PS 3-4) are not available. Based on report from National Comprehensive Cancer Network guidelines, several cycles of platinum-based regimens could be recommended as so called standardized treatment for patients with NSCLC (National Comprehensive Cancer Network, 2013). And these regimens usually consist of cisplatin or carboplatin with another cytotoxic agent, sometimes in combination with a biologic agent, e.g., bevacizumab. In this setting, the second-line or third-line treatments recommended for patients with NSCLC could be a platinum with docetaxel, erlotinib, pemetrexed or gemcitabine (Shepherd et al., 2000; Hanna et al., 2004; Shepherd et al., 2005; Leighl et al., 2012). These platinum are mainly cisplatin and carboplatin. Because gemcitabine

has emerged as an ideal partner for platinum compounds, and its theoretical ability of interfering with the inhibition of repair of platinum-induced DNA damage. Based on the results of several phase III trials, (Crino et al, 1999; Cardenal et al, 1999; Sandler et al, 2000; Schiller et al, 2002; Scagliotti et al, 2002) gemcitabine in combination with a platinum now represents a commonly used first-line treatment for patients with advanced NSCLC.

Nedaplatin is an analogue of cisplatin, with relatively low neurotoxicity and nephrotoxicity, and high in vivo bioavailability, indicating an important role as a component in the regimens for treating patients with NSCLC (Kameyama et al, 1990). Previous phase I/II study of nedaplatin and irinotecan suggested a response rate (RR) of 31.0% in treating patients with NSCLC (Oshita et al, 2003). In this clinical study, toxicities were mild (Oshita et al, 2003). In further phase II investigation on this combination suggested that it is feasible to apply this regimen in treating elderly patients with NSCLC (Oshita et al, 2004). One possible mechanism of the efficacy demonstrated by nedaplatin is supposed by a remarkable synergistic effect produced by nedaplatin and other chemotherapeutic agents (Kanzawa et al, 2001).

According to this background, we hypothesize that a combination of gemcitabine and nedaplatin could be established as an optimal schedule in treating Chinese patients with non-small-cell lung cancer.

## Materials and Methods

### Search strategy

We searched PUBMED, by using the following search terms: (non-small-cell lung cancer) and (gemcitabine and nedaplatin). All clinical studies evaluating the impact of gemcitabine and nedaplatin on the response or survival and side effects for patients with non-small-cell lung cancer published in English prior to May 2015 were identified. If samples of two studies overlap, only the newest 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 gemcitabine with nedaplatin, that were used for patients with NSCLC; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified non-small-cell lung cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) of less than 2. Studies were excluded if one of the following existed: (a) duplicate data; (b) 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, country of the first or corresponding author, the number of patients. Outcome presented in at least 3 studies were extracted for combined analysis.

## Results

There were 18 papers relevant to the search words by the 3rd of August 2015. Via steps of screening the title and reading the abstract, 4 studies were identified (Shirai et al., 2006; Masago et al., 2011; Sugiyama et al., 2011; Yang et al., 2012). These studies had been carried out in Japan and in China. 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 studies included in this analysis are presented as short-term outcomes: the response rate of Shirai, et al. was 30.3% (10/34), of Sugiyama et al. was 45.7 % (16/35), of Masago et al. was 62 % (8/13), and of Yang et al. was 37.5 % (11/30). Totally, 112 patients were enrolled and 45 patients achieved CR or PR, the pooled response rate thus was 45/112 (40.2%). Main side effects included

Grades 3-4 neutropenia, thrombocytopenia, and anemia. Grades 3-4 nonhematological toxicities included nausea and vomiting, diarrhea, and hepatic dysfunction. There were no treatment-related deaths.

## Discussion

Lung cancer is a serious problem for human being. Many patients with lung cancer will be diagnosed with advanced disease and will be systemically treated with palliative chemotherapy. For clinical practice, many patients with advanced NSCLC would receive palliative chemotherapy, in which platinum doublets were still recommended as first-line, pemetrexed or docetaxel as second-line, and erlotinib as second- or third-line therapy (Hanna et al., 2004; Scagliotti et al., 2007; Schiller et al., 2002; Fossella et al., 2000; Shepherd et al., 2000; Feld et al., 2006; Shepherd et al., 2005). Significant improvements were achieved in the treatment of advanced NSCLC since 2010. Treatment strategies are now heavily influenced by histologic type of NSCLC (Ellis et al., 2011), and multiple trials have examined the sequence of subsequent lines of therapy, especially, the clinical use of newly developed medications.

Gemcitabine combined with cisplatin is a chemotherapy considered one of the most active regimens for patients advanced NSCLC, with a reported overall response rate (ORR) of 22-38% and median survival of 8.1-9.8 months in previous studies (Crinò et al, 1999; Scagliotti et al, 2002; Schiller et al, 2002). One possible reason is because of mild toxicity profile of gemcitabine, including low haematological toxicity and visceral side effects. This resulted in its use as a combination with platinum. Several clinical studies on new platinum-based doublets (Kelly et al, 2001; Schiller et al, 2002; Smit et al, 2003) produced similar results, but a meta-analysis suggested an absolute 1-year survival benefit of 3.9% for gemcitabine-cisplatin chemotherapy when compared to other platinum-containing regimens (Le Chevalier et al, 2005). Cisplatin is one of the most widely used platinum derivatives, however it is considered to link with significant toxicities, including severe nausea /vomiting, ototoxicity and neuropathy and renal toxicity, thus requiring adequate hydration. Nedaplatin is an analogue of cisplatin, with reported low neurotoxicity and nephrotoxicity, and high in vivo bioavailability (Kameyama et al, 1990).

Previous research to retrospectively evaluate the safety and efficacy of a combination of gemcitabine and nedaplatin for patients with advanced non-small-cell lung cancer was conducted in Showa University School of Medicine of Japan (Shirai et al., 2006). In this study, they registered 34 patients (24 men and 10 women) with a mean age of 69 years (range, 39-75 years) and all patients were treated every 3 weeks with gemcitabine (1,000 mg/m<sup>2</sup> (2) on days 1 and 8) and nedaplatin (100 mg/m<sup>2</sup> (2) on day 1). Four patients had stage IIIB disease and 30 patients had stage IV disease. This study revealed that none of the 33 patients achieved a complete response, but 10 achieved a partial response, thus with a response rate of 30.3%. One patient could not be evaluated for response because only one course of chemotherapy had been administered due

to grade 3 eruption. The median survival time was 9.0 months (range, 1-17 months) (Shirai et al., 2006). Grades 3-4 hematological toxicities included leukopenia in 47% of patients, neutropenia in 62%, thrombocytopenia in 56%, and anemia in 44%. Grades 3-4 nonhematological toxicities included nausea and vomiting in 6% of patients, diarrhea in 3%, and hepatic dysfunction in 9%. There were no treatment-related deaths. The dose intensities were 89.6% and 86.7%, respectively, of the planned doses of gemcitabine and nedaplatin (Shirai et al., 2006). In conclusion, Shirai et al. suggested that the combination of gemcitabine and nedaplatin is an acceptable treatment for patients with previously untreated advanced non-small-cell lung cancer (Shirai et al., 2006). In a retrospective study by Sugiyama et al., they analyzed 35 Japanese patients with previously untreated NSCLC, including 7 females and 28 males (Sugiyama et al., 2011). All 35 patients received gemcitabine (800 mg/m<sup>2</sup> on days 1 and 8) and nedaplatin (80 mg/m<sup>2</sup> on day 1) every 3 weeks. In this study, the overall response rate was 45.7% (95% confidence interval 28.8-63.4). The median survival time was 14 months (range 3-44). Grade 3-4 toxicities included neutropenia in 74.3%, thrombocytopenia in 48.6%, anemia in 34.3%, hepatic dysfunction in 11.4%, and infection in 2.9%. There were no treatment-related deaths. There were no differences in response rate and survival between patients aged 75-79 years and patients ≥80 years, although grade 3-4 thrombocytopenia and anemia were significantly more frequent in patients ≥80 years (Sugiyama et al., 2011). In conclusion, this study indicated that the combination of gemcitabine and nedaplatin is effective and well tolerated for selected elderly patients with advanced NSCLC (Sugiyama et al., 2011). In a study by Masago et al., they enrolled 13 patients with advanced NSCLC (Masago et al., 2011). In their results, they suggested that the response rate to gemcitabine (days 1 and 8) and nedaplatin (day 8) was 62%. The most frequent toxic effects were thrombocytopenia and neutropenia; grade 3 or 4 thrombocytopenia was observed in 23% of patients, and grade 3 or 4 neutropenia was seen in 46% of patients. Non-hematologic toxicities were mild. Grade 3 fatigue, nausea/vomiting, and appetite loss occurred in two patients (Masago et al., 2011). Thus in conclusion, Masago suggested that doses of 800 mg/m<sup>2</sup> gemcitabine and 70 mg/m<sup>2</sup> nedaplatin should be recommended and the combination of gemcitabine together with nedaplatin is active and well tolerated (Masago et al., 2011). In another study by Yang et al., they enrolled 30 Chinese patients with advanced NSCLC and treated by a combination of nedaplatin together with gemcitabine (Yang et al., 2012). In their results, they suggested that median progression-free survival was 6.0 months and response rate of the combination of gemcitabine with nedaplatin was 37.5% (Yang et al., 2012). Therefore, in their conclusion, they indicated that gemcitabine together with nedaplatin seems to be superior over gemcitabine together with carboplatin for patients with advanced NSCLC, but further investigation is needed to validate this superiority. (Yang et al., 2012).

Our current study was designed to evaluate the efficacy and safety of a combination of gemcitabine and nedaplatin in treating patients with non-small cell lung

cancer. Our results demonstrated that when gemcitabine and nedaplatin based regimens was used as a palliative treatment, the pooled response rate was 40.2% (45/112) of this combination. Main side effects included Grades 3-4 neutropenia, thrombocytopenia, and anemia. Grades 3-4 nonhematological toxicities included nausea and vomiting, diarrhea, and hepatic dysfunction. There were no treatment-related deaths. In conclusion, our current systemic analysis suggests that gemcitabine and nedaplatin based regimens are associated with good response rate and accepted toxicities for treating patients with advanced non-small cell lung cancer.

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