RESEARCH ARTICLE

Irinotecan as a Second-line Chemotherapy for Small Cell Lung Cancer: a Systemic Analysis

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Abstract

Purpose: This analysis was conducted to evaluate the efficacy and safety of irinotecan based regimens as second-line chemotherapy in treating patients with small cell lung cancer. Methods: Clinical studies evaluating the efficacy and safety of irinotecan based regimens as second-line chemotherapy for patients with small cell lung cancer were identified using a predefined search strategy. Pooled response rates (RRs) of treatment were calculated. Results: In irinotecan based regimens as second-line chemotherapy, 4 clinical studies which including 155 patients with small cell lung cancer were considered eligible for inclusion. In all chemotherapy consisted of irinotecan with or without nedaplatin. Pooled analysis suggested that, in all patients, the pooled RR was 27.1% (42/155) in irinotecan based regimens. Nausea, vomiting, diarrhea and myelosuppression were the main side effects. No grade III or IV renal or liver toxicity was observed. No treatment related death occurred with the irinotecan based treatments. Conclusion: This systemic analysis suggests that irinotecan based regimens as second-line chemotherapy are associated with mild response rate and acceptable toxicity for patients with small cell lung cancer.

Keywords: Irinotecan - second-line chemotherapy - small cell lung cancer

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Introduction

Lung cancer is a leading cause of cancer-related mortality worldwide (Herbst et al., 2008). According to an annual report of 2012 Chinese cancer registration , more than 3 million new cases of lung cancer will be diagnosed every year, and an approximately 2.7 million deaths from lung cancer will account for 13% of all mortalities with poor treatment results and prognosis (Fei et al., 2013; Cui et al., 2014; Huang et al., 2014; Ji et al., 2014). Small cell lung cancer (SCLC), accounting for 15%–20% of total lung cancer, is an aggressive neuroendocrine malignancies characterized by high growth rate, widespread metastases and poor prognosis (Jackman et al., 2005; van Meerbeeck et al., 2011). According to recent analyses, improved median survival time (MST) and 5-year survival rate of limited stage (LS)SCLC over the last 30 years was reported, MST of LS-SCLC is 15–20 months and the 5-year survival rate is up to 15% (Chen et al. 2010; Govindan et al. 2006). With regard to extensive stage (ES)-SCLC, a MST of 9.4–12.8 months and 2-year survival of 5.2–19.5% are disappointing (Maalouf et al., 2007; Noda et al., 2002). SCLC patients with prior treatment include refractory patients whose disease progressed during first-line chemotherapy or progressed within 60 days; and sensitive patients who could respond to first-line chemotherapy and relapsed after a treatment-free interval for at least 60 days. Sensitive patients are more likely to respond to second-line chemotherapy than refractory patients (von Pawel et al., 2003). And further, 80% of senior patients (≥70 years) with lung cancer generally have complications, e.g., chronic obstructive pulmonary, heart , and cerebrovascular disease, as well as malnutrition, osteoporosis and dementia (Johnson, 1997). Evidence-based standard treatment for these patients with relapsed SCLC is not established.

Investigation reported that retreatment with previous drugs used in initial chemotherapy was justified for sensitive relapsed cases [Rosti et al. 2006]. However, refractory relapse is chemoresistant and response rates (RRs) was less than 10% and usually obtained with single-agent chemotherapy (Glisson, 2003). Consequently, although a large number of chemotherapy was evaluated in clinical trials and some have shown a promising activity, no evidence-based standard treatment has been established for second line chemotherapy in this setting.

Irinotecan and its active metabolite, SN-38, interacts with cellular topoisomerase I complexes and has S-phase-specific cytotoxicity by preventing religation of the DNA strand, resulting in double-strand DNA breakage and cell death (Liu et al., 2000). In the second-line setting, Pallis and colleagues performed a randomized phase II study

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comparing irinotecan alone with a combination with gemcitabine (Pallis et al. 2009). The result showed no complete or partial response (CR or PR) was observed in the irinotecan alone group. The efficacy in the treatment of relapsed SCLC as second-line chemotherapy has not yet been confirmed (Masuda et al., 1992).

According to this background, we hypothesize that irinotecan originated regimen could be established as an optimal schedule in second-line chemotherapy for patients with SCLC.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search terms: (small cell lung cancer) and (irinotecan). All clinical studies evaluating the impact of irinotecan on the response or survival and side effects for small cell lung cancer published in English prior to December 2014 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, conbined with cisplatin, carboplatin, nedaplatin or others; (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 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 810 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 (Ohe et al., 2012; Matsubara et al., 2013; Yu et al., 2013; Morise et al., 2014). 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 studies included in this analysis are presented as short-term outcomes: the response rate of Morise, et al. was 32% (18/57), of Yu et al. was 29 % (9/34), of Ohe et al. was 75 % (9/12), and of matsubara et al. was 18.8 % (6/32). Totally, 155 patients were enrolled and 42 patients achieved CR or PR, the pooled response rate thus was 42/155 (27.1%). Observation on toxicities: major adverse effects were hematological toxicities, gastrointestinal disturbance, and neurosensory toxicity .

Discussion

Previous research reviewed medical charts of small cell lung cancer patients who had received second-line chemotherapy at the National Cancer Center Hospital of Japan between April 2003 and June 2012 (Morise et al., 2014). They administered irinotecan (60 mg/m2) on Days 1, 8 and 15 every 4 weeks) for a consecutive 57 patients. This study reveled that the median age of this patient cohort was 70 years (range, 51-83). Fifty-two (91%) were male, 36 (63%) had an Eastern Cooperative Oncology Group performance status 0-1 and 26 (46%) were sensitive relapse (Morise et al., 2014). The median number of chemotherapy cycles was 2. The objective response rate was 32% (95% confidence interval: 20-45%). The median progression-free survival and the median overall survival were 2.9 months and 5.3 months, respectively. The incidence of Grade 3/4 neutropenia, diarrhea and nausea/vomiting was 21, 4 and 5%, respectively (Morise et al., 2014). In conclusion, Morise et al.suggested that low-dose irinotecan monotherapy for recurrent small cell lung cancer might be effective with favorable toxicity (Morise et al., 2014). In a retrospective study by Yu et al., they analyzed 1, 140 Chinese patients who diagnosed small cell lung cancer from April 2009 to April 2012. Of all the patients, 34 patients were treated with irinotecan and nedaplatin (irinotecan 60 mg/m2 on days 1, 8 nedaplatin 85 mg/m2 day 1, every 3 weeks) , and 20 patients were treated with irinotecan and cisplatin (irinotecan 60 mg/m2 on days 1, 8 cisplatin 75 mg/m2 day 1, every 3 weeks) as a second-line treatment. The results of Yu et al. suggested that of all 54 eligible patients, median progression free survival (PFS) was 4.9 months, and median OS was 13.3 months. Median PFS was 5.4 months for irinotecan plus nedaplatin and 4.9 months for irinotecan plus cisplatin, respectively (P=0.465). Median OS was 14.3 months and 13.3 months, respectively (P=0.704). The toxicities were mild, while toxicity profile was slightly different for each of the arms: hematologic toxicity was higher in IN group, and diarrhea was higher in IC group. In conculsion, Irinotecan plus platinum is effective and tolerable for refractory and relapsed small cell lung cancer. Irinotecan plus nedaplatin is non-inferior to irinotecan plus cisplatin in terms of efficacy and safety. In a study by Matsubara et al., they enrolled 32 patients (median age, 60 years) from December 2007 to April 2009 (Matsubara et al., 2012). Six partial responses to irinotecan monotherapy were observed (ORR, 18.8%). The disease control rate was 78.1%,

median PFS was 4.0 months, and median survival time was 10.4 months. Grade 3-4 neutropenia was observed in 22% of patients, No patients had grade 3-4 diarrhea or treatment-related death (Matsubara et al., 2012). Of 15 patients for whom progressive disease represented the best response to previous treatment regimens, 2 exhibited a partial response and 9 showed stable disease after irinotecan monotherapy, with a disease control rate of 73.3%, median PFS of 4.4 months, and MST of 8.2 months. Thus in conclusion, Matsubara suggested that irinotecan monotherapy is effective for advanced NSCLC patients who have previously failed 2 or more treatment regimens (Matsubara et al., 2012). Another Japanese study was conducted by Ohe et al.In this study, patients with relapsed SCLC were treated with irinotecan at 50 mg/m2 on days 1 and 8 and nedaplatin at 50 mg/m2 every 4 weeks for 4 cycles (Ohe et al., 2012). The outcomes of Ohe et al. demonstrated that 12 patients (9 male and 3 female; age range 48-76 years, median 62 years) were retrospectively analyzed (Ohe et al., 2012). Seven of the patients showed sensitive relapse. Two patients had a performance status of 2. Nine of patients received 4 to 6 courses of irinotecan and nedaplatin. Grade 3 or 4 anemia, neutropenia and thrombocytopenia occurred in 25.0%, 50.0% and 41.7% of patients, respectively. No grade 3 or 4 non-hematologic toxicities except for febrile neutropenia in 1 patient was reported, no treatment-related death occurred (Ohe et al., 2012). In this study, 9

patients achieved PR, and the objective response rate was 75.0% (Ohe et al., 2012). The median survival time was 11.1 months and the 1-year survival rate was 50.0% (Ohe et al., 2012). Ohe et al. concluded that irinotecan and nedaplatin in combination are effective and safe for patients with RSCLC.

Our current study was designed to evaluate the efficacy and safety of irinotecan based regimens as second-line chemotherapy on response and safety for patients with small cell lung cancer. Our results demonstrated that when irinotecan based regimens was used as second-line chemotherapy, the pooled RR was 27.1% (42/155). Nausea, vomiting, diarrhea and myelosuppression were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in these irinotecan based treatments.

In conclusion, our current systemic analysis suggests that irinotecan based regimens as second-line chemotherapy are associated with mild response rate and accepted toxicities for treating patients with small cell lung cancer.

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