RESEARCH COMMUNICATION

Irinotecan as a Second-line Monotherapy for Small Cell Lung Cancer

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Abstract

Objectives: The present study was designed to investigate the efficacy of irinotecan monotherapy as a second-line treatment for small cell lung cancers (SCLCs). Methods: Irinotecan monotherapy was administered to 46 SCLC patients who were previously undergone cisplatin based chemotherapy protocols. Response to treatment, time to progression (TTP), overall survival rates and adverse events associated with irinotecan monotherapy (300mg/m2; total 153 cycles; mean 3.78 ± 1.98) were determined, retrospectively. Results: Limited stage disease was diagnosed in 19.6% of patients (n=9) while 80.4% (n=37) were diagnosed with extensive stage cancer preceeding the irinotecan monotherapy. None of the patients had complete response to irinotecan. Partial response and stable disease were achieved among 17.5% of patients. Mean time to tumor progression (TTP) was determined to be 11.3±5.94 weeks while overall survival was 13.3±6.83 months. Considering adverse events, grade 3 and 4 toxicity was encountered in 8.9% and 4.5% of patients, respectively. Irinotecan monotherapy in brain metastasized tumors was found to be associated with significantly higher survival times compared with tumors lacking brain metastasis (15.0±5.95 vs 10.7±4.82 months; p<0.05). Conclusions: Irinotecan as a monotherapy in the second-line treatment of SCLC seems to have an acceptable level of toxicity and significant palliative effects. The prominent survival step-up effect particularly in brain metastasis patients appears worthy of note.

Keywords: Small-cell lung cancer - second-line chemotherapy - irinotecan - survival

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Introduction

Lung cancer is the leading cause of cancer related deaths worldwide (Jemal et al., 2007). The two thirds of small-cell lung cancer (SCLC) are as extensive disease (Govindan et al., 2006). The combination chemotherapy with etoposide and cisplatin along with chest radiotherapy has been applied in patients with limited stage disease, while combination chemotherapy of either irinotecan or etoposide with cisplatin (Noda et al., 2002) has been known as the standard regimens in patients with extensive stage SCLC (Jemal et al., 2007; Kim et al., 2008).

Although SCLC is a quite chemosensitive malignancy with overall response rates of 80–95% and 60–80% in patients with limited and extensive stage disease, respectively; most patients relapse within a year of initial treatment and more than 95% of them eventually die from disease progression (Jackman et al., 2005). It has been reported that second-line chemotherapy in relapsed SCLC usually fails leading approximately 2-3 months of median survival time (Jackman et al., 2005; Jemal et al., 2004).

Since results of several randomized trials concerning optimal duration of chemotherapy suggested a little role for maintenance chemotherapy (Le Chevalier et al., 1997; DeVore et al., 1998), first-line chemotherapy on responding SCLC patients has been intended to be discontinued after 4–6 months rather than longer 2 year-protocols (Von et al., 1999, Ettinger, 2001). Additionally, when patients were randomly selected for chemotherapy or for supportive care alone after tumor progression, survival was shown to be compromised in patients with supportive care alone but not in those who had received chemotherapy (Negoro et al., 1991).

Despite the high response rates observed with first-line treatment, results of second-line treatment for patients with relapsing or progressing disease are generally poor, with a median survival from the time to progression of 4–5 months (Von et al., 1999). In an effort to achieve higher survival rates in this destructive disease, the novel agents such as topotecan, docetaxel, paclitaxel, irinotecan, and gemcitabine have been introduced in first- and second-line treatment of SCLC (Ettinger et al., 2001, Kelly 2000).

Among them, irinotecan, a water-soluble camptothecin derivative, has been reported to be active in pre-treated

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patients with SCLC (Le Chevalier et al., 1997, DeVore et al., 1998, Masuda et al., 1992). Antitumor activity of irinotecan against a variety of human xenografts via intravenous, intraperitoneal and oral administration was shown to be excellent (Hattori et al., 2009). Accordingly, cisplatin/irinotecan combination was reported to be associasted with significant difference in survival compared to "standard" doublet of cisplatin/etoposide as a first-line treatment in extensive stage SCLC (Noda et al., 2002).

However, past studies concerning second line treatment of SCLC revealed somehow inconsistent and puzzling results that whether irinotecan could be applied as combination chemotherapy or a monotherapy to elderly patients with the extensive stage SCLC have not been evaluated in a satisfactory manner (Kim et al., 2008).

The present study therefore was designed to investigate the efficacy of irinotecan monotherapy as a second-line treatment in patients with SCLC presenting either with extensive or limited stages of the disease.

Materials and Methods

Study Design and Patient Selection

This observational and retrospective study aiming to evaluate the safety and efficacy of irinotecan monotherapy in the second line treatment of SCLC was conducted with 46 patients (45 males and 1 female; mean age was 55.3±10.13 years) with histologically or cytologically confirmed SCLC who were previously treated with cisplatin based chemotherapy protocols.

Small-cell lung cancer patients presented either with limited-stage or extensive-stage were accepted for the evaluation of response to treatment, time to progression (TTP) and overall survival rates associated with irinotecan monotherapy according to the inclusion and exclusion criteria of the study presented in Table 1.

Before irinotecan treatment; baseline assessment comprised of a complete medical history, physical examination and vital signs, complete blood cell count with differential and blood biochemistry, electrocardiography, chest X-rays and computed tomography scans of the chest, abdomen and brain and a whole-body radionuclide bone scan were performed. Irinotecan was administered on a single day as a 90-min i.v. infusion, at a dose of 300 mg/m^2. Treatment was repeated every 3 weeks as long as the disease progression or the appearance of untolerable adverse event was not encountered.

Table 1. Inclusion and Exclusion Criteria for the Study

Inclusion criteria
histologically confirmed small-cell carcinoma
extensive-stage or limited-stage disease
age over 18 years old
adequate haematologic parameters (haemoglobin concentration of at least 9.0 g/dL, absolute neutrophil count ≥1500/mm3, platelet count ≥100,000/mm3), renal functions (serum creatinine ≤1.5 mg/dl), and liver function (total bilirubin ≤1.5 mg/dl, level of serum transaminase twice the upper limits of normal or less)
prior cisplatin-based chemotherapy
Exclusion criteria
active infection
prior irinotecan chemotherapy
uncontrolled congestive heart failure or hypertension
uncontrolled diabetes mellitus
prior second primary cancer, except for cervix cancer in situ or skin cancer.

Statistical analysis

Database was transferred to SPSS (Statistical Package for Social Sciences) and statistical analysis was made using Student's t-test, ANOVA or ANCOVA tests for parametric variables and Mann-Whitney U test and Kruskal-Wallis tests for nonparametric variables to compare independent group means. The degree of relationship between numerical variables was determined using Pearson correlation analysis. Chi-square and Fisher's tests were used for the comparisons including categorical data. The duration of response was measured from the day of the first documentation of response to chemotherapy until disease progression. The time to tumor progression (TTP) was measured from study entry until the day of the first evidence of disease progression whereas the overall survival (OS) from study entry to death or last contact. Data were expressed as "mean±standard deviation (SD)" and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

Results

A total of 46 subjects (age 55.26±10.13 years, 45 males and 1 female) with histologically confirmed SCLC who were previously treated with cisplatin based chemotherapy protocols were included in the study. Disease was determined to be at the limited stage in 19.6% of patients (n=9) and at the extensive stage in 80.4% of patients (n=37) before the administration of the second-line irinotecan treatment.

A total of 153 chemotherapy cycles using irinotecan were administered with a mean cycle number of 3.78±1.98. Considering adverse events/toxicity related to irinotecan monotherapy, overall grade 3-4 toxicity was encountered among 8.9% and 4.5% of patients, respectively. Among grade 3-4 toxicity, the mostly encountered grade 3-4 toxicity was neutropenia (5.1%). Febrile neutropenia and thrombocytopenia was observed in 1.3% and 0.6 % of patients, respectively. There was no treatment-related death. The most frequent non-haematological toxicity was nausea/vomiting occurred in 41.9% (Grade 1), 17.4% (Grade 2) and 3.8% (Grade 3) of patients, respectively. The second common nonhematologic toxicity was diarrhea occurring in 36.1% (Grade 1) and 7.0% (Grade 2) of patients. Constipation (Grade 1-2) was observed among 13.5% of patients. All other haematological and non-hematological toxicities were relatively infrequent and tolerable. Table 2 summarizes all of these irinotecan-related adverse events.

Considering efficacy of irinotecan, none of the patients was detected to achieve a complete response (CR). Progression of the disease was observed among 81.8% of patients (n=36) whereas stable disease was achieved for only 11.4% and partial response for 6.8% of patients

Table 2. Adverse Events Encountered during Irinotecan Monotherapy

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Nausea / vomiting	65 (41.9%)	27 (17.4%)	6 (3.8%)	0
Diarrhea	56 (36.1%)	11 (7.0%)	2(1.3%)	2 (1.3%)
Constipation	18 (11.6%)	3 (1.9%)	0	0
Stomatitis	8 (5.2%)	5 (3.2%)	0	0
Alopecia	16 (10.3%)	5 (3.2%)	0	0
Allergy	2 (1.3%)	0	0	0
Neutropenia	19 (6.5%)	2 (1.3%)	5 (3.2%)	3 (1.9%)
Febrile neutropenia	0	0	0	2 (1.3%)
Trombocytopenia	0	0	1 (0.6%)	0

involved in the study. Mean time to tumor progression (TTP) was determined to be 11.3±5.94 weeks while overall survival (OS) was shown to be 13.5±6.83 months. Distant metastases were found in 80.4% of patients all of which were patients with extensive stage disease. Most frequent single site for the distant metastasis was the brain (23.9%). Other possible locations of distant metastases including liver, adrenal gland and bone either alone or in various combinations in-between.

The average latent period passed from the initial diagnosis until the initiation of second-line irinotecan treatment was found to be 8.65±4.2 months in our patients. The time passed before the administration of the irinotecan monotherapy was similar when limited (8.5±2.32 months) and extensive (8.7±4.54 months) stages of SCLC were compared to each other ($p>0.05$). There was a significant positive correlation between survival (13.45 ± 6.83 mo) and the time passed between the first diagnosis of the disease and the initiation of the irinotecan monotherapy (8.65±6.8 mo; $p<0.02$). However there was no relation between survival and the time passed between the first–line treatment and initiation of the irinotecan monotherapy (7.94±3.4 mo; $p>0.05$).

Regarding overall outcome, 71.7% of patients (n=33) died and only 5 out of 46 patients (10.8%) were found to be alive at the end of 6, 17, 22, 35 and 36 months from the initial diagnosis, respectively. This represented 11.1% of patients with limited disease (1 out of 9) and 10.8% of those with extensive disease (4 out of 37) The outcome was not known for 17.4% of patients (n=8) due to failure to record data.

There was no statistical difference between metastatic or limited stage disease in terms of the treatment response and TTP ($p>0.05$). Despite the similarity concerning TTP values between metastatic and limited stages, the presence of brain metastasis was found to have a significant effect on survival ($p<0.05$). There was no significant difference in survival and TTP with respect to use of irinotecan as a second-line (n=38) or a third-line (n=8) chemotherapeutic ($p>0.05$).

Although there was a tendency towards higher survival among patients with limited stage disease (17.8±9.9 months), this was not significant statistically when compared to survival among patients with extensive stage disease (12.5±5.7; $p>0.05$). The mean duration of the second-line irinotecan monotherapy was 3.86±1.98 months (range 1-8). Limited and extensive stage SCLC were also found to be similar in terms of duration of irinotecan chemotherapy (4.4±2.06 mo and 3.72±1.96 mo, respectively; $p>0.05$).

Blood biochemistry was shown to be similar between patients with limited and extensive stage diseases, except for uric acid levels which were found to be significantly higher among patients with extensive stage disease (5.27±1.44 vs 3.81±1.09; $p<0.05$). The single variable associated with both survival and TTP was the serum hemoglobin level. High hemoglobin levels were found to be positively correlated with survival ($p<0.05$) and TTP ($p<0.01$).

Discussion

The vast majority of patients with SCLC become candidates for second-line therapy due to high relapse rates associated with the disease. The time between the administration of the first-line treatment and the experience of relapse, the response rate to first-line treatment and the type of drugs administered as first-line therapy were among the factors considered to influence the success of second-line therapy (Pallis et al., 2009). Accordingly, patients lacking a remarkable response to the first-line therapy or having a relapse within 3 months following the therapy were considered to be treatment resistant, whereas the presence of respectable treatment response and the occurrence of relapse in > 3 months were the factors in favor of treatment sensitivity (Jackman et al., 2005).

In fact, despite 80% of our survived patients were detected to present with the extensive form of the disease at the beginning, the interval between first and second-line treatments was independent from the stage and presentation of the disease. Furthermore the time passed between the first and second-line chemotherapy administration was not found to be related to survival rates obtained among our patients. This may highlight the value of natural treatment-free course of the disease preceding the first-line treatment as long as the overall quality of life and high relapse rates were concerned.

The main prognostic factors for the SCLC were stated to be the stage of the disease, i.e., the better and longer response rates with smaller tumors, and the clinical condition of the patient at the diagnosis (Spiro, 1985). Similarly, past studies concerning combination treatments lasting approximately 18 months (range 4-24 mo) for SCLC were recently reviewed and the overall survival rate at two years was calculated to be 7.0% (representing 13% of patients with limited disease and only 2% of those with extensive disease) (Morstyn et al., 1984). In contrast to above studies, our study revealed similar treatment responses, TTP and survival time between extensive and limited stages of the disease despite the administration of shorter term irinotecan monotherapy (1-8 cycles with a 3-week intervals). Nevertheless, our findings are compatible with the consideration in the literature that a chemotherapy cure rate of 25% for those with limited disease was a useless early hope that have not been realised (Oldham and Greco, 1980).

Moreover, survival chance with irinotecan monotherapy was found to be more prominent among patients having

extensive stage disease with brain metastasis. Thus receiving irinotecan treatment seems to increase survival among brain metastatic patients, significantly. Certifying this finding, patients presenting with extensive disease especially those who have cerebral or hepatic metastases were shown in the liteature to be related with poor prognosis. On the other hand those with an isolated bone metastasis or single positive result at marrow aspiration biopsy may, however, were stated to respond as well as patients with limited disease (Hande 1984).

Reduced and tolerable adverse event profile associated with the irinotecan monotherapy in our study may be related to administration of irinotecan for a shorter time period compared to up to 12 to 18 months usage in the past (Feld 1984). This reduction in adverse effects may also be associated with the common belief that benefits from treatment tend to occur early but side effects appear much later becoming more noticeable as treatment is prolonged (Spiro 1985). Additionally our findings related to short term administration of irinotecan monotherapy seems to be compatible with the results of recent studies showing no difference between longer term treatments and shorter regimens including with three and six courses of chemotherapy followed by chest irradiation in terms of median survival (Feld et al., 1984; Spiro, 1985).

Combination therapy in SCLC was reported to be associated with almost 50% complete response rates in some series, and also with nearly a third of partial response. In patients who have presented with widespread disease a quarter has had a complete response and half a partial response with the combination treatments (Spiro 1985). The achievement of a complete response was stated to be the main determinant of long term survival (Morstyn et al., 1984). In this vein, when mean cycle number of irinotecan treatment was considered, it is clear that most of the patients died before the completion of chemotherapy and therefore, complete response was not achieved among our patients. However, partial response rates plus stable disease achievement was observed in 17.5% of patients, when compared to overall response rate of 10–50% reported with irinotecan / gemcitabine combination (Pallis et al., 2009). Therefore, iritonecan monotherapy seems to have a moderate palliative effect since mean survival time approaching 14 months with irinotecan monotherapy was indeed comparable to 4-14 months survival obtained by irinotecan/ gemcitabine combined treatment (Ohyanagi et al., 2008).

In fact adverse events encountered in our study were much milder than reported with irinotecan monotherapy in the literature. For instance 22.6% of the patients in the irinotecan monotherapy arm (300 mg/m^2) developed grade 3-4 toxicity in a past study (Pallis et al., 2009) when compared to much lower incidence (4.1%) obtained among our patients with the same dose of irinotecan monotherapy (300 mg/m^2). Such a marked difference in the neutropenia encounter may appear as a result of ethnic differences between study populations including Greek and Turkish cancer patients similar to white blood cell count shown to be lower among African American women with breast cancer both at baseline and as a result of chemotherapy compared with white women with breast cancer (Hershman 2003). Diarrhea on the other hand was the most frequent non-hematological toxicity also in the present study, similar to the literature (Pallis et al., 2009).

Far from a declaration of a certain variable that influence survival per se, but in attempt to link prognosis with the results of simple laboratory tests, we have found that hemoglobin levels were associated with a favorable outcome similar to previously shown association between survival and high serum albumin concentration (Spiro 1985). The results of biochemical tests were similar between patients with limited and extensive stage disease except for uric acid levels which were found to be significantly higher among patients with extensive stage disease.

Irinotecan/gemcitabine combination was reported to have better outcome in terms of response rate (23.7% vs. 0%) and TTP (3.9 months vs. 1.7 months) but the difference concerning survival was not shown to be significant (6.8 months vs. 4.6 months) (Pallis et al., 2009). Similarly, complete response was also absent in our trial concerning irinotecan monotherapy but both TTP (range 3-24 weeks) and survival (4 months to 35 months) seem to approach and even to go beyond the values obtained by the combination treatment. Survival obtained in our patients with irinotecan monotherapy was also comparable to survival of 125 days reported in a previous study (Le Chevalier 1997) including administration of irinotecan as a monotherapy at doses (350mg/m^2) similar to our study to sensitive or refractory patients with SCLC. In fact administration of irinotecan as a monotherapy at much lower doses was also reported (DeVore RF 1998) to be associated with similar survival rates obtained in our study. On the other hand in a past study with irinotecan monotherapy (300mg/m^2), the reported survival was much lower than we had obtained (Pallis et al., 2009).

In fact, longer survival detected among our patients may be attributable to the presence of concomitant brain metastasis which was shown to lead significant increment on the survival in lung cancer compared to its absence. Interestingly, despite a survival advantage of brain metastasis was also reported in the literature concerning breast cancer patients, this advantage was not correlated with better control of the brain metastases (Kirsch 2005). Hence survival advantage after brain metastasis has been considered to be result from better control of extracranial systemic disease in cancer patients (Lower 2003). Moreover, in a randomized controlled trial it was concluded that aggressive therapy for a single brain metastasis from a variety of primary cancers improves survival only if extracranial disease is controlled (Noordijk et al., 1994). On the other hand recently reported response rate of 65% in the intracranial disease of 14 SCLC patients with known brain metastases (Chen et al., 2009) seems to indicate the better chance of the metastatic patients in terms of treatments targeting brain due to longer survival associated with their condition. Accordingly, based on the evaluation of published reports concerning patients who received chemotherapy for brain metastases from SCLC, the response rate of brain metastases from SCLC to a variety of chemotherapy was suggested to range from 22% to 85% and the median survival of patients was determined

to be 3-9 months (Chen et al., 2008).

When issues concerning irinotecan monotherapy were considered such as the lack of therapeutic discrimination between limited and extensive stages of the disease, brain metastasis specific survival chance and the achievement of similar survival rates accompanied with reduced adverse event frequency and severity; it becomes inevitable to justify the present questioning regarding achievement of long term survival, toxicity and long term side effects and finally the necessity of chemotherapy for patients with SCLC (Spiro 1985).

The reasons for these conflicting results concerning the efficacy of irinotecan in second-line setting are not obvious. In fact survival does not guarantee being tumor-free in SCLC. In the literature about half of the long term survivors had either some form of disease or limitation of lifestyle related to previous treatment, in addition to running the risk of relapse (Morstyn et al., 1984). Hence the treatment of patients with SCLC remains difficult, and in dealing with an aging population the potential toxicity of treatment must be weighed against the potential for improved survival rates and possible long term survival (Spiro, 1985). In addition longer survival observed among brain metastatic SCLC patients with irinotecan monotherapy may indicate a much better chance concerning the management of brain metastasis in these patients.

In conclusion, while irinotecan monotherapy in the second-line treatment of SCLC seems to have an acceptable level of toxicity and significant palliative effect indicating that a SCLC related promise of responding to second-line chemotherapy, larger prospective randomized trials are mandatory to be able to discriminate the shorter courses of chemotherapy enabling symptomatic relief in patients with extensive stage disease.

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