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Running title: CPT-11 plus pegylated doxorubicin salvage treatment in SCSL

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Abstract

Purpose To evaluate efficacy and toxicity of a combination of pegylated liposomal doxorubicin and irinotecan in patients with refractory small-cell lung cancer.

Patients and methods Thirty-one patients with early relapse after first-line therapy with cisplatin/etoposide were treated with pegylated liposomal doxorubicin 15mg/m^2 and irinotecan 125mg/m^2 on days 1 and 15. Treatment was repeated every 28 days.

Results A total of 144 chemotherapy courses were administered. All patients were evaluable for toxicity and twenty-six (84%) for response. Grade 3 neutropenia occurred in two (6.5%) patients and grade 1 thrombocytopenia in one (3.2%). Fatigue was the most frequent grade 3 non-haematologic toxicity and was observed in seven patients (23%). Four (12.9%; 95% C.I: 1.1%-24.7%) patients achieved a partial response and disease stabilization was observed in additional two (6.5%) patients (Tumor Growth Control: 19.4%; 95% C.I: 5.5%-33.3%). The median TTP was 2.03 months and the median survival time was 3.16 months.

Conclusions The combination of pegylated doxorubicin and irinotecan is very well tolerated but with modest activity in patients with refractory SCLC.

Keywords Pegylated Doxorubicin; CPT-11; SCLC, Second line treatment

Introduction

Small cell lung cancer (SCLC) is staged as limited or extensive disease according to a two-stage system developed by the Veteran's Administration Lung Cancer study group based on whether the disease can be encompassed within a reasonable radiation port. Patients with limited disease are treated with combined chemo-radiotherapy with the potential of cure, but these patients represent only about one third of the cases [1]. In the majority of patients, disease is diagnosed as extensive and treatment is undertaken with palliative intent. Chemotherapy is the backbone of therapy at any stage of disease. Platinum-based regimens remain the treatment of choice in the first-line setting. Cisplatin or carboplatin in combination with etoposide is the gold standard treatment achieving response rates ranging between 60% and 90% depending on the stage of the disease [2;3].

Despite the initial high chemotherapy sensitivity, SCLC remains an incurable disease, as the majority of the patients relapse commonly within the first year after initial treatment [4]. The probability of response to second line chemotherapy is mostly dependent on the treatment-free interval after the completion of first-line treatment [5]. In patients relapsing at intervals of 3 months or longer from the front-line chemotherapy, re-administration of the induction regimen is frequently associated with a new response which may substantially impact survival of SCLC patients [6]. Patients progressing while on treatment or within 3 months after its completion are considered as resistant to the drugs used in the induction regimen. For these patients various alternative combinations with drugs that have demonstrated activity in chemotherapy-naive SCLC patients have been tested in several clinical trials but with modest or borderline activity [7].

The effectiveness of doxorubicin-containing regimens in the treatment of SCLC has been demonstrated several years ago. Pegylated liposomal doxorubicin is a novel formulation of doxorubicin in which the drug is encapsulated in polyethylene glycol-coated liposomes. This is associated with an enhanced uptake by cancer cells and reduced drug delivery to normal tissues [8]. The substitution of doxorubicin by pegylated liposomal doxorubicin in the CAV regimen (cyclophosphamide, doxorubicin and vincristine) represents an active option in relapsed SCLC patients, with acceptable response and manageable toxicity [9].

Irinotecan is a semisynthetic derivative of camptothecin. The inhibition of topoisomerase-I by its active metabolite SN-38 eventually leads to double-strand DNA breakage and termination of both DNA replication and transcription [10]. The efficacy of irinotecan in the first-line treatment of SCLC has been established. The substitution of etoposide by irinotecan in platinum-based regimens provides at least the same clinical benefit with less hematologic toxicity [11]. As second-line treatment, irinotecan has been extensively evaluated in several phase II clinical trials demonstrating substantial activity, either as single agent [12], or in combinations with cisplatin [13], etoposide [14] or gemcitabine [15].

Based on these data and in preclinical studies that have shown synergistic activity between topoisomerase I and II inhibitors [16;17], we designed a two-stage phase II study to evaluate the efficacy of a pegylated doxorubicin-irinotecan combination in patients with refractory SCLC. The doses and schedule employed was based on unpublished data of a phase I study in patients with advanced solid tumors conducted by Hellenic Oncology Research Group. In this study, the maximum tolerated dose for pegylated doxorubicin and irinotecan was 15mg/m^2 and 125mg/m^2,

respectively, given in a biweekly schedule on days 1 and 15 every 28 days. The dose limiting toxicities were grade 4 neutropenia and grade 3 thrombocytopenia.

Patients and Methods

Patients

Patients who were eligible for this study were at least 18 years old with a WHO performance status of 0-2, an estimated life expectancy >3 months, histologically or cytologically proven SCLC and documented progressive disease within 3 months after the completion of first line chemotherapy with cisplatin and etoposide. Patients with brain metastases were allowed provided that they had been irradiated and had clinical and radiological improvement. Additional eligibility criteria included: adequate hematologic parameters (absolute granulocyte count >1500/mm^3, platelet count >100,000/ mm^3 and hemoglobin level >9 g/dL), adequate hepatic (serum bilirubin <1.5 mg/dL, transaminases <2x the upper limit of normal) and renal function (serum creatinine <1.5 mg/dL); adequate cardiac function (left ventricular ejection fraction >45%). Patients with pre-existing severe diarrhea, uncontrolled angina pectoris, myocardial infarction less than 3 months before the enrolment were excluded from the study. Patients with severe cachexia or malnutrition (>20% loss of body weight), active infection, or a second primary tumor other than skin squamous cell carcinoma or in situ cervical carcinoma, were not eligible. The study protocol was approved by the Ethical and Scientific Committee and all patients gave a written informed consent before enrolment.

Treatment Schedule and Dose Modifications

Pegylated doxorubicin was administered as a 1-h intravenous infusion at a dosage of 15mg/m^2 followed by irinotecan administered as a 90min infusion at a dosage of 125mg/m^2 with both drugs being given on days 1 and 15 in an outpatient setting. All patients received anti-emetic therapy consisting of an intravenous 5-HT3 antagonist. The treatment cycles were repeated every 4 weeks until disease progression, unacceptable toxicity or patient's refusal to continue further treatment.

Minimum requirements for chemotherapy administration were an absolute neutrophil count >1500/mm^3, platelets count ≥75,000/mm^3, and no grade 2 or higher non-hematologic toxicity. In case of grade 3/4 or febrile neutropenia granulocyte-colony stimulating factor (rhG-CSF) was administered on days 3 to 9 after chemotherapy. If febrile or grade 3/4 neutropenia occurred despite rhG-CSF administration, both drug doses were adjusted to 75% of the calculated dose. A similar reduction was done in case of grade 3/4 thrombocytopenia. In case of any grade 3/4 non-hematological toxicity (except nausea/vomiting and alopecia) both drug doses reduced by 15%. Additional 10% dose reduction was applied in case of repeated grade 3 or 4 non-hematological toxicity.

Baseline and follow-up assessments

The baseline assessment had to be performed within 2 weeks before study entry and included a complete medical history and physical examination, complete blood count (CBC) with differential and platelet count, blood chemistry, computed tomography (CT) scans of the chest, abdomen and brain and whole body bone scans. Left ventricular ejection fraction (LVEF) was monitored by echocardiography or multiple-gated acquisition scan at the baseline assessment and every 3 cycles of therapy;

electrocardiography was performed as clinically indicated. During treatment, a limited history taking, physical examination, assessment of toxicity, complete blood cell count with differentials and blood chemistry were performed before each chemotherapy administration.

All patients who received at least 3 cycles were evaluable for response. Response was assessed by CT scans every 3 cycles or sooner, if clinically indicated, using the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) [18]. All patients who received at least one cycle were evaluable for toxicity. Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria (version 2.0) [19].

Statistical considerations

Sample size was based on overall response rate. According to Simon's two-stage optimal design [20], assuming that the expected overall response rate will be at least 25% and the minimum acceptable response rate 5%, a sample of 22 patients will be required in the first step. If a minimum of 2 responses is observed a total of 30 patients will be accrued. Thereby, if at least 5 responses occur the treatment will be declared sufficiently promising. The probability of accepting a treatment with a real response rate of less than or equal to 5% will be 5%. On the other hand, the risk of rejecting a treatment (at the second stage) with a response rate of at least 25% will be 10%.

An intent-to-treat analysis was performed. Response rate, the primary end point of the study, was calculated as the ratio of the number of patients who achieved a complete or partial response to the number of enrolled patients. All responses were confirmed 4 weeks after the first documentation of response, and imaging studies

were reviewed by an external panel of radiologists. Secondary end points were: time to progression (TTP, determined by the interval between the initiation of treatment to the first date that disease progression was objectively documented), overall survival (OS, calculated from study entry to death or last contact), and safety. OS and PFS were assessed by the Kaplan-Meier method and the 95% confidence interval (95% CI) for the median time to event was computed.

Results

Patient characteristics

From April 2004 to September 2009, 31 consecutive patients with refractory SCLC were enrolled onto the study. The median age was 64 years (range 48-77). Twenty-six (84%) patients had ECOG PS of 0-1. All had received cisplatin/etoposide in the front-line setting. Median interval between prior treatment and study entry was 2.4 months (range, 0.03-3 months). Baseline patients' characteristics are shown in Table 1.

Drug administration

A total of 144 chemotherapy cycles were administered (median: 4, range: 1-20). Twenty (14%) chemotherapy cycles were delayed for the following reasons: hematologic toxicity (n=3), non-hematologic toxicity (n=1) and other reasons not-related to disease or treatment (pending imaging studies for treatment evaluation and patients' request for personal reasons; n=16). The median treatment delay was 7 days (range, 3-11 days). In 40 (28%) chemotherapy cycles, rhG-CSF administration was required. Dose modification was required in 4 cycles due to hematologic (n=1) and non-hematologic (n=3) toxicity. The median delivered dose intensity for pegylated

doxorubicin was 7.27mg/m^2/week (97% of the protocol planned dose) and for irinotecan 60mg/m^2/week (96% of the protocol planned dose).

Toxicity

All patients were evaluable for toxicity. The treatment was generally well tolerated. Treatment related adverse events are shown in Table 2. Two (6.5%) patients developed grade 3 neutropenia and one (3.2%) grade 2 thrombocytopenia. There was no febrile episode. Anemia was relatively mild, but more frequent; grade 1/2 anemia was observed in 25 (80%) patients. The most significant grade 3 non-haematologic toxicity was fatigue which was observed in seven (23%) patients. Grade 3 diarrhea occurred in one (3.2%) patient, grade 2 in two (6.5%) and grade 1 in three (9.7%) patients. Hand-foot syndrome grade 1 and 2 occurred in two (6.5%) and one (3.2%) patients, respectively. Other non-hematologic toxicities were mild consisting mainly of grade 1/2 nausea in five (16%) patients, grade 1/2 constipation in three (9.7%) and grade 1/2 alopecia (48%). There was no toxic death.

Response to Treatment and Survival

Twenty-six (84%) patients were evaluable for response. Five patients discontinued chemotherapy before the first evaluation; three refused further therapy after first or second cycle and two patients were dropped out after the second cycle due to performance status deterioration. Non-evaluable patients were included in the intent-to-treat analysis.

Four (12.9%) patients achieved a partial response. Two additional patients (6.5%) experienced stabilization of their disease. The overall disease control rate was 19.4%. After a median follow-up period of 18.8 months (range, 0.9-24 months) all

patients had disease progression. The median TTP (Fig. 1) for patients with progression disease was 1.86 months (range: 0.5-4.97 months) and for patients with stable disease or partial response 8.63 months (range: 1.73-11.6 months). Twenty-five of 31 patients have died during the follow-up period. The median overall survival was 3.16 months (range: 0.9-24 months; 95% CI: 1.8-4.5 months) and the 1-year survival rate19.9% (Fig. 2).

Discussion

Today, there are more than 80 published studies of second-line therapy in SCLC reporting response rates ranging from 0% to 73% providing conflicting conclusions, especially for refractory patients [21]. The efficacy of second line chemotherapy in relapsed SCLC is largely dependent on the treatment-free interval, the extent of response and the residual toxicity from first-line therapy, as well as the performance status of the patient [22;23]. Nevertheless, even in late relapse, treatment with other agents is often less effective than the initial chemotherapy; the response rate with the approved second-line therapy, topotecan, is only about 20% [24]. For patients who fail to respond to or who relapsed shortly after the completion of first-line chemotherapy the response to most agents or regimens is poor and currently there is no standard second-line treatment [7].

In our study, the combination of pegylated doxorubicin and irinotecan demonstrated modest activity in refractory SCLC, with confirmed responses in 12.9% of patients; moreover, disease stabilization occurred in an additional 6.5% of the patients along with a median TTP of about 2 months and an overall survival of 3.1 months. Even if the efficacy outcomes achieved are considered comparable to those seen in other studies, the pre-defined criteria for characterizing the treatment effective

were not met. A possible explanation for the modest efficacy of the regimen could be the relatively low dosing of the combination. As we have already discussed, the dose and schedule was based on a previous phase I study in patients with refractory neoplasms who had received multiple lines of treatment. The latter may have impacted the defined maximum tolerated dose at the combination in that phase I study. In the present study the majority of our patients had a performance status of 0-1 and this may also account for the acceptable tolerance of the chemotherapy regimen.

Indeed, with respect to toxicity, the regimen was very well tolerated and treatment-related adverse effects were mild and easily manageable. Grade 3 neutropenia was observed only in two (6.5%) patients but was of short duration and easily manageable with rhG-CSF. There were no episodes of febrile neutropenia. Severe anemia and thrombocytopenia were infrequent with only one patient experiencing grade 3 anemia. Regarding the non-haematologic toxicity, only fatigue was a treatment problem. Although it is difficult to differentiate this type of toxicity from the symptoms of a generalized disease such as SCLC, grade 2-3 fatigue affected fourteen (45%) patients. Biweekly administration of irinotecan may be an additional reason for the high incidence of this type of toxicity. The rare incidence of severe hand-foot syndrome (only 10% of patients' experienced grade 1 and 2 hand-foot syndrome) could be attributed to the relative low dose of pegylated doxorubicin administered (15mg/m^2 every 14 days).

In conclusion, although the results presented here are from a relatively small phase II study and the study was not designed to draw strong conclusions, the results suggest that pegylated doxorubicin plus irinotecan combination after early failure to cisplatin/etoposide is well tolerated, but with modest activity. However, given the mild toxicity profile of the regimen, it would merit further investigation at different

doses or schedule in patients with refractory SCLC. Another possibility could be the replacement of pegylated doxorubicin with amrubicin, a third generation synthetic anthracycline, with potentially promising results, either as monotherapy [25], or in combination with topoisomerase-I inhibitor topotecan [26].

Disclosures

None

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Table 1 Patient characteristics

Characteristic	***n***	**%**
Number of patients	31	
Evaluable for response	26	
Evaluable for toxicity	31	
Age, years (range)	64 (48-77)	
Gender		
Male	28	90.3
Female	3	9.7
Performance status		
0	5	16.1
1	21	67.7
2	5	16.1
No. of distant metastatic sites		
1	1	3.2
2	8	25.8
≥3	22	71.0
Metastatic sites		
Liver	16	51.6
Nodes	21	67.7
Lung	27	87.1
Bones	8	25.8
CNS	7	22.6
Pleura	7	22.6
Other	10	32.3

Table 2 Hematologic and non-hematologic toxicity

Toxicity	**WHO grade**			
	1	**2**	**3**	**4**
	n (%)	n (%)	n (%)	n (%)
Neutropenia	7 (22.6)	3 (9.7)	2 (6.5)	- -
Febrile Neutropenia	- -	- -	- -	- -
Anemia	19 (61.3)	6 (19.4)	1 (3.2)	- -
Thrombocytopenia	6 (19.4)	1 (3.2)	- -	- -
Nausea	2 (6.5)	3 (9.7)	- -	- -
Vomiting	- -	2 (6.5)	- -	- -
Constipation	2 (6.5)	1 (3.2)	- -	- -
Diarrhea	3 (9.7)	2 (6.5)	1 (3.2)	- -
Stomatitis	3 (9.7)	- -	- -	- -
Hand-Foot Syndrome	2 (6.5)	1 (3.2)	- -	- -
Neurotoxicity	3 (9.7)	1 (3.2)	- -	- -
Allergy	1 (3.2)	1 (3.2)	- -	- -
Fatigue	8 (25.8)	7 (22.6)	7 (22.6)	- -
Alopecia	7 (22.6)	8 (25.8)	- -	- -

Legends to figures

Fig. 1 Kaplan-Meier time to progression curve for patients with progression disease (PD) and patients with stable disease or partial response (SD/PR)

Fig. 2 Kaplan-Meier survival curve for all patients

Figure 1

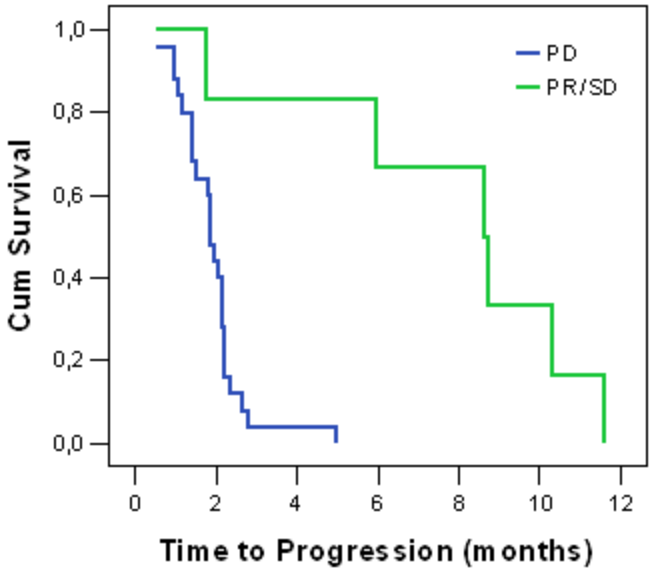
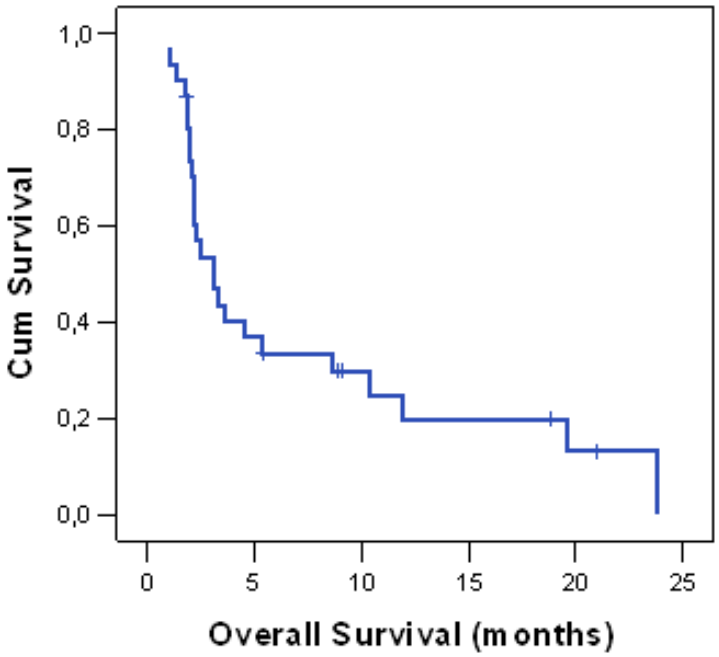

1,0
0,8
0,6
0,4
0,2
0,0
Cum Survival
PD
PR/SD
0
2
4
6
8
10
12
Time to Progression (months)

Figure 2


1,0
0,8
0,6
0,4
0,2
0,0
Cum Survival
0
5
10
15
20
25
Overall Survival (months)