

Clinical Studies

Pegylated Liposomal Doxorubicin HCL (Caelyx®) in Combination with Sandostatin LAR® as Salvage Therapy in Patients with Small-cell Lung Cancer

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Abstract. *Background:* The aim of the present study was to evaluate the efficacy of Pegylated Liposomal Doxorubicin (Caelyx) combined with Sandostatin LAR as salvage treatment of small cell lung cancer (SCLC) in platinum-pretreated patients. *Patients and Methods:* Nine pretreated patients (median age 53.5 years, PS: 0-1) with histologically confirmed SCLC were treated with Caelyx 40 mg/m² (i.v.) on day 1 and Sandostatin LAR 30 mg (i.m.) on day 1 every 28 days. Four (44%) out of the nine patients had received two prior regimens and five (55%) were refractory to front-line chemotherapy. *Results:* No complete or partial responses were observed. Disease stabilization was obtained in two (22%) patients. The median overall survival was 18.7 months and the median time to progression was 9.1 months. *Conclusion:* The combination of Caelyx and Sandostatin LAR was inactive as salvage treatment in this poor prognosis group of patients with relapsed SCLC. However, the combination would merit further investigation in patients pretreated with one prior regimen.

Small-cell lung cancer (SCLC) accounts for between 13% and 20% of lung cancer cases. The staging of SCLC is different from that of other solid tumors; the Veterans Administration Lung Cancer Group staging system classifies patients into limited-stage disease (LD) or extensive-stage disease (ED) (1). Although SCLC is an aggressive

malignancy with a propensity for early metastasis, it has been shown to be sensitive to chemotherapy, with a small group of SCLC patients achieving long-term disease-free survival. Treating SCLC remains frustrating however, as most patients will relapse and die of their disease despite an initial early high positive response to treatment.

Approximately 50% of patients with LD SCLC receiving combination chemoradiotherapy will achieve complete clinical remission. In ED SCLC, many will show an initial response to chemotherapy but only 20-40% will go into complete remission. The survival of patients with SCLC has improved significantly since the introduction of combination chemotherapy in the 1980s, but it is far from optimal and has not greatly increased (2, 3).

Patients failing or relapsing after first-line platinum-based treatment with cisplatin-etoposide (PE) regimen might be offered further chemotherapy or best supportive care. Patients who relapse within 3 months after the completion of first-line chemotherapy are defined as refractory and tend to do poorly, while those who relapse 3 or more months after therapy are defined as sensitive and are more likely to respond to second-line treatment. The response to re-treatment with the induction regimen mainly depends on the time between the completion of front-line treatment and recurrence (4, 5). However, despite the administration of second-line chemotherapy, the median survival of patients with LD is approximately 18 months, whereas in ED the median survival does not exceed 9 months (6).

Doxorubicin is a commonly used standard regimen in combination chemotherapy of SCLC. In an effort to reduce toxicity, while maintaining the same level of activity, doxorubicin has been entrapped in liposomes. Pegylated liposomal doxorubicin (PLD) is the first antineoplastic drug derived from the new technology of liposome formulation to be introduced in clinical practice. Clinical trials have shown that PLD is active against various types of tumors,

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with palmar-plantar erythrodysesthesia (PPE) and mucositis being the two main dose-limiting toxicities. Conversely, myelosuppression, nausea, alopecia and cardiotoxicity are less common and less severe compared with free doxorubicin (7-12).

Somatostatin (SST) is characterized as an inhibitory peptide with exocrine, endocrine, paracrine and autocrine activity (13). It inhibits the release of growth hormone and all known gastrointestinal hormones and selectively decreases splanchnic and portal blood flow without affecting mucosal blood distribution (14-20). According to the current knowledge, the effect of SST is thought to be mediated via specific SST receptors (SSTRs). The activation of the receptors is thought to decrease intracellular cAMP concentration, but the exact intracellular mechanisms effected by different SSTRs with regards to cellular proliferation and possibly induction of apoptosis are still under investigation.

Somatostatin receptors have been described on the cell membranes of tumors derived from the APUD system and their presence has also been demonstrated on SCLC cells both *in vitro* (cell line cultures and biopsies from SCLC patients) and *in vivo* (SCLC grown in nude mice) at a percentage of 50-75% (21, 22). Since SS and its analogs have shown relevant antiproliferative action in lung cancer with SS receptors, the *in vivo* characterization of the receptor status of lung cancer could influence the therapeutic approach (23-25).

A phase II study with administration of PLD HCl combined with Sandostatin LAR was conducted to assess the response/palliation in patients previously treated with the cisplatin-etoposide (PE) regimen or CAV (cyclophosphamide, doxorubicin, vincristine).

Patients and Methods

Patients. A group of 9 patients with histologically confirmed of SCLC were classified according to the Lung Cancer Group staging system as ED. Somatostatin Receptor Scintigraphy with ^{111}In -labelled somatostatin analog, pentetreotide (Octreoscan®, Mallinckrodt Medical B.V., Petten, The Netherlands) was performed at the baseline evaluation and was positive (Figure 1).

Patients should have had at least one prior platinum-based chemotherapy regimen, with or without radiation. Patients with brain metastases were permitted. Disease progression could occur earlier or after 90 days of the completion of all prior therapy. A known history of congestive heart failure and an ejection fraction (EF) less than 50% resulted in ineligibility. The eligibility criteria included: ECOG performance status (PS) of less than 2, life expectancy of two months or more and evidence of adequate bone marrow function (absolute neutrophil count $\geq 1,500/\mu\text{l}$, platelet count $\geq 100,000/\mu\text{l}$, and hemoglobin $\geq 10\text{gr/dl}$), liver function (bilirubin $\leq 1.5\text{mg/dl}$) and renal function (urea $\leq 1.5 \times \text{ULN}$, creatinine $\leq 1.5\text{mg/dl}$). Patients were required to be 18 years of age or older. All patients signed informed consent documents.

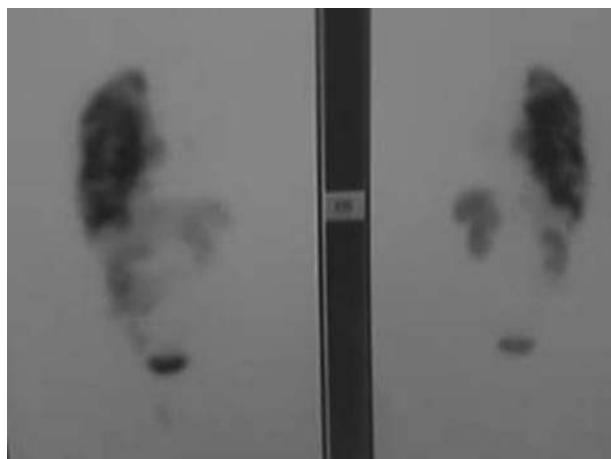


Figure 1. Somatostatin Receptor Scintigraphy with the ^{111}In -labelled somatostatin analogue, pentetreotide (Octreoscan), in a SCLC patient.

Methods. Patients received PLD (Caelyx®) at a dose of 40 mg/m^2 as a 30-min *i.v.* infusion on day 1 and Octreotide Acetate (Sandostatin LAR® Depot) at a dose of 30 mg administered by deep *i.m.* injection (into the gluteal muscle) at the same day, of a 28 day cycle for 6 cycles.

All patients received standard anti-emetic pre-treatment which consisted of 8mg dexamethasone plus 8 mg *i.v.* ondasetron. Complete blood counts and chemistry assessments including liver function studies were obtained at the beginning of each cycle. Disease was reassessed by physical examination every visit and by computed tomography scans every three cycles. The tumor response was measured by using response evaluation criteria in solid tumors (RECIST) (26). Quality of life was assessed in these 9 patients. All of the patients received the European Organization of Research and Treatment of Cancer (EORTC) Core Questionnaire, the EORTC QLQ-C30 version 3.0.

The endpoints included primarily the overall survival (OS) as well as the time-to-tumor progression (TTP). OS was measured from the time of diagnosis until death. TTP was measured from the enrollment in the study until the day of the first evidence of disease progression or death. All clinical data were analyzed with the SPSS program. For time events, the actuarial survival function was estimated by the Kaplan-Meier method.

Results

The accrual of this study was 9 patients, all of whom were evaluable for efficacy analysis. The patient characteristics are presented in Table I.

All patients had received PE in the front-line setting. In 5 (55%) patients the front-line treatment consisted of the PE regimen in combination with topotecan administered either sequentially or alternatively. Three patients received the CAVE (cyclophosphamide, doxorubicin, vincristine, etoposide) regimen in combination with cisplatin-topotecan alternatively as the front-line treatment. As second-line treatment, two patients were treated with gemcitabine plus

Table I. Patient characteristics.

	No of Patients	%
	9	100
Age (years)		
Median	53.5	
Range	47-72	
Gender		
Male	7	78
Female	2	22
Stage at the time of initial diagnosis		
Extensive disease	6	67
Limited disease	3	33
Performance Status (ECOG)		
0	1	11
1	8	89
2	0	0
Pack years		
>65	4	44
<65	5	56
Median	71.5	
Range	30-120	
Prior treatment		
First line chemotherapy	9	100
Second line chemotherapy	4	44
Radiotherapy	7	78
Response to first line chemotherapy		
CR,PR	1	11
SD	6	67
PD	2	22
Response to second line chemotherapy		
CR,PR	none	0
SD	1	25
PD	3	75
Response CR/SD/ PR to previous treatment (unmaintained)		
0-3 mos	5	56
3-6 mos	2	22
6-12 mos	1	11
12+ mos	1	11
Prior sites of radiation		
Chest	5	56
Brain	4	44
None	2	22
Number of metastatic sites		
0	2	22
1	3	34
2	4	44

CR, complete response ; PR, partial response; SD, stable disease; PD, progressive disease.

vinorelbine or irinotecan and two others had taken PE regimen. Thirty-two cycles were administered to eligible patients (range 1-6, median 4 per patient).

No complete (CR) or partial responses (PR) were observed. Two patients (22%) achieved disease stabilization (SD) lasting for 5 and 41.5 months respectively, and seven

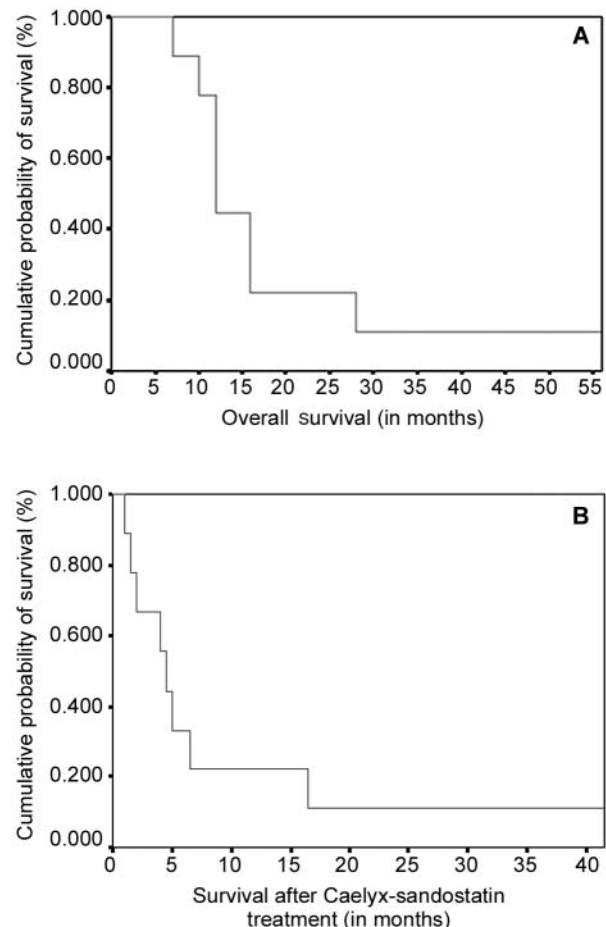


Figure 2. Survival analysis of the group of patients studied. Overall survival (A); Survival after Caelyx-Sandostatin treatment (TTP) (B).

patients (78%) had progressive disease (PD). From the patients with SD the first had a PR after the first-line treatment and was stable after the second regimen, while the second was stable after first and second-regimen.

The median overall survival was 18.7 months (range, 7-56 months) for all patients, 32 months (range, 12-56 months) for patients with LD and 12.1 months (range, 7-16 months) for patients with ED. The median time to progression (TTP) for the whole group was 9.1 months (range 1-41.5 months). Moreover, the median survival for the two patients with SD was 28.7 months (range 16-41.5) (Figure 2).

The results of this trial indicated that the drug doses were well tolerated by patients. None of the patients experienced grade III-IV toxicities and no dose reductions were required. The most common side-effects the patients faced were diarrhea and mucositis, which occurred in 22% and 11%, respectively.

There was no clear improvement in quality of life in patients. It should be noted that due to the low number of

patients, the power to detect differences in quality of life in our study is low.

Discussion

There is no standard salvage treatment for patients suffering from SCLC who fail or relapse after front-line treatment. Sensitive patients, those who relapse three or more months after therapy, could be rechallenged with the induction regimen achieving response rates as high as 50 to 67%. Objective responses of up to 27% are obtained with the combination of CAV administered as second-line treatment after the PE regimen. However, since the median survival of patients with recurrent SCLC remains poor, newer agents are currently being studied either as a monotherapy, or in combination with standard chemotherapy, in order to improve the disease outcome.

In this trial, the combination of PLD (Caelyx) and Sandostatin LAR as salvage treatment in SCLC failed to produce any objective response. The prognosis with further treatment in patients with SCLC depends on the response to first-line chemotherapy (27). The poor results observed in our study could be explained by the small number of patients included and by the fact that most patients suffered from refractory disease. Patients with highly advanced disease and a high tumor burden do not appear to be optimal candidates for therapeutic trials.

The SST analog that we have used (Octreotide) here has a distinct receptor affinity and usually does not bind to all five currently characterized SSTRs with comparable affinity. In addition, a positive scan result does not automatically indicate expression of respective SSTRs on tumor cells. Radiolabelled octreotide has been used to image granulomatous inflammatory sites.

Finally, the influence of chemotherapeutic agents on SSTR expression in pre-treated patients and the interaction between chemotherapy and concurrently administered SST analogs are still unknown.

Our data are similar to previously published results that demonstrated no therapeutic activity of lanreotide, as monotherapy, in SCLC refractory to chemotherapy at any of the doses examined. Lanreotide is a SST derivative which has a good affinity for SSTR5 as well as SSTR2 (28, 29).

In summary, the combination of PLD (Caelyx) and Sandostatin LAR was not active as a salvage treatment in this poor prognosis group of SCLC patients. However, this combination merits further investigation in patients pretreated with one regimen. There is a need of carefully designed clinical studies, including investigation of SSTR status, before treatment and assessment of optimal combination of chemotherapy with SST analogs. Additionally, new generation peptides with a broader receptor affinity are warranted. This regimen may play a

role in the prolongation of survival of sensitive patients with LD.

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