VAC chemotherapy with valproic acid for refractory/relapsing small cell lung cancer: a phase II study

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ABSTRACT Salvage chemotherapy (CT) for relapsing or refractory small cell lung cancer (SCLC) remains disappointing. *In vitro* experiments showed that valproic acid increases apoptosis of SCLC cell lines exposed to doxorubicin, vindesine and bis(2-chloroethyl)amine. The primary objective of this phase II study was to determine whether epigenetic modulation with valproic acid in addition to a doxorubicin, vindesine and cyclophosphamide (VAC) regimen improves 6-month progression-free survival (PFS).

Patients with pathologically proven SCLC refractory to prior platinum derivatives and etoposide were eligible. After central registration, patients received VAC plus daily oral valproic acid.

64 patients were registered, of whom six were ineligible. Seven patients did not receive any CT, leaving 51 patients assessable for the primary end-point. The objective response rate was 19.6%. Median PFS was 2.8 months (95% CI 2.5–3.6 months) and 6-month PFS was 6%. Median survival time was 5.9 months (95% CI 4.7–7.5 months). Toxicity was mainly haematological, with 88% and 26% grade 3–4 neutropenia and thrombopenia, respectively.

Despite an interesting response rate, the addition of valproic acid to VAC did not translate into adequate PFS in relapsing SCLC or SCLC refractory to platinum–etoposide.

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Introduction

Small cell lung cancer (SCLC) accounts for <15% of all lung cancer [1]. SCLC is usually initially chemotherapy (CT)-sensitive and first-line treatment is associated with high objective response rates (RRs) (45–75%). As observed in meta-analyses [2, 3], platinum derivatives and etoposide are the most active drugs and are currently considered as the standard for first-line treatment. However, in most of the patients, SCLC will recur and these patients will be candidates for second-line CT. A randomised trial [4] and systematic reviews [5, 6] suggested that better survival is observed in patients receiving second- or third-line treatment in comparison with supportive care only. Nevertheless, the efficacy of salvage CT depends on the response to first-line CT and the time interval before recurrence, with nonresponding patients (refractory) or those with a delay <3 months (resistant) having a poorer prognosis in comparison with those with sensitive tumours (objective response with a delay >3 months before recurrence), whatever the RR (p=0.0001) or median survival time (MST) (p=0.0035) [7].

There have been few phase III trials to determine the best CT regimen for relapsed SCLC, mainly testing VAC (vincristine, doxorubicin and cyclophosphamide) and topotecan. In a phase III trial, VON PAWEL et al. [8] compared VAC to oral topotecan in patients relapsing ⩾60 days after first-line CT. RR and MST were 18.3% and 24.7 weeks and 24.3% and 25 weeks, respectively, without any statistically significant difference. More grade 4 thrombocytopenia (p<0.001) and grade 3/4 anaemia (p<0.001) occurred in the topotecan arm. Two other randomised trials compared intravenous to oral topotecan [9, 10]. No significant differences were found for RR or MST. Haematological toxicity was important in both arms. Based on these data showing similar efficacy but increased toxicity with topotecan, VAC appears an adequate salvage CT.

As the results of second-line CT remain disappointing, original therapeutic concepts have to be considered. In a previous phase II study performed in malignant mesothelioma [11], we showed that adding valproic acid, a histone deacetylase (HDAC) inhibitor, to CT allowed an increase in RR in comparison with historical controls. As lysine deacetylase inhibitor, valproic acid decondenses chromatin and induces gene transcription. Since valproic acid has been widely used for treatment of epilepsy, its pharmacology and toxicology have been very well characterised, including potential interactions with conventional CT. In addition, we demonstrated a synergistic effect on the apoptotic rate in four SCLC cell lines by adding valproic acid to vindesine, doxorubicin and 2-chloroethylamine (the active cyclophosphamide metabolite) (data presented in the associated article by HUBAUX et al. [12]).

The primary objective of this phase II study was to determine whether epigenetic modulation with valproic acid in addition to a VAC regimen can improve 6-month progression-free survival (PFS).

Material and methods

This phase II study was an academic trial (EudraCT identifier number 2008-004278-41). The protocol is available on from www.elcwp.org and www.clinicaltrials.gov (identifier number NCT00759824). The study was approved by all ethical committees of the participating institutions as well as the national representatives.

To be eligible, patients had to fulfil the following eligibility criteria: histological or cytological SCLC diagnosis; SCLC refractory to a prior CT regimen including platinum derivatives (cisplatin or carboplatin) and etoposide, either primary refractory (immediate progression or recurrence <3 months after the end of previous CT) or secondary refractory (sensitive patients to platinum plus etoposide in first-line, progressing or recurring <3 months after reintroduction of the same CT regimen); at least one evaluable or measurable lesion; adequate haematological (neutrophils >2000 mm^{-3}, platelets >100 000 mm^{-3}), hepatic (serum bilirubin <1.5 mg per 100 mL and/or transaminases more than twice the normal range) and renal (serum creatinine <1.5 mg per 100 mL) function; availability for participating in the detailed follow-up of the protocol; and having provided signed informed consent. Criteria for ineligibility were: previous treatment with anthracycline, vinca-alkaloid derivatives or cyclophosphamide; performance status <60 on the Karnofsky scale; history of prior malignant tumour, except nonmelanoma skin cancer, in situ carcinoma of the cervix or of the bladder, or cured malignant tumour (>5-year disease free interval); history of HIV infection; abnormal coagulation tests (activated partial thromboplastin time (PTT), PTT or prothrombin time) and/or decreased fibrinogen; recent myocardial infarction (<3 months prior to date of diagnosis), congestive cardiac failure (ejection fraction of the left ventricle <50%) or uncontrolled cardiac arrhythmia; uncontrolled infectious disease; active epilepsy needing a specific treatment; concomitant treatment with monoamine oxidase inhibitors, carbamazepine, mefloquine, phenobarbital, primidone (desoxyphenobarbital), phenytoin, lamotrigine or zidovudine; pregnancy or refusal to use active contraception; known allergy to valproic acid and/or doxorubicin, cyclophosphamide or vindesine; and serious medical or psychological factors that might have prevented adherence to the treatment schedule.

Initial work-up consisted of history and physical examination including weight, height and surface area measurement, recording of performance status, complete blood sampling, and ECG with isotopic or

echographic left ventricular fraction assessment. Tumour assessment included chest radiography and computed tomography, computed tomography or echography of the liver and adrenal glands, brain magnetic resonance imaging or computed tomography, and bone isotopic scintigraphy (with radiography of suspected lesions). If positron emission tomography was performed, bone isotopic scintigraphy could be avoided and abdominal computed tomography or echography were performed in the case of positive lesions. Blood counts were repeated at least once between cycles. Complete blood sampling including valproic acid dosage, chest radiography, ECG, and physical examination were performed before each new course. A complete evaluation including the same tests as in the initial work-up was performed every three cycles. During follow-up, patients had to be seen every 2 months with a clinical examination, biology and chest radiography.

Treatment plan

After central registration at the European Lung Cancer Working Party (ELCWP) data centre, eligible patients received doxorubicin (45 mg·m^{-2} on day 1), cyclophosphamide (1 g·m^{-2} on day 1) and vindesine (3 mg·m^{-2} on day 1) every 3 weeks. The next course could be given after haematological recovery (neutrophils >1500 mm^{-3} and platelet count >100 000 mm^{-3}). If myelosuppression persisted at day 36, the patient went off treatment. Valproic acid was administered orally at a dose of 20–30 mg·kg^{-1}·day^{-1} during meals in order to obtain a serum concentration in the range of the recommended values for the treatment of epilepsy (50–100 µg·mL^{-1}). The administration of valproic acid began 1 week before first cycle of VAC and continued during the whole treatment. Response was assessed after three courses and responders pursued CT until the best response was achieved, there was unacceptable toxicity or the cumulative dose of doxorubicin exceeded 500 mg·m^{-2}. At progression, the choice of treatment was left at the discretion of the treating physicians.

The following dose adaptations were proposed during treatment. If during the previous course, the nadir counts of neutrophils and/or platelets was <500 or <25 000 mm^{-3}, respectively, the doses of doxorubicin, cyclophosphamide and vindesine were reduced to 75% for the next course. In the case of asymptomatic or transient cardiac dysrhythmias, or those not requiring therapy (World Health Organization (WHO) grade 1), no change in doxorubicin administration was needed. In the case of WHO grade 3 or 4 toxicity, the treatment had to be stopped. In cases of WHO grade 2 toxicity, treatment continuation was discussed on a case-by-case basis. Treatment was stopped in cases of left ventricular ejection fraction (LVEF) reduction >10% from the baseline or a reduction below the absolute value of 50%. In cases of WHO grade >2 peripheral polyneuropathy or constipation, vindesine was stopped. In case of stomatitis of WHO grade ⩾3, the doses of doxorubicin, cyclophosphamide and vindesine were reduced at 75% for next course. In cases of skin toxicity WHO grade ⩾2 attributable to valproic acid, it was stopped and VAC continued without dose adaptation. In cases of any other grade ⩾3 WHO toxicity, if doxorubicin, cyclophosphamide and/or vindesine was responsible, the treatment was stopped, except for alopecia, nausea and vomiting, or anaemia, and the patient went off trial; if valproic acid was responsible, this drug was stopped and VAC continued. If the plasma level of valproic acid was outside the therapeutic range, oral doses were adapted in order to obtain concentration between 50 and 100 µg·mL^{-1} without CT delay. In cases of overdose, valproic acid was stopped and reintroduced only if all adverse events had resolved.

Response was evaluated every three cycles according to WHO criteria. Early cancer progression and stopping treatment due to excessive toxicity were considered treatment failures. Response status was assessed during regular meetings of the groups by at least three independent observers. Survival and PFS were measured from the first day of registration until death (or the last date the patient was known to be alive) or date of first progression or death, respectively. Toxicity was evaluated according to WHO criteria.

Statistical considerations

The primary end-point was PFS rate at 6 months in order to assess whether the combined treatment was potentially active enough to be further studied. The sample size evaluation relied on the following assumptions. From previous trials [13–15], it was expected to reach a median PFS and 6-month PFS rate of 2.4 months and 18%, respectively, with second-line CT in refractory SCLC patients. It appeared reasonable to expect an increase of the 6-month PFS rate to 39% (hazard ratio 0.55) with valproic acid and VAC. If true, this increase should be detected by the present trial with α=10% and β=10% after inclusion of 43 patients assessable for PFS.

Results

Between November 2008 and December 2013, 64 patients were registered, of whom six were not eligible, either because no evidence of progression was documented at time of inclusion (n=4), or because of reduced LVEF or mixed histology (both n=1). The main characteristics of the 58 eligible patients are presented in table 1.

TABLE 1 Main patient characteristics of the 58 eligible patients included in the study	
Age years median (range)	60 (32–81)
Sex	
Male	38
Female	20
Karnofsky performance status	
60	4
70	13
80	18
90	13
100	10
Previous lines of CT	
1	38
>1	19
Free interval after last CT	
<3 months	37
>3 months	14
Missing	7
Data are presented as n unless otherwise stated. CT: chemotherapy.	

Seven patients did not receive any treatment and were excluded from the analyses, five because of rapid deterioration due to lung cancer and the cause of death of the last two patients was unknown. The number of CT cycles administered is reported in table 2. Valproic acid dosages were assessed regularly in order to maintain the blood concentration between 50 and 100 $\mu g \cdot mL^{-1}$. Of the 48 patients with valproic acid data available, 19 had at least one cycle with at least one measurement <50 $\mu g \cdot mL^{-1}$ and eight had at least one cycle with at least one measurement >100 $\mu g \cdot mL^{-1}$. If we consider all valproic acid data (all cycles, n=206), we found that doses <50 or >100 $\mu g \cdot mL^{-1}$ were found in 19% and 6% of the cases, respectively.

Best response statuses are shown in table 3. Including the 51 patients receiving at least one cycle of CT, the RR was 19.6% (95% CI 8.7–30.5%) and disease control rate was 29% (95% CI 19%–43%). Of the 15 patients reaching a partial response or stable disease after three CT cycles, 10 progressed at six cycles.

The median and 6-month PFS were 2.59 months (95% CI 2.39–2.85 months) and 5% (SE 3%) when considering the 58 eligible patients (intent-to-treat analysis). When restricting the analysis to the 51 patients receiving at least one CT injection, median and 6-month PFS times were 2.75 months (95% CI 2.46–3.61 months) and 6% (SE 3%) (figure 1). No statistical difference was found between patients with recurrence >3 months after the last CT and those with a time interval <3 months (p=0.52).

Among the 58 eligible patients, MST was 5.3 months (95% CI 3.8–7.1 months). At 6, 9 and 12 months, survival rates were 44% (SE 7%), 23% (SE 6%) and 5% (SE 4%). Of the 51 patients receiving CT, 48 died within 6 months after the date of registration. MST was 5.9 months (95% CI 4.7–7.5 months). At 6, 9 and 12 months, survival rates were 50% (SE 7%), 26% (SE 6%) and 6% (SE 4%). In addition, no significant difference was found according to delay from the last CT (>3 versus <3 months) (p=0.45).

TABLE 2 Number of chemotherapy cycles administered to the 58 eligible patients	
Cycles	**Patients**
0	7
1	9
2	6
3	20
4	
5	3
6	12
7	1
Data are presented as n unless otherwise stated. CT: chemotherapy.	

TABLE 3 Best response observed among the 51 eligible patients receiving VAC plus valproic acid in refractory/relapsing small cell lung cancer	
Type of response	**Subjects n**
Complete response	0
Partial response	10
No change	5
Progression	28
Early death due to cancer	2
Early death due to toxicity	1
High toxicity	2
Not evaluable	3
VAC: doxorubicin, vindesine and cyclophosphamide.	

As expected, toxicity was mainly haematological (table 4). Only one toxic death (septic shock in febrile neutropenia) was observed. Treatment has to be stopped for excessive toxicity in two cases because of hyperammonaemia related to carbonic anhydrase Va deficiency in one and alteration of the general status of the other, possibly due to chemotherapy.

Discussion

This phase II study assessing the additive role of an epigenetic modulation by valproic acid to a conventional chemotherapy regimen including doxorubicin, cyclophosphamide and vindesine did not reach its primary objective of improving 6-month PFS despite an interesting RR and 6-month overall survival.

The efficacy of conventional CT has reached a plateau for both SCLC and non-small cell lung cancer (NSCLC). In NSCLC, major therapeutic advances have been noted with targeted therapies, mainly focusing on *EGFR* activating mutations [16] and *ALK* translocations [17], or with active immunotherapy [18]. Although a few potential targets have been discovered in SCLC, these have not yet led to therapeutic achievements. This justifies the search for original concepts using old drugs with well-known therapeutic profiles, such as valproic acid.

Valproic acid belongs to the family of HDAC inhibitors. It has major advantages: it has been used for treating epilepsy for more than 40 years, and its pharmacology and toxicology are well characterised; and among classic antiepileptic drugs, it has the lowest interaction with CT [19]. Valproic acid showed anticancer activity in various haematological and solid tumour cell lines, and in mouse models. For example, valproic acid improved the anticancer activity of cisplatin and etoposide in SCLC cell lines [20]. HDAC inhibitors have mainly been tested in haematological malignancies, with some positive results [21]. A few phase I studies have been performed in solid tumours [22–25]. In all but one study, valproic acid was given over a short period of time at a high dose and, consequently, with substantial neurotoxicity.
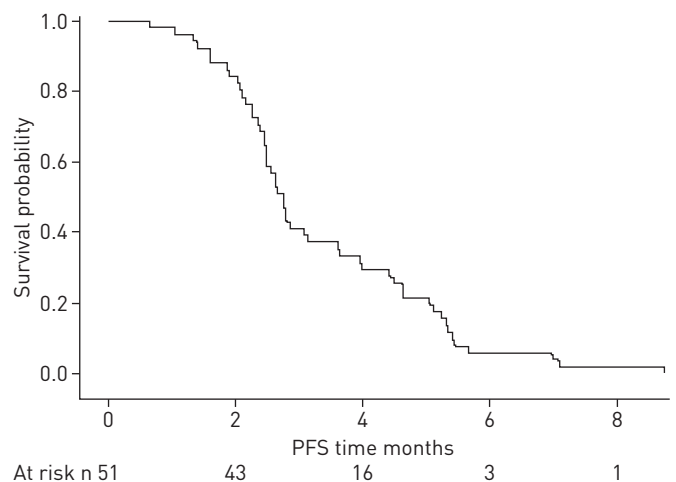

FIGURE 1 Progression-free survival (PFS) time in the 51 patients receiving at least one cycle of chemotherapy. Median PFS was 2.75 months (95% CI 2.46–3.61 months) and 6-month PFS was 6% (SE 3%).

TABLE 4 Worst grade 3–4 toxicity observed during VAC plus valproic acid administration in relapsed/refractory small cell lung cancer patients	
Nonhaematological toxicity	
Nausea and vomiting	1 (2)
Infection	2 (4)
Bleeding	1 (2)
Neurological encephalopathy	2 (4)
Respiratory	3 (7)
Cardiac	1 (2)
Febrile neutropenia	13 (26)
Haematological toxicity	
Leukopenia	43 (86)
Thrombopenia	13 (26)
Neutropenia	44 (88)

Data are presented as n (%). VAC: doxorubicin, vindesine and cyclophosphamide.

Nevertheless, our group was able to demonstrate the value of an epigenetic modulation by valproic acid in malignant pleural mesothelioma [26]. In heavily pre-treated patients, a combination of doxorubicin and valproic acid showed an interesting 16% response rate, while two previous studies demonstrated that doxorubicin alone was inactive in this setting.

Despite all this evidence, the addition of valproic acid to VAC did not result in improved PFS, the primary end-point of the present study. However, the RR (19.6%) and median overall survival (5.3 months) were comparable to those reported in a recent systematic review in resistant/refractory SCLC: 14.8% and 5.45 months, respectively [7]. If our results in terms of PFS and MST appear worse than in previous randomised trials that also included sensitive and refractory SCLC (table 5), it must be taken into consideration that our study included tumours refractory to platinum–etoposide, which have an intrinsically poorer prognosis.

Do we have any explanation for the failure of this approach in SCLC, in contrast to mesothelioma? We can consider various possibilities. First, relapsing SCLC could be very resistant tumours, particularly in the present study, where sensitive tumours to first-line CT were excluded, and that modulating gene expression cannot be sufficient to restore chemosensitivity. Despite very interesting preclinical data [20], it remains difficult to extrapolate from results obtained in cell lines to humans in the clinic. It could be hypothesised that HDACs involved in gene regulation in relapsed SCLC are not those modulated by valproic acid. Another option is that the dosage of valproic acid chosen in this study, corresponding to the

First author [ref.]	Regimen	RR %	PFS	MST	6-month survival %	1-year survival %
TABLE 5 Response rate (RR), progression-free survival (PFS) and survival in randomised trials with salvage chemotherapy for relapsing small cell lung cancer						
Von Pawel [8]	VAC	18	12.3 weeks	25 weeks	45	14.4
	Topotecan	24	13.3 weeks	25 weeks	47	14.2
O'Brien [4]	Topotecan	7	16.3 weeks	25.9 weeks	49	
	BSC			13.9 weeks	26	
Eckardt [9]	Topotecan oral	18	11.9 weeks	33 weeks		32.6
	Topotecan IV	22	14.6 weeks	35 weeks		29.2
Inoue [27]	Amrubicin	38	3.5 months	8.1 months		
	Topotecan	13	2.2 months	8.4 months		
Jotte [28]	Amrubicin	44	4.5 months	9.2 months	60	36
	Topotecan	15	3.3 months	7.6 months	54	33
Present study	VAC-VA	20	2.6 months	5.3 months	50	6

MST: median survival time; VAC: doxorubicin, vindesine and cyclophosphamide; BSC: best supportive care; VA: valproic acid.

one used for treating epilepsy, was below the concentration needed to obtain HDAC inhibition and that the 1 mM used in cell lines was higher than the one obtained in clinical practice [20]. In addition, we observed that in 19% of the measurements, valproic acid dosages were below the recommended value at least once during CT. However, as this is not uniform throughout all cycles, it seems unlikely that low dosages of valproic acid could be implicated in the limited efficacy of VAC.

A last concern could be the choice of vindesine instead of vincristine in the triplet combination. Vindesine is commonly used in SCLC. The ELCWP conducted randomised trials in first-line therapy comparing etoposide plus vindesine with and without cisplatin [29], assessing the role of accelerated CT (vindesine, ifosfamide and epirubicin) [30] with maintenance therapy with etoposide and vindesine [31]. In the second line, vindesine showed activity when added to cisplatin for refractory [32] or recurrent SCLC [33]. In all these studies, toxicity, particularly neurotoxicity, was manageable. In the few trials comparing vindesine to vincristine, including a randomised trial in combination with cyclophosphamide as first-line chemotherapy in 116 patients with SCLC [34], similar toxicity and efficacy were noted.

In conclusion, epigenetic modulation with valproic acid failed to improve the therapeutic efficacy of a conventional CT regimen for relapsed refractory SCLC, preventing further evaluation of this combination. However, as preclinical data are showing promising results, more biological information is needed in order to pursue research in this field.

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