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Randomised phase II study of amrubicin as single agent or in combination with cisplatin versus cisplatin etoposide as first-line treatment in patients with extensive stage small cell lung cancer – EORTC 08062 ☆

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ABSTRACT

Purpose: The EORTC 08062 phase II randomised trial investigated the activity and safety of single agent amrubicin, cisplatin combined with amrubicin, and cisplatin combined with etoposide as first line treatment in extensive disease (ED) small cell lung cancer (SCLC).

Patients and methods: Eligible patients with previously untreated ED-SCLC, WHO performance status (PS) 0–2 and measurable disease were randomised to 3 weekly cycles of either amrubicin alone 45 mg/m^2 i.v. day(d) 1–3 (A), cisplatin 60 mg/m^2 i.v. d1 and amrubicin 40 mg/m^2 i.v. d1–3 (PA), or cisplatin 75 mg/m^2 i.v. d1 and etoposide 100 mg/m^2 d1, d2–3 i.v./po (PE). The primary end-point was overall response rate (ORR) as assessed by local investigators (RECIST1.0 criteria). Secondary end-points were treatment toxicity, progression-free survival and overall survival.

Results: The number of randomised/eligible patients who started treatment was 33/28 in A, 33/30 in PA and 33/30 in PE, respectively. Grade (G) $\geqslant$3 haematological toxicity in A, PA and PE was neutropenia (73%, 73%, 69%); thrombocytopenia (17%, 15%, 9.4%), anaemia (10%, 15%, 3.1%) and febrile neutropenia (13%, 18%, 6%). Early deaths, including treatment

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related, occurred in 1, 3 and 3 patients in A, PA and PE arms, respectively. Cardiac toxicity did not differ among the 3 arms. Out of 88 eligible patients who started treatment, ORR was 61%, (90% 1-sided confidence intervals [CI] 47–100%), 77% (CI 64–100%) and 63%, (CI 50–100%) for A, PA and PE respectively.

Conclusion: All regimens were active and PA met the criteria for further investigation, despite slightly higher haematological toxicity.

1. Introduction

Small cell lung cancer (SCLC) represents around 15–20% of all lung carcinomas.[1] The mainstay of treatment for the majority of patients with SCLC remains chemotherapy, resulting in major responses in most patients. Standard drugs available for the treatment of SCLC include cyclophosphamide, doxorubicin, methotrexate, etoposide, vincristine, cisplatin and carboplatin. Using these in combination, response rates of 70% or more have been reported. Combination chemotherapy for SCLC has been reported to be superior to single agent treatment.[1,2] The superiority of cisplatin plus etoposide over an anthracycline-based regimen was demonstrated by a randomised study of 436 patients in Norway.[3] With conventional drugs the role of the number of courses, high dose, dose intensity, carboplatin, maintenance therapy and cross regimens has been explored, meta-analysed and reviewed.[4–6] However, this has not influenced the standard of management, which continues to be a platinum based regimen (cisplatin or carboplatin) with etoposide for 4–6 courses depending on response and tolerability.

More recent drugs used in combination with a platin include gemcitabine,[7] topotecan[8] and irinotecan[9] have not changed standard therapies. Addition of a third drug in the form of a taxane has caused more myelosuppression.[10–12] New treatments e.g. pemetrexed, targeted agent bevacuzimab, or broadly targeted agents like thalidomide were also found to be ineffective.[13,14]

Amrubicin is a synthetic anthracycline that has demonstrated more potent antitumour activity than doxorubicin in several human tumour xenografts implanted in nude mice.[15] Amrubicin and its highly active 13-hydroxy metabolite amrubicinol are more potent DNA topoisomerase II inhibitors than doxorubicin. Amrubicinol is 10–100 times more cytotoxic than amrubicin due to its selective distribution in tumours.[16]

In preclinical studies, the acute toxicity of amrubicin was found qualitatively comparable to that of doxorubicin. However, amrubicin did not exhibit the chronic cardiotoxic effects in rabbits and dogs observed with doxorubicin.[17]

At the time of protocol writing approximately 600 patients in the Japanese clinical trials received amrubicin alone or in combination with other chemotherapy agents prior to its approval. Approximately 6,500 patients with SCLC or NSCLC had been treated with amrubicin in Japan since marketing approval in 2002. A Phase 2 study was conducted in untreated ED-SCLC patients using single agent daily ×3 schedule (45 mg/m^2/d). Of the 33 eligible patients, the overall response rate (ORR) was 76% with a median survival time (MST) of 11.7 months. The 1-year and 2-year survival rates were 48.5% and 20.2%.[18]

The combination of amrubicin and cisplatin was tested in a Phase 1–2 study in 41 untreated patients with ED-SCLC. The ORR was 87.8%, the MST was 13.6 months, and the 2-year survival rate was 17.6%.[19] The majority of patients developed neutropenia, but cardiotoxicity typical for anthracyclines was uncommon.

The EORTC 08062 study was designed to confirm the activity of amrubicin in combination with cisplatin as the first line treatment in ED-SCLC in a non-Japanese population. The recommended phase II doses of combination cisplatin 60 mg/m^2 on day 1, amrubicin 40 mg/m^2 on days 1–3 was the regimen used in the PA schedule.[19] As single agent amrubicin appeared to give results comparable to a standard PE combination, we felt it reasonable to include a single agent amrubicin arm. As PA contained cisplatin, cisplatin was also chosen rather than carboplatin for the standard arm in this trial. The cisplatin, etoposide, PE, chosen was as in Sundstrom et al. described above[3]

This trial aimed to document the activity and safety of single agent A, PA, and PE as first line treatment in ED-SCLC with a view to choosing the best amrubicin arm to be further compared to standard treatment in 1st line ED-SCLC.

2. Patients and methods

2.1. General objective and outline

This was an open label randomised 3-arm multicentre late phase II study. After completion of screening investigations, eligible patients were stratified at randomisation by institution, sex, and WHO PS (0–1 versus 2) to receive:

Arm 1: 3-weekly cycles of amrubicin (45 mg/m^2, days 1–3);
Arm 2: 3-weekly cycles of cisplatin (60 mg/m^2, day 1) and amrubicin (40 mg/m^2 days 1–3);
Arm 3: 3-weekly cycles of cisplatin (75 mg/m^2, day 1) and etoposide (intravenous injection 100 mg/m^2 on day 1, oral administration 200 mg/m^2 on days 2–3) or etoposide i.v. 100 mg/m^2 for three consecutive days.

Treatment started within 7 days of randomisation. Patients were treated until progressive disease, excessive toxicity, patient refusal or clinical decision. The disease was assessed every 2 cycles until documented progression, and treatment side-effects were assessed for each cycle of therapy.

Prophylactic antibiotics and growth factors were not dictated in the original version of the protocol. Due to an update in the amrubicin investigator's brochure during the study, the protocol was amended to provide growth factor use for the remaining third of patients to be recruited.

The protocol was approved by the Ethical Committees of each participating institution (see Acknowledgement) and written informed consent was obtained from every patient.

A general outline and CONSORT diagram are provided in Fig. 1.

2.2. *Patient selection criteria*

Patients were eligible if they had histologically/cytologically proven ED-SCLC as defined by Veterans Administration Lung Group Study,[20] WHO performance status 0–2, measurable disease according to RECIST version 1[21] (imaging within 28 days prior to entry), age $\geqslant$18 years, normal baseline cardiac function (as assessed by left ventricular ejection fraction measurement according to institution normals), no prior systemic chemotherapy for SCLC, and no radiotherapy for SCLC within 14 days before treatment.

Adequate haematological function (ANC $\geqslant 1.5 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, Hb $\geqslant$ 9 g/dL) was required as was a creatinine clearance: $\geqslant$60 ml/min (Cockroft and Gault), and good hepatobiliary function (ALT/AST <2.5 × upper limit of normal); all blood tests performed within 14 days of patient inclusion.

Patients with known interstitial lung disease or pulmonary fibrosis were excluded from this study.

Prior malignancies were allowed when the patient had been disease free for >5 years, or in case of a non-melanoma skin cancer or in-situ carcinoma of the cervix. Absence of uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrolment New York Heart Association Class III or IV heart failure; uncontrolled angina; clinical significant pericardial disease or cardiac amyloidosis; absence of any psychological, familial, sociological or geographical condition potentially hampering compliance were all necessary for inclusion.

An appropriate method of contraception was necessary. Written informed consent was taken before randomisation, according to ICH/EU GCP, and national/local regulations. The protocol, patient information sheet and consent forms were translated and approved by all national/regional ethics and research board in the UK, Belgium, The Netherlands, Italy and Poland.

2.3. *End-points*

Primary end-point was ORR defined as proportion of patients responding (CR/PR) to the treatment as assessed by local

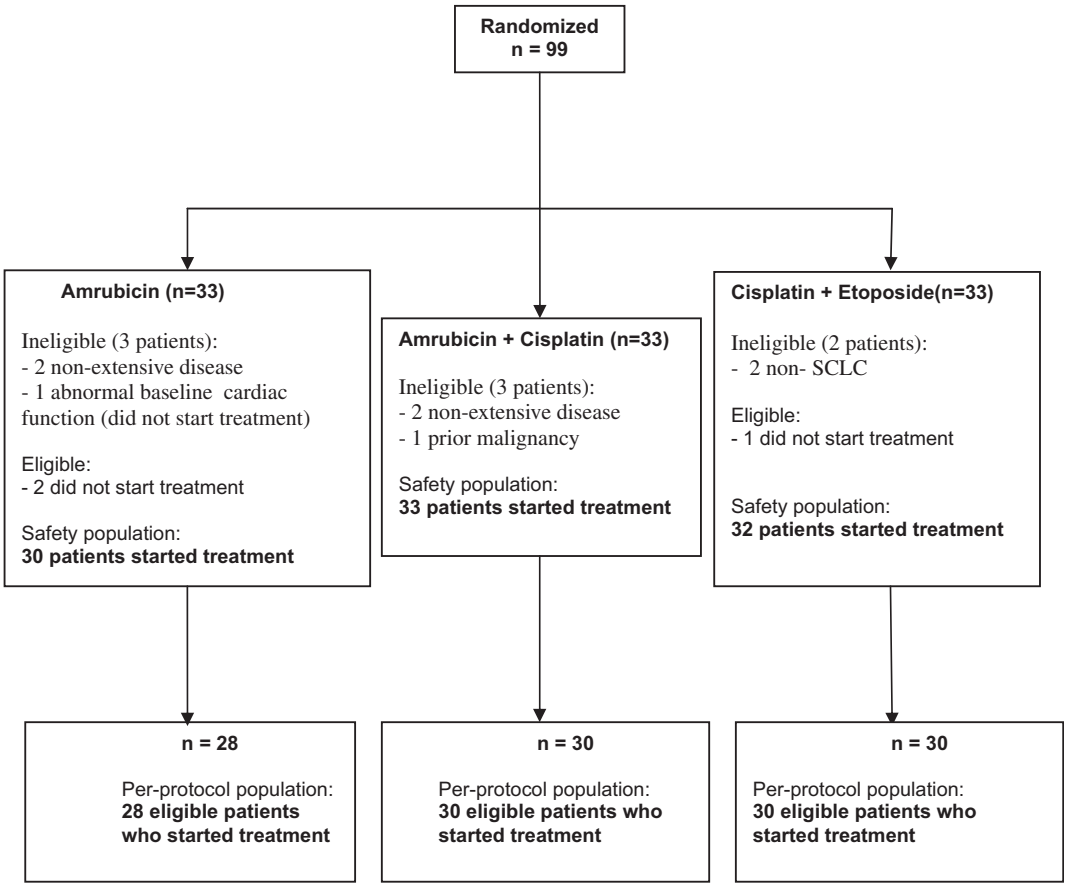

Fig. 1 – CONSORT diagram and patient flow.

investigators using RECIST 1.0.[21] Secondary end-points were toxicity of treatment (including cardiotoxicity) scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, progression-free survival (PFS) and overall survival (OS).

2.4. Sample size

To determine the "success of treatment" in an arm, a one step Fleming design was used with α set at 0.10 and β at 0.10. P_0 was set at 55% and defined as the largest response rate which if true implied that the arm did not warrant further investigation. P_1 was set at 80% and defined as the lowest response rate which if true implied that the arm did warrant further investigation. Response rate was investigator reported. Under this hypothesis the total sample size was calculated to be 27 eligible patients who started treatment in each arm. If 19 responses out of 27 would be obtained, the arm should be further investigated. In case of more than 27 eligible patients who started treatment in an arm, then the arm should be further investigated when the lower bound of 90% 1-sided confidence interval for the response rate would be >55%.

2.5. Patient populations for safety and efficacy analyses

In this article, toxicity was reported on 95 patients who started treatment (safety population), including patients subsequently found ineligible. Efficacy was reported on 88 eligible patients who started treatment (per-protocol population). Details can be found in general outline and CONSORT diagram (Fig. 1).

3. Results

The study was activated in November 2006 and closed to enrollment in July 2009. Accrual proceeded as planned. CONSORT diagram is depicted in Fig. 1. In total 99 patients were randomised from 5 countries and 16 centres. A total of 8 pa-

Table 1 – Baseline characteristics (patients who started treatment regardless of eligibility).

	Treatment			Total (N = 95) N (%)
	Amrubicin (N = 30) N (%)	Amrubicin + cisplatin (N = 33) N (%)	Cisplatin + etoposide (N = 32) N (%)	
Sex[a]				
Male	19 (63.3)	21 (63.6)	21 (65.6)	61 (64.2)
Female	11 (36.7)	12 (36.4)	11 (34.4)	34 (35.8)
Performance status[a]				
0	7 (23.3)	5 (15.2)	4 (12.5)	16 (16.8)
1	19 (63.3)	22 (66.7)	23 (71.9)	64 (67.4)
2	4 (13.3)	6 (18.2)	5 (15.6)	15 (15.8)
Age category				
36–45 years	1 (3.3)	1 (3.0)	3 (9.4)	5 (5.3)
46–55 years	7 (23.3)	11 (33.3)	7 (21.9)	25 (26.3)
56–65 years	15 (50.0)	14 (42.4)	15 (46.9)	44 (46.3)
66–75 years	5 (16.7)	6 (18.2)	7 (21.9)	18 (18.9)
>75 years	2 (6.7)	1 (3.0)	0	3 (3.2)
Presence of non-malignant associated chronic disease				
Yes	16 (53.3)	25 (75.8)	17 (53.1)	58 (61.1)
Patient is a smoker currently				
Yes	10 (33.3)	13 (39.4)	17 (53.1)	40 (42.1)
Liver metastasis				
Yes	19 (63.3)	19 (57.6)	17 (53.1)	55 (57.9)
Bone metastasis				
Yes	6 (20.0)	7 (21.2)	7 (21.9)	20 (21.1)
Brain metastasis				
Yes	3 (10.0)	3 (9.1)	7 (21.9)	13 (13.7)
Number of metastatic sites				
1	3 (10.0)	4 (12.1)	5 (15.6)	12 (12.6)
2	16 (53.3)	11 (33.3)	10 (31.3)	37 (38.9)
3	6 (20.0)	13 (39.4)	11 (34.4)	30 (31.6)
4	3 (10.0)	3 (9.1)	5 (15.6)	11 (11.6)
5	1 (3.3)	0	0	1 (1.1)
6	0	1 (3.0)	0	1 (1.1)
7	0	0	1 (3.1)	1 (1.1)
None	1 (3.3)	1 (3.0)	0	2 (2.1)

[a] Stratification factors.

tients were ineligible, 3, 3, and 2 in A, PA and PE respectively. The reasons for ineligibility were, 4 patients had non-extensive disease (2, 2 and 0 in A, PA and PE respectively), 2 patients in PE had non-SCLC, 1 patient in A had abnormal baseline cardiac function and 1 patient in PA had recent prior malignancy. Four patients did not start treatment 3, 0, and 1 in A, PA and PE, respectively. A total of 88 patients were eligible and started treatment, 28 (85%), 30 (91%) and 30 (91%) in A, PA and PE, respectively. The median follow-up time of 88 patients who were eligible and started the treatment is 17.4 months. Fig. 1 and Table 1 shows eligibility and baseline characteristics.

The groups were well balanced for all the major prognostic characteristics with most patients having a PS of 1 and age between 55 and 65 years. The sites of metastatic disease were well balanced in frequency between the 3 treatments apart from an imbalance in brain metastases (10%, 9% and 22% in A, PA and PE, respectively).

The number of cycles of treatment given is shown in Table 2. The median number of cycles was 6 in all arms with one patient on single agent amrubicin carrying on up to 22 cycles with growth factor support. The relative dose intensity for A was 91% (range 46–101%), for PA was 89% (50–101%) and 90% (32–101%), and 89% (18–104%) and 92% (46–105%) for PE.

Less prophylactic antibiotics and growth factors were used with PE than with either amrubicin arm. Prophylactic antibiotics were used in a number of patients (40%, 45% and 28% in A, PA and PE) (Table 2). Following toxicity profile data from a large phase III study in the second line SCLC (NCT00547651), prophylactic growth factors became mandatory in all arms for the first cycle to increase patient safety and the protocol was amended after 67/95 patients had been randomised. As shown in Table 2, a total of only 30.5% of patients received prophylactic growth factors at cycle 1, 36.7% (2/20 before amendment, 9/10 after) in A, 39.4% (5/24 before amendment 8/9 after) in PA, and 15.6% (2/23 before amendment, 3/9 after) in PE.

Myelosuppression was the main toxicity as shown in Table 3 with 74%, 73% and 69% of patients experiencing grade 3 or 4 neutropenia, including 13%, 15% and 6% of patients experiencing grade 3–5 febrile neutropenia in A, PA and PE, respectively, despite growth factor availability. Growth factor use decreased the number of grade 3–5 febrile neutropenia from 9/67 (13.5%) to 3/28 (10.7%) cases in total and prevented grade 4–5 febrile neutropenia (4.5% before and no cases after the amendment). One responding patient in the PA arm died of acute respiratory failure after 5 cycles (not reported with early deaths). Neither interstitial pneumonitis nor pulmonary fibrosis had been diagnosed before the onset of SCLC. Changes on the baseline CT scan lung fields were thought to represent lymphangitis carcinomatosis. No post mortem was permitted but a drug related pulmonary toxicity was assumed. Cardiotoxicity did not differ among the 3 arms but there was more pre-existing comorbidity in PA arm (Table 1).

Table 2 – Relative dose intensity and dose reductions – the use of growth factors and antibiotics.

	Treatment			Total (*N* = 95)
	Amrubicin (*N* = 30)	Amrubicin + cisplatin (*N* = 33)	Cisplatin + etoposide (*N* = 32)	
Number of cycles received				
Median	6	6	6	
Range	1–22	1–8	1–22	
Amrubicin relative dose intensity				
Median	91.1	89.9		90.7
Range	45.9–101.3	32.2–100.6		32.2–101.3
No. obs.	30	33	0	63
Cisplatin relative dose intensity				
Median		88.6	89.3	88.6
Range		50.3–101.0	17.9–103.7	17.9–103.7
No. obs.	0	33	32	65
Etoposide relative dose intensity				
Median			91.8	91.8
Range			46.2–105.2	46.2–105.2
No. obs.	0	0	32	32
Number of cycles with prophylactic antibiotic therapy given during chemo				
1	5 (16.7)	3 (9.1)	3 (9.4)	11 (11.6)
2	1 (3.3)	3 (9.1)	2 (6.3)	6 (6.3)
3	2 (6.7)	3 (9.1)	1 (3.1)	6 (6.3)
4–8	4 (13.3)	6 (18.2)	3 (9.4)	13 (13.7)
None	18 (60.0)	18 (54.5)	23 (71.9)	59 (62.1)
GCSF during cycle 1 before amendment				
Prophylactic, *n* = 67	2/20	5/24	2/23	9/67
GCSF during cycle 1 after amendment				
Prophylactic, *n* = 28	9/10	8/9	3/9	20/28
Total (GCSF during cycle 1 before and after amendment)				
prophylactic	11 (36.7)	13 (39.4)	5 (15.6)	29 (30.5)
None	19 (63.3)	20 (60.6)	27 (84.4)	66 (69.5)

Seven early deaths were reported (1, 3, and 3 patients in A, PA and PE), 4 of whom were treatment related (1 in A, 2 in PA and 1 in PE) and 3 due to other causes: 1 ischaemic cerebrovascular accident, 1 respiratory insufficiency and 1 pneumonia not clearly defined as toxicity or progression .

The investigator ORR was highest with PA (77%, CI 64–100%; Table 4). A and PE had similar response rates of 61% (CI 47–100%) and 63% (CI 50–100%), respectively. As per protocol, the independent radiology review was planned on all 71 (23, 25 and 23 patients in A, PA and PE) patients who have at least SD. Only 60 patients (18, 21 and 21 in A, PA and PE, respectively) were successfully reviewed independently. Eleven patients (5, 4, 2 in A, PA and PE, respectively) were not reviewed due to missing baseline or follow up scans. The number of patients with verified responses was 13, 19 and 17 in A, PA, PE, respectively. One patient with a PR in PA was a confirmed CR on independent review and 4, 1 and 3 patients with SD in A, PA and PE were changed to PR. No patients with PR were downgraded to either SD or PD on review. In general, investigators underscored the PR rates, but the response rate as assessed by an independent reviewer appears lower at 61%, 67% and 67% for A, PA and PE, respectively. This was because 11 patients reported to have either PR (8 patients, 4, 4, 0 in A, PA and PE) or SD (3 patients, 1, 0, 2 in A, PA and PE) by investigators had missing scans and were not assessable by independent review.

Secondary endpoints including the PFS and OS figures are shown in Figs. 2 and 3 and appear to be similar across the arms. Median OS (95% 2-sided confidence interval) was 11.1 months (7.9–14.5), 11.1 months (7.3–16.3) and 10 months

Table 3 – Grade ⩾3 toxicity.

	Treatment			Total (N = 95)
	Amrubicin (N = 30) N (%)	Amrubicin + cisplatin (N = 33) N (%)	Cisplatin + etoposide (N = 32) N (%)	N (%)
WBC				
Grade 3	7 (23.3)	10 (30.3)	9 (28.1)	26 (27.4)
Grade 4	8 (26.7)	9 (27.3)	3 (9.4)	20 (21.1)
Neutropenia				
Grade 3	8 (26.7)	7 (21.2)	10 (31.3)	25 (26.3)
Grade 4	14 (46.7)	17 (51.5)	12 (37.5)	43 (45.1)
Thrombocytopenia				
Grade 3	4 (13.3)	3 (9.1)	3 (9.4)	10 (10.5)
Grade 4	1 (3.3)	2 (6.1)	0	3 (3.2)
Anaemia				
Grade 3	2 (7)	4 (12)	1 (3)	7 (7)
Grade 4	1 (3)	1 (3)	0	2 (2)
Febrile neutropenia				
Grade 3	3 (10.0)	4 (12.1)	2 (6.3)	9 (9.5)
Grade 4	1 (3.3)	1 (3.0)	0	2 (2.1)
Grade 5	0	1 (3.0)	0	1 (1.1)
Cardiac ischaemia/infarction				
Grade 4	0	1 (3.0)	0	1 (1.1)
Mucositis/stomatitis				
Grade 3	2 (6.7)	2 (6.1)	1 (3.1)	5 (5.3)
Diarrhoea				
Grade 3	0	2 (6.1)	2 (6.3)	4 (4.2)
Vomiting				
Grade 3	1 (3.3)	2 (6.1)	1 (3.1)	4 (4.2)
Neuropathy: motor/sensory/other				
Grade 3	0/0/3	0/1/2	1/0/0	1 (1.1)
Grade 4	0/0/0	1/0/0	0/0/1	1 (1.1)
Other infection				
Grade 3	7 (23.3)	5 (15.2)	4 (12.5)	16 (16.8)
Grade 4	0	1 (3.0)	0	1 (1.1)
Grade 5	1 (3.3)	0	0	1 (1.1)
Dyspnea (shortness of breath)				
Grade 3/4	0	3/4 (9.1/3.0)	2 (6.3)	5 (5.3)
Pulmonary fibrosis				
Grade 5	0	1 (3.0)	0	1 (1.1)
Other pulmonary				
Grade 3	0	1 (3.0)	1 (3.1)	2 (2.1)
Grade 5	0	1 (3.0)	0	1 (1.1)
All other toxicity				
Grade 3	4 (13.3)	5 (15.2)	5 (15.6)	14 (14.7)
Grade 4	3 (10.0)	6 (18.2)	2 (6.3)	11 (11.6)
Grade 5	2 (6.7)	2 (6.1)	3 (9.4)	7 (7.4)

Table 4 – overall response rate as assessed by local investigators (primary endpoint) and an independent reviewer.

	Treatment			Total (N = 88)
	Amrubicin (N = 28)	Amrubicin + cisplatin (N = 30)	Cisplatin + etoposide (N = 30)	
	N (%)	N (%)	N (%)	N (%)
Best overall objective response (investigators)				
PR[a]	17 (60.7)	23 (76.7)	19 (63.3)	59 (67.0)
SD[a]	6 (21.4)	2 (6.7)	4 (13.3)	12 (13.6)
PD	3 (10.7)	2 (6.7)	4 (13.3)	9 (10.2)
Early death-malignant disease	0	1 (3.3)	0	1 (1.1)
Early death-toxicity	1 (3.6)	1 (3.3)	1 (3.3)	3 (3.4)
Early death-other	0	0	2 (6.7)	2 (2.3)
Not Assessable	1 (3.6)	1 (3.3)	0	2 (2.3)
Best Overall Response independent reviewer				
CR	0	1 (3.3)	0	1 (1.1)
PR	17 (60.7)	19 (63.3)	20 (66.7)	56 (63.6)
SD	1 (3.6)	1 (3.3)	1 (3.3)	3 (3.4)
Not assessable (IR) due to missing baseline scan	3 (10.7)	2 (6.7)	2 (6.7)	7 (8.0)
Not assessable (IR) due to missing or incompatible FU scan	2 (7.1)	2 (6.7)	0	4 (4.5)

The best overall response rates as assessed by investigators (Exact one-sided 90% Confidence Intervals): 60.7% (47%, 100%), 76.7% (64%, 100%) and 63.3% (50%, 100%) in A, PA and PE, respectively.

[a] Patients were independently assessed.

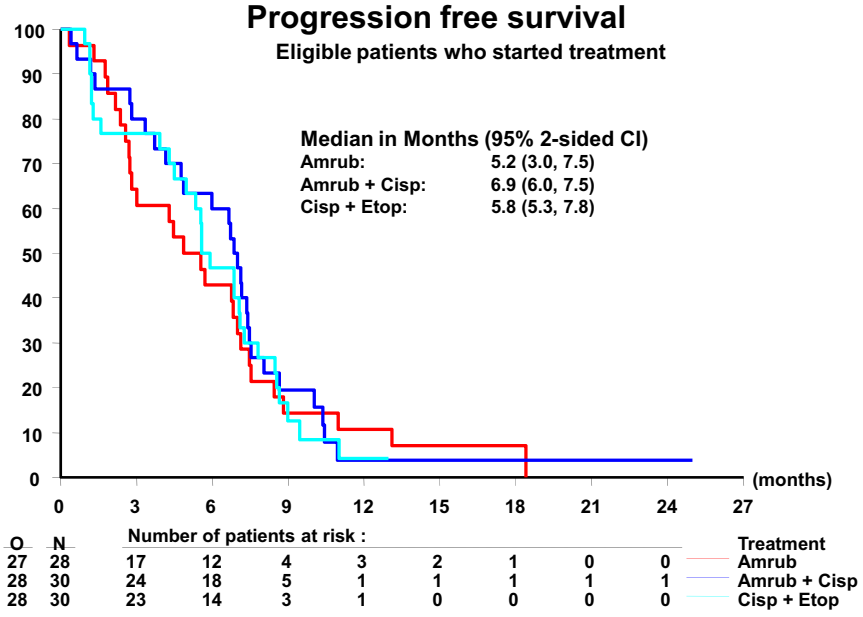

Fig. 2 – Progression free survival.

(9.2–13.3), and median PFS (95% 2-sided confidence interval) was 5.2 months (3.0–7.5), 6.9 months (6.0–7.5) and 5.8 months (5.3–7.8) months in A, PA and PE, respectively. Notably, this observation is based on small numbers of events, 26, 22 and 22 deaths for OS and 27, 28 and 28 deaths or PD for PFS in A, PA and PE, respectively. More patients progressed in the liver when initially treated with A than with PA or PE (23.3% versus 6.1% versus 9.4%, respectively), and a similar trend was noted in the brain (30% versus 15.2% versus 12.5%, respectively) for A, PA and PE. Bone was the site of progressive disease in 16.7%, 3% and 9.4% of patients receiving A, PA and PE.

Prophylactic cranial irradiation was not dictated in the protocol but the use of subsequent radiotherapy was documented in 33%, 45.5% and 46.9% of patients treated with A, PA and PE, respectively. About 75% of patients had some form of subsequent therapy; second line chemotherapy was used in 43.3%, 48.5% and 43.8% of patients initially treated with A, PA and PE, respectively.

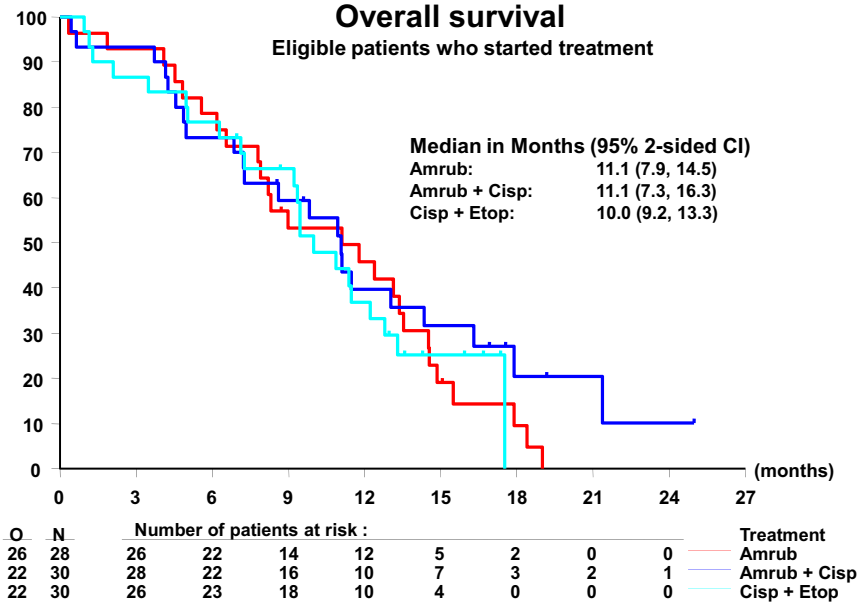

Fig. 3 – Overall survival.

4. Discussion

ED-SCLC remains a frustrating disease. Many trials have tested new combinations and approaches without making any impact on OS.[5] OS improvement remains the ultimate goal as unlike other chemosensitive cancers, second line treatment is not an option for many patients due to rapid disease progression and poor PS.[22] Third line treatment for SCLC is used very scarcely.

In this trial a PA regimen was associated with a higher ORR (the primary end-point in this study) compared to two other 2 regimens (A alone or PE). However, the results of an independent review suggest that the difference for ORR could be small and this is supported by the similarity of PFS and OS. However, due to small number of patients, these analyses have low statistical power. The results of the standard arm in this study are within the expected range. The most recent study comparing an anthracycline regimen to PE (with etoposide given orally day 2–3) showed a median survival of 8.4 months and one-year overall survival of 16% (with 30% of crossover to second line chemotherapy).[3,23] Our figures with smaller numbers are comparable, with OS of 10 months and one-year survival of 30%, with around 43% of second line use. The baseline characteristics were fairly well balanced – brain and liver metastases were more common in the A arm while chronic disease was more frequent in the PA arm.

Of the 71 patients who had a CR, PR or SD as best response, only 60 patients underwent independent radiology review. The remainder of the patients were not assessable due to either missing baseline scans or incomplete follow up scans. The results show that the local investigators were conservative in response assessment. The independent review when intended as a sensitivity analysis – did not change the conclusions of the study but gave information on underdiagnosis of bone metastases detected by their sclerotic healing in the course of patients presenting PR. Bone metastases like bone marrow involvement is probably present in more patients than expected. In our study CT scanning was the only mandatory staging investigation.

Grade 3–4 haematologic toxicity was increased in the amrubicin containing treatment arms and so was growth factor and antibiotic use. Other toxicities were predictable, with one case of acute respiratory failure probably due to amrubicin induced pulmonary toxicity. Of note, pre-existing pulmonary fibrosis or interstitial disease is a contraindication to the drug.

In this study single agent amrubicin proved to be an active and well tolerated drug – probably the most active single agent to date, and this should be explored further. In addition a few responding patients were able to tolerate prolonged treatment with amrubicin. Amrubicin would thus be a candidate for testing in a cross over maintenance trial. While this study did reach its end-point for the PA combination, it also confirmed that PE is a robust regimen that will remain a standard therapy.

Clinical trials

This study was registered in: ClinicalTrials Gov. No. NCT00227630.

Conflict of interest statement

MOB has done paid advisory work for Celgene. PL has received financial support for speaking by Pharmion 2007. No declared conflict of interest from the other authors.

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