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Original Paper

Long-term Follow-up of a Randomised Trial of Combined Chemoradiotherapy Induction Treatment, With and Without Maintenance Chemotherapy in Patients with Small Cell Carcinoma of the Lung

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The toxicity and efficacy of concomitant chemotherapy and radiotherapy as induction therapy was evaluated in patients with previously untreated small cell carcinoma of the lung (SCLC), and in responding patients the value of maintenance chemotherapy was examined. 202 patients received induction chemotherapy with cisplatin and etoposide (EP), in combination with cranial and local radiotherapy. 85 patients (42%) developed grades III and IV myelosuppression, the main toxicity of induction treatment. Of the 154 responding patients, 129 were randomised to maintenance chemotherapy with vincristine, doxorubicin and cyclophosphamide (VAC) or no further treatment. The response rate for the limited disease patients (LD) was 87%, 62% achieving a complete response (CR) and the response rate for extensive disease patients (ED) was 68%, with 26% achieving a CR. 17 patients (11%) completed 10 courses of maintenance chemotherapy. 32 patients (57%) developed grade III and IV neutropenia. Median survival for all patients was 53 weeks (LD, 70 weeks; ED, 42.5 weeks). There was no significant difference in overall survival (OS) or disease-free survival (DFS) in the two randomisation arms. This study shows that EP combined with radiotherapy is an effective induction regimen in SCLC. Maintenance chemotherapy with VAC is not associated with increased survival but has significant toxicity after such induction treatment.

Key words: small cell lung cancer, chemoradiotherapy, induction treatment, maintenance treatment
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INTRODUCTION

SMALL CELL lung cancer (SCLC) constitutes approximately 20% of lung cancer, the largest cause of cancer-related death. A number of chemotherapeutic agents have been shown to prolong survival in SCLC especially when used in combination [1]. In patients with limited disease (LD), 50–60% attain a complete remission (CR), but relapse almost invariably occurs, at which time the recurrent tumour is usually resistant to further chemotherapy, with the median survival being as short as 8 weeks.

Prophylactic radiotherapy to the thorax and cerebrum, two of the most common sites of relapse, have been widely studied. Thoracic radiation has been reported to prolong median survival [2, 3], but a recent review suggests that prophylactic cranial irradiation (PCI) does not [4].

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At the time of commencement of this trial, studies in other tumour types had suggested that maintenance chemotherapy given when patients had obtained an initial remission, could prolong survival. In a study by CALGB [5], Maurer and associates reported maintenance chemotherapy significantly prolonged survival in patients with LD with 33% of patients alive at 24 months compared with 9% who had not received maintenance chemotherapy. However, the study had a complex design using three different randomisations and has also been questioned on the basis of whether the patients, in fact, received adequate induction therapy. The regimen used in this study was prompted by a study by Sierocki and associates [6] who gave patients two courses of cisplatin and etoposide (EP) prior to four cycles of VAC. PCI was given to all patients and followed by a further course of the initial chemotherapy. Response rates were 93% in LD and 88% in extensive disease (ED), and rapid responses were seen after the EP.

Thus, a randomised prospective trial was begun to assess

initially response rates and toxicity to induction therapy with four cycles of EP combined with PCI and thoracic radiotherapy. Then to randomise patients responding to induction therapy, to no further treatment or 10 cycles of VAC to investigate the role of maintenance chemotherapy.

We now report results of this randomised prospective trial at 12 years of follow-up.

PATIENTS AND METHODS

Patient eligibility

During the period January 1981 – August 1985, all patients with histologically proven SCLC, independent of performance status, who had not received prior radiotherapy nor chemotherapy were entered into a study at the Royal North Shore Hospital (RNSH) and Repatriation General Hospital Concord. Patients with severe co-existing disease at time of entry to the study were excluded. Pre-treatment creatinine was required to be less than 0.15 mmol/l. All patients were required to have at least one site of evaluable or measurable disease.

Patient assessment

All patients had pre-treatment physical examination, full blood count, full biochemical analysis (including electrolytes, urea, creatinine and liver function tests), chest X-ray, computerised tomography (CT) of brain, liver scan (either CT or radionuclide) and bone scan. LD was defined as disease limited to one hemi-thorax and the ipsilateral supraclavicular fossa lymph nodes. Patients with pleural effusion or disease beyond the hemi-thorax were categorised as ED.

Induction treatment

Cisplatin, 80 mg/m^2, was administered intravenously (i.v.) day 1, and etoposide, 60 mg/m^2, was administered i.v. days 1, 2 and 3. Pre-hydration with 2 l of 5% dextrose over 2 h was followed by 37.5 g of mannitol administered i.v. 30 min prior to cisplatin. The cisplatin was given over 2 h followed by 2 l of 5% dextrose, each over 6 h. Etoposide was given by a 45-min infusion on days 1, 2 and 3. Induction chemotherapy was given every 21 days for four courses. Chemotherapy doses were modified according to the various toxicities such as myelosuppression and mucositis. Radiotherapy was given simultaneously to the primary, mediastinum and brain in two split courses each consisting of nine fractions of 2.2 Gy. These were given after the first and second courses of induction chemotherapy. At the completion of four courses of EP, full reassessment was undertaken with physical examination, full blood count and biochemical analysis with repeat chest X-ray and upper abdominal imaging.

Maintenance chemotherapy

Patients responding to induction treatment were randomised to either observation or maintenance therapy with vincristine 1.4 mg/m^2 (maximum 2 mg) i.v., doxorubicin 50 mg/m^2 i.v. and cyclophosphamide 750 mg/m^2 i.v., which were given on day 1 and repeated every 3 weeks for a total of 10 courses.

Randomisation and stratification

Randomisation was by selection from a bank of sealed cards at RNSH. Patients were stratified by initial disease extent (LD or ED) and by response to induction (CR or PR). Response criteria were standard World Health Organisation (WHO) criteria [7].

Ethical considerations

Verbal informed consent was obtained from each patient and the study was approved by the Ethics Committee of RNSH.

Statistical analysis

Survival curves were constructed according to the method of Kaplan and Meier and compared by the log rank test. Proportions were compared using a chi-square test. Cox's Hazards Ratio was used to obtain a measure of the sensitivity of the differences of overall survival (OS) and disease-free survival (DFS) in the randomised groups.

RESULTS

204 patients were entered into the study. Two patients were excluded when review of the pathology showed non-small cell histology. Patient characteristics are shown in Table 1. This group is representative of patients with SCLC with a male predominance, mean age of 62 years and a majority of patients with ED. Seventy-one per cent had a ECOG performance status of zero or 1.

Induction treatment

155 (77%) patients completed induction chemotherapy and, of the 47 patients who failed to complete induction therapy, 32 had an initial performance status of 2. 38 patients died during induction therapy, 27 deaths were related to malignancy, three deaths were a result of other medical illnesses and eight causes of death are not known. 154 patients (76%) responded to induction therapy. Of the 85 patients with LD, 74 (87%) responded, 53 (62%) achieving a CR. Of the 117 patients with ED, 80 (68%) responded with 30 (26%) achieving a CR.

Toxicity of induction therapy

The principal side-effects were myelosuppression, infection, thrombocytopenia and alopecia (Table 2). 85 (42%) patients

Table 1. Patient characteristics

		No. of patients	%
1. Age	Median	63	
	Mean	62	
2. Sex	Male	161	80
	Female	41	20
3. ECOG performance status	0	66	33
	1	78	39
	2	32	16
	3	16	8
	4	8	4
	Unknown	2	1
4. Disease extent	Extensive	117	58
	Limited	85	42
5. Metastatic sites	Ipsi SCF lymph nodes	10	5
	Other lymph nodes	6	3
	Brain	13	6
	Bone	17	8
	Liver	18	9
	Bone marrow/skin	5	2
	Multiple	48	24

Ipsi SCF lymph nodes: ipsilateral supraclavicular lymph nodes.

Table 2. Toxicity

	Induction	($n = 202$)	Maintenance	($n = 54$*)
	No.	%	No.	%
White cells (WHO grade 3–4)	85	42	32	59
Platelets (WHO grade 3–4)	20	10	6	11
Mucositis (WHO grade 2–3)	6	3	4	7
Renal (WHO grade 3–4)	3	1.5	1	2
Nausea/vomiting (WHO grade 2–3)	163	81	34	63
Alopecia (WHO grade 1–2)	180	89	53	98

*65 patients were randomised to receive maintenance chemotherapy, but 6 refused further treatment, and toxicity data were unavailable for 5 patients.

developed WHO grade 3–4 neutropenia, of whom 8 (4%) developed life threatening sepsis and 4 (2%) died. Although WHO grade 3–4 thrombocytopenia occurred in 10% of patients, there were no episodes of thrombocytopenic haemorrhage. Nausea and vomiting were generally well controlled with 16 patients experiencing WHO grade 3 toxicity and 147 grade 2 toxicity.

Randomisation

Of 154 responding patients, 129 agreed to take part in randomisation. The comparative demographics of the two arms are shown in Table 3. There was no significant difference between the two groups in terms of age, sex, performance status, disease extent or response to induction ($P = 0.331$).

Table 3. Randomisation

Criterion	VAC (No. of patients)	Observation (No. of patients)
Sex		
Male	54	50
Female	11	14
Disease bulk		
LD	33	28
ED	32	36
Response to induction		
CR	38	32
PR	27	32
ECOG performance status		
0	27	22
1	23	29
2	8	8
3	6	3
4	1	1
Unknown	0	1
Metastatic sites		
Ipsi SCF lymph nodes	3	3
Other lymph nodes	1	2
Brain	4	3
Bone	6	6
Liver	5	7
Other sites	2	1
Multiple	11	14

Ipsi SCF LN: ipsilateral supraclavicular lymph nodes.

Maintenance chemotherapy

5 patients were randomised to receive maintenance chemotherapy, but refused treatment and 6 patients had no recording of toxicity data. 11 patients (17%) completed the full maintenance protocol and 43% of patients completed more than four courses of maintenance chemotherapy. The numbers of patients completing each course are shown in Table 4. The reasons for not completing the treatment were withdrawal in 25 patients (38%), toxicity in 10 (15%), progressive disease in 14 (21%) and death in 5 (8%) patients. Three deaths were due to neutropenic sepsis and two deaths due to disease progression. 2 patients improved their response from PR to CR.

Toxicity of maintenance chemotherapy

The toxicity of maintenance chemotherapy was similar to induction therapy (Table 2). Again the principal toxicity was myelosuppression with 32 patients experiencing WHO grade 3–4 WCC toxicity and 3 patients dying of neutropenic sepsis. WHO grade 3–4 thrombocytopenia occurred in 6 patients which was asymptomatic. Nausea and vomiting were more

Table 4. Maximum number of maintenance chemotherapy courses completed

No. of courses	No. of patients	%
10	11	16.9
9	2	3.1
8	1	1.5
7	3	4.6
6	7	10.8
5	4	6.2
4	5	7.7
3	5	7.7
2	12	18.5
1	9	13.8
0	5	7.7

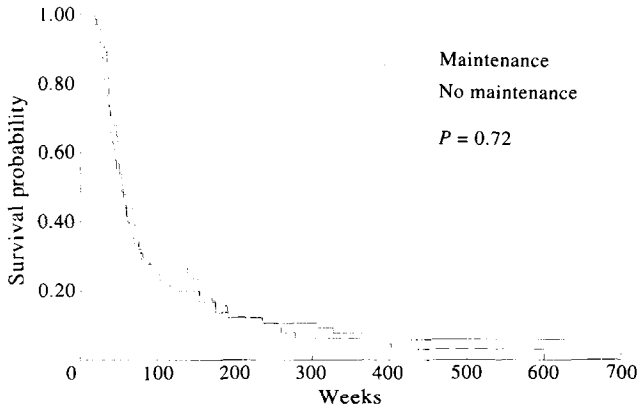

Figure 1. Survival time by randomisation.

common than with induction therapy with 34 (63%) patients experiencing grade 2–3 toxicity.

Survival data

The median survival for all eligible patients was 39 weeks (range 0–627 weeks). Results of patients randomised showed an overall median survival of 53 weeks (range 17–627 weeks), and for those receiving matinenance chemotherapy, a median survival of 54 weeks (range 19–627 weeks; 49–63 weeks 95% confidence intervals) versus 52 weeks (range 17–602 weeks; 43–70 weeks 95% confidence intervals) for the observation arm. This represents no significant difference in survival for maintenance chemotherapy ($P = 0.636$). The median survival for patients with LD was 70 weeks (range 25–627 weeks) and 42.5 weeks (range 17–541 weeks) for patients with extensive disease. The median disease-free survival (DFS) was 25.4 weeks (range 2–612 weeks). In the patients who received maintenance chemotherapy, the median DFS was 37 weeks (24–61 weeks 95% confidence intervals) compared with 23 weeks (16–31 weeks 95% confidence intervals) for the observation group ($P = 0.099$). The results show that there was no significant difference in either median DFS (37 versus 23 weeks) or median OS (54 versus 52 weeks) when comparing the maintenance group with the no further treatment group, respectively (Figures 1 and 2). Using Cox's Regression Model, the Hazards Ratio for OS is 1.068 (0.75–1.5 95% confidence intervals) and for DFS is 1.407 (0.94–2.11 95% confidence intervals). The wide confidence interval reflects the small number of patients in this study.

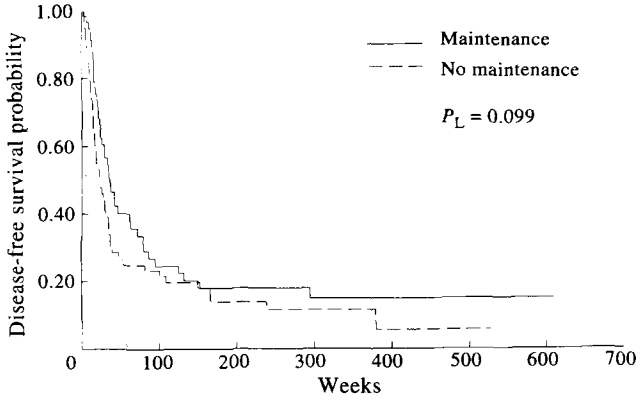

Figure 2. Disease-free survival by randomisation.

33 patients (16%) survived 2 years, of whom 15 had received maintenance chemotherapy and 18 had not. 22 of these patients were LD at initial staging and 11 were ED. These represent 26 and 9% 2-year survivals for LD and ED, respectively. Data assessed at a minimum of 7 years follow-up showed 8 survivors, 4 of who had received VAC maintenance chemotherapy and 2 who were randomised to no further chemotherapy. The other 2 patients, who had achieved a CR after induction chemotherapy, refused randomisation. 5 of these patients had LD and 3 ED, and 7 had obtained a CR and 1 a PR to induction therapy.

DISCUSSION

This study provides mature data for the use of cisplatin, etoposide and radiotherapy as induction therapy in SCLC in previously untreated patients, followed by the randomisation of the responding patients to either maintenance chemotherapy with VAC or no further treatment. The minimum follow-up is now 7 years.

It is one of the earliest large studies to use cisplatin and etoposide as first line therapy in patients, including every level of initial performance status. The induction regimen was well tolerated with 77% of patients able to complete all of the planned induction therapy and those patients failing to complete induction were predominantly those with a performance status of 2. The toxicities would have been increased by the use of concomitant thoracic and cranial radiotherapy.

The response rates (LD, 87 with 62% CR; ED, 68% with 26% CR) were impressive as were the long-term survival data, especially since these figures included patients who had a performance status of 3 and 4, who currently would not be included in clinical trials. McCracken and associates [8] have reported results after 4 years follow-up in patients with LD SCLC for similar induction therapy using three courses of cisplatin, etoposide and vincristine combined with thoracic radiotherapy and PCI, followed by two courses of vincristine, methotrexate, etoposide, doxorubicin and cyclophosphamide. Their response rate was 83%, with 56% achieving a CR and survival was 30% at 4 years follow-up. Einhorn and associates [9] reported a study of patients with LD and a median performance status of 1, a median survival of 98 weeks in patients receiving two cycles of cisplatin and etoposide after four cycles of VAC, compared with a median survival of 68 weeks in those patients receiving VAC alone.

These results and our own suggest that the combination of etoposide, cisplatin and radiotherapy is tolerable and effective induction therapy for SCLC with long-term survival comparable to, if not superior to, that reported in recent analyses [10, 11]. The induction therapy was completed within 9 weeks and the use of higher doses of etoposide may lead to even better results, although this may be associated with increased toxicity.

In terms of disease-free survival, overall or long-term survival, there was no advantage for patients receiving maintenance chemotherapy over those who did not. However, this study was small and would have only detected a large difference. Maintenance chemotherapy was poorly tolerated as reflected by only 11 patients (17%) completing the intended 10 courses of VAC. In addition, 32 patients (59%) developed grade III or IV neutropenia, necessitating dose reduction and 3 patients died from neutropenic sepsis. In terms of benefit, only 2 patients improved their response status during maintenance treatment.

Table 5. Maintenance chemotherapy in small cell lung cancer

Year [Ref.]	No. of patients	ED vs LD (%)	Induction Rx	Response to induction	Maintenance Rx	Median survival	Results
1980 [5]	258	43/45 12% not evaluable	C CME CMEV CHD-MtxV RT to I° and PCI	54% (CR 27%) 51% (CR 34%) 58% (CR 50%) 62% (CR47%)	CR — As per induction every other month until relapse		Improved survival in maintained group (33% versus 9% alive at 2 years) Median survival the same for CR
1984 [17]	320 new 147 old	52/48 55/45	New—VAC × 6 —RT to 1° and PCI Old–VAC × 3 —RT to 1°	LD 84% (CR 52%) ED 73% (CR 10%) LD 83% ED 65%	NIL All patients—CCNU.PMtx for 12 months	New LD 49 weeks ED 34 weeks Old LD 47 weeks ED 37 weeks	No advantage for maintenance
1986 [18]	309	20/80	VAC × 6 RT in LD to 1°	LD 65% (CR 12%) ED 52% (CR 19%)	CR and good response (minor residual abN) VAC × 8 at a lower dose	LD 363 weeks ED 272 weeks (maintenance 372 no maintenance 259)	ED—Advantage
1989 [15]	497	26/74	ECMtxV × 6 RT to 1°	85% (CR 11%)	In responders induction × 6	M 42 weeks NoM 30 weeks	No advantage Trend in CRs
1989 [14]	610	68/32	CVE × 4 or 8	× 4 61% (CR 12%) × 8 after 4 courses 61% (CR 9%) after 8 courses 63% (CR 15%)		× 4 LD 43 weeks ED 28 weeks × 8 LD 48 weeks ED 35 weeks	No benefit if chemotherapy given on relapse
1989 [19]	68	0/100	CisE alternating with CVMtx RT to 1° & if CR PCI	59% CR	CR— CVMtx × 6	M—14.1 months NoM–19.2 months	Disadvantage for maintenance
1990 [16]	577	100/0	VAC or VAC alt HEMtx × 6–8	61% (CR 16%) 64% (CR 23%)	CR— same drugs × 6	M 41 wks NoM 30 wks M 49 wks NoM 61 wks	Border survival advantage No advantage
1992 [13]	320	53/47	CDE × 6 L × 3	95% (CR 40%)	CR— CDE × 6	M 68 months NoM 56 months	No advantage
1993 [12]	687	48/52	CDE × 5	79% (CR 43%)	CR, PR or SD— CDE × 7	M 9.3 months NoM 9.3 months	No advantage DFS better than 2 months in M
1996 (this study)	202	58/42	CisE × 4	LD 87% (CR 62%) ED 69% (CR 26%)	CR or PR— VAC × 10	M 54 weeks NoM 52 weeks	No advantage

LD, limited disease; ED, extensive disease; Rx, treatment; CR, complete response; PR, partial response; SD, stable disease; M, maintenance chemotherapy; NoM, no maintenance chemotherapy; RT, radiotherapy; C, cyclophosphamide; Mtx, methotrexate; V, vincristine; A, D, doxorubicin; P, procarbazine; E, etoposide; Cis, cisplatin; L, lomustine, PCI, prophylactic cranial irradiation; alt, alternated; abN, abnormal; CHD-MTX, high dose methotrexate; HEMtx, hexamethylmelamine, etoposide and methotrexate.

Other groups have investigated the value of maintenance chemotherapy (Table 5) and our results tend to agree with those studies (EORTC [12], Lebeau and associates [13], Spiro and associates [14], MRC [15], Ettinger and associates [16], Feld and colleagues [17]). Studies that disagree with these results include the trial by Cullen and colleagues [18], in which the survival difference was largely accounted for by the differences in performance status and response to induction chemotherapy between the two series. In several of the studies (Maurer and associates [5], Spiro and associates [14], Cullen and associates [18], Ettinger and colleagues [16]) response rates to induction (51–65%) were lower than in our study (77%) and may be an explanation of why a longer duration of treatment with these lesser regimens was required to approach an equivalent median survival. This idea is supported by the study of Ettinger and associates [16] in which it was reported that patients receiving VAC induction benefited from maintenance chemotherapy whilst those receiving VAC–HEM did not. Two studies (Spiro and colleagues [14] and EORTC [12]) have shown a DFS advantage of 8 weeks for patients who received maintenance chemotherapy, but if chemotherapy was given at relapse, the difference was eliminated with only a small benefit in survival for prolonged chemotherapy. A study by Byrne and colleagues [19] has shown a survival advantage for the no maintenance group. This result could not be explained by higher toxicity in the maintenance arm, and other aspects, such as the small number of patients and design of the study using randomisation at diagnosis, with inevitable subsequent withdrawals, might have influenced the results.

The present trial as well as others indicates that maintenance chemotherapy is poorly tolerated as only 17% of patients completed the full 10 cycles of maintenance chemotherapy in our study. In the other trials assessing maintenance chemotherapy (Table 5) 37–51% of patients randomised to receive maintenance chemotherapy completed the planned treatment.

In conclusion, four cycles of cisplatin and etoposide combined with thoracic radiotherapy represents effective induction therapy for SCLC. This study and those reviewed in the discussion would support that between four and six cycles of induction chemotherapy is an appropriate standard treatment and maintenance chemotherapy is not justified [20, 21]. In the positive trials of maintenance therapy, induction treatment tended to be suboptimal and any survival advantage demonstrated was very small, but re-introduction of chemotherapy on relapse for patients who had not received maintenance chemotherapy was more effective than in patients who had received maintenance chemotherapy.

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