A pilot study of MVP (mitomycin-C, vinblastine and cisplatin) chemotherapy in small-cell lung cancer

TF Hickish, IE Smith*, MC Nicolson, S Ashley, K Priest, L Spencer, A Norman, G Middleton and MER O'Brien

Lung Unit, Royal Marsden Hospital, Sutton, Surrey, UK

Summary MVP chemotherapy (mitomycin C 8 mgm^{-2}, courses 1,2,4 and 6, vinblastine 6 mgm^{-2}, cisplatin 50 mgm^{-2}) is an active low-toxicity regimen in non-small-cell lung cancer (NSCLC). Based on the single-agent activity of these agents in SCLC, we have conducted a phase II trial of MVP in SCLC. Fifty chemo-naive patients with SCLC were entered in this trial. There were 33 men and 17 women with median age 66 years (range 46–83 years); 18 patients had limited disease (LD) and 32 extensive disease (ED). WHO performance status (PS) was: three patients PS 0, 33 patients PS 1, ten patients PS 2, four patients PS 3. A maximum of six cycles was given in responding patients. On completion of chemotherapy, patients with LD obtaining complete response (CR)/good partial response (PR) received thoracic irradiation and those obtaining CR were offered entry into the ongoing MRC Prophylactic Cranial Irradiation Trial. The overall response was 79% with 17% CR and 62% PR. For LD patients, 38% obtained CR but for ED only one patient achieved CR. Median response duration for LD patients was 8 months and for ED patients 5 months. Median survival was 10 months for LD patients and 6 months for ED patients. There was complete resolution of symptoms in 24%, partial improvement in 68%, no change in 2% and progressive symptoms in 6%. As regards toxicity, 24% developed WHO grade 3/4 neutropenia, 16% grade 3/4 thrombocytopenia and 6% significant hair loss. Two patients died during the first week of treatment with neutropenic infection. Quality of life using the EORTC questionnaire (QLC-C30) with lung cancer module demonstrated significant improvements from baseline levels in emotional and cognitive functioning, global QOL, of pain, dyspnoea and cough. MVP, an effective palliative regimen for NSCLC, is also active against SCLC with low toxicity and merits comparison with more toxic conventional schedules.

Keywords: MVP; chemotherapy; small-cell lung cancer

Despite its initial chemo-radiosensitivity, progress in the treatment of small-cell lung cancer (SCLC) over the last decade has been disappointing, with more than 80% of patients dying of recurrent chemoresistant disease within 2 years of diagnosis. Combination chemotherapy remains the cornerstone of current management of this disease and two different approaches to its use can be identified.

On the one hand, there is the dose-intensive approach, which has failed to yield incremental benefits (Harper and Souhami, 1985; Ihde et al, 1986; Klasa et al, 1991) but has now been revisited with the evaluation of growth factors (Woll et al, 1995) or high-dose chemotherapy with stem cell rescue (Leyvraz et al, 1995). On the other hand, there is the low-toxicity approach in recognition of the limited impact of the dose-intensive approach with its concomitant toxicities. The concern with the latter approach is that this may result in a survival deficit and no particular quality-of-life advantage (Joss et al, 1995).

Recently we have reported an MVP (mitomycin C, vinblastine and cisplatin) chemotherapy schedule in advanced non-small-cell lung cancer emphasizing symptom relief and low toxicity (Ellis et al, 1995a). The objective response rate (32%) was similar to that achieved in trials of other active regimens, yet only 3% developed significant alopecia or WHO grade 3/4 nausea and vomiting and 69% had marked alleviation of tumour-related symptoms. Cisplatin and the vinca alkaloids have single-agent activity in SCLC. Although

mitomycin C has not been shown to be active as a second-line agent in phase II trials in SCLC, it displays synergy with cisplatin in vitro and has been used in combination chemotherapy studies in SCLC (Murray et al, 1985; McHale and Einhorn, 1986; Inada, 1988; Broder et al, 1994). Accordingly, our experience with the MVP regimen encouraged a phase II pilot trial in previously untreated small-cell lung cancer combined with a quality-of-life assessment.

PATIENTS AND METHODS

Patient characteristics

Fifty sequential previously untreated patients with histologically or cytologically proven SCLC were entered into this study between July 1993 and September 1994. Inclusion criteria included normal full blood count, satisfactory renal function (^{51}Cr EDTA clearance $\geq$ 60 ml min^{-1}) and liver function (LFTs less than twice upper limit of normal) and WHO performance status (PS) $\leq$ 3. Patients with cerebral metastases were not excluded from the study.

Patient characteristics and sites of disease involvement are summarized in Table 1. There were 33 men and 17 women. The median age was 66 years (range 46–83 years). Sixteen patients had limited disease (LD) and 34 extensive disease (ED) according to the two-stage system of the Veterans Administration Lung Group. WHO performance status was as follows: three patients PS 0, 33 patients PS 1, ten patients PS 2, four patients PS 3.

All patients had pretreatment physical examination, plasma electrolytes, urea and creatinine, serum liver function tests, chest radiography (or computerized tomography (CT) of thorax if disease not measurable on chest radiograph), an imaging examination of the liver (either ultrasound or CT) and ^{51}Cr EDTA clearance. Isotope

Table 1 Patient characteristics

Number of patients	50
Sex	
Male	33
Female	17
Age (years)	
Median	66
(range)	(46–83)
Limited disease	18
Extensive disease	32
WHO PS	
0	3
1	33
2	10
3	4
Median PS	1

Table 2 Objective response

Stage	Patients	CR	PR	Overall response	NC	PD
LD	18	7	10	17 (94)	1	0
ED	30	1	21	22 (73)	7	1
Total	48	8	31	39 (81)	8	1

Numbers in parentheses are percentages. Two patients not evaluable.

Table 3 Overall symptomatic response

Complete resolution of symptoms	28%
Improved symptoms	64%
No change in symptoms	2%
Symptoms worse	6%

Three patients not evaluable

Table 4 Haematological toxicity

	WHO grade (% for any course)		
	0	1–2	3–4
Anaemia	28	54	18
Leucopenia	42	34	24
Thrombocytopenia	68	16	16

Table 5 Non-haematological toxicity

	WHO grade (% for any course)		
	0	1–2	3–4
Infection	58	30	12
Nausea/vomiting	32	58	10
Alopecia	48	46	6
Mucositis	70	30	–
Diarrhoea	88	8	4
Neuropathy	80	20	–
Nephrotoxicity	96	4	–
Constipation	60	38	2

bone scan, bone marrow aspiration and brain CT were only performed when clinically indicated.

Before each treatment patients had a physical examination, full blood count and biochemistry and chest radiography performed. Restaging of chest and upper abdomen and other known sites of disease was performed after four cycles of treatment or earlier if clinically indicated.

Treatment

All patients received the following regimen: mitomycin-C 8 mg m^{-2} i.v. day 1 (given on alternate courses), vinblastine 6 mg m^{-2} (maximum 10 mg) i.v. day 1 and cisplatin 50 mg m^{-2} i.v. day 1, repeated every 21 days. Intravenous pre- and post-treatment hydration was given with cisplatin according to the Unit's protocol. The duration of administration was 8 h enabling treatment to be delivered as a day-case when appropriate. The decision whether to administer MVP chemotherapy as a day-case or in-patient was necessarily flexible and depended on factors such as home circumstances, availability of transport and tolerance of previous treatment. Patients received prophylactic anti-emetic therapy with a 5HT3 antagonist and dexamethasone. Renal function was checked with ^{51}Cr EDTA clearance before alternate courses and the dose of cisplatin reduced as follows: EDTA ≥ 60 ml min^{-1}, full dose; 40–60 ml min^{-1}, 25% dose reduction; < 40 ml min^{-1}, no treatment with cisplatin. Our policy at the time of this study was not to use prophylactic antibiotics. Treatment with MVP chemotherapy was continued until the development of progressive disease, unacceptable toxicity or to a maximum of six cycles in patients achieving objective response and/or symptomatic relief.

After the completion of chemotherapy, patients under 70 years of age with limited disease obtaining CR or good PR received thoracic irradiation to 40 Gy in 15 fractions over 3 weeks. Where necessary this was given in two phases to keep the spinal cord dose within tolerance. Patients obtaining CR were offered entry into an ongoing MRC prophylactic cranial irradiation trial (PCI). Those patients who received PCI had fractionated whole-brain radiotherapy to total doses between 24 and 36 Gy.

Response, toxicity and survival analysis

Tumour response was defined according to standard criteria (Miller et al, 1981). CR was defined as the disappearance of all clinical, radiological and biochemical evidence of disease for at least 4 weeks and PR was defined as a reduction in the product of two diameters of measurable disease by at least 50% for at least 4 weeks, without the appearance of new lesions or progression of any one lesion. Stable disease (SD/NC) was defined as < 50% decrease or < 25% increase in the size of the measurable disease, without the appearance of new lesions or progression of any lesion > 25% for 1 month. Progressive disease (PD) was defined > 25% increase in one or more of the measurable lesions of the appearance of a new lesion(s). Toxicity was also graded according to standard WHO criteria (Miller et al, 1981).

Tumour-related symptoms were recorded at the start of treatment under the following general headings: malaise, pain, cough, dyspnoea or 'other', which was then specified. Symptoms were then reassessed independently of the medical team by research nurses following each course of treatment with patients asked to grade change in symptoms using simple descriptive criteria as follows: (1) complete disappearance of symptoms (CR); (2) good
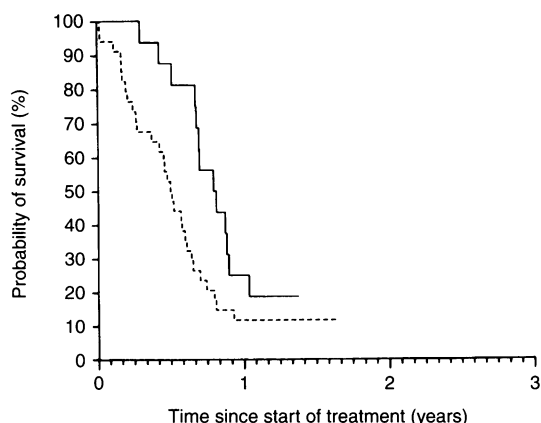
Figure 1 Survival: limited (——) vs extensive (- - -) disease

Table 6 Symptom response – change from baseline

	MVP no. 1	MVP no. 2	MVP no. 3	MVP no. 4
Pain	0.002	0.003	0.025	0.036
Cough	0.001	0.001	0.001	0.001
Dyspnoea	0.001	0.001	0.001	0.001
Malaise	0.003	0.002	0.002	0.005

P-values. Significance calculated using the Mann–Whitney test.

Table 7 Quality of life – change from baseline

QoL item	3 weeks	6 weeks	9 weeks	12 weeks	Direction
Physical functioning	NS	NS	NS	NS	NS
Role functioning	NS	NS	NS	NS	NS
Emotional functioning	0.037	NS	NS	0.022	Better
Cognitive functioning	NS	NS	NS	0.044	Better
Social functioning	NS	NS	NS	NS	NS
Global QoL	0.005	NS	0.035	NS	Better
Fatigue	NS	NS	NS	NS	NS
Nausea and vomiting	NS	NS	NS	NS	NS
Pain	0.005	NS	0.041	NS	Less
Dyspnoea	0.006	NS	0.022	NS	Less
Sleep disturbance	NS	NS	NS	NS	NS
Appetite loss	NS	NS	NS	NS	NS
Constipation	NS	NS	NS	NS	NS
Diarrhoea	NS	NS	NS	NS	NS
Financial impact	NS	NS	NS	NS	NS
Lung module					
Cough	0.005	0.007	0.196	0.037	Less
Dyspnoea	NS	NS	NS	NS	NS
Swallowing	NS	NS	NS	NS	NS
Toxic effects	0.038	0.014	NS	NS	More
Pain	0.039	NS	NS	NS	Less

P-values for difference from baseline.

improvement of symptoms (PR); (3) minor or no change in symptoms (NC); (4) worse (PD).

Response duration and survival were calculated from the date of first treatment using the standard life-table method of Kaplan and Meier (Kaplan and Meier, 1958).
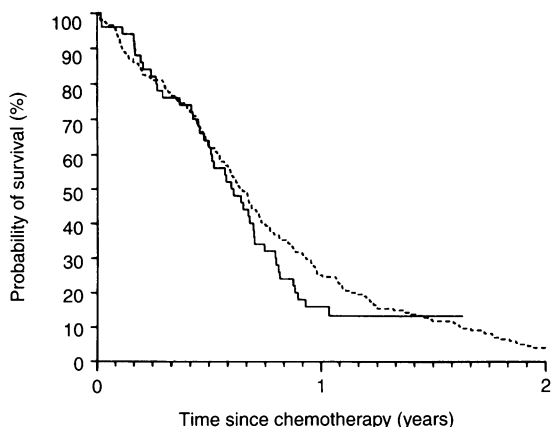

Figure 2 Overall survival for patients treated in this trial (——) and controls (- - -) matched for age, stage, performance status and disease extent treated in a series of chemotherapy trials in the Lung Unit at the Royal Marsden Hospital. Each patient had four matched controls. Details of the chemotherapy regimens used in these trials are given in the following: Smith et al (1985, 1987, 1990), Smith (1992), Jones et al (1991, 1993), Ellis et al (1995*b*). The chi-squared test was used to detect any difference between the two survival curves

Quality-of-life assessment

A measurement of quality of life was defined using the European Organization for Research and Treatment of Cancer (EORTC) questionnaire (EORTC QLC-C30) with lung cancer module. Patients were given standard instructions and invited to make ratings before starting treatment – baseline, and before each subsequent cycle of MVP (i.e. every 3 weeks) and at follow-up after the completion of treatment. Responses were scored according to the EORTC QL Group guidelines with conversion to a 0–100 scale using the recommended algorithm.

Ethics

This study was conducted in accordance with the declaration of Helsinki and approved by the Royal Marsden Hospital Ethical Committee. Witnessed informed consent was obtained from all patients according to guidelines laid down by the Committee.

RESULTS

Of the 50 patients initially entered into this study, 48 were assessable for response and all were evaluable for toxicity. Two patients died during the first week of treatment with neutropenic infection. All patients were included in survival analysis.

Response

Overall, 38 patients (81%, 95% CI 78–96%) obtained an objective response with eight CR (17%) and 31 PR (65%). In limited disease (LD) patients, an overall response rate of 94% (95% CI 83–100%) was obtained with 38% CR. For patients with extensive disease (ED), 73% (95% CI 66–96%) of patients achieved a response but only one patient (2%) achieved CR. Details of response by stage are shown in Table 2. Median response duration from initiation of chemotherapy for LD patients was 8 months, for ED patients 5 months, with an overall response duration of 5 months. Median response duration measured from the end of chemotherapy for LD

patients was 12 weeks, for ED patients 6 weeks, with an overall response duration of 7 weeks. Median survival from initiation of chemotherapy was 10 months for LD patients and 6 months for ED patients; the overall value being 7 months (Figure 1). Median survival measured from the end of chemotherapy for LD patients was 6 months, for ED patients 3 months; the overall value being 4 months.

The overall symptom response was 64%, with 28% of patients experiencing complete relief of symptoms (Table 3). The change from baseline was significant for all the major symptoms (pain, cough, dyspnoea and malaise).

Toxicity

Twenty-four per cent of patients developed WHO grade 3/4 neutropenia (Table 4). There were two deaths associated with neutropenic infection and these occurred during the first week of treatment. Sixteen per cent of patients developed grade 3/4 thrombocytopenia at any stage during treatment (Table 4). Non-haematological toxicity was minimal. Sixty-eight per cent of patients experienced some degree of nausea and vomiting over the course of treatment. Just 6% developed alopecia and there was no significant nephrotoxicity or neurotoxicity (Table 5).

Number of cycles of MVP chemotherapy

The number of cycles per patient of MVP chemotherapy was as follows: one cycle, five patients; two cycles, seven patients; three cycles, six patients; four cycles, six patients; five cycles, ten patients; six cycles, 16 patients.

Dose reductions and delays

Four patients had 25% dose reductions (due to anaemia, one patient; repeated chest infections, one patient; neutropenia/fever, one patient; and low EDTA/nephrotoxicity, one patient. Four patients had dose delays (due to chest infection, one patient; cellulitis, one patient; infection, one patient; and general malaise with fever/shivers, one patient).

Quality of life

Quality-of-life baseline data are available for 41 patients and 12-week follow-up data are available for 25 patients (Table 6 and 7). Thereafter attrition on quality-of-life data was high with insufficient data available for analysis. Over the initial 12 weeks of treatment there was improvement in a range of quality-of-life items that appeared to mirror the symptom response data. There was no evidence of a deterioration in other quality-of-life measurements.

Database comparison with other chemotherapy regimens given as first-line therapy for SCLC

We have conducted a survival analysis comparison (Kaplan–Meier survival curves) of patients entered in this trial with patients matched for age, stage, performance status and disease extent (ED, LD) treated in the context of a series of Royal Marsden chemotherapy trials (Smith et al, 1985, 1987, 1990; Smith, 1992; Jones et al, 1991, 1993; Ellis et al, 1995*b*). Each patient in the current trial had four matched controls. There was no difference in the survival between the two groups (*P* > 0.1) (Figure 2).

DISCUSSION

This study demonstrates that a moderate-dose MVP regimen is active in SCLC and combines the benefits of symptom relief and mild toxicity seen with its use in NSCLC (Ellis et al, 1995*a*).

The response rate and survival data for this pilot trial are similar to those from other reported series using platinum/etoposide and doxorubicin-based regimens (Ellis et al, 1995*b*; Bishop et al, 1987; Evans et al, 1988; Fukuoka et al, 1991; Roth et al, 1992). There was no survival difference between patients entered in this trial and matched controls treated in a series of chemotherapy trials with data entered prospectively on our database (Figure 2).

For survival, these data are less impressive than the median survival data reported with dose-intensive regimens supported with growth factors or peripheral stem cell transplantation in the treatment of selected patients (Brugger et al, 1995; Woll et al, 1995; Fetscher et al, 1997). In a recent update of a non-random-ized study evaluating multimodality therapy including high-dose chemotherapy with peripheral stem cell transplantation, a survival advantage for this approach appeared to accrue to young, good performance status, LD patients (Fetscher et al, 1997). To date, only one small randomized trial has compared conventional dose chemotherapy with high-dose chemotherapy supported by stem cell rescue (in this case ABMT), and this demonstrated improved disease-free survival in the high-dose arm (Humblet et al, 1987). As such, a dose-intensive approach may yield a survival advantage for selected patients and, for these, MVP chemotherapy would represent undertreatment.

However, for older, poor performance status/ED patients, reduction in toxicity with maintenance (ideally with improvement) of the survival fraction is the current goal of trials. The possibility that a 'more gentle' chemotherapy regimen may have inadequate activity in SCLC was demonstrated in a recent trial in which patients with advanced disease were randomized to receive either weekly carboplatin and teniposide or cisplatin, doxorubicin and etoposide alternating with cyclophosphamide, methotrexate, vincristine and lomustine (Joss et al, 1995). The trial was closed before the planned accrual because of a significant survival difference in favour of the more intensive alternating regimen (1 year survival: 30% vs 4%). Toxicity was greater with the more intensive regimen but there was no difference found in patient-related tumour symptoms or general quality-of-life categories. Likewise, that a regimen initially conceived to have low toxicity with acceptable anti-tumour activity may not do so is exemplified by the MRC randomized trial of oral etoposide in comparison to intravenous multidrug chemotherapy (Girling et al, 1996). In this trial, the oral etoposide schedule was associated with greater toxicity and a poorer median survival. However, another MRC randomized trial of a two-drug regimen (EV: etoposide, vincristine) with a four-drug regimen (ECMV: etoposide, cyclophosphamide, methotrexate, vincristine) for poor performance status patients demonstrated how toxicity can be reduced significantly without a survival deficit (Bleehen et al, 1996).

The anti-tumour response achieved with the MVP regimen in this trial was matched by symptom relief and patients overall had an improvement in a range of quality-of-life items (during the initial 12 weeks of treatment), as measured by the EORTC Quality of Life Assessment instrument.

As we have reported previously (Ellis et al, 1995*a*), this MVP regimen has a low cost. Furthermore it is pragmatic and represents a reasonable alternative when diagnostic uncertainties arise and

the tumour cannot be confidently defined as small-cell or non-small-cell.

Moderate-dose MVP chemotherapy has acceptable anti-tumour activity and toxicity in small-cell lung cancer. It offers an appropriate comparator in future randomized trials for poor performance status patients in which minimization of toxicity and enhancement of quality of life are emphasized.

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