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The Multidrug Resistant Phenotype in Clinical Practice; Evaluation of Cross Resistance to Ifosfamide and Mesna after VP16-213, Doxorubicin and Vincristine (VPAV) for Small Cell Lung Cancer

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Abstract—*Eight-eight previously untreated patients with small cell lung cancer were treated with a combination of VP16, adriamycin and vincristine (VPAV) for three courses. Resistance to these drugs is associated with the multidrug resistance (MDR) membrane glycoprotein in cell lines* in vitro. *The clinical relevance of this mechanism of resistance was assessed by using a second line treatment with intravenous infusions of ifosfamide/mesna* 5 g/m^2 *every* 3 *weeks in patients with only partial responses or non-responders. Cross-resistance to alkylating agents is rare in the MDR. Ifosfamide produced partial responses in six* (43%) *of* 14 *patients unresponsive to prior therapy.*

Intravenously infused ifosfamide/mesna was also used in consolidation therapy with only minor bone marrow or urinary tract toxicity. This did not prevent CNS relapse.

The overall response rate to VPAV was 69% *and for all treatment modalities,* 75%. *Median survival for all patients ws* 39.5 *weeks and* 59 *weeks for all patients attaining complete response.*

The addition of large fraction chest irradiation given with the final course of induction chemotherapy to those with good chemotherapy responses produced a further response in 44% *of assessable patients. Combined modality treatment resulted in moderate and reversible toxicity.*

The lack of improved survival with ifosfamide and the resistance of the majority of patients to salvage with ifosfamide/mesna suggested that the MDR is not the major mechanism of resistance in the clinic, since cross-resistance to alkylating agents of this type is not a feature of MDR cells.

INTRODUCTION

Cytotoxic chemotherapy produces high response rates in small cell lung cancer (SCLC), but most patients relapse and die with few long-term disease free survivors [1–3].

It is uncertain if more than approx. 3 months chemotherapy contributes to survival [4–6] and maintenance therapy may not be necessary [7]. This suggests that drug resistance develops early in the course of treatment or before treatment has started. To overcome resistance, high dose cyclophosphamide has been assessed in SCLC with major marrow toxicity. Ifosfamide, an oxazaphosphorine cytotoxic closely related to cyclophosphamide, has antitumour activity in cancers such as osteosarcoma [8] and pancreatic cancer [9] and has been combined with other cytotoxics to treat SCLC [10]. Ifosfamide is less toxic to the bone marrow than is cyclophosphamide [11], but a major toxicity is haemorrhagic cystitis, which can be circumvented by the uroprotector mesna [11–13].

Cytotoxic drug resistance in cancer cells is complex and partly may be mediated through the emergence of a multidrug resistance phenotype (MDR) which enhances cellular efflux of cytotoxic drugs, amongst other mechanisms. This malignant phenotype has been described in Chinese hamster ovary

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cells, and has been associated with over-expression of a cell surface glycoprotein in murine and human tumour cell lines [14, 15]. Evidence for the existence of multidrug resistant cells in human SCLC cell lines has been shown [16]. Cross-resistance to cytotoxic drugs, including VP16, adriamycin and vincristine, is a major feature of the MDR phenotype [17]. However, there is no cross-resistance to alkylating agents other than melphalan.

We therefore undertook a study to assess the clinical relevance of this MDR phenotype. Drugs known to be active in SCLC but also involved in MDR were used to induce remission by short courses. Ifosfamide was introduced as a second line therapy if there was failure to respond or only partial response occurred.

The use of ifosfamide for consolidation therapy was assessed in patients with good response to first line therapy. Following preliminary experience with large fraction radiotherapy in small cell lung cancer [18], a final aspect of the trial was to integrate large fraction radiotherapy with chemotherapy to control local disease.

PATIENTS AND METHODS

Eighty-eight patients with histologically and/or cytologically proven SCLC were treated. No patient had prior chemotherapy and on entry into study and before each chemotherapy course, patients had chest X-rays, full blood counts, serum urea, creatinine, sodium, chloride, calcium, bilirubin, alkaline phosphatase and aspartate transaminase estimations. Nadir full blood counts were not routinely performed. Seventy-one patients (81%) had bone marrow aspirate or trephine examinations. Isotope scans of brain, liver and bone and computed tomographic scans were performed if there were clinical and/or biochemical abnormalities indicating possible metastatic disease.

Fifty patients had disease confined to within one hemithorax with ipsilateral supraclavicular fossa (SCF) node metastases in five and ipsilateral pleural effusions in three. Five other patients had, in addition to disease within one hemithorax, contralateral SCF node metastases (3 patients) or contralateral pleural effusions (2 patients) but no other detected site of metastases. These latter five patients were combined with the former 50 and designated as limited stage patients. Thirty-three patients had extensive stage SCLC and included seven patients whose only site of extrathoracic spread was bone marrow. Some extensive stage patients had multiple detected sites of metastatic disease. Liver metastases were present in 12 patients, bone metastases in 12 and bone marrow metastases in 12 patients also. Two patients had skin metastases and two patients had brain metastases. Performance status (PS) was defined by World Health Organisation (WHO) criteria [19] and patient characteristics are given in Table 1.

Table 1.

	Limited stage	Extensive stage
No. of patients	55	33
Median age (years) (range)	58 (32–76)	60 (46–75)
Male:female ratio	34:21	24:9
Serum sodium <134 mmol/l (normal ≥134 mmol/l)	12 (24%)	12 (36%)
WHO performance status*		
0, 1	47 (85%)	20 (62%)
2	8 (15%)	13 (39%)

*There were significantly more extensive stage patients with performance status 2, χ^2 test, $P < 0.03$.

The trial design was to induce remission with three courses of VPAV. Local radiotherapy was to be given 4 days after the third course was started in patients with complete or partial response with a residual mass less than 5 cm. Consolidation therapy with two courses of ifosfamide was then given.

For patients with no response or progressive disease, or less than a partial response after two courses, crossover to ifosfamide was carried out. The ifosfamide was given for three courses in total.

Drug dosages were VP16 100 mg/m^2, adriamycin (doxorubicin) 40 mg/m^2 and vincristine 2 mg, all intravenously (i.v.) on day 1. VP16 200 mg/m^2 was given orally on days 2 and 3.

Cycles were repeated every 3 weeks. The first two VPAV courses were given at the participating District General Hospital and patients were referred to the Regional Radiotherapy and Oncology Centre for the third VPAV course with chest irradiation or crossover to ifosfamide/mesna.

Ifosfamide/mesna started 3 weeks after VPAV, but the interval was extended to 4 weeks for those with prior VPAV plus irradiation. Ifosfamide/mesna was given every 3 weeks to a maximum of three courses. Ifosfamide was given as a 24 h i.v. infusion of 5 g/m^2 in 3 l. of dextrose saline preceded by 1 g/m^2 i.v. bolus of mesna. Four g/m^2 of mesna was given i.v. over a 32 h period starting at the same time as ifosfamide, and mesna and ifosfamide were both given in the same infusion fluid. Intravenous frusemide 40 mg was given at the start of therapy and as necessary to maintain an average urine output of 100 ml an hour.

Chest irradiation was given to those achieving complete response (CR). Patients achieving partial response (PR) were given chest irradiation only if the residual chest X-ray hilar mass was ≤ 5 cm in its maximum diameter. Residual masses larger than this were not irradiated, as it was thought they were

Table 2. Numbers of patients with complete, partial or no response (NR) by treatment and initial stage

Treatment modalities	Limited stage CR	PR	NR	Extensive stage CR	PR	NR
VPAV	17/55	23/55	15/55	0/33	21/33	12/33
VPAV + irradiation	23/32	8/32	1/32	—	—	—
Ifosfamide/ mesna	25/48	14/48	9/48	0/22	17/22	5/22

One of 17 patients with CR to VPAV did not have chest irradiation, but did crossover to ifosfamide/mesna. Two patients with CR to prior therapy did not receive ifosfamide/mesna. Denominators refer to numbers of patients, by initial disease stage, receiving a particular treatment modality.

too extensive to treat to the planned high dose.

The planned dose was 24 Gy in four fractions, each fraction given on alternate days, excepting weekends, and irradiation was started within 4 days of previous VPAV. The dose was calculated at mid plane, no lung allowance was made and the supraclavicular areas were not included. Average field length was 13 cm and average width 9.5 cm and target volume included mediastinum plus residual tumour if present.

Response was defined by standard WHO criteria, but routine rebronchoscopies after treatment were not performed.

During therapy, a variety of antiemetics were prescribed. During ifosfamide and mesna, patients were given either high dose i.v. metoclopramide or oral high dose domperidone and dexmethasone.

RESULTS

Response and toxicity with VPAV

Seventeen of 55 (31%) limited stage patients had CR to VPAV. Confidence limits for this percentage response were 19.1–44.8%, 95% confidence level. No extensive stage patient had CR. Twenty-three of 55 (42%) limited stage patients (95% confidence limits 28.6–55.8%) and 21 of 33 (64%) extensive stage patients (95% confidence limits, 45.1–79.6%) had PR to VPAV. Thus 61 (69%) of 88 patients (95% confidence limits, 58.5–78.7%) had an objective response to VPAV. Responses to treatment modalities are summarised in Table 2.

There were 13 early deaths, 12 after one cycle and one after two VPAV cycles in patients who were either extensive stage disease or PS 2 or had both poor prognostic variables at the start of VPAV. One death was due to progressive cerebral metastases, three deaths occurred in leukopenic febrile patients and nine patients died at home between treatment cycles.

Patients who were early deaths were classified as non-responding patients. The haematological and neurotoxicity of VPAV, documented by WHO grading [16] , (Table 3) was otherwise mild. In addition, one reversible septicaemia and three episodes of anaemia requiring blood transfusions occurred. Patients who received two or more courses of VPAV all had moderate to severe alopecia.

Table 3. WHO graded toxicity during VPAV multiple treatment courses in 88 patients

	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	13	11	1	4
Thrombocytopenia	1	2	—	—
Stomatitis	—	—	1	—
Peripheral neuropathy	—	7	—	—

Response and toxicity with combined VPAV and chest irradiation

Thirty-two limited stage patients had chest irradiation and 16 of these were already in CR with prior VPAV. Seven PR patients converted to CR with irradiation and eight PR patients did not show radiographic change and remained in PR after irradiation. One PR patient had radiographic disease progression despite irradiation. Thus, seven (44%) of 16 patients (95% confidence limits, 19.7–70.1%) with residual disease had a further response to radiotherapy plus a third course of chemotherapy.

Toxicity of irradiation in association with VPAV was oesophagitis in 11 patients, in one case requiring i.v. hydration in hospital. Three patients developed febrile illness during periods of neutropenia and two did not complete four fractions of radiotherapy but all recovered with intensive antibiotic therapy. One patient, whilst still in clinical and radiographic CR, developed progressive paraplegia, thought to be due to treament-induced

spinal myelopathy 4 months after the end of therapy.

Twenty-three patients were in CR after chest irradiation given with VPAV and 10 had first detected recurrence in the chest or SCF nodes. This first relapse was outside the irradiation field in nine patients but subsequently evidence of involvement within the irradiated field became apparent. Five of the 10 patients had multiple metastases detected before death. Four of 23 CR status patients had isolated brain relapse as first manifestation of recurrent disease.

Eight patients remained in PR when assessed immediately after chest irradiation and three of these subsequently converted to CR with ifosfamide. In the eight patients, first evidence of relapse was in the chest lesions in five and was in the brain in three without evidence of chest relapse.

Response and toxicity with ifosfamide/mesna

Forty-three patients were given a median of two ifosfamide/mesna courses, 10 patients had one and 17 patients three courses. Eighteen patients did not receive ifosfamide/mesna and comprised 13 who died during VPAV, two CR patients who had serious intercurrent non-neoplastic illness, and two PR patients and one VPAV resistant patient who refused further chemotherapy after VPAV. Thus, at the start of ifosfamide/mesna, 22 patients were already in CR, 34 were in PR, and 14 were resistant to previous therapy.

The latter 14 patients comprised 13 who had had no previous objective response and one who had a PR with VPAV but progressed during chest irradiation. Twenty-two patients in CR remained thus after ifosfamide/mesna, and three of 34 PR patients converted to CR with isosfamide/mesna. Twenty-five patients remained in PR and six progressed despite ifosfamide/mesna. Ifosfamide/mesna induced PR in six (43%) of 14 patients (95% confidence limits 17.6–71.1%) who were progressing immediately prior to ifosfamide/mesna. Toxicity of ifosfamide/mesna included recurrence of oesophagitis in one patient associated with melaena and reversible septicaemia and one episode of cardiac failure likely related to i.v. delivery fluids in a patient with ischaemic heart disease and hypertension. Frank haemorrhagic cystitis occurred once in a patient with co-existing bacterial urinary infection and false positive ketonuria on urinalysis occurred in most patients [20]. One patient had marginal elevation of serum creatinine levels after ifosfamide and mesna and one other patient had elevated serum creatinine levels before and after ifosfamide/mesna.

One premenopausal woman developed reversible galactorrhoea and one patient had a neuropsychiatric event (fainting and long lasting fatigue). Two episodes of leukopenia (grade 1 and 2) and one episode of grade 3 thrombocytopenia occurred in a total of three patients during ifosfamide/mesna therapy.

Concomitant administration of high dose i.v. metoclopramide or oral high dose dexamethasone (a total of 16 mg 24 h per course) and oral domperidone, controlled emesis in approximately two-thirds of ifosfamide/mesna treated patients and approximately one-third of patients requested additional antiemetic drugs.

Survival

Life tables for subgroups were constructed by the method of Peto *et al.* and the log-rank test was used to examine differences between curves [21]. Median survival times and ranges are shown in Table 4.

There was a significant survival advantage ($P < 0.001$) to those with limited stage disease compared with extensive stage patients (Fig. 1). Patients attaining complete response had significant survival advantage ($P < 0.001$) compared to those with partial response to therapy.

All responding patients (CR and PR) had significant survival advantage ($P < 0.001$) when compared with non-responding patients. When survival of all 39 patients whose best response was partial was examined by initial stage of disease, then there was significant survival advantage ($P < 0.01$) to 18 PR limited stage patients compared with 21 PR extensive stage patients. When all 27 patients who attained CR were subdivided into those attaining CR with VPAV only (17 patients) and those attaining CR with additional therapy (10 patients), there was no significant difference in survival ($P > 0.1$).

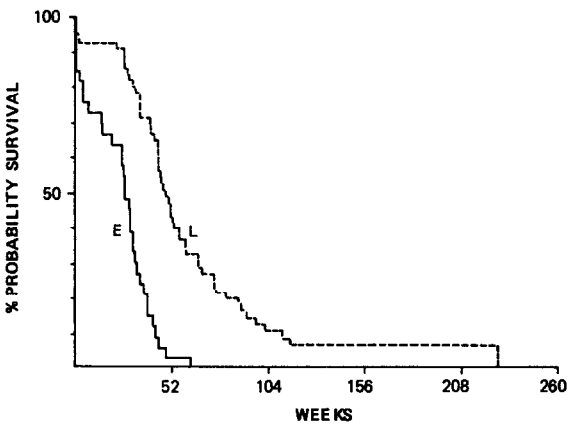
Twenty-five patients survived for 52 weeks or more from entry into study and seven patients survived from > 100 weeks from first treatment time. Six patients survived for 2 years after first treatment, four without evidence of recurrence. These latter four patients all had limited stage disease and complete response to treatment. Of these four patients (all women), one died with disease recurrence after 228 weeks and the other three are alive and free of recurrence at 196, 188 and 168 weeks, respectively. In addition, two limited stage CR patients died from cardiovascular related events at 46 and 59 weeks, respectively, from first treatment, while still in clinical and radiographic CR.

DISCUSSION

With short courses of chemotherapy including ifosfamide, 75% of all patients had objective responses (CR plus PR), results similar to other series [22]. Median survival times for patients with limited stage disease and also those with CR to therapy were very similar to other reports using

Table 4. Survival times in weeks

No. of patients		Median	Range
88	Patients	39.5	1–228
55	Limited stage patients	48	1–228
33	Extensive stage patients	27	1–62
27	CR patients	59	29–228
17	CR patients with VPAV	57	35–228
10	CR patients with additional therapy	74.5	29–112
18	Limited stage patients with PR as maximum response	44.5	22–102
6	Limited stage patients with PR to isosfamide/mesna	47.5	41–102
21	Extensive stage patients with PR as maximum response	31	14–62
22	Patients with no response	4	1–66



PATIENTS AT RISK AT START AND AT INTERVALS OF 52 WEEKS THEREAFTER

L	55	23	6	4	1	0
E	33	1	0	0	0	0

Chi-square (log rank) = 31.8, d.f. = 1, $p < 0.001$

L = limited stage disease, E = extensive stage disease

Three patients are alive without recurrence at 168, 188 and 196 weeks from first treatment.

Fig. 1. Life table of patients by extent of disease.

short courses of chemotherapy [5]. The important prognostic impact of tumour burden at start of therapy as assessed by staging was apparent with greater likelihood of CR to therapy and also greater survival advantage to those with limited stage disease. These prognostic implications of stage of disease are well known [23, 24].

Because high fraction sizes of radiation might have been more effective against residual drug resistant tumours, the toxicity of this regime was assessed in combination with the final VPAV course. Combined modality irradiation plus VPAV was feasible and resulted in moderate and in most cases reversible toxicity.

The addition of chest irradiation to patients with limited stage disease showing only PR to VPAV converted 44% of patients to complete response, although this conversion might have occurred with the final VPAV course alone. The addition of the novel high dose radiotherapy schedule in this study to good response and limited stage patients appeared to delay relapse within the radiation field at least in patients attaining complete radiographical response to therapy. There was a high initial relapse rate in the chest or adjacent nodal sites outside the irradiated area. Our results suggest patterns of relapse can be altered by the novel radiotherapy schedule in this study, but it is not possible to determine the effect on survival of the addition of chest irradiation to VPAV in a subgroup of patients. Combined chest irradiation and chemotherapy in randomized studies resulted in better complete response rates and relapse-free survival when compared with combination chemotherapy without chest irradiation [25, 26]. However, in a large randomized study, chest irradiation produced no survival advantage to those who received it [27] and it is difficult to demonstrate an overall survival gain by addition of chest irradiation to combination chemotherapy [28].

Ifosfamide/mesna was active in patients resistant to prior treatment, producing regressions in 43% of assessable patients. In patients already responding to prior therapy, ifosfamide may have contributed to further tumour regression, but did not produce CR in most. Ifosfamide with VP16 after cyclical alternating chemotherapy for SCLC did not increase CR rate or prolong survival [29] but this was not surprising as ifosfamide and VP were 3rd line chemotherapy. Ifosfamide, although inducing a 43% partial response rate, in our experience failed to produce any complete responses in patients resistant to prior therapy, indicating the existence of substantial cytotoxic drug resistance at the time of ifosfamide administration Goldie and Coldman [30] suggested that resistance of neoplasms to

chemotherapy can occur as a result of random mutations which are selected into prominence by the presence of the chemotherapeutic agent. A similar mechanism is relevant to gene amplification and selection of cells with particular amplified target genes. The genes coding for multidrug resistance (P glycoprotein) have been identified in many cells *in vitro*. In clinical practice, drugs to which multidrug resistance can develop are often used in combination and would therefore be expected to be potent selectors for MDR. If the MDR phenotype were the major cause of clinical resistance in SCLC, then a greater response to ifosfamide might have been expected, since resistance to ifosfamide by the MDR phenotype has not been demonstrated. Our results suggest that factors other than the MDR phenotype underlay the observed results with crossover to ifosfamide. Other mechanisms of drug resistance with or without the presence of MDR were likely to have been operative in our patients on crossover to ifosfamide. Clonal heterogeneity of SCLC suggests that drug resistance in many cases may exist prior to the start of any therapy [22].

Toxicity of short courses of ifosfamide with uroprotection by mesna was mild with minimal marrow suppression as assessed by pre-treatment cycle full blood counts, suggesting that ifosfamide/mesna could be safely combined with other cytotoxics and used earlier in the course of SCLC. Some of our patients had brief courses of high dose corticosteroids with ifosfamide and there are possible interactions between corticosteroids and alkylating agents. Chlorambucil, nitrogen mustard and phenyl acetic mustard were potentiated by steroids in two solid tumours and therapeutic index was enhanced [31]. However, the systemic toxicity of melphalan and cyclophosphamide was greater with steroids but the drug activity was increased against two alkylating agent resistant tumours. In general, there was enhancement of activity against alkylating agent resistant rodent tumour cell lines [31]. In patients, there are few randomized studies but the addition of continuous prednisone to adjuvant cyclophosphamide, methotrexate and 5-fluorouracil did not modify the effectiveness of the regimen, although it increased tolerance [32].

Late intensification with high dose cyclophosphamide after induction with VP16, doxorubicin and vincristine resulted in high responses but no apparent survival benefit in SCLC [33]. This approach produced an overall median survival of 11 months and induced severe myelotoxicity despite autologous marrow support in some patients. Similarly, late intensification therapy with high dose cyclophosphamide with or without other cytotoxics and autologous marrow support has yet to show significant survival benefit [34, 35].

Our data suggests that late intensification with short courses of ifosfamide 5 g/m^2 and mesna uroprotection could be used for patients in response to induction therapy without loss of survival benefit and with little toxicity and expense by comparison with high dose cyclophosphamide. Despite the activity of ifosfamide in SCLC, it was not effective in preventing cerebral metastases.

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