Pergamon

European Journal of Cancer Vol. 30A, No. 3, pp. 299–303, 1994
Printed in Great Britain.
0959–8049/94 $6.00+0.00

VP-16, Ifosfamide and Cisplatin (VIP) for Extensive Small Cell Lung Cancer

W.K. Evans, D.J. Stewart, F.A. Shepherd, D. Logan, G. Goss, J.A. Maroun, R. Wierzbicki, E. Warner, J. Latreille and S. Dahrouge

Thirty-seven extensive disease SCLC patients were treated with ifosfamide 1.0 g/m² (maximum 1.75 g), VP-16 (etoposide) 75 mg/m² and cisplatin 20 mg/m² (VIP) daily for 5 days in hospital. Mesna was given as a continuous infusion until 12 h after the last ifosfamide dose. Treatment was reduced to 4 days after the first 8 patients experienced serious myelotoxicity. 30 patients were evaluable for response. 8 (27%) achieved a complete response and 60% had a partial response. The median duration of response was 23 weeks. The median survival of all 37 patients was 41 weeks, and 47 weeks for the 30 evaluable patients. Fifty per cent and 26% of the evaluable treatment courses were associated with grade 4 and 3 granulocytopenia, respectively. There were eight febrile events including four treatment-related deaths from sepsis on the 5-day regimen. Although the response to VIP was generally rapid, the proportion achieving complete response (27% of evaluable patients) and the median survival is similar to standard chemotherapy regimens which are less toxic and less complex to administer.
Eur J Cancer, Vol. 30A, No. 3, pp. 299–303, 1994

INTRODUCTION

EXTENSIVE SMALL cell lung cancer (SCLC) patients have a poor prognosis. Only 20% achieve a complete remission (CR) and their median survival time is approximately 33 weeks [1]. Etoposide and cisplatin (EP), one of the most clinically active regimens, is commonly used alone or is alternated with CAV (cyclophosphamide, doxorubicin, vincristine) [2, 3]. EP produces response rates and survival comparable or superior to CAV [4], it induces responses in >50% who fail CAV [5] and can be given successfully with thoracic irradiation without unacceptable toxicity [6].

Ifosfamide, a cyclophosphamide analogue with different metabolism and pharmacokinetics [7], lacks clinical cross resistance with cyclophosphamide [8]. The single-agent response rate in previously untreated SCLC is 70% [9], and it has been studied in combination with other cytotoxic agents [10, 11]. The risk of haemorrhagic cystitis has been reduced significantly by giving the uroprotective agent mesna [12]. As ifosfamide is less myelotoxic than cyclophosphamide and is active against SCLC, we studied VP-16 (etoposide), ifosfamide and cisplatin (VIP) in patients with measurable extensive SCLC.

PATIENTS AND METHODS

Patients were entered on to the study from May 1988 to October 1991 from four Canadian cancer treatment centres. All patients had histological or cytological proof of SCLC and extensive disease by standard definition including cytology-positive pleural effusion. No patient had received prior chemotherapy or radiotherapy.

Correspondence to W.K. Evans at the Ottawa Regional Cancer Centre, 190 Melrose Avenue, Ottawa, Ontario K1Y 4K7, Canada.
W.K. Evans, D.J. Stewart, D. Logan, G. Goss, J.A. Maroun and S. Dahrouge are at the University of Ottawa and Ottawa Regional Cancer Centre, 190 Melrose Avenue, Ottawa, Ontario K1Y 4K7; F.A. Shepherd and E. Warner are at The Toronto Hospital; J. Latreille is at the Hotel Dieu de Montreal; and R. Wierzbicki is at the Cancer Treatment and Research Foundation of Nova Scotia, Canada.
Revised 30 Sep. 1993; accepted 11 Oct. 1993.

At entry, patients had a history and physical examination, body surface area estimate, performance status assessment, renal and hepatic biochemical tests, a chest X-ray, and imaging of brain, bone and liver. Bone marrow aspiration and biopsy were optional. All patients had bidimensionally measurable lesions of at least 2 cm diameter, white cell count > 4.0×10^9/l, absolute granulocyte count > 2.0×10^9/l, platelet count > 125×10^9/l, serum albumin > 35 g/l and an Eastern Cooperative Oncology Group (ECOG) performance status < 3. Initially, patients had to be < 65 years, but during the study this was modified to < 70 years. Similarly, patients had to have a creatinine clearance of > 1.5 ml/s but this criteria was waived during the study if the serum creatinine was < 130 μmol/l.

Patients were ineligible if they had no measurable disease, mixed histology, a previous malignancy or had a history of myocardial infarction within 3 months, decompensated heart failure, an ejection fraction > 10% below normal, or irreversible arrhythmias. Also excluded were patients with brain metastases or active infections.

Chemotherapy administration

Initially, VIP was given over 5 days. However, due to grade 3–4 myelosuppression in the first 8 patients, therapy was reduced to 4 days resulting in a 20% dose reduction. On day 1, patients were hospitalised, prehydrated with 500 ml of normal saline (N/S) over 2 h and given dexamethasone 10 mg intravenously (i.v.), prochlorperazine 10 mg orally (p.o.) and metoclopramide 20 mg i.v. This was followed by mesna 100 mg/m² in 50 ml of N/S over 5–10 min, etoposide 75 mg/m² in 250 ml of N/S over 60 min, cisplatin 20 mg/m² in 250 ml of N/S over 60 min and, finally, ifosfamide 1.0 g/m² (maximum 1.75 g) in 100 ml of N/S over 15–20 min. A continuous infusion of mesna 900 mg/m² in 750 ml of N/S was given over the remainder of the 24 h following chemotherapy on each of the treatment days. Twelve hours after the last dose of ifosfamide, the infusion of mesna was stopped. Prochlorperazine [10 mg p.o. or intramuscularly (i.m.)] and dexamethasone (2 mg i.v. or p.o.) were given every 6 h during chemotherapy. If there were > 10 red blood cells per high-

power field on the daily urinalysis, ifosfamide was withheld and mesna was infused until the haematuria resolved. Patients were observed closely for ifosfamide-induced encephalopathy.

Chemotherapy was repeated every 21–28 days. Drug dosages were adjusted according to nadir and treatment day blood counts. Doses were reduced by 25% for a nadir granulocyte count $< 0.2 \times 10^9$/l or platelet count $< 50 \times 10^9$/l or for treatment day granucloctye counts of $1.5–1.99 \times 10^9$/l. Therapy was withheld until granulocytes rose to $> 1.5 \times 10^9$/l. Cisplatin and ifosfamide were given if the serum creatinine was < 130 μmol/l, and withheld until recovery when this level was exceeded. Narcotics, anxiolytics and sedating antiemetics were to be avoided to permit detection of ifosfamide-induced encephalopathy. If severe drowsiness occurred within 24–72 h of therapy without obvious cause, ifosfamide was reduced by 25% or discontinued.

Patients with a CR or partial response (PR) were considered for prophylactic cranial irradiation using 20 Gy in five fractions after the fourth cycle. Maintenance chemotherapy was not given. If disease progression occurred during or after VIP treatment, patients were treated with CAV or a phase II trial agent.

Response criteria

Response to therapy was determined by monthly clinical assessment, chest X-ray, liver function tests and periodic imaging studies as clinically indicated. Standard response criteria were used. Bronchoscopy was not repeated to define the completeness of response. Response duration was calculated from documented CR or PR to relapse or last follow-up. Time to progression (TTP) was calculated from the start of therapy to disease progression or last follow-up. Survival was measured from first treatment to the date of death from any cause or last follow-up. Kaplan–Meier estimates were made for TTP, response duration (RD) and survival duration (SD) [13]. Toxicity was graded using American National Cancer Institute toxicity criteria.

The study protocol was reviewed by the ethics review boards of all participating institutions. Each patient entered on the study gave written informed consent.

RESULTS

38 patients were entered on to the study. One patient with limited disease was excluded from analysis. The characteristics of the 37 patients are shown in Table 1. Seventy-six per cent of patients were ECOG performance status 0 or 1, 19% were ECOG 2 and 5% were ECOG 3. Liver and bone were common sites of metastases (59 and 35%, respectively).

A number of patients (14) did not meet all eligibility criteria. 5 patients had baseline creatinine clearances < 1.5 ml/s and were entered prior to protocol revision allowing entry if the serum creatinine was normal. 2 patients had pretreatment platelet counts $< 125 \times 10^9$/l which in one case was due to documented bone marrow involvement. 3 patients had mixed histology. 2 patients had brain metastases, 1 of whom had mixed histology. One patient, aged 69 years, was admitted to the study when the eligibility criteria was < 65 years. 2 patients had a performance status of 3. These patients were included in the response, survival and toxicity analyses.

Initially, VIP was given for 5 days, but this was reduced to 4 days due to severe myelotoxicity. 6 patients received all four cycles as 5-day VIP and 2 patients received three cycles of 5-day VIP and one cycle of 4-day VIP. Efficacy and toxicity data for the two regimens have been analysed separately and together.

Table 1. Characteristics of 37 patients with extensive small cell lung cancer treated with VIP

Characteristic	Total no. (%)
Sex	
Male	23 (62)
Female	14 (38)
Age (years)	
Median	60
Range	38–70
ECOG performance status	
0	6 (16)
1	22 (60)
2	7 (19)
3	2 (5)
Metastatic sites	
Liver	22 (59)
Bone	13 (35)
Abdominal lymph nodes	6 (16)
Adrenal gland	6 (16)
Bone marrow	5 (14)
Pleural effusion	4 (11)
Brain	2 (5)
Pancreas	1 (3)

Response

7 of 37 patients are inevaluable for response. 2 patients died of sepsis, 13 and 17 days after the first treatment. A third patient died from pneumonia after the second cycle before full evaluation. One patient was lost to follow-up, and 1 refused further therapy after the first cycle. Another patient was removed from the study due to a significant decrease in renal function after the first cycle. Finally, 1 patient received radiation for haemoptysis not due to disease progression.

8 of the 30 evaluable (27%) patients acheived a CR (Table 2). 18 patients (60%) had a PR. Among the PRs was 1 patient who had a CR radiologically but died before the response duration criteria were met; a second patient who attained CR only after radiotherapy and a third patient with bone metastases who had complete regression in lung and liver but whose bone disease was not re-evaluated. Seven per cent of patients had stable

Table 2. Analysis of response and survival by treatment regimen in 30 evaluable patients treated with VIP

	Best response to chemotherapy regimen		
	4-day ($n = 24$)	5-day ($n = 6$)	Both ($n = 30$)
Complete response	5 (21%)	3 (50%)	8 (27%)
Partial response	15 (63%)	3 (50%)	18 (60%)
Stable disease	2 (8%)	0 (0%)	2 (70%)
Progressive disease	2 (8%)	0 (0%)	2 (70%)
Median time to progression*	25	29	27
(range)	(13–112)	(15–50)	(13–112)
Median response duration*	19	26	23
(range)	(8–108)	(6–43)	(6–108)
Median survival duration*	47	50	47
(range)	(1–118)	(2–200)	(1–200)

*Time in weeks.

disease and 7% had disease progression. The median duration of response was 23 weeks (range 6–108). The median time to progression was 27 weeks in the 28 responding or stable patients. A Kaplan–Meier survival curve for all 37 patients is shown in Fig. 1, and the median survival of all study patients was 41 weeks (range 1–200). The median survival time for the 30 evaluable patients was 47 weeks.

For the 8 patients who received all or part of their therapy as 5-day VIP, response rates, TTP, response duration and survival did not differ from those receiving 4-day VIP.

Performance status improved in 10 patients and remained stable in 12. For the 5 patients with disease progression and 10 patients with substantial treatment-related toxicity, performance status deteriorated. Similarly, for those without disease progression or substantial toxicity, 8 gained weight, 11 maintained their pretreatment weight and 3 suffered weight loss.

Side-effects

The worst side-effects experienced by each patient are listed in Table 3. This analysis and the analysis of toxicity by treatment cycle indicate that the most important side-effect of VIP was myelosuppression. Of the 113 treatment cycles for which complete haematological data were available, 29 (26%) were associated with grade 3 granulocytopenia and 56 (50%) with grade 4 ($< 0.5 \times 10^9$/l). Grade 4 granulocytopenia was more severe for 5-day VIP than for 4-day VIP (67 versus 46%). The median nadir granulocyte count was 0.345×10^9/l for 5-day VIP (range 0–2.68) and 0.583×10^9/l for 4-day VIP (range 0–11.9) ($P = 0.08$, Mann–Whitney U-test). During the 5-day VIP, all 7 evaluable patients had at least one episode of grade 4 granulocytopenia, and there were eight febrile events during the 24 treatment cycles. There was one febrile neutropenia without a source of infection, two urinary tract infections, one upper respiratory infection, two deaths from septic shock, one death from pneumonia and one death from necrotising colitis. After the 20% dose reduction, there were seven episodes of neutropenic fever, five upper respiratory tract infections and one urinary tract infection in 29 patients over 97 cycles of 4-day VIP and no septic deaths.

Grades 3 and 4 thrombocytopenia were also more frequent with 5-day VIP (41 versus 16%). Anaemia occurred with approximately the same frequency on the two regimens based on the total number of cycles analysis. According to the protocol, dose reductions for myelotoxicity should have been made in 24 instances but were done in only 9.

Table 3. Analysis of worst grade of toxicity experienced by each of the 37 patients according to treatment regimen

Toxicity	Grade	Treatment regimen: 4-day cycle ($n = 29$)	5-day cycle ($n = 8$)	All cycles ($n = 37$)
Granulocytopenia				
	0	1 (3%)	0 (0%)	1 (3%)
	1	0 (0%)	0 (0%)	0 (0%)
	2	4 (14%)	0 (0%)	4 (11%)
	3	5 (17%)	0 (0%)	5 (14%)
	4	19 (66%)	8 (100%)	27 (73%)
Thrombocytopenia				
	0	7 (24%)	0 (0%)	7 (19%)
	1	11 (38%)	2 (25%)	13 (35%)
	2	1 (3%)	0 (0%)	1 (3%)
	3	6 (21%)	4 (50%)	10 (27%)
	4	4 (14%)	2 (25%)	6 (16%)
Anaemia				
	0	2 (7%)	0 (0%)	2 (5%)
	1	8 (28%)	1 (13%)	9 (24%)
	2	12 (41%)	4 (56%)	16 (43%)
	3	6 (21%)	2 (25%)	8 (22%)
	4	1 (3%)	1 (13%)	2 (5%)
Nausea/vomiting				
	0	4 (14%)	1 (13%)	5 (14%)
	1	15 (52%)	5 (63%)	20 (54%)
	2	10 (35%)	1 (13%)	11 (30%)
	3	0 (0%)	1 (13%)	1 (3%)
	4	0 (0%)	0 (0%)	0 (0%)
Diarrhoea				
	0	26 (90%)	5 (63%)	31 (84%)
	1	3 (10%)	2 (25%)	5 (14%)
	2	0 (0%)	1 (13%)	1 (3%)
	3	0 (0%)	0 (0%)	0 (0%)
	4	0 (0%)	0 (0%)	0 (0%)
Mucositis				
	0	23 (79%)	6 (75%)	29 (78%)
	1	3 (10%)	2 (25%)	5 (14%)
	2	3 (10%)	0 (0%)	3 (8%)
	3	0 (0%)	0 (0%)	0 (0%)
	4	0 (0%)	0 (0%)	0 (0%)

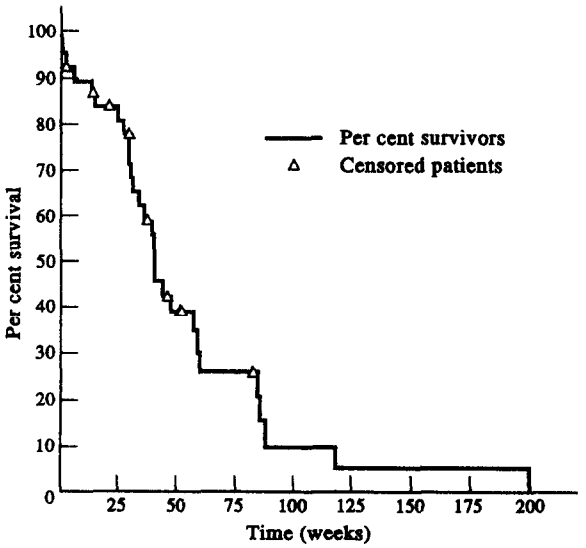

Fig. 1. VIP in small cell lung cancer (all 37 patients).

Other treatment toxicities were much less severe. In 36% (43/121) of all treatment cycles there was no nausea or vomiting, while 49% (59/121) experienced grade 1 nausea and vomiting, and 16% required parenteral antiemetics. For all cycles, grades 1 and 2 diarrhoea occurred in 7%, grade 1 or 2 mucositis in 8%.

With regard to ifosfamide encephalopathy, a significant number of symptoms were reported, but none were directly attributable to ifosfamide. The only serious neurological problem was the development of seizures in a patient with a normal computed tomography scan who suffered a fatal septic episode. In all other cases, the symptoms resolved without sequelae upon withdrawal of neurotropic drugs.

Urinary tract problems were infrequent. Ten of 121 treatment cycles were associated with microscopic haematuria, of which one was due to early mesna discontinuation. No episode of haematuria prevented further ifosfamide therapy. 4 patients had a decline in creatinine clearance and/or a modest rise in serum

creatinine. 1 patient had serious renal toxicity as the serum creatinine rose to 316 μmoles/l, but recovered when therapy was discontinued.

The large volume of fluid administered with the chemotherapy resulted in mild oedema in 6 patients (10 cycles) and grade 2 oedema in 4 patients (five cycles). All patients developed alopecia.

No patients developed metabolic acidosis or the syndrome of inappropriate antidiuretic hormone secretion secondary to ifosfamide.

DISCUSSION

Treatment results for extensive SCLC plateaued in the early 1980s. None of the recent innovative approaches have proven superior to standard regimens. This includes the use of dose-intensive weekly drug administration [14], alternating non-cross resistant chemotherapy regimens [15], consolidation chemotherapy with autologous bone marrow transplantation [16] and the addition of active new agents to standard regimens.

In this trial, we added ifosfamide to the standard EP regimen because it was an alkylating agent with broad spectrum antitumour activity [7], it was synergistic with cisplatin in preclinical studies [7] and it had demonstrated a 70% response rate in previously untreated patients with SCLC [9]. Also, the efficacy of VIP in testicular cancer refractory to etoposide–cisplatin was extremely encouraging [17]. Full doses of ifosfamide were added as this drug was less myelosuppressive than cyclophosphamide [8] in a randomised phase II trial in soft tissue sarcomas. As SCLC patients are older and less likely to tolerate intensive chemotherapy, the drug doses used were slightly less than those reported by Loehrer for testicular cancer treatment [17]. In particular, the ifosfamide dose was reduced from 1.2 to 1.0 g/m^2 daily for 5 days. Unfortunately, the same amount of drug that heavily pretreated testicular cancer patients tolerated could not be delivered [17]. The four early deaths among the first 8 patients probably occurred because our patients were older (average age 60 years), they were all smokers with chronic chest disease and they were hospitalised for their therapy during which nosocomial colonisation may have occurred. Even after dosage reduction, serious myelosuppression occurred with a median nadir granulocyte count of 0.583×10^9/l.

Although VIP can be given in an outpatient setting, we hospitalised our patients to ensure continuous mesna administration to prevent haemorrhagic cystitis and to permit close observation of ifosfamide encephalopathy. Neither of these side-effects occurred frequently.

The antitumour effects of VIP were significant, but not dramatically different from other regimens. The overall response rate of 87% in evaluable patients is similar to our prior experience with EP alone in extensive disease [4], and is similar to the National Cancer Institute of Canada's experience with alternating CAV and EP [2]. The CR rate of 27% in evaluable patients is also similar to our previous studies (20%), but the 95% confidence limits around this response rate are quite wide (8.7–35.3%)

This study's results are nearly identical to those reported by Loehrer and coworkers in 40 extensive SCLC patients. They also found the 5-day VIP to be excessively myelosuppressive [18], with two septic deaths in the first 11 patients, and a total of five early deaths in the course of the study. The overall response rate in both our study and that of Loehrer was 71%, while the CR rate in the Loehrer study was higher (37%) than in our study (27%). This latter difference may not be significant, as patient survival was almost identical (41 versus 42 weeks). Based on their results, the Hoosier Oncology Group is conducting a study randomising extensive SCLC patients between EP and VIP.

Two other phase II studies incorporating ifosfamide have yielded encouraging results. Thatcher combined etoposide 120 mg/m^2 i.v. days 1 and 2 and 240 mg/m^2 p.o. day 3 with 5 g/m^2 ifsofamide day 1 and 300 mg/m^2 carboplatin day 1 every 4 weeks for six cycles [10]. The response rate in 37 patients was 95% with a 60% CR. Similarly, Smith gave etoposide 100 mg/m^2 days 1 to 3 with ifosfamide 5 g/m^2 day 1 and carboplatin 400 mg/m^2 day 1 every 4 weeks for six cycles [11]. 26 of 27 patients (96%) responded, with 11 CRs.

Despite these results, the role of ifosfamide will only be determined through randomised controlled clinical trials. The Hoosier Oncology Group study should help to define whether ifosfamide increases survival over that achieved with EP alone in the palliation of extensive SCLC patients. If a higher CR rate is confirmed, the VIP regimen might have greater utility in the treatment of limited SCLC, where the achievement of CR is a necessary prerequisite for long-term survival and possible cure.

1. Seifter EJ, Ihde DC. Therapy of small cell lung cancer: a perspective on two decades of clinical research. *Sem Oncol* 1988, **15**, 278–299.
2. Evans WK, Feld R, Murray N, *et al.* Superiority of alternating non-cross-resistant chemotherapy in extensive small cell lung cancer: a multi-centre, randomized clinical trial by the National Cancer Institute of Canada. *Ann Int Med* 1987, **107**, 1451–1458.
3. Roth BJ, Johnson DH, Einhorn LH. A randomized study of cyclophosphamide, doxorubicin, vincristine versus etoposide and cisplatin versus alteration of these two regimens in extensive small cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992, **10**, 282–291.
4. Evans WK, Shepherd FA, Feld R, *et al.* VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985, **3**, 1471–1477.
5. Evans WK, Osoba D, Feld R, *et al.* Etoposide (VP-16) and cisplatin: an effective treatment for relapse in small cell lung cancer. *J Clin Oncol* 1985, **3**, 65–71.
6. Turrisi AT, Glover DJ, Mason B, Tester W. Long term results of platinum-etoposide + twice daily (BID) thoracic radiotherapy for limited small-cell lung cancer: results on 32 patients with 48 month minimum followup. *Proc Am Soc Clin Oncol* 1992, **11**, 292 (abstract 975).
7. Dechant KL, Brogden RN, Pilkington T, Faulds D. Ifosfamide/mesna. A review of its antineoplastic activity, pharmacokinetic properties and therapeutic efficacy in cancer. *Drugs* 1991, **42**, 428–467.
8. Bramwell VHC, Muridsen HT, Santoro A, *et al.* Cyclophosphamide versus ifosfamide: a final report of a randomized phase II trial in adult soft tissue sarcoma. *Eur J Cancer Clin Oncol* 1987, **23**, 311–321.
9. Warenius HM, Hurman DC, Cottier B. High-dose ifosfamide in small cell lung cancer. *Br J Cancer* 1986, **54**, 216 (abstract).
10. Thatcher N, Lind MJ, Smith DB, *et al.* Carboplatin, ifosfamide, etoposide with mid-course vincristine for limited small cell lung cancer. *Br J Cancer* 1989, **60**, 98–101.
11. Smith IE, Perren TJ, Ashley SA, *et al.* Carboplatin, etoposide and ifosfamide as intensive chemotherapy for small-cell lung cancer. *J Clin Oncol* 1990, **8**, 899–905.
12. Bryant B, Ford H, Jarman M, *et al.* Prevention of ifosfamide-induced urothelial toxicity with 2-mercaptoethane sulphonate sodium (mesna) in patients with advanced carcinoma. *Lancet* 1980, **2**, 657–659.
13. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1981, **53**, 457–481.
14. Murray N, Shah A, Osoba D, *et al.* Intensive weekly chemotherapy for the treatment of extensive-stage small-cell lung cancer. *J Clin Oncol* 1991, **9**, 1632–1638.
15. Osterlind K. Alternating versus sequential chemotherapy in small cell lung cancer. *Lung Cancer* 1989, **5**, 173–177.
16. Sculier JP, Klastersky J. High-dose chemotherapy of small-cell lung

cancer with and without bone marrow transplantation. In Hansen HH, ed. *Basic and Clinical Concepts of Lung Cancer*. Boston, Kluwer Academic Publishers, 1989, 259–274.
17. Loehrer PJ, Laurer P, Roth BJ, *et al.* Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. *Ann Int Med* 1980, 7, 540–546.
18. Loehrer PJ, Rynard S, Ansari R, *et al.* Etoposide, ifosfamide, and cisplatin in extensive small cell lung cancer. *Cancer* 1992, **69**, 669–673.

Acknowledgements—The authors wish to thank Chris Allen for careful preparation of the manuscript and Brenda Waterfield for data collection.

Pergamon

European Journal of Cancer Vol. 30A, No. 3, pp. 303–307, 1994

0959–8049/94 $6.00+0.00

0959-8049(93)E0033-M

Subsequent Primary Cancers Following Bladder Cancer

E. Salminen, E. Pukkala, L. Teppo and S. Pyrhönen

The incidence of a subsequent primary cancer was investigated among 10 014 patients with cancer of the urinary bladder diagnosed in 1953–1989 in Finland. During the follow-up period of 1953–1989, 652 new metachronous cancers were diagnosed. The number equals the expected number based on the national incidence figures. There were 195 second cancers of the lung. The standardised incidence ratio (SIR) for lung cancer was 1.3 among males [95% confidence interval (CI) 1.1–1.4] and 2.6 among females (95% CI 1.4–4.5). An increased SIR for larynx cancer in males (SIR=1.7, 95% CI 0.91–2.8) and for kidney cancer in females (SIR=3.6, 95% CI 1.8–6.2) was observed. The risk of a second cancer was greater among patients less than 60 years of age at the time of first diagnosis than among older patients. No consistent differences were observed in the risk of new cancer between bladder cancer patients treated with or without radiotherapy.

Key words: urinary bladder cancer, second primary cancer, standardised incidence ratio, radiotherapy
Eur J Cancer, Vol. 30A, No. 3, pp. 303–307, 1994

INTRODUCTION

WITH THE increase in the incidence of cancer and improvement in both early diagnosis and treatment, the number of surviving cancer patients is increasing [1]. Therefore, knowledge of the risk of new primary cancers is important. Second primary cancer is defined as an independent new primary malignant tumour arising after the diagnosis of the first neoplasm [2]. Each tumour must be distinct and must present a definite pattern of malignant disease. Metastases from other organs must also be excluded. In multiple cancer studies both aetiological aspects and treatment-related factors can be investigated. The purpose of the present study was to estimate the risk of a subsequent new cancer among urinary bladder cancer patients, especially after radiation therapy.

Correspondence to E. Salminen at the Department of Oncology, Turku University Central Hospital, Kiinamyllynkatu 4–8, 20520 Turku, Finland.
E. Pukkala and L. Teppo are at the Finnish Cancer Registry, Liisankatu 21B, 00170 Helsinki; and S. Pyrhönen is at the Department of Radiotherapy and Oncology, Helsinki University Central Hospital, 00290 Helsinki, Finland.
Revised 11 Oct. 1993; accepted 11 Nov. 1993.

MATERIALS AND METHODS

The files of the Finnish Cancer Registry (founded in 1952) cover all cancer cases diagnosed in the country. They include cancers diagnosed and/or treated in hospitals or by medical practitioners, those verified in pathological and cytological laboratories and those mentioned in death certificates. The percentage of microscopic verification (i.e. histology or cytology) increased from about 50% in the mid-1950s to over 90% in the early 1970s [3]. The records for the period from 1953 to 1989 were analysed to assess the risk of patients with cancer of the urinary bladder of developing a new malignant tumour. Papillomas of the bladder were excluded from the patient material. One should notice, however, that in the 1950s and 1960s the diagnosis of papilloma was more widely used than today when these tumours are often designated as carcinomas grade I. Thus, the more recent part of the urinary bladder carcinoma material includes tumours that in the past would have been called papillomas.

The follow-up started 5.5 months after the diagnosis of bladder cancer, and ended at the date of death, emigration or on December 31 1989, whichever came first. Subsequent cancers diagnosed during the follow-up time were tabulated according to sex, primary site, age at the time of diagnosis of the new cancer and time since the date of diagnosis of the first primary.