Eur J Cancer, Vol. 28A, No. 6/7, pp. 1081–1084, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Teniposide as Single Drug Therapy for Elderly Patients Affected by Small Cell Lung Cancer

Diego Tummarello, Pierpaolo Isidori, Felice Pasini, Gianluigi Cetto and Riccardo Cellerino

From January 1987 to December 1990, 26/105 previously untreated patients affected by small cell lung cancer (SCLC), not suitable for intensive SCLC treatment since 19 of them were older than 70 years and 7 suffered from severe chronic diseases, received induction therapy consisting of teniposide alone, 60 mg/m² on days 1–5, every 3 weeks until disease progression. After a minimum of two courses, 24 patients were evaluable for response: 13 with limited disease (LD) and 11 with extensive disease (ED) (2 patients were unevaluable: 1 early death and 1 protocol violation). Response rate, by disease stage, was: in the 13 LD, 1 complete response (CR), 8 partial responses (PR), 2 minor responses and 2 failures; in the 11 ED, 1 CR, 4 PR and 6 failures. The overall response rate was 58% (14/24) (95% confidence limits = 38–78%), comprising 8% CR and 50% PR. Median duration of response was 7 months (range 2–32). Median overall duration of survival was 9 months (range 1.5–36+). Toxicity was haematological WHO grade III in 13% of courses delivered, whereas no further important side-effects were recorded, excluding alopecia, which was common. Teniposide used alone appeared a safe and effective palliative treatment for poor-risk patients; the major limitation was the low CR rate.
Eur J Cancer, Vol. 28A, No. 6/7, pp. 1081–1084, 1992.

INTRODUCTION

PEOPLE AGED 70 years and more are increasing in number in most western countries; the frequency of malignancies increases sharply with age and lung cancers make no exception to this rule [1–3]. As a result, elderly patients with lung cancer are growing in number and more studies are needed on these age groups [4, 5].

Small cell lung cancer (SCLC) accounts for about a quarter of all lung cancers and old patients represent about 18–25% of all new cases of SCLC [6, 7]. SCLC is a disease chemosensitive to numerous cytotoxic drugs such as alkylating agents, anthracyclines, platinum compounds, vinca alkaloids and podophyllotoxin derivatives, both used alone and in combination. At conventional doses, 3–4 drug combinations have been firmly established to be more effective than single-agent therapy; however, toxicity by multidrug combinations is also higher [8].

Elderly patients affected by SCLC, either with organic impairments or the presence of chronic diseases, are more susceptible to toxic complications [9, 10]. Usually, they do not comply with standard multidrug SCLC protocols and, often, are excluded from intensive chemotherapy studies because of their association with a high morbidity and mortality rate. Therefore, in many instances, these patients receive little or inadequate therapy and more appropriate regimens need to be defined [11, 12].

Recently, to limit toxic complications, single-agent therapy with podophyllotoxin derivatives such as etoposide or teniposide, drugs very active against SCLC, was reconsidered for elderly patients with SCLC [13–15]. Based on schedules with single moderate doses delivered over 3–5 consecutive days, early studies on series of elderly patients, previously untreated, appeared extremely promising.

Smit *et al.* [13], using etoposide orally given over 5 consecutive days, found 71% antitumoural response rate, whereas Bork *et al.* [14], with teniposide intravenously administered, reported up to a 90% response rate with moderate toxicity. However, more recent observations in the literature have been less optimistic as well as conflicting, with response rates ranging from 33% to 71% [16–18]. Therefore these results, though interesting, still remain undefined and further confirmations are needed.

In the present study we evaluated teniposide as a single-agent schedule in previously untreated patients affected by SCLC who, being aged over 70 years and/or suffering from severe chronic diseases, did not fulfil criteria for standard protocol entry.

PATIENTS AND METHODS

From January 1987 to December 1990, 26 out of 105 admitted patients with histologically or cytologically proven SCLC were entered into this study. Requisites for entry were: age older than 70 years or concurrent chronic diseases that did not meet the eligibility criteria of our SCLC standard protocol; Karnofsky score ≥70; life expectancy ≥2 months; normal blood cell counts; evaluable or measurable disease; and no prior chemotherapeutic treatments. Patients with central nervous system (CNS) metastases were also evaluated and were treated with additional brain irradiation. Before treatment, all patients underwent standard staging procedures according to the international guidelines for SCLC. Clinical investigations included: complete history, physical examination, blood chemistry, chest X-rays, bronchoscopy, isotopic bone scan, brain and chest computed tomography (CT), abdominal ecography and bone marrow biopsy. Extent of disease was assessed as limited (LD) when confined to 1 hemithorax, the mediastinum and ipsilateral hilar and

Correspondence to D. Tummarello.
D. Tummarello and R. Cellerino are at the Oncologia Medica, Universita' di Ancona, Ospedale Torrette, 60020 Ancona; F. Pasini and G. Cetto are at the Department of Medical Oncology, University of Verona, Verona; and P. Isidori is at the Division of Pneumology, Hospital of Pesaro, Pesaro, Italy.
Received 16 Dec. 1991; accepted 19 Dec. 1991.

supraclavicular limph nodes; all other conditions were considered as extensive disease (ED) [19].

Treatment employed consisted of: teniposide 60 mg/m^2 dissolved in 500 ml of 5% glucose or 0.9% saline solution and administered intravenously in 1 h, on days 1–5, every 3 weeks, until progression. When indicated, drug doses were adjusted or treatment was delayed according to blood cell counts. Patients failing to respond to teniposide and those relapsed after a tumoural remission were not scheduled to receive second-line chemotherapy. Palliative or consolidating radiotherapy was delivered when clinically indicated.

Response categories

Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were assessed after a minimum of two cycles of chemotherapy based on WHO accepted criteria [20]. Also, minor response (MR) was defined as unequivocal tumour reduction which did not fulfil the criteria of PR. Patients classified as complete responders following restaging procedures were submitted to bronchoscopy plus biopsy, to confirm the response histologically or cytologically.

The duration of response as well as extent of survival was computed starting from the first day of teniposide therapy. The actuarial survival curve was plotted according to the Kaplan–Meier method. Toxicity, by the WHO scale, was assessed by calculating the number of courses associated with toxicity in relation to the total courses of teniposide delivered to the patients.

RESULTS

Patients enrolled in this study were the 24.7% of the total population observed over 4 years (26/105). All the 26 examined patients were evaluable for survival; 24 of them were fully evaluable for response and 2 were not (1 patient, suffering from cardiopathy, died soon after the first cycle of therapy of unclear cause and was considered an early death; 1 patient was not evaluated because after the first course of teniposide he refused further therapy and periodical follow-up).

Among the 26 patients, 19 were aged more than 70 years (range 64–79) and 7, aged 64–69 years, were also included in the study because they suffered from debilitating chronic diseases: 3 were severe chronic bronchitis, 3 were heart diseases and 1 was a diabetic angiopathy. Because of such conditions they did not fulfil criteria for entry in our standard protocol.

The main characteristics of patients are summarised in Table 1. Median age was 73 years (range 64–79); male/female ratio was 23/3; performance status (Karnofsky index) was over 70 in 19 patients and equal to 70 in 7 patients; the stage of disease was limited (LD) in 14 patients and extensive (ED) in 12. Metastatic involvement was single in 5 patients (2 liver, 2 bone and 1 brain) and multiple in the remaining 7 patients.

The results of treatment are reported in Table 2. Following 2 cycles of teniposide, there were 2 CR, 12 PR, 2 MR, 5 SD and 3 PD. According to the stage of disease, major response rate was as follows: 1 CR and 8 PR in the 13 LD patients (69%), 1 CR and 4 PR in the 11 ED patients (45%). On the whole, we observed 14/24 (58%) major responses (CR+PR) with 95% confidence limits ranging from 38% to 78%. Median duration of response was 7 months (range 2–32).

4 patients with LD, 2 partially responsive and 2 stable on teniposide, in addition to chemotherapy, underwent chest radiotherapy up to 45 Gy, but no further change occurred in response rate. The patient with brain metastasis, simultaneously to chemotherapy, also received cranial irradiation (50 Gy). Patients who progressed or relapsed after treatment received no further chemotherapy.

Table 1. Characteristics of evaluable patients

No. of patients	26
Median age, years (range)	73 (64–79)
Male/female	23/3
Karnofsky index	
>70	19
=70	7
Stage of disease	
Limited	14
Extensive	12
Liver	6
Bone	5
Lymph nodes	4
CNS	1
Skin	1
Adrenal	1
Major chronic diseases	
Severe bronchitis	3
Diabetes and angiopathy	1
Heart diseases	3

Median suvival time was 10 months (range 3–36+) in LD patients and 9 months (1.5–21) in ED patients; overall, median survival was 9 months (1.5–36+) (Fig. 1). Toxicity secondary to treatment is summarised in Table 3.

Of the total courses of teniposide delivered, 124/130 (95%) were evaluable for toxicity. The main side-effects recorded were haematologic and gastrointestinal; WHO grade III myelosuppression was observed in 16/124 (13%) courses, while 4/124 courses were complicated by severe gastrointestinal effects. Only 1 course was complicated by WHO grade IV myelosuppression, recorded in the cardiopathy patient and stated as early death after the first cycle of therapy; however, it is uncertain if this death was directly related to drug toxicity or to heart failure. No other remarkable toxicities were recorded excluding alopecia, which was common.

DISCUSSION

Treatment of patients affected by SCLC in advanced age and/or with concomitant chronic diseases represents a major

Table 2. Response to treatment

	Stage of disease	
	LD	ED
No. of patients	13	11
Response		
CR	1	1
PR	8	4
MR	2	—
SD	1	4
PD	1	2
Median duration of response (range)	7 months (2–32)	

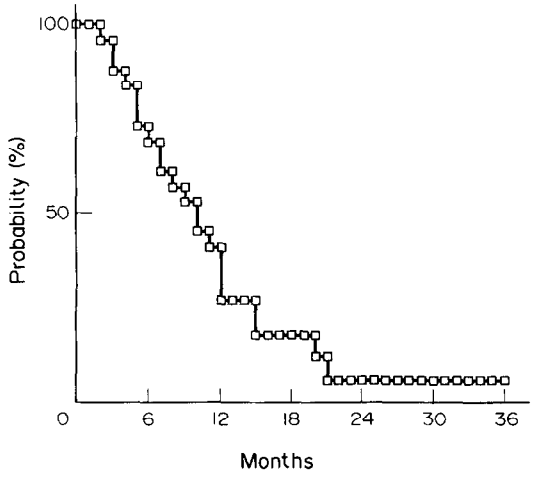

Fig. 1. Cumulative survival curve in the 26 patients.

*Table 3. Cycles of teniposide associated with toxicity**

	Toxicity: WHO grading				
	0	I	II	III	IV
Haematological	67	18	22	16	1
Gastrointestinal	97	15	8	4	

*Toxicity was evaluated on 124/130 cycles delivered.

problem in oncologic practice. Although old age, *per se*, has not been reported as an established factor capable of affecting treatment outcome [1], age-related changes in drug pharmacokinetics (i.e. alteration of drug absorption and distribution, drug clearance reduction etc.) or impaired recovery following drug toxicity have been considered adverse determinants for successfully intensive chemotherapy [21–24]. Therefore single-agent therapy with effective moderately toxic drugs appeared a reasonable alternative to supportive care or to the use of novel drugs in an experimental setting, the latter if ethically acceptable [25, 26].

Recently, Carney *et al.* [7] using etoposide alone, given orally for 5 days, observed 17 % of CRs and 62 % of PRs in a series of 53 subjects aged 70–95 years; toxicity was minimal and median survival was 9.5 months. Bork *et al.* [14] in an early phase II study with teniposide at a dose of 60 mg/m^2 on days 1–5, in a series of 33 untreated patients (all with WHO performance status <2 and 21 with LD), 27 of whom were older than 70 years, reported a 90% response rate including 30% CR; toxicity was mild, median duration of response was 8 months and median survival time 8.7 months (range 1.9–20).

Conversely, Cerny *et al.* [16], in a similar study, found less favourable results. Treating 30 elderly patients (median age 73 years) with a higher dose of teniposide (100 mg/m^2 for 5 consecutive days) they observed a 30% response rate and no CR. They mentioned 9 early deaths during the first 2 cycles of therapy, 5 of them due to septic complications. The differences compared with the results of Bork *et al.* [14] were in part explained by a higher rate of poor performance status (23% vs. 0%) and frequency of extensive disease (50% vs. 36%). Also Holoye *et al.* [17], employing the same schedule as Bork *et al.* [14], observed moderate results. In 24 untreated patients with extensive disease (WHO grade I–II performance status), they obtained 12 PR (50%) and no CR; neither response duration or median survival time were mentioned; toxicity was found moderate. Giaccone *et al.* [27] in a study carried out on both treated and untreated patients, using higher doses of teniposide (120–140 mg/m^2) given on days 1, 3, 5, every 3 weeks, reported a 36% response rate, including 1 CR, in the small subset of 12 untreated patients older than 70 years; toxicity was haematological WHO grade III–IV in 43% of cases (leukopenia), and in 13% of cases was thrombocytopenia; severe vomiting occurred in 30% of cases and no therapy related deaths were described.

Again Bork *et al.* [18], in a recent extensive study, compared at random teniposide to its analogue compound etoposide. Maximum teniposide doses used were 80 vs. 90 mg/m^2 of etoposide. Both schedules were given sequentially in 5 days, repeated every 3 weeks. Response rate was 71% (23% CR) with teniposide vs. 65% (24% CR) with etoposide; response duration with teniposide was 9 months and median survival 11.3 months vs. 8 months and 8.5 months for etoposide. Data were similar statistically and the authors concluded that both drugs have equivalent activity against SCLC, though a more frequent myelosuppression occurred with teniposide.

Table 4. Main recent studies on teniposide alone for treatment of elderly patients affected by SCLC

Studies	Schedule*	Patients & stage (LD/ED)	Median (years)	Response (%) CR	Response (%) PR	MDR (months)	MS (months)
Bork *et al.* [14]	60	21/12	73	30	60	8.0	8.7
Cerny *et al.* [16]	100	15/15	73	—	33	5.4	5.6†
Holoye *et al.* [17]	60	0/24	66	—	50	—	—
Giaccone *et al.* [27]	140	12‡	70	8	28	7.6	7.0
Bork *et al.* [18]	70–80	35/13	73	23	48	8.0	11.3
This study	60	13/11	73	8	50	7.0	9.0

*mg/m^2 daily for 5 consecutive days every 3 weeks, except Giaccone *et al.* 3 consecutive days, every 3 weeks.

†9 patients were early deaths, 5 of them due to toxicity.

‡The classification in stages was not reported.

MDR = median duration of response; MS = median survival.

In our study we obtained a 58% overall response rate with only 2 CR (8%), results which were closer to those of Holoye *et al.* [17] than to those of Bork *et al.* [14, 18]. Drug toxicity was modest, with WHO grade III myelosuppression in 13% of courses delivered, and without other important toxicities. Treatment was well accepted and the schedule appeared feasible and well tolerated. A list of major teniposide trials on old patients with SCLC is reported in Table 4. In these studies, total doses employed, per course, ranged from 350 to 500 mg/m^2. Schedules more intensive than ours, such as the last employed by Bork *et al.* [18], produced a higher response rate, but by increasing doses further, as in the study of Cerny *et al.* [16] or in that of Giaccone *et al.* [27], it seemed that toxicity alone increased without any further gain in response rate.

Median survivals ranged from 5.6 to 11.3 months, similar to those from younger series of patients, at poor risk, treated with intensive multidrug regimens. Undoubtedly the comparison with defined multidrug standard programs for SCLC is arbitrary, and teniposide as monochemotherapy should not be proposed as a treatment of choice. It may be considered a safe and effective palliative treatment, its major drawback being its low CR rate. Perhaps optimising dose and time schedule, and/or combining teniposide with other active agents such as carboplatin or hexamethlmelamine, given sequentially or in alternating fashion, could improve response without increasing toxicity. However, further, larger studies should be undertaken.

1. Smith EF, Postmus PE, Sleijfer DTh. Small cell lung cancer in the elderly. Factors influencing the results of chemotherapy: a review. *Lung Cancer* 1989, 5, 82–91.
2. Kennedy BJ. Aging and cancer. *J Clin Oncol* 1988, **6**, 1903–1911.
3. Baronowsky A, Myers MH. Cancer incidence and survival in patients 65 years of age and older. *CA Cancer J Clin* 1986, **36**, 26–41.
4. Shepherd F, Goss P, Evans W, *et al.* Treatment of small cell lung cancer (SCLC) in the elderly. *Proc ASCO* 1991, **10**, 241.
5. Kennedy BJ. Needed: clinical trials for older patients (Editorial). *J Clin Oncol* 1991, **9**, 718–720.
6. Teeter SM, Holmes FF, McFarlane MJ, *et al.* Lung carcinoma in the elderly population: influence of histology on the inverse relationship of stage to age. *Cancer* 1987, **60**, 1331–1336.
7. Carney DN, Grogan L, Smit EF, Harford P, Berendsen HH, Postmus PE. Single-agent oral etoposide for elderly small cell lung cancer patients. *Semin Oncol* 1990, **17** (Suppl 2), 49–53.
8. Minna JD, Pass H, Glatstein E, Ihdi DC. Therapy of small cell carcinoma of the lung. In: De Vita VT jr, Hellman S, Rosemberg SA, eds. *Cancer: Principles and Practice of Oncology*, 3rd edn. Philadelphia, JB Lippincott, 1989, 666–687.
9. Hoagland HC. Hematologic complications of cancer chemotherapy. *Semin Oncol* 1982, **9**, 95–102.
10. Poplin E, Thompson B, Whitacre M, Aisner J. Small cell carcinoma of the lung: influence of age on treatment outcome. *Cancer Treat Rep* 1987, **71**, 291–296.
11. Samet JM, Hunt WC, Key CR, *et al.* Choice of cancer therapy varies with age of patient. *JAMA* 1986, **225**, 3385–3390.
12. Fentiman IS, Tirelli U, Monfardini S, *et al.* Cancer in elderly: why so badly treated? *Lancet* 1990, **335**, 1020–1022.
13. Smit EF, Carney DN, Harford P, Sleijfer DT, Postmus PE. A phase II study of oral etoposide in elderly patients with small cell lung cancer. *Thorax* 1989, **44**, 631–633.
14. Bork E, Hansen M, Dombernowsky P, Hansen SW, Pedersen AG, Hansen HH. Teniposide (VM-26) an overlooked highly active agent in small cell lung cancer. Results of a phase II trial in untreated patients. *J Clin Oncol* 1986, **4**, 524–527.
15. Clark PI, Cottier B, Joel SP, *et al.* Prolonged administration of single-agent oral etoposide in patients with untreated small cell lung cancer (SCLC). *Proc ASCO* 1990, **9**, 226.
16. Cerny T, Pedrazzini A, Joss RA, Brunner KW. Unexpected high toxicity in a phase II study of teniposide (VM-26) in elderly patients with untreated small cell lung cancer (SCLC). *Eur J Cancer Clin Oncol* 1988, **24**, 1791–1794.
17. Holoye PY, Winn RJ, Craig K, *et al.* Phase II study of teniposide in small cell bronchogenic carcinoma. *Proc ASCO* 1989, **8**, 243.
18. Bork E, Ersboll J, Dombernowsky P, Bergman B, Hansen M, Hansen HH. Teniposide and etoposide in untreated small cell lung cancer: A randomized study. *J Clin Oncol* 1991, **9**, 1627–1631.
19. Stahel RA, Ginsberg R, Havemann K, *et al.* Staging and prognostic factors in small cell carcinoma of the lung. Consensus report. *Lung Cancer* 1989, 5, 119–126.
20. World Health Organization. *Handbook for Reporting Results of Cancer Treatment.* WHO Offset Publication No. 48, Geneva, 1979.
21. Wynne H, Woodhouse KW. The disposition of cytotoxic drugs in the elderly. In: Hamblin TJ, ed. *Haematological Problems in the Elderly. Clinical Haematology.* London: Balliere Tindall, 1987, Vol. 1, 513–531.
22. Friedman SA, Raizner AE, Rosen H, Salomon MA, Sy W. Functional defects in the ageing kidney. *Ann Int Med* 1972, **76**, 41–45.
23. Ouslander JG. Drug therapy in the elderly. *Ann Int Med* 1981, **95**, 711–722.
24. Dodion P. Chemotherapy in the elderly. *Eur J Cancer Clin Oncol* 1987, **296**, 1833–1835.
25. Cullen MH. Evaluating new drugs as first treatment in patients with small cell lung carcinoma: guidelines for an ethical approach with implications for other chemotherapy sensitive tumours. *J Clin Oncol* 1988, **6**, 1356–1357.
26. Ettinger DS, Finkelstein DM, Abeloff MD, *et al.* Justification for evaluating new anticancer drugs in selected untreated patients with a chemotherapy-sensitive advanced cancer: an ECOG randomized study. *Proc ASCO* 1990, **9**, 224.
27. Giaccone G, Donadio M, Bonardi G, Testore F, Calciati A. Teniposide in the treatment of small-cell lung cancer: the influence of prior chemotherapy. *J Clin Oncol* 1988, **6**, 1264–1270.

Acknowledgements—We express our gratitude to Miss Ersilia Tarabelli and Mr Luciano Giorgini for their excellent secretarial assistance.