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Sequential chemotherapy in good-prognosis patients with small-cell lung cancer*

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Summary. A sequential combination chemotherapy regimen was evaluated in 23 patients with small-cell lung cancer (16, limited disease; 7, extensive disease). All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, normal serum sodium and albumin levels and alkaline phosphatase values of <1.5 times the upper limit of normal. Treatment comprised ifosfamide and either vindesine or vincristine given on weeks 0, 2 and 4; cisplatin and etoposide given on weeks 6, 9 and 12; and doxorubicin and methotrexate given on weeks 15 and 17. The overall response rate at the end of chemotherapy was 91% and the complete response rate was 43%. Treatment was generally well tolerated and the delivered dose intensity was 83% of that projected. Median survival was 54 weeks, with 4 patients (17%) being alive 2 years after the completion of therapy.

Introduction

Although chemotherapy has considerably improved the short-term prognosis of patients with small-cell lung cancer (SCLC), only 6% of them survive for 2 years [10]. We have previously identified a group of patients whose prognosis is relatively good following conventional chemotherapy [11] and in whom more intensive treatment might increase the chances of cure. This is the first of two studies in this group of patients during which drugs were rescheduled to increase the frequency of administration. In this study, we investigated sequential treatment, giving short courses of three different chemotherapy regimens with activity in SCLC and using dosages at which toxicity was likely to be manageable. Treatment intervals were reduced in an attempt to increase dose-time intensity, and regimens were given sequentially since this may enable the observation of patterns of chemosensitivity.

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Patients and methods

A total of 23 patients (16, limited disease; 7, extensive disease) with histologically proven, previously untreated SCLC were treated. All had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, normal serum sodium and albumin levels and serum alkaline phosphatase values of <1.5 times the upper limit of normal on entry to the study. There were 14 men and 9 women with a median age of 59 years (range, 42–72 years).

The treatment plan is shown in Table 1. If the white blood count was $<3 \times 10^9$/l or the platelet count was $<100 \times 10^9$/l on the day chemotherapy was due, treatment was delayed until these levels were reached. Drug dosages were modified according to the nadir blood count of the previous course of chemotherapy. Ifosfamide was given as a 1-h infusion [14] in combination with mesna (2-mercaptoethane sulphonate), which was given in divided doses at 60% of the ifosfamide dose. The first 14 patients received 3.5 mg/m^2 vindesine with ifosfamide as the initial regimen; because of subsequent treatment delays due to myelosuppression, vincristine was substituted for vindesine in the remaining 9 patients.

Response to chemotherapy was assessed according to WHO criteria [8] after each of the three regimens. Bronchoscopy was not performed for the confirmation of a complete remission as observed on chest radiograph after the completion of all chemotherapy. Patients showing disease progression at any time during the first two chemotherapy regimens stopped their current treatment and received the next planned drug combination. Consolidation thoracic radiotherapy and prophylactic cranial irradiation were not included in the treatment protocol. Patients who relapsed after completing the chemotherapy received symptomatic treatment, including radiotherapy but not further chemotherapy.

Table 1. Treatment protocol used for sequential combination chemotherapy in 23 patients with SCLC. *IV*, 5 g/m^2 ifosfamide given by 1-h infusion in combination with mesna on day 1 and either 3.5 mg/m^2 vindesine (14 patients) or 2 mg vincristine (9 patients) given i. v. on day 1; *CE*, 25 mg/m^2 cisplatin and 120 mg/m^2 etoposide each given i. v. on days 1–3, *DM*, 50 mg/m^2 doxorubicin and 40 mg/m^2 methotrexate given i. v. on day 1

Week	0	2	4	6	9	12	15	17
Chemotherapy	IV	IV	IV	CE	CE	CE	DM	DM

Treatment toxicity was assessed according to WHO criteria [8]. Where indicated results are expressed with 95% confidence intervals (CI). The delivered dose-time intensity was calculated using the formula:

$$\text{Dose-time intensity } \% = \frac{\%\text{ planned dose delivered}}{\%\text{ planned time for treatment}} \times 100.$$

For patients who did not complete all chemotherapy, the treatment time was taken as 17 weeks.

Results

All patients were evaluable for response, survival and treatment toxicity, with a minimum follow-up of 40 months. The overall response rate was 100%; this included two patients whose disease progressed during treatment with cisplatin and etoposide but who achieved a complete remission after receiving doxorubicin and methotrexate. However, two other patients showed disease progression whilst receiving this final regimen. Therefore, the final response rate after the completion of all chemotherapy was 21/23 (91%; CI, 73%–98%). During the course of treatment, the complete remission rate rose from 17% after treatment with ifosfamide and the vinca alkaloid to 30% following cisplatin and etoposide therapy, finally reaching 43% after the completion of chemotherapy with doxorubicin and methotrexate. Six patients (26%) relapsed in the brain, and for 5 this was the first site of disease progression. The median survival was 54 (CI, 39–82) weeks, with 4/23 patients (17%; CI, 2%–33%) being alive at 2 years after the completion of therapy.

Treatment was generally well tolerated. All patients developed extensive but reversible alopecia (WHO grade III). Only one subject experienced intractable (WHO grade IV) vomiting, and there were no episodes of WHO grade III or IV infection. None of the patients required admission to hospital because of infection or myelosuppression. There were no episodes of encephalopathy or haemorrhagic cystitis following ifosfamide treatment. Two patients refused to continue chemotherapy, in one case due to grade IV vomiting.

Of the 153 treatment courses given, 58 (38%) were delayed by myelosuppression (occurring in 50% of patients after ifosfamide and vindesine, and 26% after ifosfamide and vincristine; in 26% after cisplatin and etoposide; in 50% after doxorubicin and methotrexate). Dose reductions were carried out for 26 (17%) treatment courses, 9 of which were also delayed. The mean dose-time intensity achieved was 83% (CI, 79%–87%) of that projected.

Discussion

There is a need for new approaches to treatment in SCLC [5]. The current study explored the use of sequential combination chemotherapy in a well-defined group of good-prognosis patients. This approach has previously been investigated in both non-randomised [9] and randomised trials [1–3]. However, in this study we gave short courses of each regimen and attempted to reduce the intervals between courses of chemotherapy. This study confirms that such an approach is feasible. Although the number of patients studied was small, the response rate was similar to that seen with very high-dose regimens using autologous bone marrow rescue [4, 12] and was higher than that we previously observed following conventional treatment given every 3 weeks [13]. Moreover, this high response rate was achieved with minimal hospitalization and with considerably less toxicity than that usually associated with very high-dose chemotherapy regimens.

Despite the high response rate obtained, the 2-year survival for this highly selected group of patients remains disappointing and is probably no better than that previously reported for other combination chemotherapy regimens [5]. Nevertheless, in the current study the proportion of *complete* responders was high and rose as new regimens were introduced. This cannot be attributed solely to the activity of new regimens introduced sequentially against resistant cell lines, since continued treatment with any one regimen may have had the same effect. However, both patients who progressed during the first two regimens achieved a complete remission when a new drug combination was introduced, suggesting some non-cross-resistance between these regimens.

Increasing the dose-time intensity of treatment further has been investigated in high-grade non-Hodgkin's lymphoma [6], and this may represent a useful step forward in the management of SCLC. We have pursued this approach using a weekly chemotherapy regimen [7], and a randomised comparison with standard chemotherapy given every 3 weeks is now in progress.

References

1. Daniels JR, Chak LY, Sikic BI, Lockbaum P, Kohler M, Carter SK, Reynolds R, Bohnen R, Gandara D, Yu J (1984) Chemotherapy of small cell cancer of the lung: a randomized comparison of alternating and sequential combination chemotherapy programs. J Clin Oncol 2: 1192
2. Evans WK, Feld R, Murray N, Willan A, Coy P (1987) Superiority of alternating non-cross-resistant chemotherapy in extensive small cell lung cancer. Ann Intern Med 107: 451
3. Feld R, Evans WK, Coy P, Hodson I, MacDonald AS, Osoba D, Payne D, Shelley W, Pater J (1987) Canadian multicenter randomised trial comparing sequential and alternating administration of two non-cross-resistant chemotherapy regimens in patients with limited small-cell lung cancer. J Clin Oncol 5: 1401
4. Humblet Y, Symann M, Bosly A, Delaunois L, Francis C, Machiels J, Beauduin M, Weynants P, Longueville J, Prignot J (1987) Late intensification chemotherapy with autologous bone marrow transplantation in selected small-cell carcinoma of the lung: a randomised study. J Clin Oncol 5: 1864
5. Klastersky J (1988) Therapy of small cell lung cancer: anything new? Eur J Cancer Clin Oncol 24: 107
6. Klimo P, Connors JM (1985) MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann Intern Med 102: 596
7. Miles D, Earl H, Souhami R, Rudd R, Harper PG, Ash CM, James L, Tobias JS Spiro SG (1991) Intensive weekly chemotherapy for good prognosis patients with small cell lung cancer. J Clin Oncol 9: 280
8. Miller AB, Hoogstraten B, Straquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207
9. Postmus PE, Sleijfer DTh, Meinesz AF, Kerstjens HAM, Lo GT, Sluiter HJ (1986) No response improvement after sequential chemotherapy for small cell lung cancer. Eur J Respir Dis 68: 279

10. Souhami RL, Law K (1990) Longevity in small cell lung cancer. Br J Cancer 61: 584
11. Souhami RL, Bradbury I, Geddes DM, Spiro SG, Harper PG, Tobias JS (1985) Prognostic significance of laboratory parameters measured at diagnosis in small cell lung cancer. Cancer Res 45: 2878
12. Souhami RL, Hajichristou HT, Miles DW, Earl HM, Harper PG, Ash CM, Goldstone AH, Spiro SG, Geddes DM, Tobias JS (1989) Intensive chemotherapy with autologous bone marrow transplantation for small-cell lung cancer. Cancer Chemother Pharmacol 24: 321
13. Spiro SG, Souhami RL, Geddes DM, Ash CM, Quinn H, Harper PG, Tobias JS, Partridge M, Eraut D (1989) Duration of chemotherapy in small cell lung cancer: a Cancer Research Campaign trial. Br J Cancer 59: 578
14. Thatcher N, Anderson H, Smith DB, Steward WP, Webb K, Hilton A, Rahman A (1986) Ifosfamide by bolus as treatment for advanced non-small cell lung cancer. Cancer Chemother Pharmacol 18 [Suppl 2]: S30