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ETOPOSIDE VERSUS METHOTREXATE IN SMALL CELL BRONCHIAL CARCINOMA

A randomized study of two types of four-drug chemotherapy regimens

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Seventy-nine patients with small bronchial carcinoma randomly received cyclophosphamide, doxorubicin, vincristine, and methotrexate, alternating after four cycles with cyclophosphamide, lomustine, vincristine and methotrexate or the same with replacement of methotrexate by etoposide in lomustine cycles. Patients with limited disease received radiotherapy with 40 Gy. In 34 patients with extensive disease the total response in the groups with and without etoposide was 89% and 69% and the median survival 10.9 and 8.2 months respectively. In 45 patients with limited disease, the complete remission rates in the groups with and without etoposide were 57% and 67%, partial remission rates 38% and 25%, and the median survival times 12.3 and 17.8 months respectively. The disease-free survival exceeding 5 years in the respective groups was 4.2% and 14.3%. A slightly better response in extensive disease and a tendency to better long-term survival in limited disease was noted but the price was increased toxicity in the latter group.

In a previous study we found that addition of radiation treatment to chemotherapy regimens in small cell bronchial carcinoma patients with limited disease gave a slight benefit as to better long-term survival (1). To further improve the same treatment, inclusion of etoposide in one of the chemotherapy arms was tested in a prospective randomized study. The efficacy of etoposide had been shown to be promising (2). The intention was to look for better long-term survival. Prolonged median survival was not expected. Quality of life should also have been studied but there was for the time being no appropriate instrument available for detailed follow-up measurements like the EORTC questionnaire today (3).

Material and Methods

During the 4-year period from January 1, 1984 to December 31, 1987, all patients with suspected or verified small cell bronchial carcinoma admitted to the Department of Lung Medicine at the University Hospital in Uppsala, Sweden were enrolled in the study. In this period, 109 consecutive patients were referred to the department from six counties.

In three of the counties the patients were only referred due to suspicion of other lung malignancy. Five such patients were excluded from the material since they only started the treatment at the Department of Lung Medicine in Uppsala after confirmation of the diagnosis and completed it at home departments. Two patients with suspected small cell carcinoma proved not to have this disease. Thus, of the original 109 patients, 102 had verified small cell bronchial carcinoma and are reported on herein.

Diagnostic procedures

No patients were excluded from the study on the grounds of age, performance status, or expected short survival. Only patients with a verified histologic or cytologic diagnosis of small cell carcinoma were included. Patients who were operated on for a suspected tumour of unclear type, which then proved to be small cell carcinoma, were excluded from randomization, except in cases of non-excisional thoracotomy. The World Health Organization (WHO) system was used for histologic classification (4). The diagnostic

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procedures included clinical examination, chest radiography, bronchoscopy, transthoracic fine-needle biopsy, mediastinoscopy, sputum cytology, ultrasonic liver scanning, radionuclide isotopic scanning of the skeleton, roentgenography of the skeleton in cases of suspected bone metastases, bone marrow aspiration from the sternum and the iliac crest unilaterally, and computed tomography of the brain on suspicion of cerebral metastases.

Definitions

Limited disease was defined as carcinoma confined to one hemithorax, excluding verified pleural and thoracic wall metastases. Contralateral supraclavicular lymphoglandular metastases were included in patients with limited disease. All other patients were classified as having extensive disease. Complete remission (CR) was defined as complete disappearance of all recognizable lesions. Partial remission (PR) was defined as a decrease by more than 50% of the tumour size as the product of the longest diameter and the diameter perpendicular to it on the chest radiograph. In patients with tumour deposits outside the thorax, the decrease by more than 50% of the tumour volume was counted for all tumour lesions together. No response (NR) was defined as any response less than partial remission. The term 'not evaluable' was defined as a follow-up period of less than one month from the date of a recognized response or from the start of therapy in patients with no response. The duration of survival was calculated from the start of chemotherapy. The duration of remission was calculated from the date of recognized response to the first sign of progression or to death, or, in surviving patients, to the respective follow-up times. Stable disease was defined as no change after tumour response (CR or PR). Tumour progression was defined as first appearence of tumour expansion or recurrence at primary site or in metastases. No patients were lost to follow-up. The study was approved by the Ethics Committee of the Medical Faculty of Uppsala University. Informed consent was obtained from each patient.

Chemotherapy regimens

Regimen A included cyclophosphamide 750 mg/m^2 body surface area intravenously (i.v.) on day 1; vincristine 2 mg i.v. on day 1; doxorubicin 50 mg/m^2 i.v. on day 1; methotrexate 100 mg/m^2 i.v. as a 2-h infusion on day 1, diluted in 1 000 ml of 5.5% glucose or 0.9% NaCl; leucovorin rescue after the infusion on day 2: 12 mg intramuscularly and 15 mg by the oral route every fourth hour for a total dose of 75 mg.

The cardiac toxicity limit for doxorubicin was 550 mg/m^2.

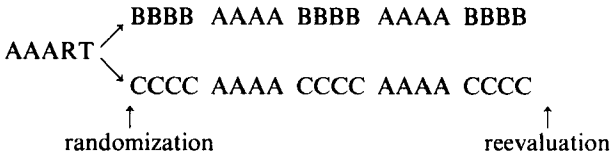
Regimen B included lomustine (CCNU) 40 mg/m^2 by the oral route (given only every second chemotherapy course because of its delayed hematological toxicity) on day 1; cyclophosphamide 750 mg/m^2 i.v. on day 1; vincristine 2 mg i.v. on day 1; methotrexate 100 mg/m^2 i.v. given as in regimen A.

Regimen C was the same as regimen B except that methotrexate was replaced by etoposide 80 mg/m^2 i.v., given for 0.5 to 1.5 h on days 1, 2 and 3. The total dose limit of etoposide was 400 mg/m^2 and chemotherapy course.

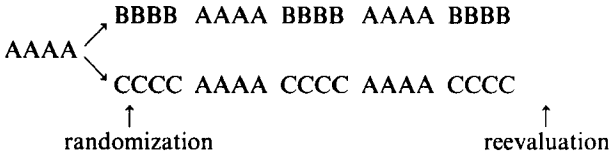
All chemotherapy courses were given at 3-weekly intervals. In order to diminish the rate of septicemia, the interval was lengthened to four weeks at the middle of the study period, after eight courses had been given. If the blood leukocyte count was below 2×10^9/l and/or the blood thrombocytes were below 80×10^9/l, the chemotherapy course was postponed until the limitation level was again reached. Dose reductions were not applied except in elderly patients.

Treatment schedules

Limited disease:



Extensive disease:



When complete remission was confirmed at reevaluation, no further treatment was given. If the tumour remained, treatment was continued. The treatment was given either for a total period of 18 months or in a total of 24 courses. During the last six months of the study period the total treatment time was reduced to 12 months or to a total of 16 courses because of patient refusal. (After closing the study the number of treatment courses has been further reduced in order to diminish the toxicity.)

Radiation treatment

Irradiation (RT) with a total dose of 40 Gy (2 Gy/day, 5 days a week, 4 weeks) to the primary tumour and the adjacent mediastinum was given to all patients with limited disease instead of the fourth course of chemotherapy. The treatment is described in a previous article (1).

All patients who obtained complete remission were given prophylactic brain irradiation (PBI) at a total dose of 30 Gy.

Palliative regimens

Palliative radiation treatment was administered independently from study protocol schedules to all patients with the superior vena cava syndrome, cerebral metastases, or skeletal metastases causing severe pain. When presenting with the superior vena cava syndrome, the study schedule chemotherapy was given.

Supportive care included corticosteroid therapy at the terminal stage. Solitary brain metastases were operated on if the patients had achieved complete remission.

Statistical methods

The χ^2-test, Mann-Whitney U test, life table analysis, and the log-rank test were used for calculation (5).

Results

During the 4-year period of 1984–1987, 102 patients with small cell bronchial carcinoma were diagnosed at the Department of Pulmonary Medicine in Uppsala, Sweden. There were 77 males and 24 females (M : F = 3.1 : 1.0) with median age 66 years (range 27 to 87). Ninety-seven per cent were smokers. Forty-nine per cent of the patients had limited disease and 51% extensive disease. The autopsy rate among the 97 deceased patients was 77%.

Two patients were initially diagnosed as having not definitely verified small cell carcinoma and were thus operated on and thereafter treated with combined chemotherapy and radiation. One patient was initially diagnosed as not having small cell carcinoma but subsequently received radiation therapy and chemotherapy. These three patients were thus not included in the randomization. One patient refused further treatment after four courses of chemotherapy. Nineteen patients (16 with extensive disease and 3 with limited disease) died before the randomization was performed. Five of them died of a combination of carcinoma and septicemia, and two died of carcinoma and pulmonary emboli. Of the 102 patients with verified small cell carcinoma, a total of 23 patients could not be randomized for the aforementioned reasons. Thus, 79 patients (45 with limited disease and 34 with extensive disease) were randomly allocated to the described treatment groups. The median survival in all 102 patients was 10.3 months (range 0.1 to 36). Thirty-six per cent (37 of 102) had complete remissions, 36% (37 of 102) partial remissions, 16% (16 of 102) showed no response, and 12% (12 of 102) were not evaluable. Five per cent (5 of 102) were alive free of disease at 3 years and 4% (4 of 102) at 5 years.

The pretreatment characteristics are presented in Tables 1 and 2, and the response rates are given in Tables 3 and 4. There were no significant differences in pretreatment characteristics between the two groups of patients receiving chemotherapy regimens AB and AC, either among those with extensive or among those with limited disease. The differences in response rates between the chemotherapy groups AB and AC with extensive disease (Table 3) were not significant (CR $\chi^2 = 0.06$, $p = 0.8$; PR $\chi^2 = 0.97$, $p = 0.3$; NR $\chi^2 = 2.10$, $p = 0.1$). Nor were the corresponding differences significant in patients with limited disease (Table 4)(CR $\chi^2 = 0.43$, $p = 0.5$; PR $\chi^2 = 0.90$, $p = 0.3$; NR $\chi^2 = 0.23$, $p = 0.6$). The latency times from the start of therapy to remission are also given in Tables 3 and 4, as well as the duration of the remissions. The differences in latency times between the chemotherapy groups AB and AC with extensive disease were not significant. Nor were

Table 1

Pretreatment characteristics of the patients with extensive disease

	Chemotherapy AB	Chemotherapy AC
Male	81% (13/16)	89% (16/18)
Female	19% (3/16)	11% (2/18)
Age (mean and range)	66 yr (27–79)	64 yr (46–79)
Karnofsky's index (6) (median, range)	70% (50–90)	70% (50–80)
Carlen's index (7) level (performance status during 3 days before admission) (median, range)*	0.8 points (0.2 → 0.8)	0.8 points (0.2 → 1.2)
Distribution of distant metastases		
hepatic	44% (7/16)	53% (9/18)
skeletal	38% (6/16)	24% (4/18)
bone marrow	56% (9/16)	35% (6/18)
cerebral	0% (0/16)	11% (2/18)
other types of metastases	44% (7/16)	29% (5/18)
two metastatic sites	25% (4/16)	24% (4/18)
three or more metastatic sites	25% (4/16)	12% (2/18)

* Corresponds approximately to Karnofsky's index as follows, but cannot be directly translated: 0.4 points ≈ 40–50%; 0.8 points ≈ 50–70%; 1.2 points ≈ 70–80%; 1.6 points ≈ 80–90%

Table 2

Pretreatment characteristics of the patients with limited disease

	Chemotherapy AB	Chemotherapy AC
Male	75% (18/24)	62% (13/21)
Female	25% (6/24)	38% (8/21)
Age (mean and range)	65 yr (46–78)	64 yr (53–74)
Karnofsky's index (6) (median, range)	70% (60–100)	70% (60–100)
Carlen's index (7) level (performance status during 3 days before admission) (median, range)*	0.8 points (0.2–1.2)	0.8 points (0.6–1.2)

* Corresponds approximately to Karnofsky's index as follows, but cannot be directly translated: 0.4 points ≈ 40–50%; 0.8 points ≈ 50–70%; 1.2 points ≈ 70–80%; 1.6 points ≈ 80–90%

Table 3

Response rates in extensive disease

	Chemotherapy AB	Chemotherapy AC
Complete remission (CR) rate	19% (3/16)	22% (4/18)
Latency time from start of therapy to CR (median, range)	3.2 mo. (2.1–4.3)	2.3 mo. (0.1–4.4)
Duration of CR (median, range)	1.0 mo. (1.0–2.5)	10.9 mo. (9.2–14.8)
Partial remission (PR) rate	50% (8/16)	67% (12/18)
Latency time from start of therapy to PR (median, range)	2.0 mo. (0.4–4.1)	1.8 mo. (0.5–4.3)
Duration of PR (median, range	3.4 mo. (0.8–7.7)	5.5 mo. (0.7–9.1)
No response (NR)	31% (5/16)	11% (2/18)

the corresponding differences significant in patients with limited disease. The differences in the duration of both complete and partial remissions between groups AB and AC with extensive disease were significant at a low level ($p = 0.03$). There were patients with distant metastases only in the bone marrow in the AC group but not in the AB group, but due to the small number of patients no definite conclusions can be drawn in this respect. The differences in the duration of remissions were not significant in patients with limited disease. When extensive and limited disease patients were pooled together there were no significant differences in duration of CR ($p = 0.6$) or PR ($p = 0.4$).

Survival rates

The survival curves for extensive disease calculated from life tables are given in Fig. 1. There were no statistically significant differences in the survival, calculated by this method, between the chemotherapy groups AB and AC ($\chi^2 = 2.53$, $0.10 < p < 0.20$). The median survival for the AB group was 8.2 months (range 2.7 to 20.4) and for the AC group 10.9 months (range 3.7 to > 36.0). In the AC group one patient did survive for more than 3 years but had residual cerebral metastases and died 5 months later.

The corresponding survival curves for patients with limited diseases are shown in Fig. 2. There was no statistically significant difference in the survival calculated by

Table 4

Response rates in limited disease

	Chemotherapy AB	Chemotherapy AC
Complete remission (CR) rate	67% (16/24)	57% (12/21)
Latency time from start of therapy to CR (median, range)	1.7 mo. (0.4–7.5)	2.6 mo. (0.7–4.1)
Duration of CR (median, range)	12.1 mo. (0.8 → 36.0)	6.9 mo. (1.5 → 36.0)
Partial remission (PR) rate	25% (6/24)	38% (8/21)
Latency time from start of therapy to PR (median, range)	2.5 mo. (1.4–4.1)	1.5 mo. (0.6–3.3)
Duration of PR (median, range)	4.2 mo. (1.2–10.9)	4.3 mo. (1.5–12.0)
No response (NR)	8% (2/24)	5% (1/21)

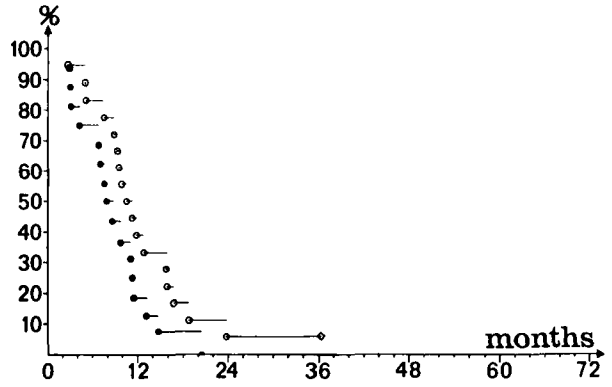


Fig. 1. Life tables for the chemotherapy AB and AC groups with extensive disease. Time of death: ● for AB and ○ for AC. Trial times for surviving patients: ◆ for AB and ◇ for AC. The number of patients still alive and under observation at entry and annually thereafter were for AB 16, 3 and 0, and for AC 18, 7, 1 and 1.

the life table method between groups AB and AC ($\chi^2 = 0.000008$, $0.990 < p < 0.999$). The median survival in group AB was 17.8 months (range 7.0 to > 52.5) and in group AC 12.3 months (range 3.8 to > 46.5). In the AB group 16.7% of the patients (4 of 24) and in the AC group 23.8% (5 of 21) survived for more than 2 years. This difference was not statistically significant ($\chi^2 = 0.36$, $p = 0.55$). In the AB group 4.2% (1 of 24) and in the AC group 19.0% (4 of 21) survived free from disease for more than 2 years. This difference was not statistically significant ($\chi^2 = 2.51$, $p = 0.11$). However, it indicates a slight advantage of the treatment modality including etoposide (regimen AC) in terms of long-term survival. In the follow-up, 4.2% (1 of 24) in the AB group and 14.3% (3 of 21) in the AC group survived disease-free for more than 3 and 5 years. This difference was not statistically significant ($\chi^2 = 1.42$, $p = 0.23$).

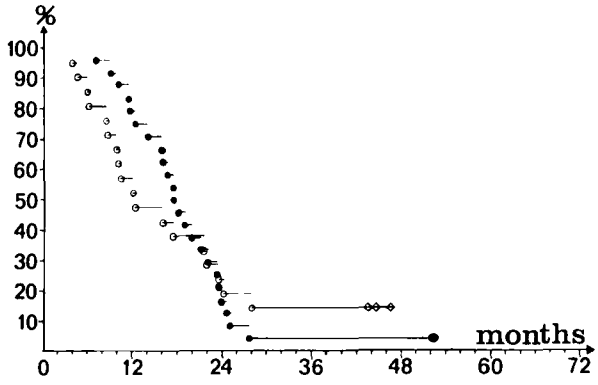


Fig. 2. Life tables for the chemotherapy AB and AC groups with limited disease. Time of death: ● for AB and ○ for AC. Trial times for surviving patients: ◆ for AB and ◇ for AC. The number of patients still alive and under observation at entry and annually thereafter were for AB 24, 19, 4, 1 and 1, and for AC 21, 12, 5, and 3.

Two male and two female patients with limited disease survived for more than 5 years.

The median numbers of chemotherapy courses given from start of treatment to patients with extensive disease were 10 (range, 4 to 24) in the AB group and 12.5 (range 6 to 30) in the AC group. The corresponding numbers in patients with limited disease were 15 (range 5 to 27) and 13 (range 5 to 33) respectively (all patients received planned radiation treatment). The major side-effects are reported in Tables 5 and 6. The recurrence rates are given in Tables 7 and 8 and the end results in deceased patients are described in Tables 9 and 10.

The difference in nadir leukocyte count between the different groups with limited disease was statistically not significant ($p = 0.13$), nor was the corresponding difference in nadir thrombocyte count ($p = 0.56$). There was no significant difference in septicemia frequency ($p = 0.24$) but there was a slight tendency, to higher toxicity in the AC group among the patients with limited disease.

The difference between the treatment arms regarding 'only primary tumour remaining' in deceased patients with limited disease was not statistically significant ($\chi^2 = 1.51$, $p = 0.22$).

Discussion

In the present study no histologic subclassification of small cell bronchial carcinomas was carried out, since there is evidence that this is irrelevant for prognostic and therapeutic decisions (8). Otherwise the randomized study groups were similar in pretreatment characteristics. The total long-term survival rate during the observation period of more than 5 years in 102 patients with small cell bronchial carcinoma, of whom 79 could be randomized, was 4%. In an analysis of treatment in 3 681 patients with small cell bronchial carcinoma, 5.9% survived for more than two years and 3% for up to seven years (9).

Since high response rates of above 85% can be expected with combinations including etoposide (2), this drug has become a natural choice in chemotherapy regimens (10). The advantage of replacing methotrexate with etoposide in regimens comparable to one of the alternating 4-cycle type regimens used in our previous study has also been pointed out by others (11). The results regarding median survival have remained within a range that can be expected with the best small cell bronchial carcinoma treatment (12). Yet there are now reports from randomized studies that inclusion of etoposide in regimens, consisting of cyclophosphamide, methotrexate, lomustine, doxorubicin and vincristine, does not significantly influence response rate, duration of response and survival (13). Moreover, it has been claimed that addition of etoposide to cyclophosphamide, doxorubicin and vincristine regimens produces increased toxicity with no significant survival benefit (14). On the other hand, improvement of long-term sur-

Table 5

Side-effects of treatment in extensive disease

	Chemotherapy AB	Chemotherapy AC
Leukocyte count (10^9/l) nadir (median, range)	0.3 (0.1–1.7)	0.3 (0.1–2.9)
Thrombocyte count (10^9/l nadir (median, range)	27 (10–280)	22 (10–205)
Hemoglobin (g/l) nadir (median, range)	83 (69–125)	86 (73–109)
No. with septicemia (median, range)	3 (0–5)	3 (0–12)
Other serious side-effects (number and type)	2 (severe neuropathy)	0
No. of blood transfusions (median, range)	9 (0–28)	14 (0–48)
No. of thrombocyte transfusions (median, range)	—	—

Table 6

Side-effects of treatment in limited disease

	Chemotherapy AB	Chemotherapy AC
Leukocyte count (10^9/l) nadir (median, range)	0.3 (0.1–3.9)	0.1 (0.1–2.8)
Thrombocyte count nadir (median, range) (10^9/l)	23.5 (8–194)	18 (8–238)
Hemoglobin (g/l) nadir (median, range)	85 (57–107)	82 (76–93)
No. with septicemia (median, range)	2 (0–7)	3 (0–10)
Other serious side-effects (number and type)	4 (cardiomyopathy (1), bleeding (1), severe neuropathy (1), severe pneumonitis (1))	4 (pericarditis (1), severe pneumonitis with esophageal fistula and mediastinitis (1), severe pneumonitis with respiratory insufficiency (1), severe pneumonitis bilaterally (1).
No. of blood transfusions (median, range)	7 (0–28)	12 (2–38)
No. of thrombocyte transfusions (median, range)	0 (0–48)	0 (0–0)

Table 7

First site of recurrence or tumor progression — Extensive disease

	Chemotherapy AB	Chemotherapy AC
In the lung (primary tumor site) (rate)	69% (11/16)	56% (10/18)
In the lung and distant metastases combined (rate)	6% (1/16)	0%
In site of distant metastases only (rate)	6% (1/16)	28% (5/18)
Stable disease (rate)	6% (1/16)	11% (2/18)
No response (rate)	13% (2/16)	6% (1/18)

Table 8

First site of recurrence or tumor progression — Limited disease

	Chemotherapy AB	Chemotherapy AC
In the lung (primary tumor site) (rate)	58% (14/24)	62% (13/21)
In the lung and distant metstases combined (rate)	0%	0%
In site of distant metastases only (rate)	33% (8/24)	19% (4/21)
Stable disease (rate)	4% (1/24)	19% (4/21)
No response (rate)	4% (1/24)	0%

Table 9

Autopsy results and clinical evaluations in deceased patients — Extensive disease

	Chemotherapy AB	Chemotherapy AC
Occurrence of primary tumor and distant metastases in combination	82% (13/16)	82% (14/17)
Only primary tumor remaining	6% (1/16)	0% (0/17)
No primary tumor remaining but distant metastases	6% (1/16)	6% (1/17)
Other causes of death		
septicemia	0% (0/16)	6% (1/17)
acute myocardial infarction	6% (1/16)	0% (0/17)
cerebral infarction	0% (0/16)	6% (1/17)

The autopsy rate in all deceased patients was 79% (23 of 29)

Table 10

Autopsy results and clinical evaluations in deceased patients — Limited disease

	Chemotherapy AB	Chemotherapy AC
Occurrence of primary tumor and distant metastases in combination	52% (12/23)	50% (9/18)
Only primary tumor remaining	26% (6/23)	44% (8/18)
No primary tumor remaining but distant metastases	13% (3/23)	0% (0/18)
Other causes of death		
cardial insufficiency and cerebral infarction	4% (1/23)	0% (0/18)
cardial insufficiency and other malignancy	4% (1/23)	0% (0/18)
severe bilateral pneumonitis	0% (0/23)	6% (1/18)

The autopsy rate in all deceased patients was 73% (30 of 41)

vival in extensive disease has been observed after addition of etoposide to cyclophosphamide-doxorubicin-vincristine regimens (15). It is possible, however, that substitution of etoposide for doxorubicin or vincristin in a cyclophosphamide-doxorubicin-vincristine combination may improve the survival in patients with extensive disease but not in those with limited disease (15, 16). In the present material there was a significantly longer duration of both complete and partial remission in the etoposide-containing treatment arm in extensive disease.

In a randomized study of 231 patients with limited stage small cell cancer treated with cyclophosphamide, doxorubicin and vincristine with or without etoposide, all of whom receiving thoracic irradiation with 37.5 Gy, there was no significant improvement of median survival but higher toxicity among those who received etoposide. These results are consistent with those of the present study (17). The survival curve for the present patients with limited disease showed a higher early death rate in the etoposide-containing treatment arm, indicating higher early toxicity. There was also a slight tendency to better long-term survival which, however, was not statistically significant.

In summary, the inclusion of etoposide in the present treatment regimens might slightly improve the results in extensive disease. In limited disease, however, it seems to produce a slightly higher toxicity and the suggested gains in long-term results cannot be statistically proven. The number of chemotherapy cycles given and the design of the present cycles, however, could have added to the toxicity. In order to substantially improve the results, quite new and differently acting principles need to be found for treatment of small cell bronchial carcinoma. Prolonged treatment is not indicated any more and as a consequence of toxicity we have reduced the number of cycles after closing the study. Instead, intensive therapy over a shorter time period with the use of growth factors to reduce the problems with granulocytopenia is being evaluated.

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