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FULL CHEMOTHERAPHY IN ELDERLY PATIENTS WITH SMALL CELL BRONCHIAL CARCINOMA

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Data on small cell lung cancer (SCLC) in elderly patients with full chemotherapy are sparse. We present material of 345 patients treated with chemotherapy (CT) with no age limits. CT was given with 2 different types of 4-drug combinations, including cyclophosphamide, doxorubicin, vincristine, methotrexate, lomustine and etoposide. Radiotherapy 40 Gy was given to 85% of the limited disease (LD) and 15% of the extensive disease (ED) patients. In 345 consecutive SCLC patients (50% LD and 50% ED) with a median survival time (MST) of 10 months and a disease-free 5-year survival 3.8%. Multivariate analysis showed clear correlation between stage of disease and survival as well as between age and survival though less pronounced. One hundred and ten patients were >70 years of age with a median survival time of 7.4 months (LD 12.3 and ED 4.6) and 235 patients <70 years of age had a median survival time of 10.9 months (LD 14.4 and ED 7.5) and a disease-free 5-year survival of 5.1%. The survival differences were statistically significant. Treatment toxicity was higher in patients >70 years of age. Seventy-seven patients 70–75 years of age had an MST of 9.5 months (LD 13.2 and ED 6.2) and a disease-free 5-year survival of 1.3%. The survival differences between patients 70–75 years old and those <70 years of age were small but statistically significant in LD at 5% level but not in ED. There were more septicemias per courses CT given in all patients 70–75 years of age and also more lethal septicemias in ED patients. Patients with LD SCLC 70–75 years of age might benefit from full treatment in terms of median and long-term survival.

It has been confirmed that for elderly patients (>65) with small cell bronchial carcinoma, patients with extensive disease and those with a poor performance status the prospects of recovery or long-term survival are remote with current therapeutic regimens (1).

It has also been stated that patients over 65 years of age, while accounting for a significant proportion of lung cancer cases, have frequently been overlooked when new approaches against lung tumours are tested (2). Tendencies towards later diagnosis and less aggressive therapy for elderly patients has also been regarded of great significance (2).

Since a majority of therapeutic studies on small cell bronchial carcinoma have excluded elderly patients data on treatment with full chemotherapy are sparse (3). Evaluation of the impact of age on the outcome of treatment for small cell bronchial carcinoma patients has also yielded conflicting results (4). In order to evaluate full cancer chemotherapy in elderly patients a 12-year material was analyzed.

Material and Methods

All patients with suspected or verified small cell bronchial carcinoma admitted to the Department of Lung Medicine at the University Hospital in Uppsala, from

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January 1, 1980 to December 31, 1992, were enrolled in the evaluation. In that period, 376 consecutive patients were referred to the deparment from six counties. Twenty-six patients with suspected small cell carcinoma proved not to have this disease. Leaving 350 patients with verified small cell bronchial carcinoma. Five of these 350 patients were discovered only at autopsy and thus did not receive any cancer treatment. The remaining 345 patients are included in this study. Two-thirds of these patients were included in clinical trials (5, 6).

Diagnostic procedures

No patients were excluded from the study because of high age, poor performance status or expected short survival. Nor was old age a reason for being excluded from the treatment protocols. Only patients with a verified histologic or cytologic diagnosis of small cell carcinoma were included. The World Health Organization (WHO) system was used for histologic classification (7).

The diagnostic 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. Patients with contralateral supraclavicular lymphoglandular metastases were included in the group with limited disease. All the 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 on the chest radiograph. In patients with tumour deposits outside the thorax, a decrease by more than 50% of the tumour volume was counted for all tumor 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 a 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 appearance of tumour expansion or recurrence at primary site or in metastases. No patients were lost to follow-up.

Informed consent was obtained from each patient included in the two studies that comprise two thirds of the patients. The remaining patients were treated according to regular clinical schedules and informed accordingly.

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 on day 1; methotrexate 100 mg/m^2 IV as a 2-hour 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 (i.m.) and 15mg p.o. every 4 hours to 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 p.o. (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 per chemotherapy course.

Regimen D included carboplatinum 150 mg/m^2 i.v. on day 2 and 3; tenoposide 50 mg/m^2 i.v. on day 1–5; vincristine 2 mg i.v. on day 1.

All chemotherapy courses were given at 3-week intervals. In order to diminish the rate of septicemia, the interval was prolonged to 4 weeks in 1986, when 8 courses had been given. If the blood leukocyte count was below 2×10^9/l and/or the blood thrombocytes below 80×10^9/l, the chemotherapy course was postponed until the limitation level was regained. Dose reductions were not applied except in a few elderly patients.

Treatment schedules

Limited disease

1. AAARTBBBB AAAA BBBB AAAA BBBB
2. AAAABBBBAAAABBBBAAAABBBB
3. AAARTCCCC AAAA CCCC AAAA CCCC
4. AAAACCCCAAAACCCCAAAACCCC
5. D was given in case of recurrencies in no-study patients.

Extensive disease

The same regimens were given except for number three. When complete remission was confirmed at reevaluation, no further treatment was given. If the tumour remained, treatment was continued. The treatment was given either at a total period of 18 months or in 24 courses totally. From July 1, 1987, the number of courses was reduced to 16 and from January 1, 1989 to 12 and finally from April

1, 1992, further reduced to 8. The reduction of the course numbers was made in order to diminish the toxicity since less courses given were reported to give the same results.

Radiation treatment

Radiotherapy (RT) to 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 85% of the patients with limited disease instead of the fourth course of chemotherapy. Fifteen per cent of the patients with extensive disease also received radiation treatment in the same way. Radiotherapy portals comprised only the primary tumours with a 1–2 cm margin and adjacent mediastinum. The mediastinal regions above and below the tumour level and the supraclavicular regions were not included. If no tumour remained after the first three chemotherapy courses, the radiation therapy was given to the former primary tumour area exclusive of a 2 cm margin and to the adjacent mediastimum. The treatment source was an 8- or 16 mV linear accelerator.

Two-thirds of the 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 independent from study protocols or regular 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 or regular 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

Cox's proportional hazards method, Mann-Whitney U-test, Kaplan-Meier life-table analysis, Gehan's generalized Wilcoxon test and the χ^2-test were used for calculation.

Results

During the 12-year period 1980–1992, 345 patients with small cell bronchial carcinoma were treated at the departments of pulmonary medicine and oncology in Uppsala, Sweden. There were 243 males and 102 females (M:F = 2.4:1.0) with a median age of 65 years (range 27 to 87). The age distribution is given in Fig. 1. Thirty-two per cent of the patients (110) were >70 years of age and 99% were smokers (ex-smokers included). Fifty per cent of the patients had limited disease and the rest extensive disease. The autopsy rate of the 334 deceased patients was 74%.

The median survival in all 345 patients was 10 months (range 0.02 to 160). Thirty-five per cent (n = 121) had complete remissions, 37% (n = 127) partial remissions, 17% (58) showed no response, and 11% (39) were not evaluable. Thirteen of the 345 patients (3.8%) were alive free of disease at 5 years. Three disease-free patients had not completed 5-year follow-up at time of writing (27.0, 36.7 and 49.4 months follow-up respectively).

Data on performance status were obtained only in one-third of the patient material and are therefore not included in the analysis.

Multivariate analysis of survival versus stage of disease and age

The survival of all 345 patients was analyzed according to Cox's proportional hazards method. Stage of disease expressed as limited disease and extensive disease showed the strongest correlation to survival, t-value = 9.1826 and p = <0.0001. Age gave also significant correlation to survival, although not as pronounced; t-value = 3.5643 and p = 0.0004.

Comparison of results in different age groups

The survival curves for all patients more than 70 years of age and less than 70 years of age are given in Fig. 2. The difference between the survival curves is statistically significant (p = 0.0002). The median survival time (MST) of the 110 patients >70 years of age was 7.4 months (range 0.02–72.6) and for the 235 patients <70 years of age 10.9 months (range 0.02–160). The disease-free 5-year survival rate was 0.9% in patients >70 years of age and 5.1% in patients <70 years of age. The difference is not statistically significant ($\chi^2 = 3.64$, p = 0.0564). One surviving patient >70 years of age had not reached 5-year survival (36.7 months follow up) as well as two patients <70 years of age (27.0 and 49.4 months follow-up). There were no major differences in response rates between the age groups. The median remission time was 2.3 months in the older age group and 4.3 months in the younger one. The difference is statistically significant (p = 0.007). The median numbers of course given were 7 and 11 respectively and the difference was statistically significant (p = 0.0001). The side-effects are given in Table 1.

The median survival time of 53 patients with limited disease >70 years of age was 12.3 months (range 0.3–72.6) and for 118 the patients <70 years of age 14.4 months (range 0.4–160). MST of 57 extensive disease patients >70 years of age was 4.6 months (range 0.02–15.7) and for the 117 patients <70 years of age 7.5 months (range 0.02–40.9).

The survival curves for all 77 patients between 70 and 75 years of age and 235 < 70 years of age are given in Fig. 3. The difference between the survival curves was statistically

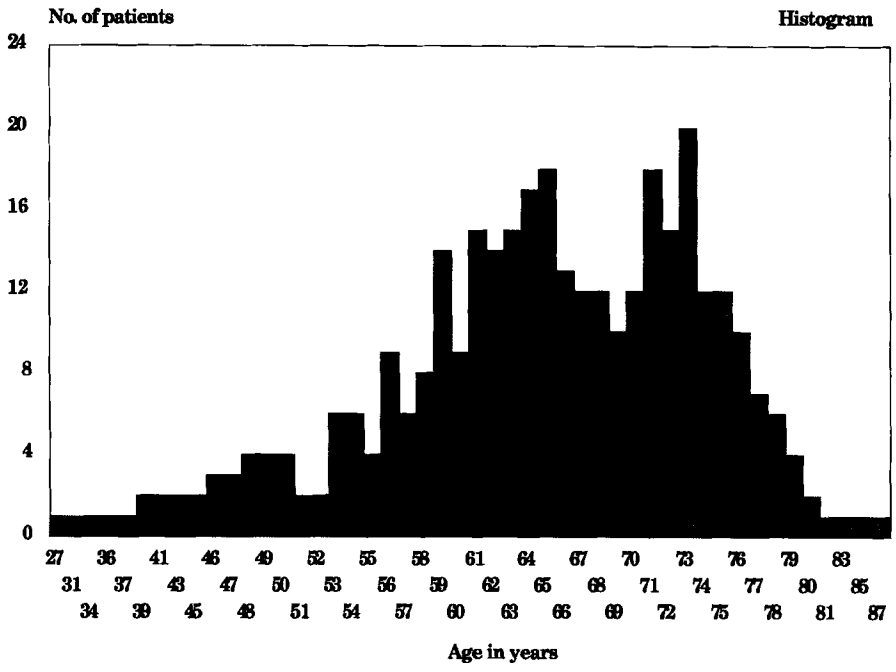

Fig. 1. Histogram of age distribution in the total material of 345 patients.

Table 1

Side effects of treatment — Comparison >70 years of age and <70 years of age groups

	>70 years of age	<70 years of age	
Leukocyte count (10^9/l) nadir (median)	0.4	0.5	N.S.
Thrombocyte count (10^9/l) nadir (median)	48	42	N.S.
Hemoglobin (g/l) nadir (median)	86	86	N.S.
No. with septicemia (median, range)	2 (0–12)	1 (0–10)	$p = 0.05$
No. of septicemias/No. of courses given (median)	0.26	0.13	$p = 0.0001$
Other serious side-effects (per cent, number)	6.4% (7)	8.5% (20)	N.S.
Lethal septicemias (per cent, number)	7.2% (8)	5.4% (12)	N.S.
Other lethal treatment complications (per cent, number)	0.9% (1)	1.4% (3)	N.S.

Table 2

Side-effects of treatment – Comparison 70–75 years of age and <70 years of age groups

	70–75 years	<70 years	
Leukocyte count (10^9/l) nadir (median)	0.3	0.5	N.S.
Thrombocyte count (10^9/l) nadir (median)	36	42	N.S.
Hemoglobin (g/l) nadir (median)	84	86	N.S.
No. with septicemia (median, range)	2 (0–12)	1 (0–10)	$p = 0.0027$
No. of septicemias/No. of courses given (median)	0.29	0.13	$p = 0.0001$
Other serious side-effects (per cent, number)	6.5% (5)	8.5% (20)	N.S.
Lethal septicemias (per cent, number)	8.0% (6)	5.4% (12)	N.S.
Other lethal treatment complications (per cent, number)	1.3% (1)	1.3% (3)	N.S.

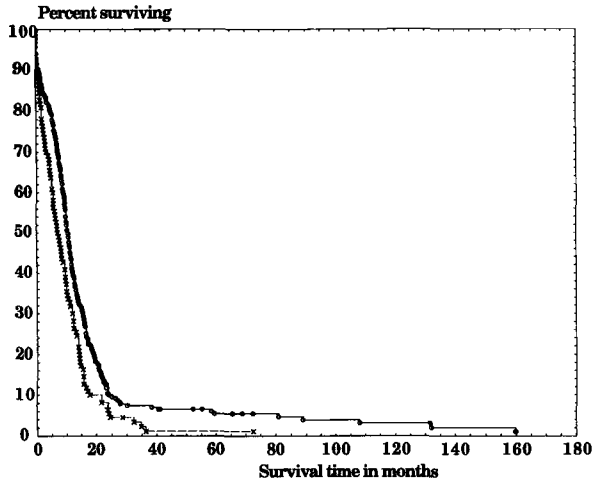

Fig. 2. Life table calculated survival of patients <70 years of age (○) and patients >70 years of age (×).

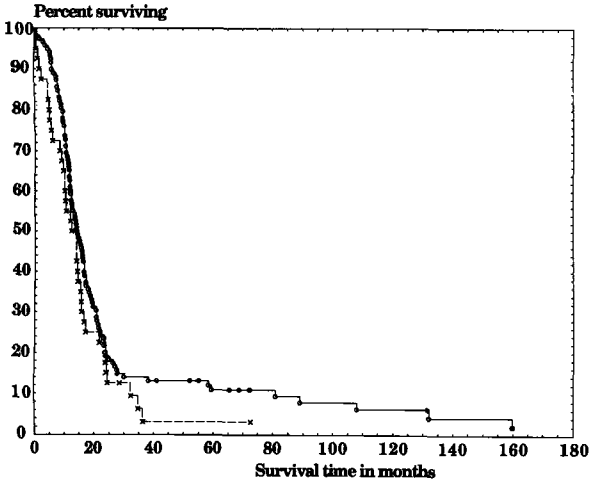

Fig. 3. Life table calculated survival of patients <70 years of age (○) and patients 70–75 years of age (×).

significant (p = 0.02233). MST of patients 70–75 years of age was 9.5 months (range 0.3–72.6) and of the patients <70 years of age 10.9 months (range 0.02–160). The disease-free 5-year survival rate was 1.3% in patients 70–75 years of age and 5.1% in patients <70 years of age. The difference was statistically not significant ($\chi^2 = 2.11$, p = 0.1467). One surviving patient in the 70–75 years of age group had not reached 5-year survival (36.7 months follow-up), nor had two patients <70 years of age (27.0 and 49.4 months follow-up). There were no major differences in response rates between the age groups. The median remission time was 2.7 months in the older age group and 4.3 months in the younger one. The difference was statistically not significant. The median numbers of courses given was 9 and 11 respectively and the difference were statistically significant (p = 0.0068). The side-effects are given in Table 2.

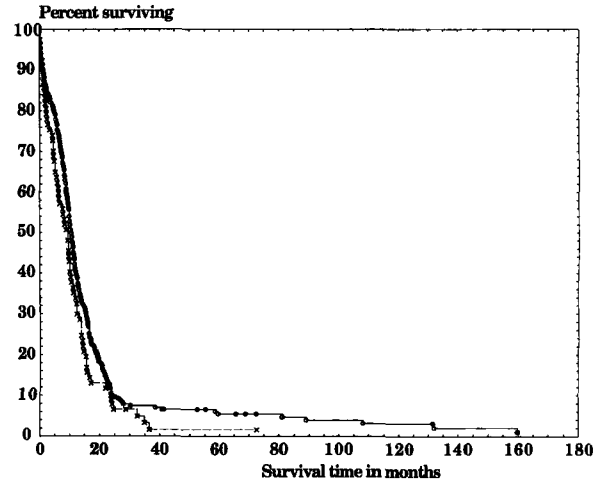

Fig. 4. Life table calculated survival of limited disease patients <70 years of age (○) and patients 70–75 years of age (×).

The survival curves for 40 limited disease patients 70–75 years of age and 118 < 70 years of age are given in Fig. 4. The difference between the survival curves was statistically significant (p = 0.04456). MST of patients 70–75 years of age was 13.2 months (range 0.3–72.6) and of the patients <70 years of age 14.4 months (range 0.4–160). The disease-free 5-year survival rate was 2.5% in patients 70–75 years of age and 10.2% in patients <70 years of age. The difference was statistically not significant ($\chi^2 = 2.33$; p = 0.1271). One surviving patient among the patients 70–75 years of age had not reached 5-year survival (36.7 months follow-up) as also two patients among the patients <70 years of age (27.0 and 49.4 months follow-up). There were no significant differences in remission rates between the groups. (CR: $\chi^2 = 1.49$; p = 0.2221). The median remission time was 5.7 months in the older and 7.5 months in the younger age group. The difference was statistically not significant (p = 0.1049). The median numbers of courses given were 10 and 13 respectively and the difference was statistically significant (p = 0.0075). The side-effects are given in Table 3

The survival curves for 37 extensive disease patients 70–75 years of age and 117 < 70 years of age are given in Fig. 5. The difference between the survival curves was statistically not significant (p = 0.11527). MST of patients 70–75 years of age was 6.2 months (range 0.3–15.7) and for patients <70 years of age 7.5 months (range 0.02–40.9). No patients survived disease-free for more than 5 years. There were no major differences in response rates. The median remission time was 1.3 months in the older age group and 1.6 months in the younger one. The difference was statistically not significant. The median numbers of courses given were 7 and 8 respectively and the difference was statistically not significant (p = 0.2828). The side-effects are given in Table 4.

Table 3

Side effects of treatment — Comparison 70–75 years of age and <70 years of age groups with limited disease

	70–75 years	<70 years of age	
Leukocyte count (10^9/l) nadir (median)	0.5	0.6	N.S.
Thrombocyte count (10^9/l) nadir (median)	43	47	N.S.
Hemoglobin (g/l) nadir (median)	85	86	N.S.
No. with septicemia (median, range)	1 (0–8)	1 (0–10)	N.S.
No. of septicemias/No. of courses given (median)	0.20	0.09	p = 0.0107
Other serious side-effects (per cent, number)	10% (4)	6.4% (15)	N.S.
Lethal septicemias (per cent, number)	0%	5.8% (6)	N.S.
Other lethal treatment complications (per cent, number)	2.6% (1)	1.9% (2)	N.S.

Table 4

Side effects of treatment — Comparison 70–75 years of age and <70 years of age groups with extensive disease

	70–75 years	<70 years of age	
Leukocyte count (10^9/l) nadir (median)	0.3	0.4	N.S.
Thrombocyte count (10^9/l) nadir (median)	36	40	N.S.
Hemoglobin (g/l) nadir (median)	84	85	N.S.
No. with septicemia (median, range)	2 (0–12)	1 (0–6)	p = 0.039
No. of septicemias/No. of courses given (median)	0.40	0.17	p = 0.0001
Other serious side-effects (per cent, number)	2.7% (1)	4.3% (5)	N.S.
Lethal septicemias (per cent, number)	16.2% (6)	5.1% (6)	p = 0.0283
Other lethal treatment complications (per cent, number)	0% (1)	0.9% (1)	N.S.

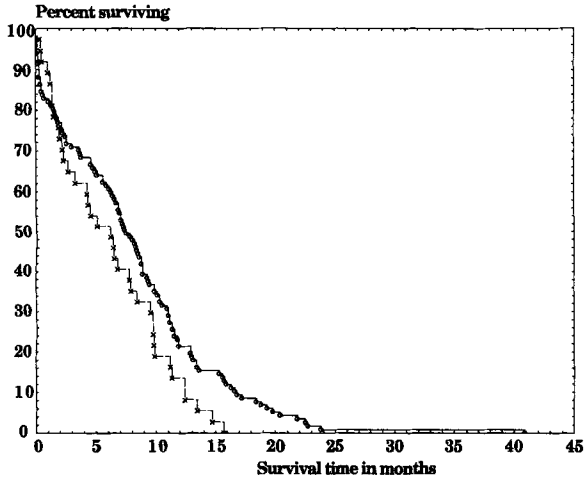

Fig. 5. Life table calculated survival of extensive disease patients <70 years of age (○) and patients 70–75 years of age (×).

The median survival in 33 patients >75 years of age was 5.5 months (range 0.02–21.8). Twenty-seven per cent had complete remissions, 30% partial remissions and 18% showed no response. No patient was alive free of disease at 5 years. Median remission time was 1.0 months (range 0–12.7). The median number of chemotherapy courses given was 5 (range 1–24) and median number of septicemias per courses given was 0.20. There were 6.1% lethal septicemias and 6.1% other serious side-effects.

Discussion

In small cell bronchial carcinoma studies 25–30% of the patients have been estimated to be >65 years of age (4). Others have estimated the proportion of small cell bronchial carcinoma patients >70 years of age at 20–27% (3). According to the west Swedish cancer registry 44% of all patients with small cell carcinoma during the period

1985–1990 were >70 years of age at diagnosis (3). In present material 32% of the patients were >70 years of age. Patients with no treatment given were not included. Thus one-third of these patients are of high age and the problem has to be dealt with.

Retrospective data have suggested that combination chemotherapy is feasible in selected elderly patients, but associated with an increased risk of severe toxicity in poor prognosis patients (3, 8). In the discussion of treatment in elderly patients, material with full treatment to all patients must be of value for decision-making, especially since the age limit varies (65–70 years) in different materials. Appropriate selection, staging, and careful consideration of treatment in elderly patients may allow an outcome similar to that seen in younger patients (4). Methotrexate has been identified as a cause of increased haematologic toxicity in the elderly (3). This might somewhat explain the tendency to more lethal septicemias in extensive disease patients 70–75 years of age in the present material.

The survival difference between patients >70 years of age and less is clear and significant and so is the toxicity in terms of number septicemias per number of courses given, but there were no significant differences in other serious side-effects and lethal treatment complications.

When looking at patients >75 years of age the results in median survival were very poor and no long-term survival was obtained.

The most interesting comparison is that between the patients 70–75 years of age and those <70 years of age, in the present material there was a small but significant difference in median survival. When analyzing the results in limited disease the difference in median survival was even smaller; MST 13.2 and 14.4 months respectively. The difference was also statistically significant even at the 5% level. There was no statistically significant difference in disease free 5 year survival even though the number in the higher age group was small. There was a significant difference in number of septicemias per number of courses given but otherwise there were no significant differences in side-effects. These results speak in favour of aggressive chemotherapy at least in limited disease patients 70–75 years of age.

Comparable results have been reported in 101 limited disease patients >65 years of age compared to 117 patients <65 years of age (9).

In the present material of extensive disease patients 70–75 and <70 years of age respectively there was no statistically significant difference in median survival; MST 6.2 and 7.5 months respectively. No long-term survivors were found. The toxicity was high in terms of number of septicemias per number of courses given as well as in percentage of lethal septicemias in the 70–75 years of age group. The toxicity might be reduced by the use of cytokines (10) but since single agent therapy with etoposide or tenoposide in elderly patients can produce responses and survival times similar to those in younger age groups with combination chemotherapy (3, 4, 11, 12) this approach seems to be more feasible. Negative impact of elderly age in treated patients with extensive disease has been reported (13). Survival benefit due to treatment will, however, be obtained in all age groups versus no treatment at all (14).

Prospective data have shown median survival times close to one year and acceptable toxicity in elderly patients with a favourable prognostic profile (1, 3). These materials, however, comprise of mixed limited and extensive disease patients. Two-year survival rates of 9% have been reported (3), but whether these therapeutic approaches have drawbacks in comparison with combination chemotherapy with regard to long-term survival remains to be proved (3, 15). In this light the present complete material could give additional information.

Multivariate analysis confirmed the strong correlation between stage of disease and survival and also to lesser degree between age and survival. The impact of performance status could not be checked due to lack of complete data, but it has been reported that performance status correlates only marginally (not significantly) with survival in elderly small cell lung cancer patients (14).

To conclude, patients with limited disease small cell bronchial carcinoma 70–75 years of age might benefit from full chemotherapy and radiotherapy in terms of median and long-term survival. In corresponding extensive disease patients and all patients >75 years of age, the same result will probably be obtained with less toxicity with single agent treatment (16).

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