Chemotherapy in elderly small-cell lung cancer patients: yes we can, but should we do it?

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Background: Twenty percent of all newly diagnosed patients with small-cell lung cancer (SCLC) are ≥75 years. Elderly patients may show more toxicity due to co-morbidity. We evaluated motives for adherence to treatment guidelines, completion of treatment and toxicity.

Patients and methods: Population-based data from patients aged ≥75 years and diagnosed with SCLC in 1997–2004 in The Netherlands were used (368 limited disease and 577 extensive disease). Additional data on co-morbidity (Adult Co-morbidity Evaluation 27), World Health Organisation performance status (PS), treatment, motive for no chemotherapy, adaptations and underlying motive and grade 3 or 4 toxicity were gathered from the medical records.

Results: Forty-eight percent did not receive chemotherapy. The most common motives were refusal by the patient or family, short life expectancy or a combination of high age, co-morbidity and poor PS. Although only relatively fit elderly were selected for chemotherapy, 60%–75% developed serious toxicity, and two-thirds of all patients could not complete the full chemotherapy.

Conclusions: We hypothesise that a better selection by proper geriatric assessments is needed to achieve a more favourable balance between benefit and harm.

Key words: elderly, population-based, small-cell lung cancer, toxicity, treatment tolerance

Introduction

Small-cell lung cancer (SCLC) accounts for ~17% of all lung tumours among males and 25% among females in the southern part of The Netherlands [1]. SCLC is an aggressive tumour that is frequently metastatised at the time of diagnosis; median survival for limited disease is ~23 months and for extensive disease 8–12 months [2]. Since SCLC is considered as a disseminated disease with subclinical distant metastases, chemotherapy plays an important role. Nowadays standard treatment of patients with limited disease who have a good performance status (PS) is combined chemoradiotherapy, while for those with extensive disease, chemotherapy alone is the standard [3]. Due to the high probability of brain metastases, prophylactic cranial irradiation (PCI) is recommended [4]. This results in better overall quality of life.

Seventy-five percent of all newly diagnosed patients with SCLC are ≥60 years, and ≥20% are aged ≥75 years [5]. Elderly patients may show higher drug-related toxic effects due to serious co-morbidity or reduced organ functions. For this reason, clinical trials have usually excluded older patients and those with serious concomitant conditions [6]. Although more trials for SCLC include elderly patients, mainly relatively healthy elderly are included. A previous population-based study from our group has shown that a substantial part of elderly patients with SCLC did not receive the standard treatment and prognosis was worse for elderly compared with younger patients [5]. In this study, we evaluated which patient characteristics were associated with adherence to treatment guidelines (and motives for non-adherence), completion of planned treatment (and motives for adaptations) and toxicity in unselected elderly Dutch SCLC patients.

Methods

Study population and data collection

Population-based data from six regional Dutch cancer registries were used. These registries record data on patients newly diagnosed with cancer in all hospitals in their region. Trained registrars routinely collect data on patient and tumour characteristics, like histology, tumour grade, localisation, morphology and stage, directly from the medical records. For the present...
study, all patients aged ≥75 years with primary SCLC (C34.0–C34.9 and International Classification of Diseases for Oncology codes 8040–8045) diagnosed during 1997–2004 in The Netherlands were included (n = 945). Patients diagnosed at autopsy were excluded. Age was classified as 75–79, 80–84 and 85+ years. Clinical stage of disease was classified as limited (tumours confined to one hemithorax without pleural effusion and no distant metastases) and extensive (distant metastases in the contralateral chest or at distant sites). Treatment of SCLC was classified as distant metastases (distant metastases) and extensive (distant metastases in the contralateral chest or at distant sites). Treatment of SCLC was classified as chemoradiation (CT + RT), chemotherapy alone (CT) and other including ‘best supportive care’ (BSC). Recommended treatment of limited disease in this period was cyclophosphamide–doxocubicin–etoposide (CDE) followed by thoracic irradiation (45–50 Gy) or cisplatinum–etoposide (CE) with concurrent thoracic irradiation. Recommended treatment of patients with extensive disease was CDE. PCI was analysed separately.

Additional data on co-morbidity according to the Adult Co-morbidity Evaluation 27 (ACE-27) classification [7], World Health Organisation (WHO) PS, living alone, living independently, detailed information on type of treatment, number of cycles, motive for no chemotherapy, adaptations and underlying motives and grade 3 or 4 toxicity according to the Common Toxicity Criteria [8] were gathered from the medical records.

The ACE-27 index is a validated 27-item co-morbidity index for patients with cancer. Twenty-seven co-morbid conditions were gathered from the medical records. Each condition was graded to severity and classified as grade 1 (mild decompensation), grade 2 (moderate decompensation) and grade 3 (severe decompensation). In case of two or more co-morbid conditions, the highest grade was count, and two or more grade 2 conditions were counted as grade 3. Patients who were not living in institutions were classified as ‘living independently’ but they could also receive home care.

Statistical analysis
Treatment and completion were described according to patient characteristics. Differences between subgroups were tested with chi-square test. Motives for suboptimal treatment and treatment adaptations were described. Furthermore, toxicity (total, haematological, cardiovascular and renal) was described according to the patient characteristics.

Results
Patient characteristics
The general characteristics of the patients are shown in Table 1. Three hundred and sixty-eight patients with limited disease were included and 577 with extensive disease. Six hundred and forty-nine of these patients (69%) were aged 75–79 years, 239 patients (25%) 80–84 years and 57 patients (6%) were diagnosed at age ≥85 years. Seventy-eight percent of all patients had co-morbidity at the time of cancer diagnosis (21% grade 1, 31% grade 2 and 26% grade 3). The most common co-morbid conditions were cardiovascular diseases (44%) and chronic obstructive pulmonary diseases (29%). Sixty-nine percent of patients were living independently and 27% were living alone. However, for about one-third of patients, information on institutionalisation or cohabitation status was not noted in the medical records. PS was also often (39%) missing, but of those with known PS, 321 (55%) had PS 0 or 1 and 258 (45%) 2–4.

Treatment and completion
Of all patients, 48% did not receive chemotherapy. Details of treatment and completion of treatment of each stage of disease are described below.

Limited disease. Among patients with limited disease, the proportion receiving chemoradiation decreased from 23% of those aged 75–79 years to 15% of those aged 80–84 years to zero of those aged ≥85 years, while the proportion receiving chemotherapy alone remained almost 40% (Figure 1). Women received less frequently chemoradiation as compared with men (12% versus 22%). Combined chemoradiation also decreased with co-morbidity (from 24% of those without co-morbidity to 13% of those with grade 3 co-morbidity) and with decreasing PS (from 27% of those with WHO 0–1 to only 8% of those with WHO 2–4). PCI was introduced in 1999 and was applied to only 4% between 1999 and 2004 (all <85 years). Of patients receiving chemotherapy, 56% received CDE, 18% a two-drug combination of cisplatin or carboplatin and etoposide (CE, mainly after 2001) and 25% other chemotherapy (mainly oral etoposide). Since 2003, the proportion receiving carboplatin–etoposide was 23% compared with 17% cisplatin–etoposide and 42% CDE.

The two most common motives for not receiving chemotherapy were a combination of high age, co-morbidity and poor PS (30%) on the one hand and refusal by the patient or family (29%) on the other hand (Table 2). Thirty percent did not receive chemotherapy because of short life expectancy and another 3% had died before start of treatment. For only 7% the motive for not receiving chemotherapy was unknown. The motive for not receiving radiotherapy was unknown in 31%, wait-and-see policy in 40% and high age, co-morbidity or poor PS in 9%. In 7%, the patient had already died before start of radiotherapy.

In 70% of all patients receiving chemotherapy dose (32%), number of cycles (42%), type of chemotherapy (8%) or time between courses (25%) was adapted (Table 3). Dose of chemotherapy was reduced before start of treatment in 13%. The most common motives for adaptations were haematological toxicity (30%, of which 3% were due to decreased bone marrow function in combination with an infection), dying during treatment (10%) or progression (8%) (Table 4). The proportion of adaptations in chemotherapy was clearly higher among men (74%) than among women (56%) and was 54% among patients without co-morbidity compared with 73% among those with co-morbidity. Adaptations were not associated with age or PS. The proportion of patients receiving less than four cycles of chemotherapy was 44% among patients receiving CDE and 35% among those receiving CE. The number of cycles was not significantly associated with gender, age, co-morbidity or PS.

Extensive disease. Among patients with extensive disease, the proportion receiving chemotherapy clearly decreased with increasing age from 55% of patients aged 75–79 years to 32% of those aged 80–84 years and 23% of those aged 85+ years (Figure 1). In contrast, the proportion receiving only BSC was 45% among younger patients, but increased markedly up to 77% among those aged ≥85 years. Administration of chemotherapy slightly decreased with co-morbidity (from 54% of those without co-morbidity to 49% of those with grade 3 co-morbidity) and was lower for those with poor PS (69% for those with WHO 0–1 and 34% for those with WHO 2–4). Of patients receiving chemotherapy, 57% received CDE, 13%
a two-drug combination of cisplatin (or carboplatin) and etoposide (CE) and 30% other chemotherapy (mainly oral etoposide).

The three most common motives for not receiving chemotherapy were poor PS (22%), refusal by the patient or family (21%) and short life expectancy (21%) (Table 2). Nine percent had already died before the start of treatment. In 8%, a motive for not receiving chemotherapy was unknown.

In 62% of all patients receiving chemotherapy dose (28%), number of cycles (44%), type of chemotherapy (3%) or time

| Table 1. Characteristics of patients with small-cell lung cancer, according to stage and age |
|---------------------------------------------|----------------|----------------|----------------|----------------|
| Stage                                      | Limited        |                | Extensive      |                |
| Age                                       | 75–79 years    | 80–84 years    | 85+ years      | 75–79 years    | 80–84 years    | 85+ years      |
| Gender                                     |                |                |                |                |                |                |
| Male                                       | 179 (72)       | 73 (78)        | 23 (88)        | 294 (73)       | 125 (86)       | 26 (84)        |
| Female                                     | 69 (28)        | 21 (22)        | 3 (12)         | 107 (27)       | 20 (14)        | 5 (16)         |
| Treatment                                  |                |                |                |                |                |                |
| CT + RT                                    | 58 (23)        | 14 (15)        | 0              |                |                |                |
| CT                                         | 98 (40)        | 35 (37)        | 10 (38)        | 222 (55)       | 46 (32)        | 7 (23)         |
| Other                                      | 92 (37)        | 45 (48)        | 16 (62)        | 179 (45)       | 99 (68)        | 24 (77)        |
| Co-morbidity (total score ACE-27)          |                |                |                |                |                |                |
| 0                                          | 33 (13)        | 9 (10)         | 9 (35)         | 78 (19)        | 21 (14)        | 8 (26)         |
| 1                                          | 46 (19)        | 21 (22)        | 3 (12)         | 81 (20)        | 37 (26)        | 6 (19)         |
| 2                                          | 82 (33)        | 38 (40)        | 7 (27)         | 117 (29)       | 41 (28)        | 9 (29)         |
| 3                                          | 77 (31)        | 21 (22)        | 6 (23)         | 103 (26)       | 36 (25)        | 5 (16)         |
| Unknown                                    | 10 (4)         | 5 (5)          | 1 (4)          | 22 (5)         | 10 (7)         | 3 (10)         |
| Performance status (WHO)                   |                |                |                |                |                |                |
| 0–1                                        | 98 (40)        | 37 (39)        | 12 (46)        | 133 (33)       | 32 (22)        | 9 (29)         |
| 2–4                                        | 48 (19)        | 23 (25)        | 6 (23)         | 120 (30)       | 47 (32)        | 14 (45)        |
| Unknown                                    | 102 (41)       | 34 (36)        | 8 (31)         | 148 (37)       | 66 (46)        | 8 (26)         |
| Living independentlyb                      | 185 (75)       | 70 (74)        | 20 (77)        | 266 (66)       | 93 (64)        | 21 (68)        |
| Living aloneb                              | 66 (27)        | 40 (43)        | 12 (46)        | 88 (22)        | 38 (26)        | 15 (48)        |

0 = absent, 1 = mild decompensation, 2 = moderate decompensation, 3 = severe decompensation.

Proportion of known; about one-third was unknown.

CT, chemotherapy; RT, radiotherapy; ACE-27, Adult Co-morbidity Evaluation 27; WHO, World Health Organisation.

Figure 1. Small-cell lung cancer, treatment according to stage and age (1997–2004).
The proportion of adaptations in chemotherapy was lower with an infection) and dying during treatment (19%) (Table 4). Haematological toxicity (32%, of which 7% were combined with an infection) combined with a co-morbidity or PS. The proportion developing toxicity decreased with age from 81% in age group 75–79 years to 66% in age group 80–84 years to 56% in those aged ≥85 years. Furthermore, toxicity was higher in those with co-morbidity (72%–90%) as compared with those without co-morbidity (59%) and was also higher in those with PS 2–4 (81%) than PS 0–1 (65%). Seven patients died due to complications of treatment, all of them already suffering from serious co-morbidity at diagnosis of SCLC.

Sixty-nine percent of patients with limited disease who received chemotherapy developed any grade 3 or 4 toxicity during or after treatment; 43% consisted of haematological toxicity (of which 10% was combined with an infection). Only six patients (3%) developed cardiac toxicity and none of the patients developed renal failure. The proportion developing toxicity decreased with age from 81% in age group 75–79 years to 66% in age group 80–84 years to 56% in those aged ≥85 years. Furthermore, toxicity was higher in those with co-morbidity (72%–90%) as compared with those without co-morbidity (59%) and was also higher in those with PS 2–4 (81%) than PS 0–1 (65%). Seven patients died due to complications of treatment, all of them already suffering from serious co-morbidity at diagnosis of SCLC.

Our study shows that almost half of all elderly SCLC patients did not receive chemotherapy. The most common motives for withholding chemotherapy were refusal by the patient or family, short life expectancy or a combination of high age, co-morbidity and poor functional status. Although only relatively fit elderly were selected for chemotherapy or combined chemoradiation, 60%–75% developed toxicity, and two-thirds of patients could not complete the full chemotherapy. The question raises whether a treatment decision should be supported with better tools to predict toxic effects, for instance a more balanced geriatric assessment. On the other hand, it is difficult to deny treatment opportunities after informing patient and family of all side-effects. Although our study is a unique study since we were able to analyse motives of non-adherence to guidelines, we could not analyse patient preferences towards acceptance of chemotherapy.

treatment and toxicity
Up to the year 2000, combination chemotherapy of CDE was the standard treatment of SCLC. Thereafter, the two-drug combination of cisplatin (or carboplatin) and etoposide (CE) has gradually been implemented as the standard of care for both limited- and extensive-stage SCLC [9]. In our study, we found that women received chemoradiation less often as compared with men. Previous studies have shown that women with SCLC suffer from more toxicity of treatment, treatment is more often adapted, but response rates are similar as compared to men [10, 11].
In accordance with previous studies [3, 12, 13], elderly tended to receive less intense treatment, due to less frequent use of chemotherapy or radiotherapy [5, 12–15]. The less intense treatment could be related to either expected toxicity or the reluctance of physicians to treat elderly patients with full dose treatment. In our study, we have shown that the most common motives for not receiving chemotherapy were refusal by the patient or family, short life expectancy or a combination of high age, co-morbidity and poor PS. The same was found in a recent international study [16]. A previous study has shown that elderly patients with lung cancer accept less toxicity for a given gain in survival [17]. In case of highly toxic chemotherapy for a lethal disease, more patients preferred BSC if survival is <6 months [18].

Previous studies report inconsistent findings with regard to increased toxicity for elderly patients with SCLC [5, 12, 13, 19, 20]. Most of these studies were clinical trials and may therefore be biased due to trial eligibility criteria (most of them only including relatively healthy elderly patients) [21]. We found a rather high proportion of elderly patients who developed toxicity (60%–75%) and this was the underlying motive for adapting treatment in ~40%. In our study, almost half of all patients developed grade 3 or 4 haematological toxicity. However, this was lower than proportions found in a study of two clinical trials among patients aged 70–80 years: 64% showed grade 4 neutropenia and 15% grade 3 or 4 thrombocytopenia [22]. In cisplatin–etoposide-based studies, great differences in toxic effects were found once the subpopulations >70 years were analysed: Yuen et al. [23] showed 84% grade 3 and 4 haematological toxic effects and 10% fatal toxic effects while Schild et al. [24] found these toxic effects in 50% and 6%, respectively. Haematological toxicity is significantly higher with doxorubicin-containing regimens [25] that have mainly been used before 2003 in The Netherlands. It should be noticed that many side-effects can be managed better nowadays [26].

Within our study population of elderly patients with limited SCLC, the prevalence of toxicity decreased with every 5 years increase in age, which can be related to stricter selection for chemotherapy at higher age. However, treatment among those aged ≥80 years was adapted as often as among those aged 75–79 years. Perhaps, toxicity among the oldest old leads to earlier adaptation. In our population-based study, the dose of chemotherapy was already reduced before start of treatment in 14% of patients. Another 50%–60% of patients receiving chemotherapy needed adaptations in dose, time between cycles, number of cycles or type(s) of chemotherapy during treatment, mainly due to haematological toxicity (~30%), early death (10%–20%) or progression of disease (6%–8%). A previous clinical study has shown that significantly lower doses were delivered to patients aged 70–80 years as compared with younger patients, and only 69% of elderly were able to complete the full treatment, which is comparable to our study [22]. It seems that more modest levels of toxicity led to dose reductions among elderly patients as compared with younger patients, perhaps due to a greater reluctance on the part of both the physician and the older patient to risk or accept severe grade 3 or 4 toxic effects [17].

Once the reduction in efficacy in case of adapted chemotherapeutic regimens is taken into account [27], one can argue that in the elderly the benefit gained by few patients is paid for by a large group of patients that will not achieve the benefits. We hypothesise that a better selection of patients is needed to achieve a more favourable balance between benefit and harm. We found that toxicity was higher among those with serious co-morbidity at cancer diagnosis. Others underlined the association between severe toxicity and, independent from each other, PS, depressive symptoms and instrumental activities of daily living dependency [28]. Therefore, no chemotherapeutic treatment should be started before these effect-modifying parameters are explicitly taken into account. It has to be studied which of the many parameters are most predictive for toxicity [29].

This study gives a rather unique insight into everyday practice, motives for treatment decisions, adaptations of treatment and toxicity in unselected elderly SCLC patients. However, we should keep in mind that this is a retrospective observational study in which there was selection for treatment. Our finding that within the group of elderly patients toxicity decreased with increasing age might confirm this. Furthermore, not all characteristics could be retrieved from the medical records. PS, for example, was missing in almost 40%.

Prospective studies are needed, not only for giving insight into the risks and benefits of treatment of this group of patients with a short life expectancy but also for evaluating the predictive value of patient characteristics. This would enable physicians and elderly patients to balance benefits, efforts and harm on a more individualised basis.

In conclusion, a better selection of patients by proper geriatric assessments is needed to achieve a more favourable balance between benefit and harm.

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**disclosure**

The authors declare no conflict of interest.
references