



Survival and treatment patterns in elderly patients with advanced non-small-cell lung cancer in Manitoba

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ABSTRACT

Lung cancer is the leading cause of cancer death worldwide. Non-small-cell lung cancer (NSCLC) is the most common form of lung cancer, with a median age at diagnosis of 70 years. These elderly patients are often underrepresented in the randomized clinical trials upon which chemotherapy plans are based. The objective of the present study was to determine the patterns of treatment and survival in elderly patients with advanced NSCLC in Manitoba.

An eligible cohort of elderly patients over 70 years of age at diagnosis ($n = 497$) with advanced NSCLC was identified from the provincial cancer registry database for the period 2001–2004. Of the 497 patients identified, only 147 had been evaluated by a medical oncologist, and 82 of the 147 had received chemotherapy treatment, which is 16.5% of the initial cohort.

Patients who received chemotherapy were younger than those who did not receive chemotherapy. Most patients receiving chemotherapy (84%) received doublet chemotherapy, with an almost equal split between cisplatin and carboplatin treatment. The median survival times for patients in this cohort were 64 weeks (stage III NSCLC) and 56 weeks (stage IV) with chemotherapy treatment, and 46 weeks (stage III) and 26 weeks (stage IV) without chemotherapy.

Although 50% of patients with advanced NSCLC are more than 70 years of age, few are evaluated by a medical oncologist and even fewer are treated with chemotherapy. However, it should be noted that, in the elderly patients who were treated, survival times are comparable to those experienced by younger patients, which is indicative of a benefit of chemotherapy treatment for those elderly patients.

KEY WORDS

Non-small-cell lung cancer, elderly patients, chemotherapy

1. INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide¹. It is the most common type of cancer in terms of incidence (12.4% of all new cancers diagnosed) and mortality (17.8% of all deaths from cancer)¹. Histologically, lung cancer can be classified into non-small-cell lung cancer (NSCLC) and small-cell lung cancer. Non-small-cell lung cancer accounts for 85% of cases of lung cancer, and approximately 65% of patients will present with advanced-stage (III or IV) disease. The current median age for lung cancer in Canada is 70 years^{2,3}. Although many risk factors can contribute to an increased risk of lung cancer, the risk of developing the disease also rises with increasing age. Unfortunately, even though 50% of NSCLC patients are more than 70 years of age, this group of older patients is very much underrepresented in the clinical trials on which treatment decisions are based⁴. That underrepresentation makes it difficult to evaluate treatment options for this older group.

Results from a number of published studies have shown that rates of chemotherapy treatment are low in elderly patients^{4–8}. Several factors have been found to be associated with chemotherapy treatment not being started, including diagnosis of stage IIIB or IV NSCLC, age, and multiple comorbidities^{4–8}. Regardless, some studies have shown that chemotherapy treatment in the elderly may be beneficial. In clinical trials, it has been shown that single-agent therapy does offer a survival benefit in older patients with advanced NSCLC⁹. When single-agent vinorelbine was compared with best supportive care, patients receiving chemotherapy experienced a higher quality of life⁹. However, in those trials, increased toxicity was also reported among the elderly patients^{4,9}.

In the present retrospective study, we evaluated, outside the setting of a clinical trial, the patterns of treatment and survival in patients who, from 2001 to 2004, were diagnosed with advanced NSCLC and who were more than 70 years of age at diagnosis.

2. METHODS

2.1 Study Population

Using the provincial cancer registry, we identified an initial study population consisting of all patients who, from 2001 to 2004, had advanced NSCLC (stage III or IV) and who were more than 70 years of age at diagnosis. In a more detailed review, that cohort was narrowed down to the individuals who also had received chemotherapy at CancerCare Manitoba. Information such as date of diagnosis, age at diagnosis, date of death, treatment, type of first-line chemotherapy, and tolerability and toxicity of the chemotherapy were captured by chart review.

2.2 Statistical Analysis

The primary objective of our study was to determine treatment patterns in elderly patients in our study population. A variable *t*-test method with unequal variances was used to assess differences. We also wanted to determine if the type of chemotherapy used varied in any particular way—for example, by patient age or sex. To determine differences in chemotherapy treatment by sex, we used a continuity-adjusted chi-square analysis. To assess differences in the tolerability of chemotherapy, we used a Fisher exact test¹⁰. Tolerability of chemotherapy was defined as the ability to complete the required number of cycles of treatment (4 cycles in our study). Survival analysis was also performed to compare survival for patients distributed by NSCLC stage and chemotherapy treatment; to that end, Kaplan–Meier survival curves were calculated¹¹. Unadjusted survival was compared using a log-rank test.

3. RESULTS

For the study period, we identified 892 patients from the Manitoba Cancer Registry who had stage III or IV NSCLC and who were more than 70 years of age at diagnosis. Of those 892 patients, 24.9% (*n* = 222) were excluded for incomplete chart information, and 19.4% (*n* = 173) were excluded because they had been managed by medical oncologists outside of CancerCare Manitoba and their charts were not available. The detailed chart review was therefore carried out for 497 patients (55.7%).

Of the 497 patients with available charts, only 147 (29.6%) had been assessed by medical oncologists at CancerCare Manitoba. Of those 147 patients, 103 (70.1%) evaluated in clinic were offered chemotherapy, but only 82 of them (79.6%) actually received it; 21 (20.4%) did not, although they were offered it at the initial visit. Therefore, the cohort that matched our eligibility criteria was composed of 82 patients, or 16.5% (82/497) of the initial group.

When we examined the age distribution of the entire cohort of elderly NSCLC patients (*n* = 892), we found that 36.8% were 70–74 years of age, 33.2% were 74–79 years of age, and 30.0% were more than 80 years of age (Table I). Of the 82 patients eligible for detailed review, 65.8% were 70–74 years of age, 25.6% were 75–79 years of age, and only 8.5% were more than 80 years of age (data not shown). The age range of patients in this eligible cohort was 70–83 years, with a median age of 74 years (Table II). In the group that received chemotherapy, men (63.4%) outnumbered women (36.6%, data not shown). In the group that did not receive chemotherapy, the difference was not so dramatic, at 56.1% men and 43.9% women (data not shown). We observed a statistically significant difference in treatment by disease stage, with 40.0% of stage III patients compared with 20.8% of stage IV patients receiving chemotherapy (*p* > 0.0007).

Table III lists the characteristics of first-line chemotherapy treatment in the treated cohort of patients. Most of the patients (84%) received doublet

TABLE I Distribution of age by year of non-small-cell lung cancer diagnosis

Age range (years)	Patients [n (%)] by diagnosis year			
	2001	2002	2003	2004
70–74	41 (38.3)	44 (38.3)	65 (39.6)	33 (29.7)
75–79	27 (25.2)	39 (33.9)	58 (35.4)	41 (36.9)
>80	39 (36.4)	32 (27.8)	41 (25.0)	37 (33.3)

TABLE II Age distribution of patients (pts) offered chemotherapy

Chemotherapy treatment	Pts (n)	Age	
		Median	Range
Accepted	82	74	70–83
Declined	21	77	70–92

TABLE III Distribution of chemotherapy treatment by age

Age range (years)	Single-agent ^a [n (%)]	Therapy	
		Doublet ^b	
		Cisplatin-based [n (%)]	Carboplatin-based [n (%)]
70–74	7 (53.8)	21 (65.6)	26 (70.0)
75–79	5 (38.5)	7 (21.9)	9 (24.3)
>80	1 (7.7)	4 (12.5)	2 (5.4)
TOTAL	13 (15.8)	32 (39.0)	37 (45.0)

^a Monotherapy with platinum (cisplatin or carboplatin), vinorelbine, etoposide, or another chemotherapeutic agent.

^b Combination of a platinum with taxanes, gemcitabine, or another compound.

chemotherapy with a platinum-based agent; only 15% received single-agent chemotherapy. Of the patients who received doublet chemotherapy, more were treated with a carboplatin-based combination (45%) than with a cisplatin-based combination (39%). Of the patients 70–79 years of age receiving doublet chemotherapy, 35 (approximately 56%) received a carboplatin-based combination, and 28 (approximately 44%) received a cisplatin-based combination. In the 6 patients more than 80 years of age, only 1 patient received single-agent therapy; the rest all received doublet chemotherapy.

Of the treated patients, 42% were able to complete the chemotherapy regimen as set out by the medical oncologist. The reasons that the other 58% of patients were not able to complete the chemotherapy regimen were intolerability (45.8%), myelosuppression (25%), disease progression (18.8%), stable disease (6.3%), and patient request (4.2%).

Almost 70% of the elderly patients in our cohort survived more than 12 weeks from the date of the last chemotherapy treatment (Table IV). Figure 1 shows the Kaplan–Meier survival curves. Patients with stage III NSCLC who were treated with chemotherapy experienced better survival than did those not so treated (median survival: 64.3 weeks vs. 56.6 weeks respectively). Similarly, patients with stage IV NSCLC who received chemotherapy also survived longer (median survival: 45.8 weeks vs. 26.5 weeks respectively). A log-rank test indicated that the survival

curves for stage III and IV patients are not different. However, median survival was statistically different between those who received chemotherapy and those who did not receive treatment ($p > 0.0053$).

4. DISCUSSION AND CONCLUSIONS

The proportion of NSCLC patients that are elderly is significant, and hence finding treatments that improve survival and quality of life in stage III and IV NSCLC and that are well tolerated by elderly patients is an important goal of care and research in NSCLC.

Previously published studies have examined chemotherapy for elderly patients. A study by Lang *et al.* found that only about 33% of elderly patients receive any chemotherapy⁶. Earle *et al.*¹² found that only 22% of elderly NSCLC patients (more than 65 years of age) received chemotherapy. A recent study by Davidoff *et al.*¹³ in a population-based setting found that only 30.1% of all patients more than 66 years of age received chemotherapy. We observed that, of our cohort 497 elderly patients (more than 70 years of age) diagnosed between 2001 and 2004 with advanced NSCLC, only 147 patients (30%) were assessed by medical oncologists. Of those 147 patients, 103 patients (21% of the entire cohort) were offered chemotherapy, and 16.5% ultimately received chemotherapy. That number seems low in comparison with the data from the studies by Lang *et al.* and Davidoff *et al.*, but it is comparable to the proportion reported by Earle *et al.*^{6,12,13} for a cohort of patients more than 65 years of age.

Despite evidence of benefit with chemotherapy treatment in the elderly population^{13,14,15}, approximately 60%–70% of patients are not offered any chemotherapy. However, in our study, when chemotherapy was offered, all but a small proportion of the elderly patients accepted that treatment recommendation made by their oncologist. That observation suggests that undertreatment of the elderly population is a result of medical decision-making rather than patient preference. It is a limitation of our study that we lack specific information about why 350 patients were not referred to a medical oncologist. However, it should be stated that the needs of those patients did not go unmet. Their referral information was reviewed by the chair of the thoracic disease site group, and those patients were also seen (and likely treated by) radiation oncologists. That observation suggests that the decision to offer or not offer chemotherapy is made at several levels by more than one person. Our study also did not examine the specific factors that may limit the enrolment of elderly patients with advanced NSCLC into chemotherapy treatment, and it could not be very descriptive concerning the tolerability and toxicity of the chemotherapy treatment delivered.

We examined the patterns of first-line chemotherapy treatment in our cohort, observing an inverse

TABLE IV Distribution of survival by age

Age range (years)	Patients [n (%)] surviving for		
	0–6 weeks	6–12 weeks	>12 weeks
70–74	9	6	40
75–79	7	2	12
>80	0	1	5
TOTAL	16 (19.5)	9 (11.0)	57 (69.5)

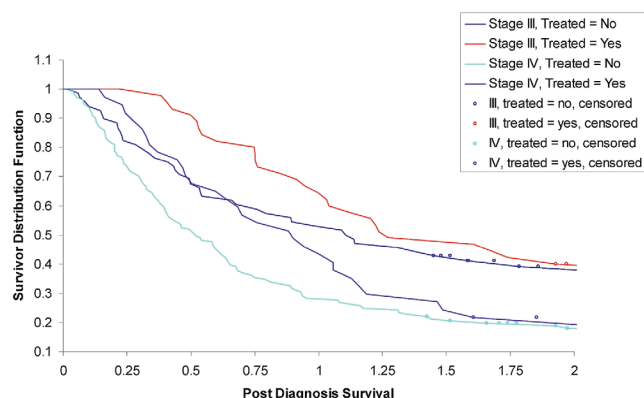


FIGURE 1 Overall survival curves for elderly patients with stages III and IV non-small-cell lung cancer.

correlation between increasing age and the ability to receive chemotherapy. More younger patients than older patients received chemotherapy. That observation has been reported in other studies of NSCLC in elderly patients and may simply reflect an assumption that older patients do not tolerate treatment well¹². Moreover, the patients who accepted chemotherapy when offered had a median age of 74 years, younger than the age of those who declined the offer of chemotherapy, who had a median age of 78 years. By contrast, we found that stage III NSCLC patients were more likely than stage IV patients to receive chemotherapy even when they were more than 70 years of age.

Davidoff *et al.* found that a large proportion of the elderly patients in their study received platinum-based doublet regimens¹³. Most of the patients (84%) in our cohort also received platinum-based doublet chemotherapy: either a carboplatin-based combination (45%) or a cisplatin-based combination (39%). Lang *et al.* determined that 69.8% of patients in their survey of the U.S. Surveillance, Epidemiology and End Results database received platinum-based doublet therapy⁶. By comparison, in an earlier survey of that database (for 1994–1999) by Ramsey *et al.*, only 20% of chemotherapy administered to elderly patients was platinum-based⁴.

Some studies specify the lines of chemotherapy administered, but our study does not. In Davidoff *et al.*¹³, 23% of all patients were treated in the first line with a platinum doublet, and 23% were treated in the second line with a platinum doublet. That finding leads to the conclusion that a doublet-based regimen is more commonly prescribed—a conclusion supported by a recent abstract in which platinum-based doublets were shown to be superior to single-agent therapy in the treatment of elderly patients more than 70 years of age¹⁶. That study found greater treatment-related toxicity in elderly patients without greater treatment-related mortality¹⁶.

Use of chemotherapy was noted to have increased during the period 1997–2002 in the United States¹³, perhaps reflecting an increase in the number of publications of positive randomized controlled trials indicating a benefit of chemotherapy versus best supportive care^{4,6,12}. Regardless, a study by Ramsey *et al.*⁴ identified several factors that influence decision-making by clinicians about treatment for elderly patients with advanced NSCLC. Those factors included sex, age older than 75 years, performance status, stage IV NSCLC, and the presence of multiple comorbidities⁴. Our study did not explicitly attempt to investigate factors that were likely to reduce the chances of an elderly patient receiving chemotherapy in Manitoba. As already mentioned earlier, patients 70–74 years of age were treated with chemotherapy more often than were patients more than 75 years of age. Age is also factor that contributes to receiving specific chemotherapeutic regimens: patients more

than 85 years of age were less likely to receive platinum and taxanes, or platinum and gemcitabine than were patients 75–84 years of age⁶.

Ramsey *et al.* examined survival in their cohort study of elderly patients and found that the Kaplan–Meier survival curves were very steep, with a large proportion of deaths occurring within the first 3 months regardless of whether chemotherapy treatment was administered⁴. A comparison of the Kaplan–Meier survival curves for stages III and IV patients treated or untreated revealed no significant differences. We observed no significant benefit of chemotherapy for survival in our study. That finding may be a result of the small sample size; however, we determined that median survival times for stages III and IV elderly NSCLC patients were both improved with chemotherapy. The median survival time for all advanced NSCLC patients on platinum-based chemotherapy has been reported to be 36 weeks^{17,18}, which is comparable to the median survival time of 45.8 weeks observed for the elderly NSCLC cohort in the present study. That observation indicates that, where appropriate, chemotherapy should be considered for all advanced NSCLC patients regardless of age. Ramsey *et al.* observed that, compared with single-agent therapy or therapy that did not include a platinum-based agent, combination therapy with a platinum-based agent was associated with improved survival⁴. Davidoff *et al.* similarly concluded that there was a clear survival benefit for chemotherapy compared with no chemotherapy¹³. Indeed, those authors observed better survival for patients treated with platinum doublets than for those treated with single agents¹³. It is possible that if we were to re-examine survival based on particular chemotherapy regimens, we might also find a survival benefit for chemotherapy.

A comment that frequently appears in other published studies on chemotherapy and elderly NSCLC patients is that chemotherapy in those patients is associated with increased toxicity. We addressed that aspect of care by examining the tolerability of chemotherapy by sex. Anecdotally, we found that there was a sex difference in the tolerability of chemotherapy treatment: women were able to tolerate more cycles of chemotherapy than men could. Increased intolerance, perhaps because of toxicity, was a major factor in the inability of patients to complete treatment. Similarly, Langer *et al.* assessed toxicity in their study of cisplatin-based therapy in elderly patients⁵ and found that of the 7 highest-grade toxic events, 4 occurred in men, and 3, in women⁵. Perhaps this ability of women to better tolerate treatment skews lung cancer outcome in their favour and plays some role in the accepted understanding that there is a sex difference in lung cancer outcomes.

In this retrospective study, we focused on the patterns of first-line chemotherapy treatment and

survival of elderly NSCLC patients. Many of our findings reflect what has previously been observed in this patient population in other geographic regions. Still, it is surprising that an exceedingly large proportion of elderly NSCLC patients are not being offered chemotherapy. However, given the evidence that chemotherapy treatment may be of benefit in this population, perhaps the number of elderly patients that should be offered chemotherapy should be re-evaluated—especially given that a new generation of better-tolerated chemotherapeutics such as erlotinib and pemetrexed have recently been developed.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no relationships with pharmaceutical companies and declare that no financial conflict of interest exists.

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