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*Age affects the choice  
of treatment regimens  
for patients with  
non-small-cell lung cancer.*

## Adjuvant Chemotherapy in Elderly Patients With Non-Small-Cell Lung Cancer

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**Background:** More than two thirds of patients who die of lung cancer in the United States are over 65 years of age. More than 50% of lung cancer patients are diagnosed over the age of 65 and about 30% over the age of 70.

**Methods:** The authors review recent data from large randomized trials on adjuvant chemotherapy in patients with NSCLC. They discuss age-related changes in organ function, comorbidities and frailty in the elderly, and chemotherapy treatment in elderly patients with NSCLC.

**Results:** Randomized trials suggest that postoperative chemotherapy improves survival after surgery in patients with stage IB to IIIA NSCLC, and awareness of the efficacy of this approach is growing in the scientific community. Clinical data obtained in the young population cannot be automatically adopted in the elderly counterpart. Elderly patients tolerate chemotherapy poorly because of comorbidity and organ failure, and after lung surgery they are considered at higher risk of chemotherapy-induced toxicity. The survival benefit obtained with platin-based chemotherapy may vanish or decrease in the elderly due to a potential higher toxic death rate or lower compliance to treatment.

**Conclusions:** Modified schedules or attenuated dose of platin-containing chemotherapy should be investigated in the adjuvant setting by specifically designed trials. Specifically designed prospective trials are needed to elucidate the role of this approach in the elderly.

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Abbreviations used in this paper: NSCLC = non-small-cell lung cancer.

## Introduction

Every year, 1.2 million new cases of lung cancer are diagnosed worldwide,<sup>1</sup> and lung cancer is the leading cause of cancer death in most developed nations. The most common type of lung cancer is of non-small cell histology, representing approximately 80%. Non-small-cell lung cancer (NSCLC) may be considered typical of advanced age. More than 50% of lung cancer cases are diagnosed in patients over the age of 65 years and approximately 30% are diagnosed in those over the age of 70.<sup>2,3</sup> Age-adjusted incidence rates for 1990-1994 reported by the National Cancer Institute Surveillance Epidemiology End Results (SEER) program are 26.7 per 100,000 individuals less than 65 years of age, while the rate grows to 345.9 among those 65 years of age or greater. More than two thirds of patients who die of lung cancer in the United States are over 65 years of age.<sup>4</sup>

Although an earlier stage of disease at diagnosis has been previously described in elderly lung cancer patients,<sup>5</sup> a recent analysis on 1,035 cases has not confirmed this,<sup>6</sup> with early and advanced stages being equally represented in the elderly and younger population. Similarly, the same series found no correlation between age and performance status (PS) at presentation as previously reported by Brown et al,<sup>7</sup> who observed a higher PS score at presentation with increasing age in 563 patients with lung cancer. Recent data from eight Italian cancer registries collected within the Itacare project<sup>8</sup> show that the 5-year relative survival of patients with lung cancer patients appear to have a poorer prognosis compared with younger patients.

Relative survival of lung cancer patients is calculated as the ratio between observed survival of patients and the expected survival of the general population with the same age, sex, and race distribution. The ratio between 5-year relative survival of patients aged 65 or more and that of patients aged 55 to 64 is 0.55, indicating that prognosis for elderly patients with lung cancer is notably worse than for younger patients. Brown et al<sup>7</sup> reported data collected by a lung cancer registry, and age alone appeared to be a major factor in influencing treatment choices. Inappropriate treatment, particularly insufficient use of chemotherapy, increased with advancing age.

## Age-Related Changes in Organ Function

Elderly patients tolerate chemotherapy poorly because of progressive organ failure related to age and comorbidities. As individuals age, hepatic clearance either decreases or remains unchanged, though generalizations are difficult to make since metabolism is affected by several factors (eg, blood flow, concurrent drug use, disease/physiologic disorders, environmental exposure,

gender, genetic differences, liver mass, nutritional intake, physical condition). Some age-related changes in liver function include declines in hepatic blood flow, hepatic organ mass, and the intracellular activity of cytochrome P450 enzymes. These declines can hinder the clearance of drugs from the system, thereby increasing the risk of drug-drug interactions. The risk of hepatic drug-drug interactions can also increase in older individuals because the incidence of polypharmacy increases with age. Declining renal function is an important risk indicator for drug-induced toxicity in elderly patients as most drugs (including metabolites) are excreted via the kidneys. Renal function is therefore an important consideration when administering therapy. Age-related changes in renal function include decreases in renal blood flow, glomerular filtration rate, and creatinine clearance that can alter drug pharmacokinetics and pharmacodynamics.<sup>8</sup>

Decreased hepatic, renal, and bone marrow functions have a negative impact on the degree of drug toxicity, in particular on cisplatin toxicity. A better understanding of the effects of chemotherapeutic agents on older patients and increased knowledge of pharmacokinetic data will help to determine their appropriate use in elderly patients.<sup>9</sup>

## Comorbidities and Frailty

It has been reported that among individuals aged 65 to 74 years, the mean number of chronic diseases is 6. The prevalence of these comorbid conditions is about twice as high as in the general population.<sup>10</sup> More than half of patients in this age group have chronic arthritis, 33% have backache, 32% have visual deficit, and 28% have exertional dyspnea.<sup>11</sup> Preliminary observations also confirm the coexistence of other diseases in elderly cancer patients.<sup>4</sup> The most important coexisting pathologies in lung cancer patients are cardiovascular and pulmonary diseases, which are common among heavy cigarettes smokers.

Another important issue is the definition of frail elderly persons. Frailty is a condition in which most functional reserve is exhausted. Frail patients depend on others for the activities of daily living primarily due to physical and cognitive dysfunctions. Generally, chemotherapy should be avoided in patients with advanced NSCLC, given the high risk of toxicity. Reliable information regarding a patient's comorbid health problems is mandatory to plan an appropriate treatment. Comorbidity influences treatment choice globally and is a predictor of outcome.<sup>12</sup> However, to date, a standard, fully satisfactory method of assessing comorbidity has not been defined.<sup>13</sup> Moreover, few authors report the number of comorbid conditions for patients entering clinical trials, and there are limited

**Table 1. — Principal Domains of Multidimensional Assessment in Elderly Cancer Patients**

Domains	Measuring Tool
Comorbidity	Charlson Comorbidity Scale Cumulative Illness Rating Scale-Geriatric
Functional status	Activities of Daily Living Instrumental Activities of Daily Living
Depressive symptoms	Geriatric Depression Scale
Mental status	Mini Mental State Examination
Nutritional state	Mini Nutritional Assessment

reports that take into consideration the degree of severity of comorbidities.<sup>14</sup>

To plan optimal treatment, a multidimensional geriatric evaluation must include not only comorbidities assessment but also functional, mental, and nutritional status. Table 1 lists the principal multidimensional assessment domains and tools. Recent studies have reported the prognostic value for overall survival of baseline assessment of functional status, comorbidity, and quality of life in 566 elderly patients with advanced NSCLC treated with chemotherapy.<sup>15</sup> Functional status was measured as activities of daily living (ADL) and instrumental ADL (IADL). Scores for pretreatment global quality of life and IADL, but not ADL and comorbidity, showed a significant prognostic value for survival of elderly patients with advanced NSCLC who were treated with chemotherapy. Using these scores in clinical practice might improve prognostic prediction for treatment planning.

As a consequence of the factors noted above, elderly patients with NSCLC, who frequently suffer tumor-related symptoms and need some type of palliative treatment, often receive untested or inadequate treatments.<sup>7,16</sup> This occurs more often in elderly patients than in their younger counterparts. Furthermore, the elderly are not generally included in clinical trials.<sup>17</sup>

## Age Cutoff

Within epidemiologic literature, the age of 65 years is usually considered a cutoff point to identify an elderly population. On the contrary, in clinical trials, the age of 70 is frequently used as the lower limit for patient selection; this is based on the consideration that patients who are 65 to 70 years of age have a general health status that is good enough to benefit from treatment strategies that are commonly applied to younger patients. Furthermore, 70 years of age may be considered as the lower boundary of senescence because the incidence of age-related changes starts to increase after the age of 70 years.<sup>18</sup>

A cutoff age of 75 years is less common. Obviously, indirect comparison of trials that include patients who

are 65 to 70 years of age and those that omit this age group may be biased. A further bias may be due to the distribution of the so-called “very old” patients, aged 80 years or more. The proportion of “very old” patients with lung cancer at presentation will increase in the next few years.<sup>4</sup> Thus, results from studies that primarily include patients in their 70s may not be completely generalizable to future generations of elderly patients. Furthermore, establishing a maximum age for chemotherapy treatment in the elderly is difficult. In clinical practice, biological instead of chronological age should be considered. Unfortunately, laboratory tests (ie, interleukin-6) and geriatric evaluation are currently inadequate in defining aging; therefore, at present, chronological age should be used as a frame of reference for clinical trials. However, any chronological definition can be considered arbitrary, and biological criteria are needed.

## Chemotherapy in Elderly Patients With NSCLC

The main clinical data on chemotherapy for elderly patients with NSCLC come from advanced disease. These data are useful for administering chemotherapy and for designing clinical trials in their early stages. The Elderly Lung Cancer Vinorelbine Italian Study (ELVIS), a phase III multicenter trial including 191 patients with advanced NSCLC, showed that single-agent vinorelbine improved quality of life and survival compared with supportive care alone (median survival, 27 vs 21 weeks,  $P=.04$ ).<sup>19</sup> Therefore, in elderly patients with advanced NSCLC, palliative chemotherapy should be considered. To improve these results with single-agent chemotherapy, some non-platin-based combinations have been developed. The most studied regimen is gemcitabine plus vinorelbine. The Multicenter Italian Lung Cancer in the Elderly Study (MILES), a large randomized phase III trial including 707 elderly patients, showed that the combination of vinorelbine plus gemcitabine is not more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC (Table 2).<sup>20</sup> Based on this background, and until results are available from prospective randomized trials of platin-based chemotherapy, single-agent chemotherapy should be considered a reasonable treatment choice in unselected elderly patients with advanced NSCLC.

Few prospective clinical experiences with cisplatin-based chemotherapy in elderly patients with NSCLC have been reported. Those that have been published show that cisplatin is particularly difficult to use in elderly patients because of renal and neurological side effects and potential hydration-related problems. The issue of cisplatin- or carboplatin-based therapy for elderly patients with advanced NSCLC has recently

**Table 2. — Principal Phase III Randomized Trials of Chemotherapy in Elderly Patients With Advanced NSCLC**

Trial	Patient Age	No. of Patients	Regimen	Objective Response (%)	Median Survival (wks)
Elderly Lung Cancer Vinorelbine Italian Study <sup>19</sup>	>70	191	BSC		21
			BSC + VNR	20	27*
Multicenter Italian Lung Cancer in the Elderly Study <sup>20</sup>	≥70	707	VNR	18.5	37
			GEM	17.3	28
			GEM + VNR	20.0	32

\* Statistically significant difference.  
VNR = vinorelbine, GEM = gemcitabine, BSC = best supportive care

been addressed in some retrospective analyses of large randomized trials.<sup>21-26</sup> Treatment outcomes of patients younger and older than 70 years of age enrolled on these trials were compared. Globally, these analyses found no differences in survival between elderly and younger patients, with a small increase in toxicity in the elderly, and suggest that advanced age alone should not preclude platin-based chemotherapy for NSCLC.

The aforementioned analyses could suffer from selection bias. In fact, elderly patients enrolled in this sort of trial could be representative not of the whole elderly population but rather of a small subgroup believed by investigators to be eligible for aggressive treatments.<sup>27</sup>

Prospective clinical trials of platin-based chemotherapy with inclusion criteria limited to the elderly population are needed. A topic of interest is exploration of innovative schedules and attenuated doses of cisplatin that could be more suitable in the elderly. Good tolerability and activity has been reported by Feliu et al<sup>28</sup> with low-dose cisplatin (50 mg/m<sup>2</sup>) plus gemcitabine and by Maestu et al<sup>29</sup> with low-dose carboplatin (AUC 5) plus gemcitabine.

## Adjuvant Chemotherapy of Elderly NSCLC Patients

A meta-analysis evaluating data available from 4,357 patients included in clinical trials comparing surgery alone to surgery plus chemotherapy showed a survival benefit of 5% at 5 years for adjuvant cisplatin-based chemotherapy.<sup>30</sup> These results have stimulated clinical research in this field.<sup>31-35</sup> The Adjuvant Lung Project of Italy (ALPI) randomly assigned 1,209 patients with stage I, II, or IIIA NSCLC to receive surgery alone or surgery plus adjuvant chemotherapy consisting of the three-drug combination of mitomycin C, vindesine, and cisplatin. This trial failed to demonstrate a statistically significant survival benefit for adjuvant chemotherapy in completely resected NSCLC.<sup>31</sup> Similarly, the Big Lung Trial, with only 381 patients enrolled, failed to observe a survival benefit with adjuvant chemotherapy.<sup>32</sup> The International Adjuvant Lung Cancer Trial (IALT)<sup>33</sup> enrolled 1,867 patients with stage I-IIIa NSCLC who

were randomly assigned to receive surgery followed by cisplatin-based chemotherapy compared with surgery alone. Chemotherapy consisted of cisplatin plus etoposide (56.5%), cisplatin plus vinorelbine (26.8%), cisplatin plus vinblastine (11.0%), or cisplatin plus vindesine (5.8%). Patients assigned to chemotherapy had a significantly higher 5-year survival rate than those assigned to observation (44.5% and 40.4%, respectively; hazard ratio [HR] for death 0.86;  $P < .03$ ). The IALT trial was the first study to observe a survival benefit for adjuvant cisplatin-containing chemotherapy.

Two recent large randomized trials of third-generation platin-based adjuvant chemotherapy have reported positive results.<sup>34,35</sup> The National Cancer Institute-Canada (NCI-C) BR10 trial randomized 482 patients with stage IB and II NSCLC to receive surgery alone or surgery followed by chemotherapy with cisplatin plus vinorelbine. Overall survival was significantly prolonged for the cisplatin plus vinorelbine arm (94 months vs 73 months; HR for death 0.69;  $P = .011$ ).<sup>34</sup> Similarly, the Cancer and Leukemia Group B (CALGB) Trial<sup>35</sup> that included 344 patients with stage IB NSCLC reported a statistically significant survival benefit for adjuvant chemotherapy with carboplatin plus paclitaxel (overall survival at 4 years was 71% in the chemotherapy group vs 59% in the observation group; HR for death 0.62;  $P = .028$ ). A recent updated analysis shows only a trend toward improvement in overall survival that is not significant (HR for death 0.80;  $P = .10$ ).<sup>36</sup> However, there is a significant improvement in disease-free survival and an advantage in the 3-year survival rate (79% vs 70%;  $P = .045$ ) favoring adjuvant chemotherapy. Thus, this updated analysis no longer shows a significant overall survival advantage for adjuvant chemotherapy in stage IB NSCLC. This study does not have adequate power to detect small differences in overall survival that may be clinically significant.

Another randomized, prospective phase III trial by the Adjuvant Navelbine International Trialists Association (ANITA) compared the effectiveness of adjuvant cisplatin plus vinorelbine in early NSCLC.<sup>37</sup> Approximately 850 patients with stage I-IIIa completely resected NSCLC were enrolled. Median survival was 65.8 months in the chemotherapy arm and 43.7 months in the observation arm (HR 1.264 [1.05-1.52];  $P = .0131$ ). The 5-year

survival rates for stage I, II, and IIIA were 62%, 52%, and 42%, respectively, in the chemotherapy arm and 63%, 39%, and 26%, respectively, in the observation arm. Thus, the ANITA results demonstrate a significant improvement in survival in patients with stage II and IIIA NSCLC treated with adjuvant cisplatin plus vinorelbine, although no benefit was observed in stage I.

Some randomized trials and a meta-analysis with data from 2,000 patients have shown that adjuvant single-agent chemotherapy with uracil/tegafur (UFT) significantly improves the survival of patients with completely resected early-stage NSCLC. In the meta-analysis, the 5-year survival rate was 81.8% in the UFT arm and 77.2% in the observation arm (HR for death 0.77;  $P=.011$ ).<sup>38,39</sup> Moreover, a meta-analysis with data from 5,716 patients has confirmed the importance of cisplatin-based chemotherapy and single-agent UFT as adjuvant chemotherapy in the treatment of resected NSCLC (HR ratio for death 0.891;  $P=.012$  for cisplatin-based chemotherapy; HR for death .799;  $P=.015$  for single-agent UFT).<sup>40</sup>

Taken globally, these data suggest that postoperative chemotherapy improves survival after surgery in patients with stage II to IIIA NSCLC. These reports also suggest that awareness of the efficacy of this approach is growing in the scientific community, although the topic is currently controversial. However, clinical data obtained in the young population cannot be automatically adopted in the elderly counterpart. In fact, elderly patients tolerate chemotherapy poorly because of comorbidity and organ failure. Also, following lung surgery, they are considered at higher risk of chemotherapy-induced toxicity. Thus, there are many doubts regarding the use of platin-based chemotherapy in adjuvant-positive trials in resected elderly patients. In fact, the survival benefit obtained with platin-based chemotherapy may vanish or decrease in the elderly due to a potential higher toxic death rate or lower compliance to treatment. An updated analysis of the CALGB trial<sup>36</sup> in stage IB NSCLC, which recently failed to show a significant improvement in overall survival, raises the question if there is sufficient promise for elderly patients to benefit from currently available adjuvant regimens to justify the toxicity and morbidity of treatment. Modified schedules or attenuated doses of platin-containing chemotherapy should be investigated in this clinical setting by specifically designed trials. The survival benefit achieved in the UFT adjuvant trials<sup>38-40</sup> suggests that new-generation single-agent chemotherapy (vinorelbine, gemcitabine, taxanes) could be investigated in future adjuvant trials for patients unsuitable for even modified or attenuated platin-containing chemotherapy as several resected elderly NSCLC patients. Specific prospective data on adjuvant chemotherapy in elderly patients are not available.

A subgroup analysis of the report from the Non-Small Cell Lung Cancer Collaborating Group using

updated data from 52 randomized clinical trials<sup>30</sup> showed no evidence that any group of patients specified by age benefited more or less from adjuvant chemotherapy. The Adjuvant Navelbine International Trialist Association<sup>40</sup> 02 study of adjuvant single-agent vinorelbine (30 mg/m<sup>2</sup> weekly for a total of 16 administrations) in patients who cannot receive cisplatin-based chemotherapy may produce interesting data, even if stopped early due to slow accrual. A recent retrospective analysis evaluated the influence of age on survival, chemotherapy delivery and toxicity in the above-mentioned positive NCI-C BR10 trial.<sup>41</sup> Pretreatment characteristics and survival benefit from treatment were compared for patients 65 years of age and less and those over age 65. Data from 327 young and 155 elderly patients were included in the analysis. Baseline prognostic factors by age were similar with the exception of histology (adenocarcinoma = 58% young, 43% elderly; squamous cell = 32% young, 49% elderly;  $P=.001$ ) and performance status (PS 0 = 53% young, 41% elderly;  $P=.01$ ). Overall survival by age showed a trend favoring the young in univariate (HR for death 0.77;  $P=.084$ ) and multivariate analysis (HR for death 0.75;  $P=.059$ ). Patients aged 75 years or more had significantly shorter survival than those aged 66 to 74 (HR for death 1.95;  $P=.02$ ). However, overall survival for patients greater than age 65 was significantly better with chemotherapy than with observation (HR for death 0.61;  $P=.04$ ). The elderly received significantly fewer doses of chemotherapy (both cisplatin and vinorelbine). Fewer elderly patients completed treatment and more refused treatment compared to the younger participants ( $P=.03$ ). There were no significant differences in toxicities, the use of granulocyte colony-stimulating factor (G-CSF), or hospitalization by age group, except for myalgias and mood alteration (more frequent among the young). Thus, this retrospective study suggests that despite receiving less chemotherapy than younger patients, those aged 65 or greater achieved improved overall survival with adjuvant chemotherapy with acceptable toxicity.

## Conclusions

Standard adjuvant treatment of NSCLC in elderly patients is a controversial topic because of the lack of specific prospective data. As occurred for large randomized trials of platin-based chemotherapy in advanced disease, retrospective subgroup analysis on elderly patients enrolled in the above-mentioned adjuvant trials performed in the young population will be presented in the near future. Although these analyses could suffer from selection bias, in the future they might be the unique source of scientific data on adjuvant chemotherapy for elderly patients with NSCLC.

Although specifically designed prospective trials are needed to elucidate the role of this approach in the elderly, the potential low accrual rate on surgical adjuvant trials could be a limit. Possible future research directions in the adjuvant treatment of elderly patients with early-stage NSCLC include attenuated-dose platinum-based chemotherapy, third-generation single-agent chemotherapy (vinorelbine, gemcitabine, taxanes), and targeted therapies with or without chemotherapy.

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