



Elisabeth Quoix



University of Strasbourg,
Chest Disease Department,
University Hospital,
Strasbourg, France



University of Strasbourg,
Chest Disease department,
University Hospital, 1 place
de l'hôpital, 67091
Strasbourg cedex, France



elisabeth.quoix@chru-strasbourg.fr

Advanced non-small cell lung cancer in elderly patients

This article aims to provide guidelines in the management of elderly patients with advanced non-small cell lung cancer. Epidemiology of lung cancer shows the considerable increase in frequency of this disease in elderly people, with a median age at diagnosis between 63 and 70 years. Thus, there is a need for a specific and appropriate approach. Studies dedicated to elderly patients are the only means to avoid selection biases which are inherent to the studies enrolling patients of any age in clinical trials. These biases preclude any generalisability of the results observed in subgroup analyses of elderly patients. Geriatric assessment is an important component of the management of elderly patients, as performance status (PS) has been shown to be insufficient to estimate accurately the general condition of these patients.

Lung cancer is the second most common cancer in males, after prostate cancer, and the third in females after breast and colorectal cancer. Also it is the leading cause of cancer-related death in males from developed or emerging countries [1] and in females in the USA since 1987, exceeding breast cancer mortality [2]. There is an exponential increase in cancer incidence with ageing and, due to the concomitant increase of life expectancy, the incidence of lung cancer in the elderly is more and more important, representing a public health problem in developed countries in which life expectancy is important. As a result, the median age of diagnosis of lung

cancer ("clinical" diagnosis, histological/cytological or both) in industrialised nations is 63 to 70 years [3–7]. Non-small cell lung carcinoma (NSCLC) represents 85% of all lung cancer cases in the elderly [8–10]. This is quite similar to what is observed in their younger counterparts. However, within NSCLC, squamous cell carcinomas are more frequent in the elderly compared with younger patients, in whom adenocarcinoma is now the main subtype [8–10]. There are also more never-smokers in elderly patients compared with younger patients and this is probably due to the fact that ageing is an important risk factor; within a recent French survey of 1,627 lung cancer patients aged ≥ 70 years, never-smokers represented 4% of 70–74 year olds, 13.4% of 75–79 year olds and 18.7% of those aged ≥ 80 [10].

Elderly people are under-represented in clinical trials [7, 11, 12] and also may not receive appropriate treatment, possibly due to the pessimism of the doctors, patients and their relatives regarding treatment relevance and toxicity in elderly patients [12].

In population-based studies, elderly patients are not offered chemotherapy in a large majority of cases. For example, in the recently published SEER database [13], only 25.8% of the 21,285 patients aged > 65 years diagnosed with NSCLC between 1997 and 2002 received first-line chemotherapy. In a recent analysis of the Manitoba registry [14], only 82 patients, 16.5% of the 497 patients aged > 70 years,

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were offered chemotherapy. Alternatively, in the aforementioned French prospective hospital-based survey of 1,627 patients, 60% received some kind of chemotherapy [10].

As a matter of fact, elderly patients differ from their younger counterparts in many respects. First, they usually display many more comorbidities, especially those linked to tobacco use (coronary disease, obliterans arteritis of lower limbs, hypertension, chronic obstructive pulmonary disease (COPD), etc.), all of which may compromise the administration of chemotherapeutic agents, for example cisplatin in the case of cardiac insufficiency or severe COPD, which do not allow hyperhydration.

Secondly, due to the number of comorbidities, elderly patients may take quite a number of medications, and special attention should be paid as they may interfere with the metabolism of chemotherapeutic drugs. Moreover, quite a number of these patients take self-prescribed drugs, which are sometimes inappropriate and not reported to their doctor [15].

Thirdly, with ageing, physiological functions decline, such as renal function and haemopoiesis. Finally, geriatric syndromes are also increasingly common with age, resulting in a potential vulnerability and frailty among this patient population. It is therefore of paramount importance to take into account comorbidities, pharmacodynamics of cancer drugs and geriatric assessment prior to the decision-making process for cancer treatment.

Comorbidities and polypharmacy

Comorbidities may be assessed using the Charlson comorbidity scale [16] (see box) or the cumulative illness rating scale geriatric (CIRS-G) (see box) both of which have been validated [17]. Although comorbidity is defined in a more restrictive way as measured by Charlson's index and in a comprehensive way as assessed using CIRS-G, there is no indication that one is more useful than the other in clinical trials carried out on elderly patients. PS may be modified by comorbidities but they are not well correlated and should thus be addressed separately [17–19]. Careful checking of all drugs taken by elderly patients should be done before any decision especially regarding chemotherapy. In fact, elderly patients with metastatic cancer have

been reported to take a median of 5–7 concomitant medications not taking into account the “over the counter” drugs and alternative or herbal remedies [15]. Contrary to general belief, alternative remedies may interact not only with chemotherapy but also with the other drugs taken before cancer treatment is initiated, such as antihypertensives, lipid-lowering, anti-platelets or anticoagulants, inducing additional toxicity.

Regarding lung cancer, there may be interaction between carboplatin, gemcitabine, paclitaxel or etoposide and warfarin (increased anticoagulant effect), between cisplatin and phenytoin with a reduced control of seizures but also with erlotinib or gefitinib with phenytoin,

Charlson comorbidity scale [16]

Comorbidity	Score
Myocardial infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Dementia	1
Cerebrovascular disease	1
Chronic lung disease	1
Connective tissue disease	1
Ulcer	1
Chronic liver disease	1
Hemiplegia	2
Moderate or severe kidney disease	2
Diabetes	2
Diabetes with complication	2
Tumour	2
Leukaemia	2
Lymphoma	2
Moderate or severe liver disease	3
Malignant tumour	6
Metastasis	6
AIDS	6

Comorbidity scores are summed and the total score predicts 10-year mortality. For each decade of age >40 years, a score of 1 is added to the total.

Cumulative illness rating scale geriatric (CIRS-G)

Severity	Score
No problem	0
Current mild problem or past significant problem	1
Moderate disability or morbidity/ requires "first line" therapy	2
Severe/constant significant disability/ "uncontrollable" chronic problems	3
Extremely severe/immediate treatment required/end organ failure/severe impairment in function	4

Each of 14 organ/biological systems is evaluated and the score totalled to give a cumulative score indicative of severity of comorbidities.

carbamazepine and primidone with a reduced activity of those targeted therapies.

Physiological alterations of functions with ageing

These are of special importance regarding renal and haematopoietic functions. These modifications may explain an increased chemotherapy toxicity [20, 21] which must be taken into account. Drugs with renal metabolism or high level of haematotoxicity should have their dosage adjusted properly. Renal function must be carefully considered if cisplatin is to be used. One must remember that although the outcome with carboplatin is slightly inferior to cisplatin in advanced NSCLC [22], it is easier to use it especially in elderly patients because the dosage is adapted to renal function and because it does not require hyperhydration which is somewhat difficult in elderly patients who may have cardiac problems.

Haematological toxicity is anticipated to be more severe in elderly patients. However, growth factors appear to have the same efficacy as in younger patients and should be considered [23]. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is of special interest as the highest incidence of toxicities which could result in the patient's

death occurring during the first cycle of chemotherapy especially in small cell lung cancer [20]. Although this has been especially demonstrated in elderly patients treated for a non-Hodgkin lymphoma, prophylactic use of G-CSF should reduce, in the same way, the risk of neutropenia in elderly patients with advanced non-small cell lung cancer when they are treated with myelotoxic drugs. A recent study evaluated in elderly patients with advanced non-small cell lung cancer the adjunction of levofloxacin *versus* placebo to chemotherapy with carboplatin plus docetaxel [24]. The infection rates were lower in the prophylactic antibiotherapy group.

Geriatric assessment

PS, even though it is an important prognostic factor in younger patients, cannot by itself predict outcome in elderly patients [17] making it mandatory to perform a geriatric assessment [25]. This geriatric assessment comprises several items (table 1) addressing cognition (mini-mental score [26]), daily activities (activity of daily living (ADL), instrumental ADL (IADL) [27]), depression, which is too often underestimated in elderly patients (geriatric depression scale [28]), nutrition [29], physical performance ("get up and go" test) and geriatric syndromes. The ADL checklist includes everything necessary for self-care (dressing, transferring, feeding, toilet, etc.). IADLs refer to the use of transportation, the utilisation of the telephone, the ability to go shopping, proper medication intake and money management, etc. The timed get-up-and-go test is the time required to get up from a chair, walk 3 metres and return back to the chair. All these evaluations are part of the comprehensive geriatric assessment (CGA), which is a highly time-consuming procedure. Screening tests have been developed in order to select patients who should really undergo a complete CGA [30].

After careful geriatric assessment, elderly patients may be classified into three groups according to Balducci (fig. 1) [31] First group: patients with no specific risk and who may be treated like their younger counterparts. Second group: patients who have treatable comorbidities and may be treated with an adapted treatment. Third group: patients who have multiple untreatable comorbidities or for dependent patients, only best supportive care should be proposed.

Table 1. Comprehensive geriatric assessment

Parameters	Assessment methods
Functional status	PS, ADL, IADL, timed get-up-and-go test
Comorbidities	Charlson comorbidity index, CIRS-G
Socio-economic status	Income, transportation possibilities, living conditions, somebody helping
Cognitive status	Folstein mini-mental score
Nutritional status	Body mass index, nutritional mini-questionnaire
Emotional status	Depression geriatric scale
Medications	Number, usefulness, interactions
Geriatric syndromes	Dementia, repeated falls, bone fractures, neglecting, abuse

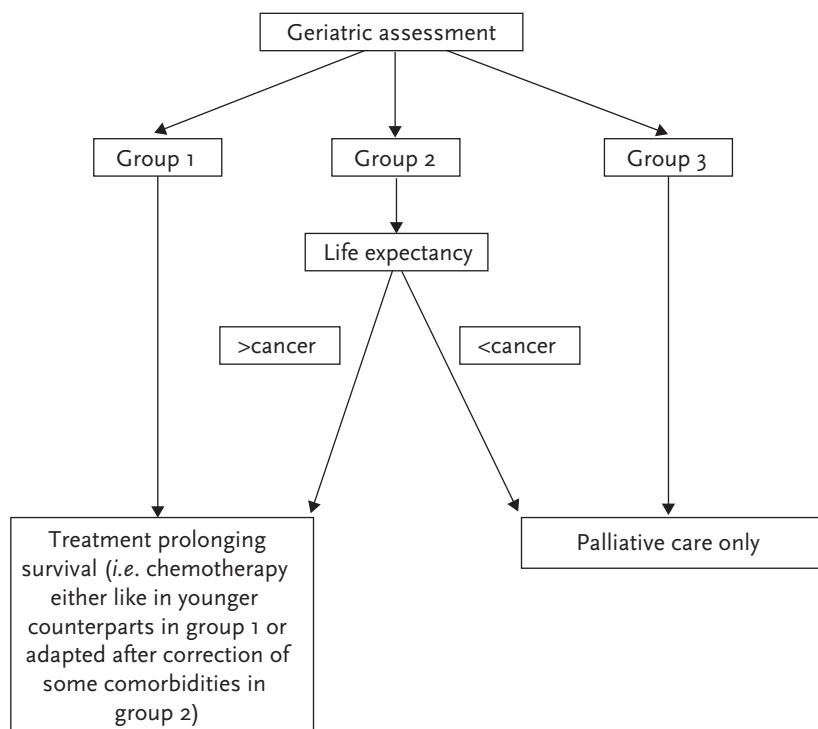
Treatment of elderly patients with advanced non-small cell lung cancer not amenable to mediastinal radiation therapy or at a metastatic stage

Treatment recommendations for fit patients (PS 0–1) with advanced non-small cell lung cancer are to administer a platinum salt-based doublet, the second drug being vinorelbine, gemcitabine, taxotere, paclitaxel or pemetrexed [32, 33]. Until the 1990s, there were no specific trials dedicated to elderly patients. As a result, no recommendations could be established for a long time and most of these patients were undertreated.

There are two approaches toward the treatment of elderly patients: first to include them in clinical trials not dedicated specifically to the elderly (*i.e.* trials with no age limits), and secondly to build trials devoted to elderly patients. In the first case, there is obviously a selection bias as those patients included in clinical trials with treatment adapted to younger patients are highly selected and are not representative. Also, the median age of the elderly patients enrolled in these studies is not very high as most of time older elderly people are not represented. For example, in a clinical trial using cisplatin-based doublet, very few patients aged above 75 years will be included. Thus, there is no generalisability of the results to the entire population of elderly patients. In the second case, the difficulty is to determine an age cutoff. Usually, there is no need to adapt treatment before 70 years and thus most of the trials dedicated to elderly patients include those aged ≥ 70 years.

Non-specific trials performed with subgroup analyses of elderly patients [34–38] are displayed in table 2. With the exception of the combined results of two Southwest Oncology Group trials reported by BLANCHARD *et al.* [38], these studies did not show any significant difference in survival between patients aged <70 years and those aged >70 years (the cut-off was 65 years in BELANI and FOSSELLA [36]).

The first randomised study dedicated to elderly patients was performed by the ELVIS Group, and published in 1999 [39]. This trial compared vinorelbine alone to best supportive care in 154 patients aged ≥ 70 years and more

**Figure 1**

The three Balducci groups. $>$ cancer: life expectancy better than that with cancer; $<$ cancer: life expectancy worse than that with cancer.

Table 2. Subgroup analyses of patients aged ≥ 70 years in non-specific clinical trials

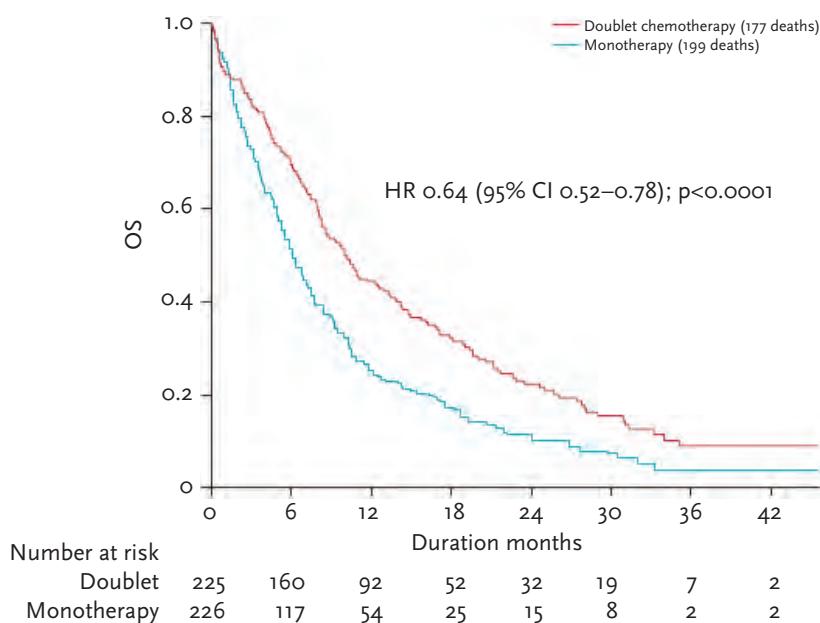
First author (year)	Total patients/ patients aged ≥ 70 years n	Treatment arms	Response rate <70 years/ ≥ 70 years %	Median survival time <70 years/ ≥ 70 years months	1-year survival rate <70 years/ ≥ 70 years %
LANGER (2002)	574/86	CDDP + VP16 versus CDDP + Pacli	21.5/23.3 [#]	9.1 [#] /8.5	38 [#] /29
LILENBAUM (2005)	561/155	Carbo + pacli versus pacli	28 [#] /36 15/21	9 [#] /8 6.8/5.8	38 [#] /33 35/31
BELANI (2005)	1218/401 [¶]	CDDP + Doc versus Carbo + Doc versus CDDP + VNR		11.0/12.6 9.7/9 10.1/9.9	44/52 37/39 41/41
ANSARI (2011)	1135/338	Carbo + Gem Pacli + Gem Carbo + Pacli	30.1/28.2 24.8/24.4 ⁺	7.7/8.8/8.0/7.2 8.9/9.8/5.9/7.8 9.4/8.4/6.1/7.9 [§]	
BLANCHARD (2011)	616/122	CDDP + VNR versus Carbo + Pacli	27/30	9/7 ($p=0.04$)	40/27

CDDP: cisplatin; VP16: etoposide; Carbo: carboplatin; Pacli: paclitaxel; Doc: docetaxel; VNR: vinorelbine; Gem: gemcitabine. [#]: global percent or median survival time for the two arms together; [¶]: 401 patients aged ≥ 65 years; ⁺: Response rate by categories of age, the three arms being combined: <70 years, 70–74 years, 75–79 years, ≥ 80 years; [§]: median survival by arm and age categories; no significant difference.

with advanced-non-small cell lung cancer. Survival benefit in the single agent chemotherapy arm was highly significant (median survival time 28 versus 21 weeks and 1-year probability of survival 32 versus 14%). After this trial demonstrating the benefit of chemotherapy in elderly patients with advanced-non-small cell lung cancer, two other studies compared single agent chemotherapy versus a non-platinum based doublet, *i.e.* vinorelbine and/or gemcitabine alone versus vinorelbine and gemcitabine. The first of these two trials published by FRASCI *et al.* [40] included only 120 patients and showed a benefit of survival in the doublet arm. However, a much larger trial including 700 patients [41] was unable to demonstrate any benefit of survival in the doublet arm. Owing to the results of these studies the recommendations for elderly patients with advanced non-small cell lung cancer were to treat them with a single agent therapy [42], the most frequently investigated being vinorelbine and gemcitabine.

In a Japanese study, vinorelbine was compared with docetaxel [43]. Response rate was significantly higher and progression-free survival was significantly longer in the docetaxel arm. There was also a trend toward a longer survival but this was not significant. The first study comparing a single agent therapy

(docetaxel) to a platin-based (carboplatin) plus docetaxel doublet was published as an abstract only and was prematurely closed after inclusion of 63 patients because of the demonstration in a pre-planned interim analysis superiority of the doublet in the 70–74 years category of age [44]. The second was published this year by the French Intergroup of Thoracic Oncology [45]. In this multicentric phase-III trial, 451 patients were included. This study compared a single agent therapy (vinorelbine 30 mg·m⁻² on day 1 and 8, or gemcitabine 1,150 mg·m⁻² on day 1 and 8 every three weeks according to the initial choice of each centre) to the doublet carboplatin (AUC 6 every 4 weeks) plus paclitaxel (90 mg·m⁻² days 1, 8 and 15). Five cycles of the single agent therapy and 4 cycles of the doublet were to be given in the absence of progression or toxicity. Median age was 77 years. Patients had either a stage-III not amenable to radiation therapy or a stage-IV disease and were included between April 2006 and December 2009. There was a significant increase in progression-free survival (6.1 versus 2.8 months) and a 4-month increase of median survival time (10.3 versus 6.2 months) in the doublet arm versus the monotherapy arm (fig. 2) with a 1-year probability of survival of 44.5 versus 24.5%. Toxic deaths were more frequent in the doublet arm: 10 (4.4% of the

**Figure 2**

Overall survival in the IFCT trial comparing a single agent therapy arm (vinorelbine or gemcitabine) and the doublet carboplatin plus weekly paclitaxel arm in patients aged ≥ 70 years with advanced non-small cell lung cancer.

patients) versus three in the single agent arm (1.3% of the patients). Also, grade 3–4 haematological toxicity was significantly more frequent in the doublet arm. This increased rate of toxic deaths and grade 3–4 haematological

toxicity stress the fact that those elderly patients should be carefully monitored with this treatment. Despite the increase in toxic deaths, the rate of early death (within 3 months) was by far inferior in the doublet arm (16.4%) compared with the single-agent arm (26.5%). Moreover, in an exploratory analysis, it appeared that the benefit of carboplatin-based doublet was observed in all subgroups of patients even in those with bad prognostic factors (PS 2, patients aged ≥ 80 years, patients with ADL <6 , patients with a body mass index <20 , etc.). The only variable not associated with a survival gain with the doublet was an MMS <24 .

Thus, the results of this study suggest that monthly carboplatin plus weekly paclitaxel could be the standard treatment for elderly patients with PS 0–2 and these results should modify the paradigm of the treatment of elderly patients with advanced non-small cell lung cancer.

Conclusion

Elderly patients with advanced non-small cell lung cancer should be treated by chemotherapy when PS is ≤ 2 . The carboplatin-based doublet provides survival gain compared

Table 3. Phase-III studies dedicated to elderly patients with advanced non-small cell lung cancer

Author (Year)	Drugs	Patients n	Response rate %	Median survival months	1-year survival rate %	p-value
ELVIS (1999)	VNR	76	19.7	6.5	32	0.03
	BSC	85	19.7	4.9	14	
FRASCI (2000)	VNR	60	22	7	13	<0.01
	Gem + VNR	60	15	4.5	30	
GRIDELLI (2003)	VNR		21	8.5	42	
	Gem	700	16	6.5	28	NS
	Gem + VNR		18.1	7.4	34	
KUDOH (2006)	VNR	182	9.9	9.9	NR	NS
	Doc	182	22.7	14	NR	
TSUKADA (2007)	Doc Carbo + Doc	63				
QUOIX (2011)	VNR or Gem	226	10	6.2	25.4	0.0004
	Carbo + weekly Pacli	225	27	10.3	44.5	

with a monotherapy in most subgroups of patients. Geriatric assessment may probably contribute to the choice between a monotherapy and carboplatin-based doublet testing procedures to discriminate between patients of group I who should be treated with a carboplatin-based doublet whereas, probably

for group II, monotherapy should be discussed. Whether geriatric assessment is only a prognostic factor or predictive of the outcome of treatments remains to be determined. Anyway, nihilism is no more appropriate in the setting of elderly patients with advanced non-small cell lung cancer.

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