

Management of elderly patients

Alain Vergnenegre^{1,2}, Romain Corre^{2,3}, Hervé Lena^{2,3}, Hervé Le Caer^{2,4}

¹Service de Pathologie Respiratoire, CHU - Limoges, France; ²Groupe Français de Pneumo - Cancerologie (GFPC), France; ³Service de Pneumologie CHU - Rennes, France; ⁴Service de Pneumologie CH - Draguignan, France

Corresponding to: Alain Vergnenegre. Service de l'Information Médicale et de l'Evaluation, Service de Pathologie Respiratoire et d'Allergologie, CHU Dupuytren, 87042 Limoges Cedex, France. Email: alain.vergnenegre@unilim.fr.

Summary: Elderly patients are often excluded from clinical trials, yet more than two-thirds of patients diagnosed with lung cancer are over 65 years old. It is therefore important to develop specific tools and trials for this specific patient population.

Methods: This chapter first examines the management specificities of elderly patients. Randomized trials specifically involving elderly patients are then described, and likely future developments are considered.

Results: Older people have several specificities. In addition to traditional criteria such as age and performance status, other important factors include the number of comorbidities and age-related changes such as cognitive deficits and depression. Specific indices taking these factors into account have been published and validated.

Single-agent therapy has been widely used to treat metastatic lung cancer in the elderly, following publication of negative results from randomized phase III trials of combination chemotherapy. Recently, however, a trial of doublet therapy gave positive results, in a subgroup of independent older patients. The benefit of patient selection based on a combination of these indices has been demonstrated in open-label and randomized trials. These results must now be confirmed in phase III trials including the use of tyrosine kinase inhibitors combined with chemotherapy.

Conclusions: Indices based on a combination of age-related factors, together with judicious use of biological markers, will further improve the prognosis of elderly lung cancer patients.

Key Words: Elderly; non-small cell lung cancer; geriatric assessment; management



Submitted Jan 18, 2013. Accepted for publication Feb 19, 2013.

doi: 10.3978/j.issn.2218-6751.2013.02.04

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Introduction

Oncogeriatric medicine has now come of age. It involves a comprehensive, multidimensional and multidisciplinary approach to the elderly cancer patient (1). Life expectancy is increasing in all western countries, and projections show that, in France in 2020, more than 10% of inhabitants will be over 70 years old (2). However, elderly individuals are very heterogeneous, and their management must take into account both medical and social problems and specific cancer therapy (3). Elderly patients are generally excluded from clinical trials, however, representing only 8-13% of patients (4). Medical evaluation of elderly cancer patients is complicated not only by their age but also by comorbidities (5), which

are independent prognostic factors.

In the United States, cancer registries show that patients over 65 years of age represent two-thirds of all lung cancer patients, and median age at diagnosis is around 70 years (6). A French observational study (7) showed that, in 2000, 32% of patients treated for lung cancer were over 70 years old, and that 18.1% were over 80.

Yet clinical trials specifically focusing on elderly patients are rare in the field of thoracic oncology, even though their value is now clear (8). Lung cancer management guidelines now include specific recommendations on the treatment of elderly patients (9,10). The international society of geriatric oncology has also issued similar guidelines (11).

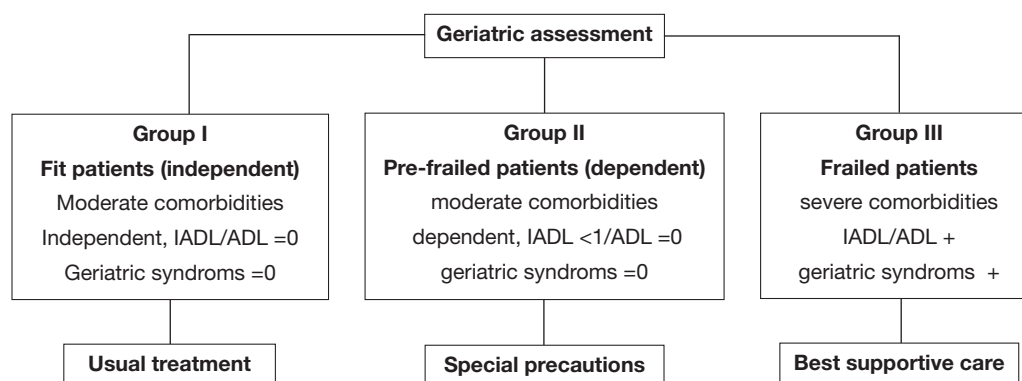


Figure 1 Subgroups of elderly patients identified using a geriatric assessment

This article examines the specific assessment of elderly cancer patients, the use of certain tools for lung cancer treatment, and likely future developments.

Specificities of lung cancer management in seniors

The selection criteria are the same whether the elderly patient is a candidate for surgery or radiotherapy, and whether the lung cancer is locally advanced or metastatic.

Aging is accompanied by a number of physiological changes, including a decreased glomerular filtration rate, impaired hepatic metabolism, decreased serum albumin, and a decreased absorption-distribution ratio (3). Elderly patients often have comorbidities: Yancik's study (12) showed that 13% of patients aged between 55 and 65 years had more than 5 comorbidities, a figure rising to 24% between 66 and 74 years and 40% after 75 years. As stressed by Extermann (13), performance status, a prognostic factor in lung cancer, does not have the same impact on patient management as comorbidities, or on tolerance of either the disease or its treatment. Validated tools are available for assessing such comorbidities, such as the Charlson index (14) and the cumulative illness rating scale - geriatric (15). However, comorbidities, performance status are independent from age in the disease prognosis (14,15).

It is crucial to assess the impact of aging by using geriatric indexes (16,17). These multidimensional tools explore cognitive functions (18), depression (19), and other geriatric disorders (20) such as falls and incontinence, nutritional status, polypharmacy, mobility and environmental conditions. These disorders are combined in the standardized comprehensive geriatric assessment (CGA) proposed by Balducci (21-23). However, as the CGA was particularly

time-consuming, a short questionnaire was developed and validated (24,25). This work allowed us to classify the elderly into three groups, as shown in *Figure 1*.

Recent studies have shown that the use of these indices influences the choice of initial care by multidisciplinary panels in about 1 in 5 cases (26-28).

Quality of life, which is widely assessed in lung cancer patients regardless of age, is particularly important in the elderly. Whatever the tool used, clinical trials must include QOL assessments to ensure that treatment does not have a major negative impact (29).

Management of early-stage lung cancer

Age itself does not contraindicate surgery (30), but elderly patients are less likely to be referred to a surgeon (31). There is a positive correlation between the survival rate and the use of limited surgery or video-assisted thoracoscopic surgery (32).

Management of patients with locally advanced lung cancer

There are currently no published trials of concurrent chemoradiotherapy in elderly patients, but trials not specifically devoted to seniors suggested that toxicity was greater in older patients (33). An ongoing French trial is studying the feasibility of using geriatric assessment for patient and treatment selection (34).

Management of patients with metastatic lung cancer

These are the patients who raise the most difficult

Table 1 Principal randomized trials in elderly subjects

Authors	Drugs	N° pts	Reponse rate	Median survival	1-year survival	P
Elvis 1999 (36)	VNR	76	19.7%	6.5	32%	0.03
	BSC	85	/	4.9	14%	
Fraschi 2000 (37)	Gem + VNR	60	15%	7	30%	<0.01
	VNR	60	20%	4.5	13%	
Gridelli 2003 (38)	VNR	233	21%	8.5	42%	ns
	Gem	233	16%	6.5	28%	
	Gem + VNR	232	18.1%	7.4	34%	
Kudoh 2006 (39)	VNR	92	9.8%	9.9	NR	ns
	Doc	90	22.7%	14	NR	
Lilenbaum 2005 (40)	Carbo + Paclitaxel	561	28%	9	38%	ns
	Paclitaxel	155	36%	8	33%	
Comella 2004 (41)	Gem	68	18%	5.1	29%	ns
	Paclitaxel	63	13%	6.4	25%	
	Gem + Paclitaxel	65	32%	9.2	44%	
	Gem + VNR	68	23%	9.7	32%	
Quoix 2010 (42)	VNR or Gem	226	10%	6.2	25.4%	0.0004
	Carbo + weekly Pacli-taxel	225	27%	10.3	44.5%	

issues. Standard treatment has consisted essentially of monotherapy, as trials conducted in the 2000s failed to show any improvement in survival with doublets. In 2010, however, Quoix *et al.* (35) showed the superiority of a weekly carboplatin-paclitaxel combination over gemcitabine or vinorelbine monotherapy, albeit at a cost of more severe hematological toxicity.

Table 1 summarizes the main phase III trials of single-agent and combination therapy in elderly patients.

It is important, in addition to traditional outcomes, to assess quality of life and particularly the impact of toxicities (29).

The choice between monotherapy and doublet therapy is still controversial, although the trial conducted by Quoix *et al.* (35) clearly marked a turning point. Des Guetz *et al.* (43) recently published a meta-analysis comparing the efficacy and safety of monotherapy versus doublet therapy in patients with metastatic lung cancer. This meta-analysis included 10 studies and 2,605 patients with an average age of 74 years. Overall survival at one year was not improved by the use of doublets versus monotherapy (HR 0.92, CI: 0.82-1.03, P=0.016). In contrast, the response rate was significantly better with doublet therapy (HR 1.51, 1.22-1.86, P>0.001). Gastrointestinal toxicity was similar in the two populations, but neutropenia, thrombocytopenia and anemia were more problematic with doublet therapy.

Among grade III/IV adverse effects, thrombocytopenia and anemia were more frequent with doublet therapy. The authors concluded that there was little additional benefit to the use of doublets versus monotherapy in these patients. Further studies are required to confirm these results (35). In addition, as the authors pointed out, these findings are applicable to independent older patients and cannot be extrapolated to frail patients, for whom the best treatment strategy remains to be defined.

In September 2012, ESMO (44) published its new guidelines favoring platinum-based doublets for elderly patients with PS =0-1 and for some selected patients with PS =2, while monotherapy should be offered to vulnerable patients and those with multiple comorbidities, owing to the higher risk of adverse effects. The “vulnerable” elderly patient was not defined.

While most of the studies presented in *Table 1* selected patients on the basis of standard criteria (age and performance status) (36-42), other teams attempted to define their geriatric patient population more precisely, based on a combination of age, performance status and a comorbidity index (Charlson score). Two open-label phase II (45,46) trials involved two distinct populations: patients who were considered to be in good general condition with few comorbidities were treated with docetaxel and

gemcitabine, while the most fragile patients were treated with docetaxel alone. Both trials were designed to assess the feasibility of the rating tools. Effectiveness was moderate in the monotherapy group, while patients treated with the combination had results similar to those observed in younger patients.

Two randomized phase II trials (47,48) were secondary published with the same selection and a targeted therapy with erlotinib into the treatment strategy. The docetaxel-gemcitabine combination followed by erlotinib gave the best results. Patients were selected on the basis of age, PS, the Charlson score, the number of comorbidities, and geriatric symptoms (falls, incontinence and dependency for ADL and IADL). The results were modest in the fragile patients treated with monotherapy (gemcitabine followed by erlotinib, or vice versa).

These latter two studies showed that geriatric assessment was feasible in clinical trials. Early use of geriatric criteria led to better-defined groups and favored the selection of patients for combination therapy or monotherapy.

Although quality of life was preserved in some clinical trials, such as that conducted by Quoix *et al.*, the risk-benefit assessment must take adverse effects into account (49).

Gradually, targeted therapies have started to be used in these patients. Numerous studies (50-53) have shown that, in Asian patients with activating EGFR mutations, EGFR-TKI significantly improved progression-free survival after frontline treatment, compared to platinum-based chemotherapy. These results were found with gefitinib in an Asian population [HR: 0.36 (0.25-0.51) (52); HR: 0.16 (0.10-0.26) (54)], and with erlotinib in a Caucasian population, HR: 0.37 (0.25 to 0.54) (53).

Following these results, gefitinib and erlotinib obtained marketing authorization for first-line treatment of advanced NSCLC in patients with activating EGFR mutations, even though these studies included very few elderly patients. The age limit for inclusion was 75 years in the studies by Maemondo *et al.* (52) and Zhou *et al.* (54), and median age was 65 years in the study by Rosell *et al.* (53). These activating mutations were a powerful predictor of intense and rapid responses [ORR 58% (53) to 73.7% (52)] to EGFR TKI, a drug with a favorable safety profile. Most elderly EGFR-mutated patients with symptoms or altered general condition (due mainly due to cancer extension) derive a major benefit. Inoue *et al.* (55) showed that some patients with activating EGFR mutations who were considered ineligible for chemotherapy because of poor PS (3 or 4) could regain a PS of 0 or 1, and that some even became eligible for second-

line chemotherapy on disease progression.

There are no specific trials of angiogenesis inhibitors in elderly lung cancer patients.

In the ECOG 4599 trial (56), comparing carboplatin-paclitaxel to carboplatin-paclitaxel-bevacizumab. Bevacizumab did not improve survival in the subgroup of patients aged 70 years or more (median 74 years), although there was a trend towards a better response rate and longer progression-free survival in the bevacizumab group. Toxicity, and especially hematologic adverse effects, was higher in the bevacizumab arm. In the AVAIL study (57) of cisplatin-gemcitabine with or without bevacizumab, progression-free survival was significantly better with bevacizumab and was similar in the older and younger subgroups, without specific toxicity in the older group; however, the median age of patients over 65 was only 68 years. In the ARIES prospective cohort study (58) evaluating the use of bevacizumab in combination with first-line chemotherapy, PFS was respectively 6.6 and 6.7 months in patients <70 years (n=1,320) and ≥70 years (n=647), and overall survival was respectively 14.2 and 12.2 months, i.e. largely inferior in patients ≥70 years. There was no excess toxicity in these latter patients.

The role of bevacizumab in combination with platinum-based chemotherapy in patients ≥70 years of age needs to be determined in a phase III trial specifically dedicated to these patients.

Future developments

While clinical practice guidelines favored the use of monotherapy in elderly lung cancer patients, recent studies supported the use of doublets in selected patients.

A phase III trial is now needed to validate the use of a geriatric index as a criterion for patient selection. Enrolment in the Esogia trial (Figure 2) is now complete and the results should be available in 2013. If the results are positive, the short geriatric assessment could become a standard selection tool for the elderly population. The use of a complete or an abbreviated form might facilitate its application (59).

Elderly lung cancer patients cannot be selected on the basis of clinical criteria alone: biological factors must also be taken into account. Rosell *et al.* (60) have shown that the prevalence of EGFR mutations is higher (41%) among patients over 70, supporting the use of EGFR inhibitors.

A recent report of the BATTLE trial (61) showed similar results in seniors and younger patients in an open trial in

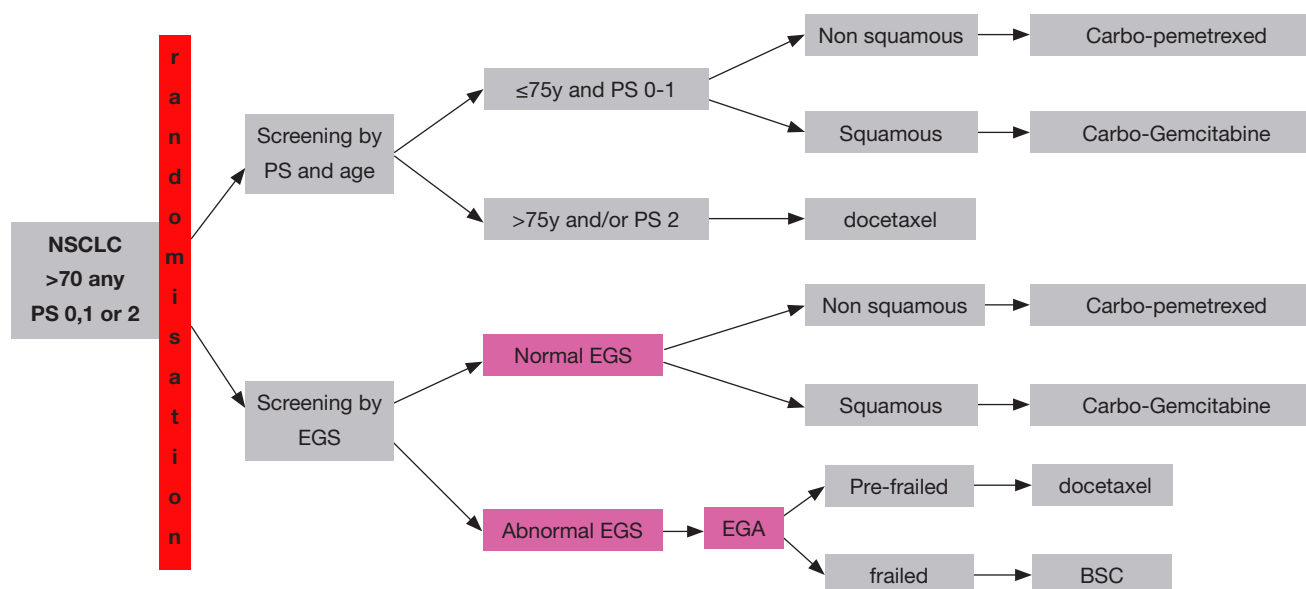


Figure 2 The ESOGIA trial

which treatment selection was based on a biomarker profile (EGFR, K-RAS, B-RAF, cyclin D1, VEGF receptor, and retinoid x receptor).

The future clearly lies in a combination of all these factors. Given the favorable harm-benefit ratio of targeted therapies (EGFR TKI and ALK inhibitors), these drugs might be used as first-line treatments for patients whose tumors bear the molecular target, including patients whose general condition is degraded by the disease. It is possible that, as new therapeutic targets and more effective and well-tolerated drugs are developed, the scope of geriatric assessment may change. Oncogeriatric tools will need to be adapted to these new treatments, including optimal use of biological markers and selection of eligible subpopulations on the basis of clinical criteria, including a geriatric assessment.

Acknowledgements

A. Vergnenegre has received honoraria from Roche, Amgen, Lilly and has received funding for clinical research from Astra-Zeneca, Chugai, Lilly, Amgen, Roche and Boehringer-Ingelheim; R. Corre has funding for clinical research from Lilly, Roche, Chugai and Sanofi Aventis; H Léna has received honoraria from Lilly for board activity and from Astra Zeneca for speaker activity; H Le Caer has received honoraria from Roche and Lilly.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Vergnenegre A, Corre R, Lena H, Le Caer H. Management of elderly patients. *Transl Lung Cancer Res* 2013;2(3):200-207. doi: 10.3978/j.issn.2218-6751.2013.02.04