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Management of non-small cell lung cancer in elderly patients

C. Gridelli[a,*], P. Maione[a], A. Rossi[a], C. Colantuoni[a], M.L. Barzelloni[a], V. Salerno[b], G. Airoma[a]

[a]*Division of Medical Oncology, "S.G. Moscati" Hospital, Avellino, Via Circumvallazione 83100, Avellino, Italy*
[b]*Facoltà di Medicina e Chirurgia, Università "Federico II", Napoli, Italy*

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Abstract

Non-small cell lung cancer (NSCLC) may be considered typical of advanced age. More than 50% of NSCLC patients are diagnosed over the age of 65 and approximately one-third of all patients with non-small cell lung cancer (NSCLC) are over the age of 70. Elderly patients tolerate chemotherapy poorly compared to their younger counterpart because of the progressive reduction of organ function and comorbidities related to age. For this reason, these patients are often not considered eligible for aggressive cisplatin-based chemotherapy, the standard medical treatment of advanced NSCLC. At present, for early stages there are no indications for adjuvant and neoadjuvant chemotherapy. Combined chemo-radiotherapy in locally advanced disease, particularly with concurrent approach should be investigated in specific trials before to be preferred in clinical practice to radiation therapy alone. In advanced disease, prospective phase II trials have demonstrated suitable toxicity profile and good antitumor activity for single agent chemotherapy with the recently developed drugs vinorelbine, gemcitabine and taxanes. Moreover, vinorelbine, compared to best supportive care in a phase III randomized trial, has proven to improve survival and quality of life. A phase III randomized trial showed that polychemotherapy with gemcitabine and vinorelbine does not improve any outcome as compared to single agent chemotherapy with vinorelbine or gemcitabine. In clinical practice, single agent chemotherapy should remain the standard treatment. Feasibility of cisplatin-based polychemotherapy remains an open issue and has to be proven prospectively. The two main research-lines to explore in the near future are the introduction of biological agents in the treatment schemes and the development of specifically designed schedules of platin-based regimens. However, practicing a multidimensional geriatric asessment for individualized treatment choice in NSCLC elderly patients is mandatory.

Keywords: Non-small cell lung cancer; Elderly patients; Single agent chemotherapy; Cisplatin-based chemotherapy

1. Introduction

Every year worldwide 1.2 million new cases of lung cancer are diagnosed [1], 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% of the total. Non-small cell lung cancer (NSCLC) may be considered typical of advanced age. More than 50% of lung cancer patients are diagnosed over the age of 65 and about 30% over the age of 70 [2,3]. Age-adjusted incidence rates for 1990–1994 reported by the National Cancer Institute Surveillance Epidemiology End Results (SEER) programme are 26.7 per 100 000 inhabitants under the age of 65, whilst the rate grows to 345.9 among people aged 65 years or more. More than two-thirds of patients dying of lung cancer in the United States are over 65 years old [4].

Although an earlier stage of disease at diagnosis has been previously described in elderly lung cancer patients [5], a recent analysis [6] on 1035 cases has not confirmed this evidence, with early and advanced stages being equally represented in the elderly and younger population. Similarly, the same series [6], found no correlation between age and performance status (PS) at presentation as previously did Brown and colleagues [7] who observed in 563 lung cancer patients an higher PS score at presentation with increasing age. Elderly patients

* Corresponding author. Tel.: +39-0825-203573; fax: +39-0825-203556.
E-mail address: cgridelli@libero.it (C. Gridelli).

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seem to have a poorer prognosis compared to younger ones. This has been shown recently by the data on 5-year relative survival of lung cancer patients, registered in 8 Italian cancer registries collected within the Itacare project [8]. 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 55–64 is 0.55, indicating that prognosis for elderly patients with lung cancer is notably worse than for the younger ones. Brown and colleagues reported data collected by a lung cancer registry and age alone appeared to be a major factor in influencing treatment choices. There was an increase of inappropriate treatment with increasing age, in particular for decreasing use of chemotherapy [7].

The majority of cases of NSCLC are diagnosed in advanced stage, and the majority of those diagnosed in early stage develop metastases in their natural history. As a consequence the large majority of NSCLC patients is candidate to a medical treatment. However, NSCLC includes a group of tumors that respond poorly to drugs. A meta-analysis showed a slight improvement in median survival for cisplatin-based chemotherapy versus best supportive care in advanced NSCLC (6 weeks) [9]. In clinical practice cisplatin-including regimens are the most widely used in the treatment of advanced NSCLC. This review will focus the treatment of elderly patients affected by NSCLC. All published papers specifically addressing treatment of elderly NSCLC patients until 15 October 2003 were searched using MEDLINE (PubMed, National Library of Medicine, Bethesda, MD, USA). Furthermore abstracts presented at the main international meetings were considered.

2. Organ function age-related changes

Elderly patients tolerate chemotherapy poorly because of progressive organ failure related to age and comorbidities. With age, hepatic clearance either decreases or remains unchanged, though generalizations are difficult to make as metabolism is affected by a number of factors such as: blood flow, concurrent drug use, disease/physiologic disorders, environmental exposure, gender, genetic differences, liver mass, nutritional intake, and physical condition [10]. Some age-related changes in liver function include: decline in hepatic blood flow, decrease in hepatic organ mass, decline in the intracellular activity of cytochrome P450 enzymes. These changes may hinder clearance of drugs from the system, thereby increasing the risk of drug–drug interactions. The risk of hepatic drug–drug interactions may 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 decreased renal blood flow, decreased glomerular filtration rate, and decreased creatinine clearance thereby altering drug pharmacokinetics and pharmacodynamics [11].

Decreased hepatic, renal and bone-marrow functions have a negative impact on the degree of 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 the elderly [12].

3. Comorbidities and frailty

It has been reported that among individuals aged 65–74 years, the mean number of chronic diseases is 6. The prevalence of these co-morbid conditions is about twice as high as in the general population [13]. Over 50% of the elderly have chronic arthritis, 33% backache, 32% visual deficit, and 28% exertional dyspnoea [14]. Preliminary observation on cancer patients also confirm the coexistence of other diseases in elderly cancer patients [4]. The most important co-existing pathologies in lung cancer patients are cardiovascular and pulmonary diseases, common among heavy cigarettes smokers.

Another important issue is the definition of frail elderly persons. The frailty is a condition in which most functional reserve is exhausted. Frail patients depend on others for the activities of daily living prevalently because of physical and cognitive dysfunctions. Generally, in these patients with advanced NSCLC, chemotherapy should be avoided considering the high risk of toxicity. Reliable information regarding patient co-morbid health problems is mandatory in order to plan an appropriate treatment. Co-morbidity influences treatment choice globally and is a predictor of outcome [15]. However, to date, a standard, fully satisfactory way to assess co-morbidity has not been defined [16]. Moreover, very few authors report the number of comorbid conditions for patients entered into clinical trials and there is practically no report accounting for the degree of severity of comorbidities [17].

In order to plan treatment, a multidimensional geriatric evaluation including not only co-morbidities assessment but also functional status, mental and nutritional status is important. Table 1 shows main multidimensional assessment domains and tools.

As a consequence of the above-reported considerations, elderly patients with NSCLC, who frequently suffer tumor-related symptoms and need some kind of

Table 1
Main domains of multidimensional assessment in elderly cancer patients

Domains	Measuring tool
Comorbidity	Charlson comorbidity scale CIRS-G CIRS-G
Functional Status	ADL IADL
Depressive Symptoms	GDS
Mental Status	MMSE
Nutritional State	Mini Nutritional Assessment

CIRS-G, Cumulative Illness Rating Scale-Geriatric; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination.

palliative treatment, often receive untested or inadequate treatments [7,18]. This happens more frequently with the elderly than with their younger counterparts. Furthermore, they are not generally included in clinical trials [19].

4. Age cut-off

Within epidemiological literature the age of 65 is usually considered as a cut-point to select elderly population. On the contrary, in clinical trials, the age of 70 is frequently used as lower limit for patient selection, based on the consideration that the general health status of patients aged 65 to 70 is usually not so bad to plan treatment strategies different from those 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 [20].

A cut-off age of 75 years is less common. Obviously, indirect comparison of trials including or not patients aged 65–70 may be biased. A further bias may be due to the distribution of the so called 'very old' patients, aged 80 or more. It is relevant that the proportion of 'very old' patients with lung cancer at diagnosis is going to increase in the next few years [4]. Thus, results coming from studies prevalently including patients in their 70s may not be completely generalizable to future generations of elderly patients. Furthermore we must consider that it is very difficult to establish a maximum age for chemotherapy treatment in the elderly. In clinical practice biological instead of chronological age should be considered. Unfortunately, to date, laboratory tests (i.e. interleukin 6) and geriatric evaluation are inadequate to define ageing; therefore, at present, chronological age should be used as frame of reference for clinical trials. However any chronological definition can be considered arbitrary and biological criteria are needed.

5. Early stages

Surgery is the only curative treatment of NSCLC. Unfortunately, only 15–20% of tumors can be radically resected, and, overall, surgically-treated patient survival is only around 40% at 5 years. For patients considered inoperable for medical reasons radical radiotherapy can be a reasonable choice. Postoperative treatments such as chemotherapy and radiotherapy have been investigated. A meta-analysis evaluating data available from 4357 patients included in clinical trials comparing surgery alone to surgery + chemotherapy showed a survival benefit of 5% at 5 years for cisplatin-based chemotherapy (95% confidence interval from 1% detriment to 10% benefit) [9]. A subgroup analysis showed no evidence that any group of patients specified by age benefited more or less from chemotherapy. These results have stimulated clinical research in that field. An American intergroup trial comparing surgery + radiotherapy to surgery + radiotherapy + chemotherapy with cisplatin and VP-16 showed no survival benefit and higher toxicity for the chemotherapy arm [21]. Furthermore, several clinical trials on platin plus new drugs, such as vinorelbine and paclitaxel, are ongoing or recently over with pending results.

However, if adjuvant chemotherapy proves effective, there will be doubts about cisplatin-based treatment tolerability in resected elderly patients. On this issue, the ongoing ANITA (Adjuvant Navelbine International Trialist Association) 02 study of adjuvant single-agent vinorelbine in patients who cannot receive cisplatin-based chemotherapy is of interest.

Regarding the role of postoperative radiotherapy, a meta-analysis demonstrated no advantage for this therapeutical approach [22]. A subgroup analysis showed no evidence that radiotherapy was more or less effective in any group of patients defined by age. To date, no postoperative treatment should be advised in clinical practice outside clinical trials in the general population and in the elderly as well.

Neoadjuvant chemotherapy in the early stages is an experimental approach under investigation in the general patient population and should not be considered in clinical practice.

6. Locally advanced disease

Meta-analysis including data from 3033 patients has shown a significant survival advantage, an absolute benefit of 2% at 5 years, for combined chemo-radiotherapy as compared to radiotherapy alone [9]. No difference in chemotherapy benefit related to age was found. However, it should be considered that the elderly have a major risk of toxicity, particularly

myelotoxicity and esophagitis. Furthermore, frequent pulmonary and cardiac co-morbidities [13] often limit aggressive approaches.

The Radiation Therapy Oncology Group (RTOG) performed a retrospective analysis of patients included in phase II–III trials [23]. A quality-adjusted survival analysis of 979 cases, treated with radiotherapy alone or combined chemo-radiotherapy, showed a critical relationship between age and ability to tolerate combined treatment. In fact, elderly patients aged more than 70 years achieved the best quality-adjusted survival with standard radiotherapy only. These results have been confirmed in another RTOG retrospective analysis of 749 locally advanced NSCLC patients enrolled in three separate trials and randomized to radiotherapy alone versus combined sequential or concurrent chemo-radiotherapy [24]. As therapy intensified, the incidence of grade 3–5 toxicities increased in the elderly group (>70 years). Unlike the overall patient population, elderly patients did not benefit from combined treatment and the authors concluded that specific trials are indicated. The same authors, two years later, retrospectively evaluating treatment outcomes in elderly versus younger patients enrolled on a randomized RTOG trial of concurrent versus sequential chemoradiotherapy, concluded not only for the feasibility of combined treatment but also for the superiority of the concurrent approach compared to the sequential one even in the elderly population [25].

In clinical practice a combined treatment, particularly if aggressive and including a concurrent schedule, should be offered to selected elderly patients only (i.e. PS 0–1, no major comorbidities). Clinical trials of combined chemo-radiotherapy specifically designed for and targeting the elderly are warranted.

7. Advanced disease

Meta-analysis of randomized trials of chemotherapy versus best supportive care showed a slight statistical survival advantage, six weeks of median survival, for cisplatin-based chemotherapy [9]. No difference related to age was observed. Recently, a retrospective trial of 6232 elderly patients from the SEER tumor registry showed that chemotherapy for metastatic NSCLC seems to have the same effectiveness as that seen in randomized trials with mostly younger patients [26]. Therefore, all suitable patients should be given the opportunity to consider palliative chemotherapy for advanced NSCLC. Based on particular clinical findings in elderly patients with reduced chemotherapy tolerability and uncertainties regarding the use of cisplatin-based combination chemotherapy, non platin-based chemotherapy was the first investigational approach.

7.1. Non platin-based chemotherapy including old generation drugs

Among first generation citotoxic agents, single-agent vindesine induced a 20% response rate in a series of 22 patients [27] and its coupling with ifosfamide did not improve activity (15% response rate) in patients over 65 years [28]. Salvati and colleagues used the combination of cyclophosphamide and lonidamine, observing a 15% of response rate with a quite long median survival of 9 months; however, in this trial 13 of 41 entered patients had stage IIIA disease with a more favorable prognosis [29]. De Marinis and colleagues performed a multicenter randomized trial comparing best supportive care versus lonidamine versus vindesine versus lonidamine + vindesine. The authors reported similar negative results in all arms. In this study about 35% of patients were lost to follow-up [30]. A low response rate (13%) has been reported with doxofluoridine in a series of 33 patients over the age of 65 [31].

7.2. Single agent chemotherapy with new generation drugs

The introduction into clinical practice of new, active and well-tolerated drugs (vinorelbine, gemcitabine and taxanes) has stimulated clinical research. Good tolerability of paclitaxel as a single-agent in the elderly has been previously described [32]. In a retrospective trial, paclitaxel showed good tolerability and activity in advanced NSCLC elderly patients [33]. Prospective data on weekly paclitaxel are being recently published. Fidias et al, used weekly paclitaxel on 35 advanced NSCLC elderly patients reporting a good tolerability and interesting results with 23% OR and 10.3 months of median survival [34]. On the contrary, Garbo and colleagues [35] and West and colleagues [36], using weekly paclitaxel in a series including unfit patients, observed a good toxicity profile but low response rate. Docetaxel has been investigated in the elderly. Yoshimura and colleagues [37] reported 18% OR but an unfavourable toxicity profile with a four-week schedule of low-dose docetaxel (60 mg/m^2). Hainsworth and colleagues reported for weekly docetaxel 18% OR, a median survival of 5 months and a good tolerability [38].

Gemcitabine is an active drug in NSCLC with a favourable toxicity profile that has allowed its use and evaluation in the elderly. Three large retrospective analyses of gemcitabine in elderly NSCLC patients have been published, suggesting that this drug could be sufficiently active and well tolerated, with no differences in terms of activity, efficacy and toxicity as compared to their younger counterparts [39–41]. In the first one, 329 patients aged over 70 had similar toxicity, response rate (25%) and survival as the patients aged under 70 [39]. In the second one, similar results were found with 24% of

objective response rate (OR) with better response rate for stage IV in the elderly (37% versus 13%) [40]. Even in the third gemcitabine showed a good response rate (26.3%), mild toxicity and promising results in terms of median survival (9.8 months) [41]. Subsequent phase II prospective trials confirmed those results with OR ranging from 16% to 33% and median survival of 29–32 weeks [42–49]. In a prospective phase 2 study in 33 patients, no grade 4 toxicity has been reported with a 24% response rate [42]. Other investigators used gemcitabine in 22 elderly patients with advanced NSCLC and observed a 41% response rate [43]. Martoni and colleagues in 30 patients reported 27% OR [44]. Ricci and colleagues in 46 patients observed a 22% response rate [45]; Gridelli et al in a randomized phase II trial enrolled 49 patients reporting a 18% response rate [46] and Altavilla and colleagues in 21 patients reported a 33% response rate [47]. Martoni and colleagues [48] and Tibaldi and colleagues [49] confirmed, in 46 and 110 patients respectively, antitumoral acitvity (22% and 14%) and a good toxicity profile.

One of the most widely studied drugs in advanced NSCLC elderly patients is vinorelbine, a vinca alkaloid with antimicrotubule mechanism of action. In phase II studies, single agent vinorelbine proved to be well-tolerated and active, with response rates of 12–39% [50–53]. Colleoni and colleagues used vinorelbine in 25 patients reporting a 16% response rate [50]. Tononi and colleagues in 25 patients not eligible for poly-chemotherapy, observed 12% OR [51]. Veronesi and colleagues treated 18 patients and observed 39% objective response. In this trial about 30% of patients had stage IIIA disease which has a more favourable prognosis [53]. Single-agent vinorelbine has also been used on advanced elderly patients with poor performance status (<4) resulting in a 5% OR but an encouraging median survival of 34 weeks [54]. Gridelli and colleagues [52] observed a 23% response rate with an improvement of ECOG performance status in one-fourth of the 43 enrolled patients; cough and pain improved in more than 40% and dyspnoea and haemophtoe in about 25% of the patients who were symptomatic at entry; overall, half of the patients had a stabilization of their symptoms. We administered vinorelbine at the standard dose of 30 mg/m^2 weekly for a maximum of 12 weeks. The median delivered dose intensity (21.4 mg/m^2/week) and patients' compliance suggests that the optimal vinorelbine schedule could be 30 mg/m^2 at days 1 and 8, recycled every 3 weeks. The Table 2 summarizes some of main phase II studies on single agent chemotherapy. The 3-week above mentioned schedule of vinorelbine was used in the subsequent phase III multicentre trial (ELVIS—Elderly Lung Cancer Vinorelbine Italian Study) comparing single-agent vinorelbine versus supportive care that enrolled 191 patients [55]. Response rate recorded in the vinorelbine arm was 20% and toxicity was mild, confirming that the 3-week schedule is an optimal way to deliver single-agent vinorelbine to elderly patients. Furthermore, the ELVIS trial showed that vinorelbine improves quality of life measured by EORTC questionnaires C30 and LC13 [56] and survival as compared to supportive care (27 versus 21 weeks of median survival, $P=0.04$). This survival advantage is similar to that reported by metanalyses for cisplatin-based chemotherapy versus best supportive care in adult patients [9].

As the ELVIS trial is the unique randomized controlled trial versus best supportive care ever performed in the treatment of elderly patients with advanced NSCLC, its result is the most reliable evidence on the efficacy of chemotherapy in this subgroup of patients.

7.3. Not platin-based combination chemotherapy including new generation drugs

In order to improve results obtained with single agent chemotherapy, the development of non cisplatin-based combinations is an interesting issue in the treatment of advanced NSCLC elderly patients. The possibility of active and well-tolerated chemotherapy while preserving patient quality of life is more attractive in the elderly. Mc Kay and colleagues used a weekly combination of gemcitabine plus docetaxel reporting good tolerability and interesting results with 27% OR and a median survival of 7.5 months [57]. The most studied non platin-based regimen is the combination of gemcitabine plus

Table 2
Main phase II studies on single-agent chemotherapy in advanced NSCLC elderly patients

Author	Drugs	Age	N. pts	%OR	MST (weeks)
Colleoni (1994) [50]	VNR	$\geqslant 65$	25	16	22.5
Gridelli (1997) [52]	VNR	>70	43	23	36
Ricci (2000) [45]	GEM	>70	46	22.2	28.9
Gridelli (2001) [46]	GEM	$\geqslant 70$	49	18.4	NR
Martoni (2001) [48]	GEM	$\geqslant 70$	46	21.7	40.5
Hainsworth (2000) [38]	TXT (W)	$\geqslant 65$	39	18	21.4
Fidias (2001) [34]	PCL (W)	>70	35	23	46.3

NSCLC, non-small cell lung cancer; OR, objective response; MST, median survival time; VNR, vinorelbine; GEM, gemcitabine; TXT, docetaxel; PCL, paclitaxel; W, weekly; NR, not reported.

vinorelbine. Some phase II studies of gemcitabine + vinorelbine have been performed [46,58,59]. Two of them also included younger unfit patients with contraindication to receive cisplatin, reporting 26% and 34.9% OR with a 1-year survival rate of 33% and 31%, respectively [58,59]. However, elderly patients and younger patients with a poor performance status ($\geqslant 2$) are two different patient populations and should not be included in the same trials. The reduction of multiorgan functions and co-morbidities must be specifically considered in the elderly, and both populations need specific treatments. In a phase II randomized study of patients all aged over 70 years, gemcitabine plus vinorelbine resulted in an 18.4% response rate and was well-tolerated [46]. Some authors performed a small phase III randomized trial comparing single-agent vinorelbine to gemcitabine plus vinorelbine combination [60]. The study randomized only 120 patients overall and was stopped with an interim survival analysis that showed a survival advantage for the combination arm (29 versus 18 weeks of median survival, respectively). The study showed a surprising short median survival for vinorelbine (18 weeks) not consistent to that reported by different large randomized trials in younger or elderly patients; furthermore that median survival is shorter to that reported for best supportive care alone [9,55]. In order to evaluate the role of non-platin doublets in advanced NSCLC elderly patients we performed a large randomized phase III trial (MILES-Multicenter Italian Lung cancer in the Elderly Study). We randomized 707 patients and single-agent chemotherapy (vinorelbine or gemcitabine) was compared to polychemotherapy with gemcitabine + vinorelbine. No comparison of single-agent gemcitabine to vinorelbine was planned because it was considered 'a priori' an equivalence question to be addressed in a different trial requiring a different approach and sample size. No statistically significant difference in terms of response rate, time to progression, survival or quality of life was found between monochemotherapy with vinorelbine or gemcitabine and polychemotherapy with the two drugs combined [61].

In the MILES trial multidimensional geriatric evaluation (Activity Daily Living Index and Instrumental Activity Daily Living Index) comparisons were performed [62]. The Table 3 summarizes some of main phase III trials performed in advanced NSCLC elderly patients.

7.4. Cisplatin-based chemotherapy

Several pharmacokinetic changes are observed with ageing. Noteworthy is the reduction of renal excretion with enhanced toxicity of renally excretable drugs, particularly cisplatin and its compounds.

Overall, very few clinical experiences with cisplatin-based chemotherapy in elderly NSCLC patients have been reported and it is self-explanatory that toxicity is the most relevant outcome in all the available reports. Cisplatin is particularly difficult to use in elderly patients because of renal and neurological toxicity. Furthermore, cisplatin administration needs aggressive hydration that could be contraindicated in these subsets of patients. In a retrospective study on toxicity and tolerability of cisplatin-based chemotherapy in advanced NSCLC in 839 patients, no correlation was found among response rate, survival, grade 3 and 4 toxicity and age categories. On the other hand, with the increase of patients age a significant rise in early death (less than 30 days from the beginning of chemotherapy) rates was noted: 0, 5 and 7% in patients aged less than 54 years and more than 70 years, respectively. The authors advised special caution in treating elderly patients with cisplatin-containing chemotherapy [63]. In another retrospective study in a series of patients, specifically evaluated for possible nephrotoxicity of cisplatin-based chemotherapy, it was found that, despite aggressive hydration with hospitalization, this toxicity was so significant as to prompt the authors to recommend clinical trials of non cisplatin-containing regimens [64]. A relevant toxicity of cisplatin-containing regimens has also been recorded in two prospective studies. Mielotoxicity was severe in a group of patients older than 75 years

Table 3
Main phase III randomized trials of chemotherapy in advanced NSCLC elderly patients

Author	Drugs	Age	N. pts	%OR	MST (weeks)
Gridelli (1999) [82]	BSC	>70	191	20	21
	versus				27[a]
	BSC + VNR				
Gridelli (2001) [46]	VNR	$\geqslant 70$	707	18.5	37
	or				
	GEM			17.3	28
	versus				
	GEM + VNR			20.0	32

NSCLC, non-small cell lung cancer; OR, objective response; MST, median survival time; VNR, vinorelbine; GEM, gemcitabine; BSC, best supportive care.

[a] Statistically significant difference.

treated with cisplatin plus vindesine and the study was discontinued after the first seven patients enrolled due to toxicity [65]. Soquet and colleagues used the MIC regimen (mitomycin C + ifosfamide + cisplatin) in a series of 16 patients, 70 years old or more, reporting 37.5% objective response (OR) but with significant toxicity. Bone-marrow and renal toxicities were the main cause of treatment discontinuation. The authors did not advise the MIC regimen in the elderly [66]. On the contrary, a further retrospective trial showed that cisplatin-based chemotherapy (cisplatin plus vindesine or cisplatin plus mitomycin C plus vindesine) was feasible and associated with a higher response rate (44% versus 28%) in the elderly [67]. The better response rate could be explained because more elderly patients had earlier disease and better performance status compared to the younger ones. A small phase II study showed that weekly cisplatin plus gemcitabine combination, in 29 patients is well tolerated and produces interesting response rate (48%) and overall clinical benefit response rate (52%). However, in this trial the cut-off age was 65 years [68]. More recently, two prospective phase II trials on cisplatin-based polychemotherapy have been presented. It is of interest because explore innovative schedules of cisplatin delivering that could be more suitable to elderly population. Berardi and colleagues reported good tolerability and response rate with a weekly schedule of cisplatin and gemcitabine [69], as did Madronal and colleagues with a low-dose cisplatin regimen (50 mg/m^2) [70].

At present, cisplatin-based chemotherapy remains the standard treatment for advanced NSCLC. Consequently it should be considered appropriate to investigate cisplatin-based chemotherapy for elderly patients with good performance status [71]. The problem is developing suitable schedules and doses for the elderly. The issue of cisplatin-based therapy for elderly patients with advanced NSCLC has been recently addressed by three retrospective analyses. The first, regarding an Eastern Cooperative Oncology Group phase III randomized trial of platinum-based chemotherapy regimens for NSCLC (ECOG 5592), compared the outcomes of elderly (>70 years) and younger patients. Response rate, toxicity and survival appeared to be similar to those in younger patients except than more frequent leukopenia and neuro-psychiatric toxicity in the elderly group. Authors concluded that advanced age alone should not preclude aggressive NSCLC treatment [72]. Similarly, Kelly and colleagues among two Southwest Oncology Group trials (# 9508 and 9308) [73], found no statistically significant differences neither in the efficacy nor in the toxicity of platin-based regimens between elderly patients and younger counterpart, although a trend toward shorter survival in older patients. Recently, Langer et al revised the ECOG 1594 phase III trial reporting similar results between younger and elderly patients [74]. The evidences from these analyses could however suffer from selection bias. In fact, elderly patients enrolled in this sort of trials could not be representative of the whole elderly population but only of a small subgroup thought to be eligible for aggressive treatments by investigators. The percentage of elderly patients among patients diagnosed with lung cancer in clinical practice is much higher than the percentage of elderly patients among patients enrolled in clinical trials for lung cancer treatment not specific for elderly population. As a consequence the generalizability of these results is poor because of possible selection bias and they could potentially put at risk many elderly patients until large prospective trials will have not shown that cisplatin is safe in the elderly [75]. Prospective clinical trials with inclusion criteria selective for elderly population are to be considered the unique tool for investigating cisplatin-based chemotherapy in this clinical setting.

7.5. *Carboplatin-based combination chemotherapy*

The substitution of carboplatin for cisplatin in younger and elderly patients alike is appealing. Carboplatin is a cisplatin analogue that causes less nausea/vomiting, nephrotoxicity and neurotoxicity than its parent drug and does not require hydration. However, it causes more myelotoxicity than cisplatin, and sometimes that toxicity is difficult to manage in the elderly. Furthermore, thrombocytopenia and neutropenia may represent serious cumulative hematological toxicity when carboplatin is combined with other myelotoxic drugs. To date carboplatin seems not inferior then cisplatin in advanced NSCLC. Recently, Rosvold and colleagues performed a retrospective analysis of carboplatin plus taxol chemotherapy in advanced elderly NSCLC patients [76]. They observed that advanced age (>70 years) is associated with a lower response rate (32% versus 50%) but with similar survival and toxicity compared to younger one. No difference in survival, as well, were found between patients younger and older than 70 years enrolled in the randomized CALGB 9730 trial comparing carboplatin plus paclitaxel versus paclitaxel alone [77]. Furthermore in the elderly subgroup was confirmed the survival advantage for combination chemotherapy versus single agent. However these data should be considered with caution because coming from a retrospective analysis. Five different studies using the carboplatin plus etoposide combination showed severe toxicity in advanced NSCLC elderly patients [78–82]. Response rates, indeed, ranged from 0 to 6.5% and significant mielotoxicity was reported in all the studies. In particular Gridelli and colleagues in 14 patients observed no objective response [82]. Carboplatin, in a weekly schedule, has also been combined with 5-fluorouracil and folinic acid in a series of 23 patients; unfortunately, no objective response has been recorded [83].

Table 4
Main phase II studies on combination chemotherapy in advanced NSCLC elderly patients

Author	Drugs	Age	N. pts	%OR	MST (weeks)
Gridelli (2001) [46]	GEM + VNR	⩾70	49	18.4	NR
Berardi (2002) [69]	CDDP (W) + GEM (W)	⩾70	46	26	40.5
Madronal (2002) [70]	CDDP (ld) + GEM	⩾70	46	37	49.5
Jatoi (2003) [86]	CBDCA (W)(ld) + PCL (W)	⩾65	49	14	NR

NSCLC, non-small cell lung cancer; OR, objective response; MST, median survival time; VNR, vinorelbine; GEM, gemcitabine; PCL, paclitaxel; CDDP, cisplatin; CBDCA, carboplatin; W, weekly; ld, low-dose; BSC, best supportive care; NR, not reported.

Two phase II studies have been performed adding carboplatin to vinorelbine, but reported activity (14% and 27% response rates) does not suggest any clinical improvement compared to single agent chemotherapy also in consideration of a significant rate and degree of mielotoxicity [84,85]. Jatoi and colleagues combined weekly low-dose carboplatin and paclitaxel producing modest antitumor activity with a mild toxicity profile [86]. Marsland et al produced good results in terms of tolerability, palliation and quality of life with a standard dose weekly schedule of carboplatin plus paclitaxel in 61 patients that included a high proportion of elderly patients [87]. Table 4 summarizes some of main phase II trials on combination chemotherapy performed in advanced NSCLC elderly patients.

7.6. *Targeted therapies*

An understanding of tumor cell biology has increased and several molecular targets for NSCLC have been identified, a number of new biologic agents have been developed. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread [88].

Gefitinib (ZD1839) (Iressa) is an orally available EGFR tyrosine kinase inhibitor. The major clinical development of gefitinib has been reported for single-agent therapy in recurrent NSCLC. In fact, recently, two large randomized phase II trials, named IDEAL-1 and IDEAL-2 (Iressa Dose Evaluation in Advanced Lung cancer), evaluating the activity of two different doses of gefitinib in pretreated NSCLC patients, demonstrated that Iressa, at a daily dose of 250 mg, is active and well tolerated [89,90]. Response rates ranged between 20% for patients pretreated with one or two chemotherapy lines (IDEAL-1 trial) and 10% for patients pretreated with two or more chemotherapy lines (IDEAL-2 trial). Considered its good safety profile, a further prospective of gefitinib use should be developed in the treatment of special patient populations such as PS 2-3 patients, elderly, and patients with major co-morbidities controindicating any chemotherapy.

Three experiences with gefitinib in the treatment of advanced NSCLC elderly patients were reported [91–93]. The results were disappointing but the treatment was well tolerated despite the patients were heavily pretreated. Single agent gefitinib is worthy to be tested in the next future to elderly and poor PS patients with advanced NSCLC even as first-line treatment.

8. Ongoing studies

The most promising fields of clinical research in the treatment of elderly NSCLC patients are the improvement of monochemotherapy, the improvement of combination chemotherapy and the introduction of new biologic agents. Our group is running a 3-arm phase II randomized study (MILES 02) evaluating activity and toxicity of single agent gemcitabine given as fixed infusion rate (10 mg/m^2/min) or cisplatin + gemcitabine or cisplatin + vinorelbine. Firstly the study will evaluate the optimal dose of cisplatin (50–60–70 mg/m^2) in the combination arms. The fixed infusion rate produce higher intracellular concentrations of active triphosphate metabolites of gemcitabine in preclinical and clinical studies [94–96] and the possibility to improve results of standard infusion (30 min) is of interest. A phase II randomized trial of pemetrexed (multitarget antifolate—MTA) alone or alternating with gemcitabine is ongoing. In another phase II randomized study we are evaluating the role of the tyrosine kinase inhibitor ZD1839 combined to vinorelbine or gemcitabine chemotherapy.

9. Conclusions

Although the number of elderly patients is increasing, and require specific attitudes and treatments, few controlled clinical trials of NSCLC chemotherapy in the elderly have been performed. However, clinical research is now focusing on this issue, and we expect in the near future some specifically designed clinical trials. In the early stages for resected patients, adjuvant or neoadjuvant approaches must be considered investigational.

For locally advanced disease, a combined approach, particularly with concurrent treatments, should be investigated in specific trials in the elderly. Cisplatin-based chemotherapy seems to be poorly tolerated in the elderly. In clinical research and practice, single-agent chemotherapy should be the standard treatment. The choice of the drug should be based on both toxicity profile of each drug and patients co-morbidities.

In the future the use of new biological agents and the development of more tolerable cisplatin-based regimens will be the main field of research.

However, to plan medical treatment in NSCLC elderly patients, and to further individualize treatments a multidimensional geriatric evaluation is mandatory.

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