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REVIEW

Advanced non-small cell lung cancer in elderly patients: A review

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Abstract

Over 50% of patients diagnosed with non-small-cell lung cancer (NSCLC) are 65 years old while 30% exceed 70 years old. Comparing elderly patients to their younger counterpart they poorly tolerate chemotherapy due to progressive reduction of organ function and age-related co-existing pathologies. Due to this reason elderly are usually excluded from platinum-based chemotherapy, which still represent the standard of care for advanced NSCLC. In every-day practice, single-agent schedule with a third-generation drug is the recommended option for elderly patients with advanced NSCLC. A modest increase in toxicity for elderly patients has been demonstrated by subgroup analyses concluding for platinum-based combination chemotherapy being similar in young patients and fit elderly. Even though the cited evidence, feasibility of chemotherapy based on platinum remains an open question. Prospective randomised trials are warranted in order to change guide lines and give the clinicians a new therapeutic option. Recent emerging role of molecular target in selecting patients for new targeted therapies suggest dedicated trials for elderly patients. The same is for more accurate evaluation of elderly patients with increasing evidence for a comprehensive geriatric assessment as a valid tool for customized treatment in NSCLC elderly patients. Suitable evidences for the treatment of elderly patients affected by advanced NSCLC together with more appropriate and validated tools for patients selection are reviewed along the manuscript.

Key words: Lung cancer; Elderly; Chemotherapy; Target therapy

Core tip: Due to progressive ageing of population in the next few years a consistent proportion of non-small-cell lung cancer (NSCLC) patients will be diagnosed over the age of 70 years old. Guide lines indications together with results from most recent phase Ⅲ trials dedicated to elderly patients are discussed along the review. Special attention has been deserved to toxicity profile. Recent emerging role of molecular target in selecting patients for new targeted therapies suggest dedicated trials as for more accurate evaluation with increasing evidence for a comprehensive geriatric assessment as a valid tool for treatment selection in NSCLC elderly patients.

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INTRODUCTION

Non-small-cell lung cancer (NSCLC) still represents the most frequent cause of cancer-related deaths in Europe and many western countries. Median age at diagnosis of NSCLC is around 70 years old with 50% and more diagnosed over 65 and 30% over 70[1,2]. Continuous shifting toward an older population will cause oncologists seeing more elderly patients with lung cancer in years to come.

The highest percentage of patients presents with metastatic disease at diagnosis with chemotherapy standing for the gold standard of management. It is demonstrated that many older patients with metastatic NSCLC are not treated due to many reasons[3,4]. Aging is cause of physiological changes in organ functions, as for example renal and liver function. Co-morbidities and and consequent drugs intake which may condition chemotherapy administration and toxicity profile[5]. An immediate consequence is a sort of under-treatment for this setting of patients[6].

It is known that these patients are not candidated to clinical trials causing difficulty in reaching evidence-based clinical recommendation. In current clinical practice the choice of treatment is still very often based on a old-believe that cancer in older people behave in a less aggressive manner[7].

A significant difference has been documented on a survey which considered trials for cancer drug registration from 1995 to 2002 with only 35% of elderly patients enrolled on clinical trials[8]. Such a discordance can greatly affect the reproducibility of trial results.

Chronological age should be no more considered the correct parameter on which candidate patients to receive specific treatment. Biological age should be defined through laboratory tests and geriatric assessment evaluation. However chronological age still represent a reference for clinical trials: 70 years old is considered a reasonable cut-off considering the incidence of age-related variations starts to increase after the age of 70[9]. Many evidences suggest an advanced median age of elderly patients in dedicated trials with milder reported toxicity respect to that reported in age-unspecified studies[10].

SINGLE-AGENT CHEMOTHERAPY

The ELVIS trial was the first phase Ⅲ trial conducted in advanced NSCLC patients aged ⩾ 70 years old. Patients were randomized to receive vinorelbine at a dose of 30 mg/m^2 on days 1 and 8 or best supportive care. Advantage in term of survival and increased quality of life (QoL) were demonstrated for vinorelbine arm[11].

Regarding the role of gemcitabine in the treatment of elderly patients affected by advanced NSCLC many specifically addressed phase Ⅱ trials confirmed its interesting role with an overall response rates (ORR) of 18% to 38% and MST of 6.8 to 9 mo. Toxicity was mild with only sporadic grade 3 to 4 hematologic toxicities in two of them[12-15].

Other specific trials demonstrated satisfying data regarding both activity and feasibility for paclitaxel and docetaxel: ORR 3%-23% and MST 6.8-10.3 mo[16]. Overall response rate (ORR) and median survival time (MST) were as follow: 3%-23% and 6.8-10.3 mo, respectively, with acceptable toxicity[16-21].

When docetaxel was compared to vinorelbine in a randomized phase Ⅲ trial no significant difference in MST was encountered, while longer progression-free survival (PFS) and higher ORR were demonstrated for docetaxel[22].

NON-PLATINUM-BASED POLICHEMOTHERAPY

Among non-platinum-based regimen the association of gemcitabine plus vinorelbine has been widely studied. At least two phase Ⅲ trials compared the combination with single agent schedule. Frasci *et al*[23] obtained survival advantage for combination respect to single agent in term of MST and ORR.

The Multicenter Italian Lung cancer in the Elderly Study (MILES) trial with its 700 elderly patients affected by advanced NSCLC, represents a milestone in this setting. Patients were randomised to receive vinorelbine or gemcitabine or combination. Considering ORR, time to progression (TTP), MST or QoL no advantage was demonstrated over single-agent therapy in favour of combination therapy. Single-agent therapy confirmed

Table 1 Results from phase Ⅲ trials of advanced non-small-cell lung cancer in elderly patients: Non-platinum based chemotherapy

Ref.	Regimen	Age (yr)	No. of patients	RR (%)	MST (mo)
Gridelli[11]	Vinorelbine	70	76	20	6.5
	vs				
	Best Supportive Care		78	NA	4.8
Frasci *et al*[23]	Vinorelbine	70	60	15	4.2
	vs				
	Vinorelbine + Gemcitabine		60	22	6.7
Gridelli *et al*[24]	Vinorelbine or	70	233	18	8.3
	Gemcitabine		233	16	6.5
	vs				
	Vinorelbine + Gemcitabine		232	21	6.9
Kudoh *et al*[22]	Vinorelbine	⩾ 70	91	9.9	9.9
	vs				
	Docetaxel		88	22.7	14.3
Quoix *et al*[54]	Vinorelbine or Gemcitabine	⩾ 70	226		10.3
	vs				
	Carboplatin/paclitaxel		225		6.2
Hainsworth *et al*[25]	Docetaxel	⩾ 65	171	17	5.1
	vs				
	Docetaxel/gemcitabine		174	25	5.5

RR: Response rate; MST: Median survival time; NA: Not applicable.

its role in this setting[24].

Hainsworth *et al*[25] demonstrated that docetaxel plus gemcitabine *vs* weekly docetaxel alone did not improve survival in a population of 350 accrued and randomized elderly patients affected by advanced NSCLC. Moreover, in these two trials the doublet was slightly more toxic than single agent treatment[25] (Table 1).

PLATINUM-BASED CHEMOTHERAPY

Cisplatin represents standard treatment for advanced NSCLC. Nephrotoxicity, ototoxicity and neurotoxicity are the most common non-haematological toxicities attributed to cisplatin in addition to haematological ones.

Carboplatin is responsible for lower incidence of nausea, nephrotoxicity and neurotoxicity, although safety remains an issue also due to its administration in combination with other myelotoxic agents.

Retrospective analyses of platinum-based chemotherapy

In the last decade many data were collected from large randomised trials not selected for elderly patients.

No significant differences in terms of efficacy were shown in retrospective analysis from ECOG 5592 comparing effects of two different platinum-based schedules in patients older than 70 years respect to younger counterpart. In terms of toxicity elderly patients had worse leukopenia and neuropsychiatric disorders[26]. ECOG 1594 trial compared four treatment combinations in first-line with no significant differences for RR and MST in retrospective subset analysis for the 227 patients (20%) aged ⩾ 70. Significant (P = 0.04) major grade 4 toxicities were reported in the elderly subgroup[27]. Always referring to retrospective analysis the Southwest Oncology Group (SWOG) 9509 trial, and the SWOG 9308 trial, documented no significant age influence on MST, TTP and toxicity[28].

In more recent years, the CALGB compared carboplatin plus paclitaxel with paclitaxel. MST was similar between patients aged > 70 and their younger counterpart. A secondary analysis evidenced a survival advantage for the doublet in the elderly patients[29].

TAX 326 compared first-line cisplatin plus vinorelbine or docetaxel. In the subset analysis considering patients aged ⩾ 65 increase in survival was obtained with docetaxel plus cisplatin respect to vinorelbine/cisplatin. Lowest incidence in toxicity was registered for docetaxel plus carboplatin arm[30].

Comparing weekly paclitaxel or standard dose paclitaxel in combination with carboplatin in the elderly, the fractionated regimen produced higher RR, TTP and MST. Significant less neuropathy was encountered in the experimental arm[31-34] (Table 2).

Platinum-based chemotherapy: Prospectives studies

Many prospective phase Ⅱ trials evaluating third-generation cytotoxic agents with modified platinum-based schedules were performed in the last 20 years. Cisplatin and gemcitabine combination was tested in four phase Ⅱ trials reaching an ORR around 40% and a MST of 10 mo[35-38]. At least three phase Ⅱ trials tested cisplatin/vinorelbine schedule with similar ORR and MST[39-41]. Both combinations demonstrated to be safe. Better results in terms of ORR and MST were demonstrated by Ohe *et al*[42] in patients aged ⩾ 75 years by adding docetaxel to weekly cisplatin[42,43].

In 2007 Gridelli *et al*[44] tested in the MILES 2P the feasibility of cisplatin with gemcitabine or vinorelbine in elderly patients. Both combinations were feasible and active with the former combination being the preferred one for a direct comparison with standard single-agent

Table 2 Retrospective data analyses of elderly patients enrolled in phase Ⅲ trials with cisplatin- or carboplatin-based chemotherapy

Ref.	Treatment	Age (yr)	No. of patients	RR	MST (mo)	*P* value
Nguyen *et al*[27]	CDDP + GEM	≥ 70	53	15%	7.7	NS
		< 70	207	29%	9.4	
Kelly *et al*[28]	CBDCA + TAX	≥ 70	117	NR	6.9	0.06
	CDDP + VNR	< 70	491	NR	8.6	
Langer *et al*[26]	CDDP + VP-16	≥ 70	86	23.3%	8.5	NS
	CDDP + TAX	< 70	488	21.5%	9.1	
Rocha Lima *et al*[32]	CDDP + VBL	≥ 70	31	16%	5.7	NS
		< 70	222	31%	8.0	
Hensing *et al*[33]	CBDCA + TAX	≥ 70	67	27%	7.1	NS
		< 70	163	20%	7.8	
Belani *et al*[30]	CDDP + TXT	≥ 65	149	NR	12.6	NS
		All ages	408	32%	11.3	
	CDDP + VNR	≥ 65	134	NR	9.9	NS
		All ages	404	25%	10.1	
	CBDCA + TXT	≥ 65	118	NR	9.0	NS
		All ages	406	24%	9.4	
Belani *et al*[30]	CBDCA + TAXw	≥ 70	70	25.7%	9.2	NR
		< 70	147	28.6%	9.6	
	CBDCA + TAX	≥ 70	63	19%	7.7	NR
		< 70	151	19.2%	11.4	
Lilenbaum *et al*[29]	CBDCA + TAX	≥ 70	77	36%	8.0	NS
		< 70	207	30%	8.5	

CDDP: Cisplatin; CBDCA: Carboplatin; TAX: Paclitaxel; TXT: Docetaxel; VNR: Vinorelbine; GEM: Gemcitabine; VBL: Vinblastine; VP-16: Etoposide; RR: Response rate; MST: Median survival time; S: Survival; NR: Not reported; NS: Not significant.

Table 3 Phase Ⅱ trials of cisplatin-based chemotherapy with third-generation agents and modified schedules or attenuated doses of cisplatin

Ref.	Regimen	CDDP dose	Age (yr)	No.of patients	RR	MST (mo)
[1]Mattioli *et al*[39]	CDDP + VNR	25 mg/m^2, weekly	> 65	36	36%	11
Pereira *et al*[40]	CDDP + VNR	60-90 mg/m^2	> 70	44	50%	7.5
Buffoni *et al*[41]	CDDP + VNR	30 mg/m^2, day 1 and 8	≥ 70	30	33%	7.4
Lippe *et al*[35]	CDDP + GEM	35 mg/m^2, weekly	≥ 65	29	48%	10
Berardi *et al*[36]	CDDP + GEM	35 mg/m^2, weekly	≥ 70	48	31.8%	9
Feliu *et al*[37]	CDDP + GEM	50 mg/m^2	≥ 70	46	35%	10.2
Moscetti *et al*[38]	CDDP + GEM	75 mg/m^2, day 2	≥ 65	46	45.6%	15
Ohe *et al*[42]	CDDP + TXT	25 mg/m^2, weekly	≥ 75	33	52%	15.8

[1]Including 3 unfit patients; CDDP: Cisplatin; VNR: Vinorelbine; GEM: Gemcitabine; TXT: Docetaxel; RR: Response rate; MST: Median survival time; S: Survival.

chemotherapy in this setting (Table 3).

Carboplatin plus vinorelbine combination was tested in two phase Ⅱ studies without any clinical benefit compared to standard treatment[45,46]. More favourable results were reported for the combination of low-dose carboplatin (AUC 4) and gemcitabine accompanied by acceptable toxicity[47].

Modified carboplatin/paclitaxel schedules reached in many trials 70% RR and 14 mo MST[10,48-53].

Recently IFCT-0501 confronted attenuated carboplatin-paclitaxel schedule *vs* standard single agent monotherapy. Combination and standard treatment showed respectively 10.3 and 6.2 mo in terms of OS. Regarding toxicity, grade 3-4 neutropenia and thrombocytopenia were 54.3% and 6.3% for doublet respect to 14.3% and 1% for single agent. Considering non-hematological toxicity, neuropathy resulted significantly more frequent in the doubletarm *vs* single agent arm. Considering QoL, role functioning and fatigue were worse in the doublet group than in single agent. Authors concluded that despite increased toxic effects for doublet, this should be considered as standard treatment in first line setting[54].

For the future better CDDP-based schedule in terms of activity and tolerability should be tested by direct comparison and considering emerging strong data about histology (Table 4).

TARGETED THERAPIES

Bevacizumab

The SAIL study assessed the addition of bevacizumab to standard chemotherapy in terms of safety and efficacy in the first-line. When evaluating incidence of anti-VEGFR related side-effects in a planned analysis including elderly patients no difference was

Table 4 Prospective trials of first line platinum-based chemotherapy in elderly patients affected by advanced non-small-cell lung cancer

Ref.	Regimen	Phase	Age (yr)	No. of patients	Efficacy
Gridelli *et al*[44]	CDDP + GEM	Ⅰ / Ⅱ	⩾ 70	159	OS 43.6 wk PFS 25.3 wk RR 43.5%
	CDDP + VNR				OS 33.1 wk PFS 21.1 wk RR 36.1%
Abe *et al*[43]	CDDP + DOC *vs* DOC	Ⅲ	> 70	221	OS 13.3 wk OS 17.3 wk
Biesma *et al*[53]	CARBO + GEM *vs* CARBO + PAC	Ⅲ	⩾ 70	181	OS 8.6 mo RR 27% OS 6.9 mo RR 19%
Quoix *et al*[54]	GEM or VNR *vs* CARBO + PAC	Ⅲ	⩾ 70	451	OS 6.2 mo RR 10.9% OS 10.3 mo RR 29.5%

CDDP: Cisplatin; VNR: Vinorelbine; GEM: Gemcitabine; CARBO: Carboplatin; RR: Response rate; OS: Overall survival.

encountered. OS (14.6 mo in both groups), TTP (8.2 mo *vs* 7.6 mo), RR (49.3% *vs* 52.4%) and disease control rate (89.3% *vs* 88.4%) were similar in both arms[55].

The ARIES trial evaluated bevacizumab in clinical practice. Six hundred and fifty enrolled patients were older than 70 and experienced similar adverse events than total population except for arterial thromboembolic events (slightly increased in patients ⩾ 70 years old). Median PFS and OS were similar in both subgroups[56].

EGFR tyrosine kinase inhibitors

Gefitinib/erlotinib: Gefitinib and erlotinib are reversible inhibitor of EGFR that competitively inhibits the binding of ATP.

Antitumor activity of single-agent gefitinib in patients unselected for EGFR status has been tested in many trials. When gefitinib was dispensed in the second line setting in an unselected populations with NSCLC obtained 5.3 mo of MST[57].

In the subgroup of elderly patients gefitinib maintained its activity and good tolerance with no grade 3 or 4 side effects experienced[58]. Cavina *et al*[59] reported encouraging efficacy data with only 10% of grade 3 skin toxicity and 3% of diarrhoea. Gridelli *et al*[60] reported in the same setting of patients similar MST and favourable safety profile. Cappuzzo *et al*[61] observed reported 5 mo MST and mild side effects. Hotta *et al*[62] studied gefitinib on patients aged ⩾ 75 years: RR 17%; SD 43%; MST 7.6 mo. Grade 3-4 toxicity was encountered in 9% of patients (Table 5).

Gefitinib addition to chemotherapy has been tested. Stinchcombe *et al*[63] combined weekly docetaxel plus daily oral gefitinib: RR 31%, MST 6.5 mo, 1-year survival 27%. The schedule resulted in excessive toxicity for elderly patients[63]. Bepler *et al*[64] added daily gefitinib to three-weekly docetaxel: RR 38%, SD 24%, MST 12.4 mo, and 1-year survival of 60%. Better tolerance was reported even if adverse effects required hospitalization in 6 patients[64]. A phase Ⅱ trial evaluated gefitinib with vinorelbine or gemcitabine. Vinorelbine plus gefitinib produced 72% of grade 3-4 neutropenia and 3 treatment-related deaths while the association with gemcitabine reported a lower activity (RR 5.7%, SD 14%, MST 9.1 mo) but a better safety profile (grade 3-4 neutropenia 11.4%; thrombocytopenia 8.6%, asthenia and diarrhoea 5.7%)[65,66] (Table 6).

At least three single-arm trials tested the role of gefitinib in patients with EGFR mutation positive tumors. A phase Ⅱ study conducted with erlotinib in patients older than 70 years in Ⅰ line setting, showing encouraging activity (RR of 10.9%, SD of 54.5%) and MST (10.5 mo). Adverse events were mild. EGFR mutations have been detected in 3 out of 5 responsive patients to erlotinib treatment[67]. Erlotinib improved also QoL and many disease related symptoms[68] (Table 7).

The EURTAC trial population with its median age of 65 years old represent an older population respect to common trial population. This trial showed that erlotinib yielded a longer progression-free survival than chemotherapy[69].

An age-unspecified trial in patients not selected for mutation status, the BR21, showed that in a second or third line setting, erlotinib improves survival but at a cost to older patients. Although older and younger patients achieved comparable PFS, OS and RRs, older patients suffered worse toxicity due to rash, fatigue and dehydration[70].

Erlotinib performed better than vinorelbine in a subgroup of EGFR mutation positive elderly patients as shown in a prospective phase Ⅱ trial while failed to gain advantage when added to gemcitabine or compared to it in molecularly not selected elderly patients[71,72].

SECOND-LINE CHEMOTHERAPY

Retrospective subgroup analysis on elderly patients from phase Ⅲ trials testing pemetrexed *vs* docetaxel obtained: TTP 4.6 mo *vs* 2.9 mo, MST 9.5 mo *vs* 7.7 mo, 12-mo survival was 20.4% *vs* 23.1%, 24-mo survival 6.1% *vs* 10.6%, respectively. Neutropenia, febrile neutropenia and anemia were more consistent in docetaxel arm[73]. Second-line cytotoxic therapy appeared feasible for good performance status elderly patients.

Pemetrexed produced a more favourable toxicity profile compared to docetaxel. In a phase Ⅱ trial a modified schedule of docetaxel (37.5 mg/m^2 on days 1 and 8 every three weeks) reported encouraging activity and acceptable toxicity profile[74].

Table 5 Retrospective analyses of gefitinib in the treatment of unselected elderly patients with advanced non-small-cell lung cancer

Ref.	Previous chemotherapy	Age (yr)	No. of patients	RR (%)	SD (%)	MST (mo)	Toxicity G ⩾ 3
Copin *et al*[58]	Yes (61%) No (39%)	⩾ 70	61	2 (3)	16 (26)	NR	None
Cavina *et al*[59]	Yes (64.5%) No (35.5%)	⩾ 70	31	0 (0)	18 (58)	3.0	G3 skin 10% G3 diarrhoea 3%
Gridelli *et al*[60]	Yes (94.5%) No (5.5%)	⩾ 70	18	0 (0)	2 (11)	4.4	None
Cappuzzo *et al*[61]	Yes (100%)	⩾ 70	40	2 (5)	18 (45)	5.0	G4 diarrhoea 2.5%
Hotta *et al*[62]	Yes (57%) No (43%)	⩾ 75	92	16 (17)	40 (43)	7.6	G3-4 toxicity 9%

RR: Response rate; SD: Stable disease; MST: Median survival time; G: Grade; NR: Not reported.

Table 6 Studies with gefitinib (250 mg/d) plus chemotherapy in the treatment of elderly patients (age ⩾ 70 years) with advanced non-small-cell lung cancer

Ref.	Treatment	Study phase	No. of patients	RR (%)	SD (%)	MST (mo)	Toxicity G ⩾ 3
Stinchcombe *et al*[63]	TXT 30-36 mg/m², days 1, 8, 15, Q4W	Ⅰ / Ⅱ	26	8 (31)	-	6.5	G3-5 toxicity 42%
Bepler *et al*[64]	TXT 75 mg/m², day 1, Q3W	Ⅱ	21	8 (38)	5 (24)	12.4	G3-4 toxicity 28.5%
Scagliotti *et al*[65]	GEM 1200 mg/m², days 1, 8, Q3W *vs* VNR 30 mg/m², days 1, 8, Q3W	Ⅱ Random	35 25	2 (5.7) 0 (0)	14 (40) 11 (44)	9.1 12.2	G3-4 neutropenia 11.4% G3-4 neutropenia 72% 3 toxic deaths

RR: Response rate; SD: Stable disease; MST: Median survival time; G: Grade; TXT: Docetaxel; GEM: Gemcitabine; VNR: Vinorelbine; Q4W: Every 4 wk; Q3W: Every 3 wk; Random: Randomised.

Table 7 Phase Ⅱ study of single-agent erlotinib in the treatment of advanced non-small-cell lung cancer elderly patients

Ref.	Previous chemotherapy	Age (yr)	No. of patients	RR (%)	SD (%)	MST (mo)	Toxicity G ⩾ 3
Jackman *et al*[67]	No (100%)	⩾ 70	58	6 (10.9)	30 (54.5)	10.5	G ⩾ 3 toxicity 30%

RR: Response rate; SD: Stable disease; MST: Median survival time; G: Grade.

Second-line cytotoxic therapy appeared feasible for good performance status elderly patients.

A recent retrospective review of elderly patients receiving a second line therapy analyzing 293 young patients (age < 70) and 168 patients (> 70) treated with second-line treatment (both chemotherapy and EGFR TKIs) showed no differences in both efficacy and toxicity between the two age group[75].

GERIATRIC ASSESSMENT

As elderly patients represent a very heterogeneous group, their functional status cannot be established only basing on chronological parameters. Comprehensive Geriatric Assessment (CGA) is a multidisciplinary and multidimensional approach including many items: co-existing diseases, socioeconomic status, nutritional status, medicine intake, and the presence of geriatric syndromes.

Many works demonstrated to add very useful informations regarding functional assessment of elderly patients permitting better evaluation in terms of prognostic aspects[76].

A meta-analysis based on 28 trials demonstrated that CGA, when applied together with geriatric interventions is capable to reduce early re-hospitalization and mortality. Nowadays no phase Ⅲ randomized trials are available.

More recent studies attributed to many CGA issues the power to predict the risk of chemotherapy toxicity[77].

Puts *et al*[78] reported data on CGA in cancer patients collected from 73 trials. Six reported a significant association with chemotherapy toxicity, 8 demonstrated association with mortality and other 2 a change of treatment indications after CGA assessment. CGA is recommended by the International Society of Geriatric Oncology (SIOG) and the EORTC[78].

CONCLUSION

NSCLC remains the major cause of cancer-related

deaths.

Altered organ functions and higher incidence of co-morbidities usually affect treatment decisions. Platinum-based treatment while is a mainstay for advanced NSCLC in younger patients is still considered questionable for elderly patients due to higher risk of toxicity. However many retrospective subset analyses demonstrated only minimal or none differences between elderly and younger counterpart patients.

Dedicated trials for elderly population are anyway needed. Research must be empowered looking for new tools and items capable of better define "biological" and "chronological" aspects of ageing. At the same time several treatment options should still be evaluated as for example: doublets with and without platinum, maintenance strategies and biologic agents[73].

A third-generation agent given alone is at the time the recommended option for elderly advanced NSCLC patients[79-81].

The choice for the best agent should consider together expected toxicities, pharmacokinetics aspects, liver-kidney function and co-existing illnesses.

Doublets employing platinum could be consider a valid indication for fit elderly patients with normal organ function. Each patient should receive a functional assessment at baseline in order to better define the therapeutic options.

Considering continuous elucidation of mechanisms that contribute to the malignant phenotype and subsequent molecular targets for anticancer therapy several biologic agents have been introduced in the treatment of NSCLC and many are still under investigation.

Trials performed with new targeted agents in molecularly selected younger population evidenced very good toxicity profile. So new biologic drugs are better candidates than chemotherapy to be tested in elderly patients. Gefitinib and erlotinib have already proven to be effective in chemotherapy-refractory NSCLC patients. Their mild toxicity profile, experienced in elderly patients with advanced disease, makes them some of the best candidates to test prospectively as single-agent first-line treatment in molecularly selected elderly population, as an alternative to chemotherapy.

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