Non-small cell lung cancer in elderly – retrospective study comparing single-agent versus doublet chemotherapy

Carcinoma de não pequenas células do pulmão em idosos – estudo retrospetivo com comparação entre monoterapia e dupleto de quimioterapia

Élia Cipriano*, Helena Magalhães, Fernanda Estevinho

Medical Oncology Department, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos.
* eliacipriano90@gmail.com

ABSTRACT

Background: In non-small cell lung cancer (NSCLC) elderly patients with advanced disease and without driver mutations, questions remain if they benefit from doublet chemotherapy (ChT) or single-agent ChT.
Methods: A retrospective study characterizing elderly NSCLC patients with advanced disease. The primary endpoint was overall survival (OS) after doublet ChT and single-agent ChT, calculated using Kaplan-Meier method and Log Rank test.
Results: Forty-six patients with locally advanced or metastatic disease were treated with ChT (22 with platinum--based doublet ChT and 24 with single-agent ChT). With a median follow-up of 26.6 months (mo.), the median OS was 8.4 mo. in doublet ChT and 7.0 mo. in single-agent ChT, p=0.441.
Conclusions: There were no statistically significant differences in survival between platinum-based doublet and monotherapy ChT in our studied population.

Key words: non-small cell lung cancer, elderly, doublet chemotherapy, single-agent chemotherapy, vulnerable

RESUMO

Introdução: Nos doentes idosos com carcinoma de não pequenas células do pulmão (CNPCP), com doença avançada, sem mutações, persiste a dúvida se estes devem ser tratados com dupleto de quimioterapia (dQT) ou com monoquimioterapia (mQT).
Métodos: Estudo retrospetivo de avaliação de doentes idosos com CNPCP, com doença avançada. Foi avaliada a sobrevivência global (SG), comparando os submetidos a dQT e mQT, usando as curvas de sobrevivência de *Kaplan-Meier* e teste *Log Rank*.

Resultados: Quarenta e seis doentes tinham doença localmente avançada ou metastizada e foram tratados com quimioterapia em 1.ª linha (22 com dQT baseado em platino e 24 com mQT). Após um *follow-up* mediano de 26.6 meses, a SG mediana foi de 8.4 versus 7.0 meses no grupo dQT versus mQT, respetivamente, p=0.441.
Conclusões: Não houve diferença estatisticamente significativa na SG mediana entre os doentes submetidos a dQT baseado em platino versus a mQT na população estudada.

Palavras-chave: carcinoma não pequenas células do pulmão, idosos, dupleto de quimioterapia, monoquimioterapia, vulnerável

INTRODUCTION

Non-small cell lung cancer (NSCLC) has a high incidence in elderly patients, with a median age at diagnosis around 70 years, and nearly 40% of patients with age ≥ 75 years at diagnosis.[1] The elderly population is frequently associated with comorbidities, especially in those with smoking history, poor physiologic reserve, geriatric syndromes, polypharmacy, functional dependence, poor nutritional status, cognitive impairment, altered emotional status and low social support. As a result of these factors, this population is more predisposed to therapeutic toxicities, drug interactions and limitations in therapeutic options like chemotherapy (ChT). The international groups and guidelines recommend the use of a comprehensive geriatric assessment that include the evaluation of all previously referred elderly associated issues.[2,3]

Nowadays, in the era of great development and constant change in the treatment of NSCLC, mostly with targeted therapies (targeting EGFR, ALK, ROS1, BRAF V600E and others molecular targets) and immune checkpoint inhibitors, which have improved outcomes comparing to classical chemotherapy, the discussion about standard chemotherapy can be considered as obsolete. But, in fact, the proportion of patients eligible for these new treatments is relatively small, and the classical chemotherapy continues to be dominant in a great proportion of NSCLC patients. Therefore, in patients with recurrent or metastatic NSCLC without driver mutations or without indication for immune checkpoint inhibitors, it is important to know if elderly patients, specifically those with more comorbidities and worse performance status, should benefit from more aggressive strategy, like double-based ChT or if the use of a harmless strategy, like single-agent ChT is more suitable.[2,4] The single-agent vinorelbine was preferred as monotherapy because it was a more convenient and less invasive treatment option compared with intravenous, and with a tolerable side-effect profile. Metronomic vinorelbine was used based on the results of phase II trials demonstrating the safety of its use, like MOVE trial.[5] A meta-analysis revealed that metronomic vinorelbine could be an active and well-tolerated strategy in patients unfit for standard ChT and manageable in frail patients.[6]

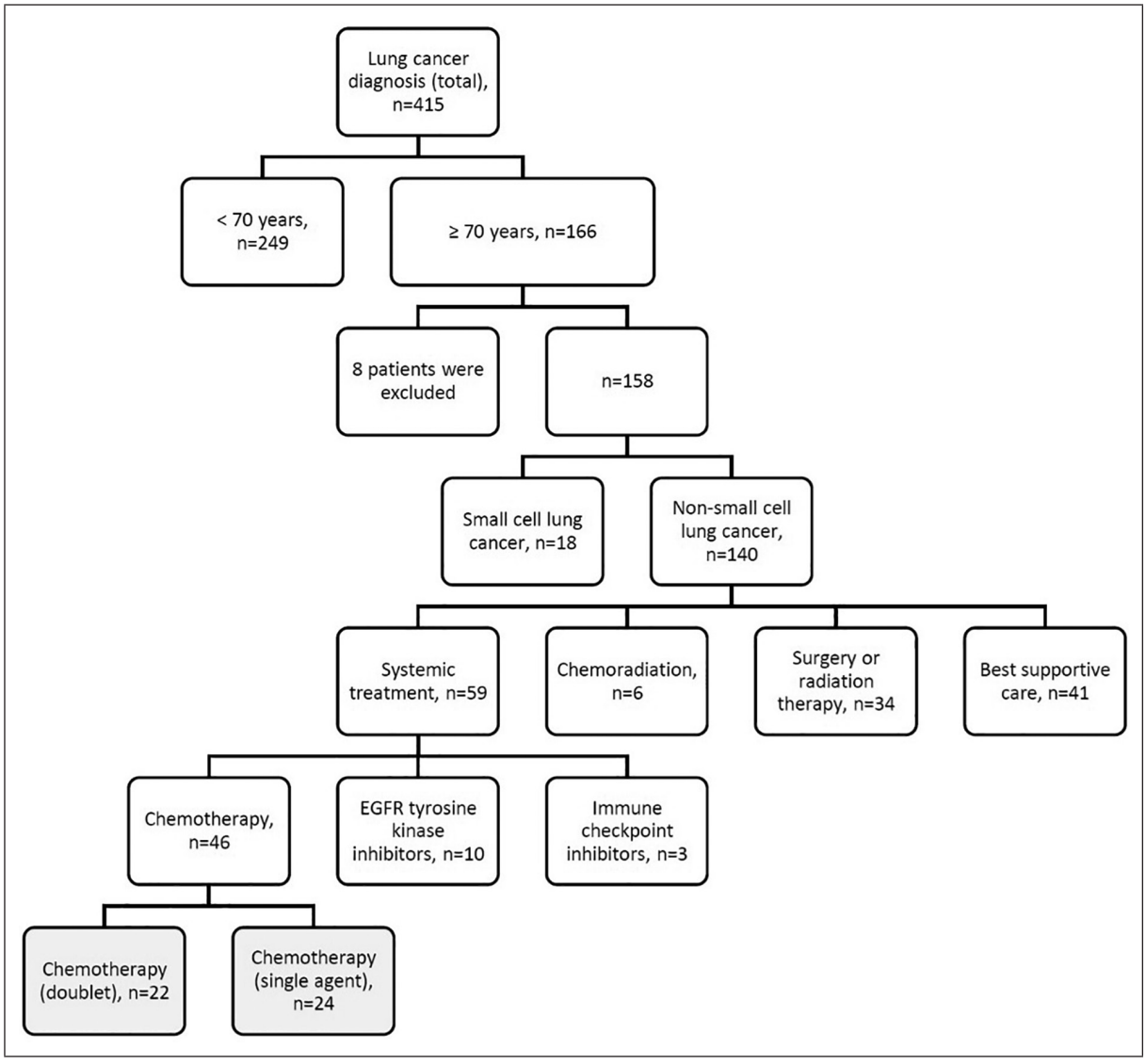
Based on this relevant topic, we studied the elderly patients diagnosed with NSCLC at our institution. We performed a population characterization and we evaluated the overall survival. The main goal was to compare the single-agent versus platinum-doublet chemotherapy as first-line treatment.

METHODS

Patients and treatment

A retrospective study, evaluating patients with a first thoracic multidisciplinary tumour board between 01/01/2015 to 31/12/2018 was performed. We selected patients with age ≥ 70 years at the time of the diagnosis, with non-small cell lung cancer histology and that received systemic therapy with chemotherapy as a 1st line treatment (Figure 1).

Figure 1. Diagram of the study



Clinicopathologic variables were collected: sex; age (median and <80/≥80 years); smoking habits; Eastern Cooperative Oncology Group (ECOG) performance status; comorbidities (<2/≥ 2 comorbidities); number of daily drugs, defining polypharmacy if taken ≥ 5 drugs/day; histology (squamous/non-squamous); stage at the start of the treatment; local of metastatic disease if stage IV; and therapeutic protocol. Patients treated with ChT at 1st line were separated in two subgroups: (1) platinum doublet ChT with carboplatin plus another drug, and, (2) single-agent ChT if patients treated with only one drug (oral vinorelbine). It was also described any-grade therapeutic side effects documented in the clinical process. Key exclusion criteria of the study were the absence of important clinical information in electronic process, like date of deceased and loss of follow-up patients to another institution.

Outcome measures

The primary endpoint was the overall survival, defined as the time between the start of systemic therapy and the date of the dead. The follow-up period was until 31/05/2019. The patients that were still alive at this time were censored at the final of the follow-up period.

Statistical analysis

Frequency tables were used to describe categorical variables, and median (min-max) was used to describe continuous variables. Mann--Witney U test was used to compare median between two groups. Median follow-up time was calculated according to *Schemper's* reverse Kaplan-Meier technique. Survival curves were described according to *Kaplan-Meier,* and it was used *Log Rank* test in comparisons between groups. Hazard ratio (HR) and the 95% confidence interval (CI) was estimated using *Cox* regression in a univariate analysis. The statistical significance of 5% was considered.

RESULTS

Patients and treatment

One hundred and sixty-six patients (n=166, 40%) had ≥ 70 years at diagnosis in the entire of 415 first lung cancer multidisciplinary consultation at our institution. It was excluded 8 patients due to loss of follow-up and missing data, being analysed 158 patients. The description of selected patients is in Figure 1. Forty-six patients (n=46; 32.9%) were treated with chemotherapy alone in the first line, and this was the population that we analysed in our study.

The clinicopathological variables of patients submitted only to ChT as first-line treatment (n=46) were described in Table I. The median age was higher in the single-agent ChT group (80 years) versus in doublet ChT (72 years), p<0.0001. As it was expected, and was a decision criteria at the start of the treatment, the proportion of ECOG performance status 1 was superior in patients that received a platinum-based doublet ChT. The single-agent subgroup had a greater proportion of patients with comorbidities ≥ 2. Male sex, history of smoking habits, drugs ≥ 5, histology and stage were proportional in the two groups.

Survival

During a median follow-up of 26.6 months, patients that started the 1st line ChT had 38 events (82.6%) – 17 deaths in platinum-based doublet ChT (77.3%) and 21 in single-agent ChT (87.5%). The median OS was 8.4 months (95% CI 1.70--15.10) in patients submitted to a platinum-based doublet ChT compared with a median OS of 7.0 months (95% CI 5.19-8.87) in patients treated with single-agent ChT in 1st line, p=0.441, HR 1.29

Table I. Characteristics of patients with locally advanced or metastatic NSCLC submitted to chemotherapy in 1st line treatment (n=46)

Characteristic	Platinum doublet ChT (n=22)	Single agent ChT (n=24)
Sex		
Male	21 (95.5%)	20 (83.3%)
Female	1 (4.5%)	4 (16.7%)
Age		
Median (min-max)	72 (70-81)	80 (70-87)
< 80	21 (95.5%)	12 (50.0%)
≥ 80	1 (4.5%)	12 (50.0%)
ECOG PS		
1	19 (86.4%)	13 (54.2%)
2	3 (13.6%)	11 (45.8%)
Smoking habits		
Ever smoker	18 (81.8%)	21 (87.5%)
Current smoker	3 (13.6%)	4 (16.7%)
Former smoker	15 (68.2%)	17 (70.8%)
Never smoker	4 (18.2%)	3 (12.5%)
Comorbidities		
< 2	9 (40.9%)	5 (20.8%)
≥ 2	13 (59.1%)	19 (79.2%)
Drugs		
< 5	12 (54.5%)	11 (45.8%)
≥ 5	10 (45.5%)	13 (54.2%)
NSCLC histology		
Non-squamous	20 (90.9%)	20 (83.3%)
Squamous cell	2 (9.1%)	4 (16.7%)
Stage		
III	1 (4.5%)	1 (4.2%)
IV	21 (95.5%)	23 (95.8%)
Local of metastatic disease at the beginning of 1st line treatment		
Central nervous system	–	2 (8.3%)
Bone	11 (50.0%)	8 (33.3%)
Contralateral lung	6 (27.3%)	9 (37.5%)
Pleural effusion	7 (31.8%)	8 (33.3%)
Liver	2 (9.1%)	1 (4.2%)
Suprarenal	2 (9.1%)	1 (4.2%)
Other localizations	2 (9.1%)	2 (8.3%)
Therapeutic protocol		
Carboplatin plus pemetrexed	18 (81.8%)	–
Carboplatin plus gemcitabine	2 (9.1%)	–
Carboplatin plus taxane	2 (9.1%)	–
Oral vinorelbine	–	24 (100%)

(95% CI 0.68-2.44) (Figure 2). At 12 months, the estimated survival rates were 43.1% in platinum--based doublet ChT group versus 25.0% in single--agent ChT group. At 24 months, the proportion of estimated survival was 16.4% in platinum--based doublet ChT compared to 11.1% in single--agent ChT. In a univariate analysis for overall survival, none of the factors analysed was positive with statistical significance for risk of death in these patients (Table II).

Figure 2. Kaplan-Meier curves for overall survival in patients submitted to chemotherapy in 1st line treatment

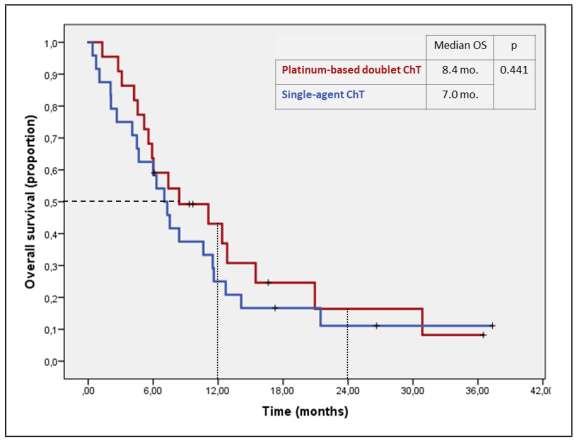


Table II. Univariate Cox regression analysis of overall survival

	n	Univariate analysis	
		HR (95% CI)	p
Treatment			
Platinum doublet ChT	22	1	0.443
Single-agent ChT	24	1.29 (0.68-2.44)	
Sex			
Male	41	1.33 (0.47-3.77)	0.592
Female	5	1	
Age			
< 80	33	1	0.113
≥ 80	13	1.77 (0.87-3.57)	
ECOG PS			
1	32	1	0.430
2	14	1.31 (0.67-2.58)	
Smoking habits			
Ever smoker	39	1.80 (0.70-4.64)	0.225
Never smoker	7	1	
Comorbidities			
< 2	14	1	0.736
≥ 2	32	1.12 (0.57-2.20)	
Drugs			
< 5	23	1	0.576
≥ 5	23	1.20 (0.63-2.74)	
NSCLC histology			
Non-squamous	40	0.80 (0.31-2.06)	0.643
Squamous cell	6	1	
Stage			
III	2	1	0.275
IV	44	1.95 (0.59-6.48)	

Adverse events

The patients proposed to platinum-based doublet ChT had more haematological side effects: 3 (17.6%) with neutropenia; 1 (4.5%) with febrile neutropenia; 1 (4.5%) with thrombocytopenia and 5 (22.7%) with anaemia. The non-haematological side effects were mucositis and emesis in 3 (13.6%); diarrhoea and asthenia in 2 (9.1%) and oedema in 1 (4.5%) patients. The most frequent adverse event in single-agent ChT group was constipation, n=7 (29.2%). Other side effects included neutropenia, infection, renal dysfunction, mucositis and asthenia in 2 (8.3%); emesis in 3 (12.5%) and diarrhoea in 1 (4.2%) patients. In our population there weren´t CTCA4 grade 5 events related to drugs analysed.

DISCUSSION

In this study we have shown that the proportion of patients with ≥ 70 years was 40%, as published in international literature.[1] This result corroborates the need to better understand how we can treat the elderly patients with NSCLC. Our results demonstrate that patients with recurrent and metastatic NSCLC treated with a more intense strategy like platinum-based doublet ChT did not have a statistically superior survival when compared to patients treated with single-agent ChT (oral vinorelbine), with a respective median OS of 8.4 months versus 7.0 months. This is a single institution data with patients that were not highly selected, as we observe in clinical trials. In ELVIS trial the patients treated with vinorelbine had an OS of 28 weeks (95% CI 23-35), which was similar

to our cohort.[7] In MOVE trial, median overall survival of patients treated with metronomic vinorelbine was 9 months (range 3-29) and in a meta-analysis of metastatic non-small cell lung cancer treated with metronomic oral vinorelbine the median overall survival was 8.7 months (95% CI 7.6-9.5).[5,6]

These results should be interpreted with some caution, given the small sample size and retrospective context. In addition, there was also bias because the two groups were not balanced for the age and performance status, which were important conditions when choosing the treatment. Despite that, these outcomes are quite comparable to some outcomes presented in randomized clinical trials published in patients with ≥ 70 years, including the patient's characteristics, the median OS and the proportion of survival at 1-year. In 2018, phase III MILES-3 and MILES-4 trials, published as a joint analysis, concluded that the addition of cisplatin to single-agent ChT for elderly patients with advanced NSCLC did not prolong OS and global health status score of quality of life. These trials compared a cisplatin-doublet ChT (with pemetrexed or gemcitabine) to a single-agent ChT (pemetrexed or gemcitabine) in patients with NSCLC and ≥ 70 years with ECOG performance status 0-1. Analysing 263 patients in cisplatin group and 268 without cisplatin, with a median follow-up of 24 months, the median OS was 7.5 months (95% CI 6.2-9.5) in monotherapy group versus 9.6 months (95% CI 8.1-11.7) in combination group, HR 0.86 (95% CI 0.70-1.05), p=0.14. Patients treated with cisplatin were more predisposed to both haematologic and non-haematologic toxicity.[8] The Japanese trial JCOG0803/WJOG4307L also demonstrated that the combination ChT with cisplatin was not associated with superior overall survival. This trial compared tri-weekly docetaxel as monotherapy to a combination therapy (weekly cisplatin plus docetaxel) in stage III or IV NSCLC with ≥ 70 years with ECOG performance status 0-1. The study analysed 139 patients in the cisplatin plus docetaxel arm and 137 patients in the docetaxel arm. The median OS was 13.3 months in doublet arm versus 14.8 in monotherapy arm, HR 1.18 (95% CI 0.83-1.69). The 1-year survival rates were 58.2% in docetaxel arm and 54.5% in the combination arm.[9] Analysing combination ChT without a platinum drug, the phase III MILES trial compared a non-platinum doublet (vinorelbine plus gemcitabine) to a single agent ChT (vinorelbine or gemcitabine). There were included 232 patients in the combination group, 233 in the vinorelbine group and 233 in the gemcitabine group. Median survival was 30 weeks (95% CI 27-36) in the combination group, 36 weeks (95% CI 30-45) in vinorelbine group and 28 weeks (95% CI 25-34) in gemcitabine group. The 1-year survival rates were 30% in combination ChT, 38% in vinorelbine group and 28% in gemcitabine group. HR 1.17 (95% CI 0.95-1.44) for doublet ChT versus vinorelbine and HR 1.06 (95% CI 0.86-1.29) for a comparison between combination ChT versus gemcitabine. In terms of quality of life, it was similar in the 3 arms.[10] On the other hand, a French phase III randomized trial (IFCT-0501) showed a better survival in patients treated with carboplatin doublet. This study compared a combination ChT (carboplatin plus weekly paclitaxel) versus vinorelbine or gemcitabine monotherapy in patients with ≥ 70 years and locally advanced or metastatic NSCLC. It was analysed 225 patients in the doublet group, and 226 in the monotherapy group. With a median follow up period of 30.3 months, the median overall survival was superior in combination ChT [10.3 months versus 6.2 months, HR 0.64 (95% CI 0.52-0.78), p<0.0001]. One-year survival rates were 44.5%

(95% CI 37.9-50.9) in combination group and 25.4% (95% CI 19.9-31.3%) in single-agent group. The group of combination ChT was more predisposed to toxicity, especially neutropenia and asthenia.[11]

Recognizing the limitations of indirect comparisons, the results of our patients are consistent with MILES-3 and MILES-4, Japanese trial and MILES trial, with no demonstrated benefit when platinum-based doublet ChT was used, compared to monotherapy. This study has some limitations. First, as a retrospective study, the information about the patient was only the data that was written in the previous observations. For example, the real proportion of adverse events was probably superior, considering the bias analysing it only through the information written in the clinical process. As a retrospective study, the patients were not randomized, so the patients that were submitted to a doublet ChT had a better performance status and less comorbidities, when compared to patients submitted to a single agent, as we can see in the distribution of these groups. The patients that received a more intensive strategy were younger, and the proportion of ECOG performance status 1 was superior. Another important limitation of this study is the comparison between the single and doublet ChT that do not use the same drug, due to its retrospective nature. Another bias in the analysis is the fact that it didn't include the second-line treatment, which could interfere in the results obtained.

CONCLUSION

In this retrospective study, the median OS in patients with locally advanced or metastatic NSCLC submitted to platinum-based doublet chemotherapy was not statistically different from the median OS in patients submitted to monotherapy. Taking account all the above, it is imperative to perform more prospective studies in elderly population with NSCLC, since this is a prevalent group in our daily practice. It will be important to investigate what could be the best treatment choice for elderly population, single-agent chemotherapy, doublet chemotherapy or immunotherapy in patients without targetable mutations, combining the best outcomes and the minimum side effects. Thus, it would be relevant to focus not only in prolonging survival but, mostly in the quality of life, patient's preferences and safety.

Elderly population is a heterogeneous group, and we have the mission to best select these patients for systemic treatment. A comprehensive geriatric assessment can be used in treatment decision making, helping to risk-stratify patients prior to potentially high-risk treatment, in order to improve the cancer management. The use of comprehensive geriatric assessment is time-consuming and not easily feasible, making their implementation in daily practise challenging. Recently, shorter geriatric tools had been developing to help evaluating and predict treatment impact in elderly patients. These tools are feasible to implement in our clinical practice and could help to optimize therapy selection in elderly patients.

REFERENCES

1. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. *Transl Lung Cancer Res*. 2018;7(3):220-233. doi:10.21037/tlcr.2018.05.06
2. NCCN Guidelines Panel. Non-Small Cell Lung Cancer. *NCCN Clin Pract Guidel Oncol*. Published online 2020.
3. Balducci L. Cancer in the Elderly : Biology, Prevention, and Treatment. In: *Abeloff's Clinical Oncology:*

Fifth Edition. Elsevier Inc.; 2018:904-913.e2. doi:10.1016/B978-1-4557-2865-7.00063-1
4. Gajra A, Akbar SA, Din NU. Management of Lung Cancer in the Elderly. *Clin Geriatr Med*. 2016;32(1):81-95. doi:10.1016/j.cger.2015.08.008
5. Camerini A, Puccetti C, Donati S, et al. Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: Results of a phase II trial (MOVE trial). *BMC Cancer*. 2015;15(1):2-7. doi:10.1186/s12885-015-1354-2
6. Pujol J-L, Coffy A, Camerini A, et al. An individual patient-data meta-analysis of metronomic oral vinorelbine in metastatic non-small cell lung cancer. *PLoS One*. 2019;14(8):e0220988. doi:10.1371/journal.pone.0220988
7. Cesare Gridelli. The ELVIS Trial : A Phase III Study of Single-Agent Vinorelbine as First-Line Treatment in Elderly Patients with Advanced Non-Small Cell Lung Cancer. *Oncologist*. 2001;6(suppl 1):4-7.
8. Gridelli C, Morabito A, Cavanna L, et al. Cisplatin--Based First-Line Treatment of Elderly Patients With Advanced Non – Small-Cell Lung Cancer : Joint Analysis of MILES-3 and MILES-4 Phase III Trials. *J Clin Oncol*. 2018;36(25). doi:10.1200/JCO.2017.76.8390
9. Abe T, Yokoyama A. Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non – Small-Cell Lung Cancer : The Intergroup Trial JCOG0803 / WJOG4307L. *J Clin Oncol*. 2015;33(6):575-582. doi:10.1200/JCO.2014.55.8627
10. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for Elderly Patients With Advanced Non-Small-Cell Lung Cancer : The Multicenter Italian Lung Cancer in the Elderly Study (MILES) Phase III Randomized Trial. *J Natl Cancer Inst*. 2003;95(5).
11. Quoix E, Zalcman G, Oster J, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer : IFCT-0501 randomised, phase 3 trial. *Lancet*. Published online 2004:1079--1088. doi:10.1016/S0140-6736(11)60780-0