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What can platinum offer yet in the treatment of PS2 NSCLC patients? A systematic review and meta-analysis

Giuseppe Bronte[a,1], Christian Rolfo[b,*,1], Francesco Passiglia[a], Sergio Rizzo[a], Ignacio Gil-Bazo[c], Eugenio Fiorentino[d], Massimo Cajozzo[e], Jan P. Van Meerbeeck[f], Cosimo Lequaglie[g], Daniele Santini[h], Patrick Pauwels[i], Antonio Russo[a]

[a] *Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy*
[b] *Phase I—Early Clinical Trials Unit, Oncology Department and Multidisciplinary Oncology Center Antwerp (MOCA) Antwerp University Hospital, Edegem, Belgium*
[c] *Department of Oncology, Clínica Universidad de Navarra, Pamplona, Spain*
[d] *Department of Surgical, Oncological and Oral Sciences, Section of Surgical Oncology, University of Palermo, Palermo, Italy*
[e] *Department of Surgical, Oncological and Oral Sciences, Section of Thoracic Surgery, University of Palermo, Palermo, Italy*
[f] *Thoracic Oncology, Multidisciplinary Oncology Center Antwerp (MOCA) Antwerp University Hospital, Edegem, Belgium*
[g] *Department of Thoracic Surgery, I.R.C.C.S.–C.R.O.B. Basilicata Regional Cancer Institute, Rionero in Vulture, Italy*
[h] *Department of Medical Oncology, University Campus Bio-Medico, Rome, Italy*
[i] *Molecular Pathology Unit, Pathology Department and Multidisciplinary Oncology Center Antwerp (MOCA) Antwerp University Hospital, Edegem, Belgium*

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Contents

Abstract

Background: Randomized phase III trials showed interesting, but conflicting results, regarding the treatment of NSCLC, PS2 population. This meta-analysis aims to review all randomized trials comparing platinum-based doublets and single-agents in NSCLC PS2 patients.
Materials and methods: Data from all published randomized trials, comparing efficacy and safety of platinum-based doublets to single agents in untreated NSCLC, PS2 patients, were collected. Pooled ORs were calculated for the 1-year Survival-Rate (1y-SR), Overall Response Rate (ORR), and grade 3–4 (G3–4) hematologic toxicities.

* Corresponding author. Tel.: +32 3 821 36 46.
E-mail addresses: christian.rolfo@uza.be, oncologiarolfo@yahoo.es (C. Rolfo).
[1] These authors contributed equally to this work.

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Results: Six eligible trials (741 patients) were selected. Pooled analysis showed a significant improvement in ORR (OR: 3.243; 95% CI: 1.883–5.583) and 1y-SR (OR: 1.743; 95% CI: 1.203–2.525) in favor of platinum-based doublets. G3–4 hematological toxicities were also more frequent in this group.
Conclusion: This meta-analysis suggests that platinum-combination regimens are superior to singleagent both in terms of ORR and survival-rate with increase of severe hematological toxicities.

Keywords: NSCLC; Chemotherapy; Performance status; Platinum; Doublet; Single agent

1. Introduction

Lung cancer is the most important cause of cancer-related death worldwide. Non-small-cell lung cancer (NSCLC) represents about 75–80% of overall lung cancer cases, and most patients have developed advanced disease at diagnosis. However the management of advanced NSCLC has significantly improved during last decade. Innovative oral targeted molecules, such as the anti-EGFR tyrosine kinase inhibitors (TKIs), gefitinib, erlotinib, and afatinib, or the ALK inhibitor, crizotinib, have shown their superiority in terms of response rate, progression-free survival (PFS) and quality of life (QoL) compared with standard chemotherapy for tumours harbouring an activating EGFR mutation or ALK-rearrangement, respectively [1–5].

Actually the use of targeted drugs is recommended as first-line treatment in 10–15% of NSCLC patients, selected according to their mutational status, while platinum-based combination remains the standard treatment of the majority of wild-type NSCLC patients with performance status (PS) 0–1. Whereas single agent chemotherapy is still recommended as the best option in the first-line treatment of PS 2 patients, platinum-based combination is considered as a possible alternative [6]; so the best treatment of these subset of patients is still uncertain and debated. PS 2 patients represent a significant proportion of the advanced NSCLC population (up of 30–40% of cases), even if the exact prevalence is still not certain [7,8]. PS is a general measure of the patient's functional status: it defines the impact of tumour symptoms, together with other pre-existing medical problems and comorbidities, on a patient's daily function and ability of self-care.

The most recent scale is the Performance Status according to the "Eastern Cooperative Oncology Group" (ECOG PS), a five points scale based on the level of symptoms interference with normal activity and on the proportion of waking hours spent in bed [9]. In fact, PS is also the most important independent prognostic factor in advanced NSCLC and a strong predictor of survival and adverse events [10]. PS 2 is associated with lower RR, shorter survival and higher risk for severe toxicity when compared to PS 0–1 [11]. However these patients represent a heterogeneous and large group, because PS 2 may be due to tumour-related symptoms (such as pain, fatigue, weight loss), pre-existing comorbidities (cardiovascular or obstructive pulmonary diseases, peripheral vascular diseases, kidney or liver diseases and age-related decline in functional status), or both, and actually we have not still known the real impact of these different factors on PS [12]. PS2 patients have been traditionally underrepresented or completely excluded by clinical trials. Subsequently treatment recommendations or guidelines about this subgroup of NSCLC patients are largely lacking [13].

Despite a worse prognosis than the PS 0/1 group, PS 2 patients appear to have a survival benefit from chemotherapy, as emerging from subgroup analysis of several trials and as previously showed in a meta-analysis of 1995, and subsequently updated in 2008 [14], which compared chemotherapy with newer third generation agents with or without platinum-compounds to best supportive care in advanced NSCLC patients, showing a 1-year survival benefit of 8% (from 20% to 28%) in favour of chemotherapy (more evident for platinum-based regimens) in general population, and an increase of 6% for PS2 subgroup. However, these patients, due to their frailty and lack of studies dedicated, have been historically considered not eligible for aggressive treatment based on combined therapies. So single-agent therapy with new generation cytotoxic agent such as gemcitabine, vinorelbine or taxane has been considered as the treatment of choice, as stated by the European experts panel consensus meeting [13] and also recommended by international guidelines.

Until now PS 2 patients have been considered not suitable combination chemotherapy as showed for elderly patients with advanced NSCLC [15–17]. However, in the last years, new prospective randomized phase III trials have been performed to evaluate the efficacy and tolerability of platinum-based doublet chemotherapy compared to single agent in this subset of patients, revealing unexpected results [18,19].

The aim of this meta-analysis is to combine and analyse simultaneously all randomized trials comparing platinum-based doublets and single-agent therapy in NSCLC and PS2 patients. This work could allow a stronger and more precise assessment of efficacy (1-year-survival rate and ORR) and toxicity profile of these treatments for the first-line treatment of PS2 patients with advanced NSCLC.

2. Materials and methods

2.1. Search for clinical trials

We performed our meta-analysis according to a predefined written protocol. We searched for all published randomized

trials, which compared efficacy and safety of platinum-based doublets to single-agent chemotherapy in untreated patients with NSCLC either wholly or partially dedicated to PS2. Publications were identified by an electronic search using PubMed online, updated in September 2014. The search for publications was made by other databases including the Cochrane Library. However the search on PubMed allowed the widest collection of publications about this topic. The following search terms were used: "randomized controlled trial", "PS 2", "performance status of 2", "NSCLC", "non-small cell lung cancer", "lung carcinoma", "NSCLC treatment". The results were supplemented with manual searches of American Society of Clinical Oncology meeting proceedings, references of selected articles and published reviews. A systematic review on this topic in the Cochrane database of systematic reviews was not found.

2.2. Selection criteria

According to this search clinical trials were taken into account if they had to fulfil all the following inclusion criteria: (1) only patients with NSCLC were included; (2) randomized phase II or III clinical trials; (3) clinical trials specifically or partially devoted to PS2 patients; (4) comparison between platinum-based doublets and single agent chemotherapy at standard doses as first-line treatment; (5) availability of specific data for PS 2 patients about 1-year survival rate (1y-SR), objective response rate (ORR), and proportion of patients who experienced grade 3 and 4 (G3–4) haematological toxicities.

2.3. Data extraction

Two authors independently selected studies according to the aforementioned inclusion criteria, and extracted and organized data according to the characteristics of the studies (i.e. first author name, journal and year of publication, design, participants, intervention and outcomes), baseline characteristics of patients (i.e. age, stage, performance status), outcome measures (i.e. 1y-SR, ORR) and G3–4 haematological toxicity rates. Data extraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. The proportion of patients for each outcome was calculated based on the percentages reported in included trials, when it was not reported as absolute number.

2.4. Statistical analysis

Primary outcome was 1y-SR, defined as the percentage of patients who remain alive one year after randomization. Secondary endpoint was ORR, defined as the percentage of patients who have a complete or partial tumor response according to World Health Organization (WHO) criteria or Response Evaluation Criteria in Solid Tumors (RECIST). Finally, severe hematologic toxicities, including grade 3–4 anaemia, neutropenia and thrombocytopenia, graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). The number of events (i.e. patients alive after 1 year, objective responses and grade 3–4 side effects) was extracted from each study or calculated from the percentage provided, and the proportion of patients was calculated for each arm; ORs (odds ratios) were presented if available. An OR greater than 1 indicated a benefit of platinum-doublet over the single agent, and subsequently a higher 1-Y-SR, RR, but also a higher grade 3–4 toxicity rate. The heterogeneity between trials was tested using the Cochran *Q*-test. A meta-analysis of ORs was performed to calculate a pooled OR for each outcome using a fixed-effect or random-effect, based on statistical significance of *Q*-test, according to Mantel–Haenszel method. All statistical analyses were performed with NCSS software (2009 version; Kaysville, Utah).

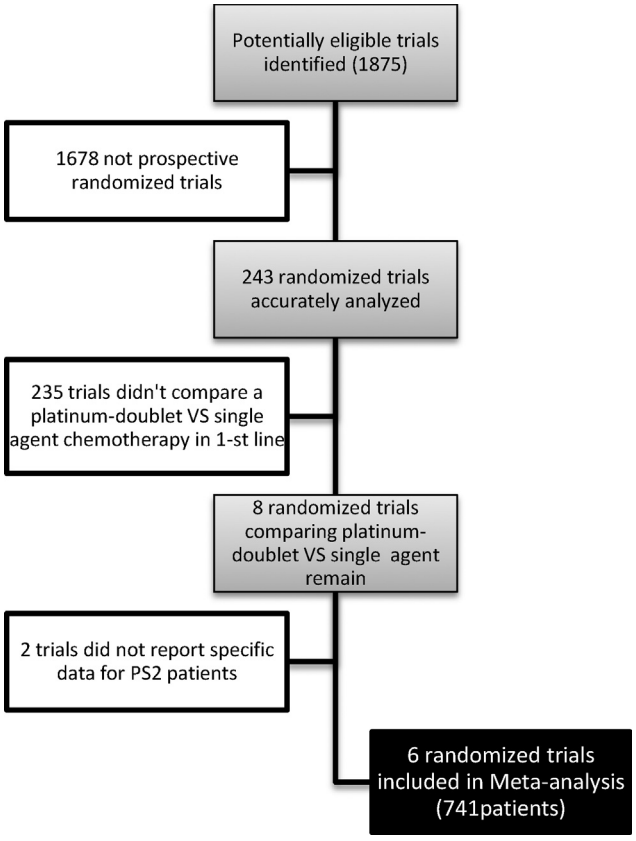


Fig. 1. Flow-chart of trials selection.

3. Results

Our PubMed search, performed in September 2014, found 1875 publications. Among these, 1632 publications were excluded because the clinical trials were not randomized; the remaining 243 trials were analysed accurately. 235 publications were considered ineligible because they did not compare platinum-based doublets with single-agent

Table 1
Primary and secondary endpoints of the 6 randomized trials included in the meta-analysis.

Trial (reference)	1y-SR *n*.* (%)	ORR *n*.* (%)	G3–4 Anaemia *n*.* (%)	G3–4 Neutropenia *n*.* (%)	G3–4 Thrombocytopenia *n*.* (%)
Zukin et al. [18]	41/103(40) 22/102(21.9)	19/79(24) 7/67(10.5)	12/103 (11.6) 4/102 (3.9)	7/103 (6.8) 1/102 (1)	1/103 (1) 0/102 (0)
Morabito et al. [19]	N/A	5/28(18) 1/28(4)	5/28 (18) 0/28 (0)	3/28 (10.7) 1/28 (3.6)	6/28 (21.5) 1/28 (3.5)
Kosmidis et al. [24]	9/43(20) 8/47(17.8)	6/43(14) 2/47(4)	3/43 (7) 1/47 (2)	3/43 (7) 1/47 (2)	3/43 (7) 0/47 (0)
Reynolds et al. [21]	26/85(31.3) 18/85(21.2)	16/85(18.8) 5/85(5.9)	12/85 (14) 6/85 (7)	46/85 (54) 9/85 (10.5)	35/85 (41) 3/85 (3.5)
Lilenbaum et al. [22]	9/49(18) 5/50(10)	12/49(24) 5/50(10)	N/A	N/A	N/A
Le Chevalier et al. [23]	11/75(14.7) 7/46(15.2)	N/A	N/A	N/A	N/A

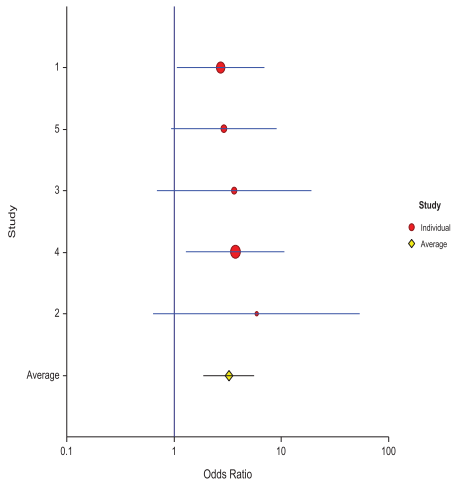
1-y-SR, 1-year survival rate; ORR, overall response rate; G3–4, grade 3–4; P, p-value; n., number of patients; N/A, not available.
* The number of patients reported corresponds to the number of patients evaluable for each specific outcome.

chemotherapy. Furthermore, two other trials were excluded because no specific data for PS2 patients were reported. So, after a careful selection procedure, only six trials met our inclusion criteria and were included in our meta-analysis. Overall 741 patients were included in these six trials (Fig. 1). Five publications [18,19,21–23] are about randomized phase III trials and one was a randomized phase II trial [24]. Four studies [18,19,21,24] were specifically devoted to PS2 patients, while two trials [22,25] reported subgroup analysis for PS2 patients (18 and 20%, respectively) within larger randomized phase III trials. All trials compared a platinum-based doublet with single-agent chemotherapy; four of these [18,21,22,24] compared carboplatin-based doublet with single agent chemotherapy: carboplatin plus pemetrexed vs pemetrexed alone [18], carboplatin plus gemcitabine vs gemcitabine alone [21,24], carboplatin plus paclitaxel vs paclitaxel alone [22,25]; the other two trials compared cisplatin plus gemcitabine with gemcitabine alone [19] and cisplatin plus vinorelbine or vindesine with vinorelbine alone [23]. In nearly every trial characteristics were well balanced between two arms. In the trial by Le Chevalier et al. [23], the two groups of patients receiving cisplatin (cisplatin plus vinorelbine and cisplatin plus vindesine) were considered as a whole group, because the aim of this meta-analysis is to explore the difference between platinum-based vs non-platinum single agent chemotherapy. The extracted data, including number of patients, PS, age, histology, stage, chemotherapy regimens, and outcomes, were reported in Table 2. Data about ORR [18,19,21,22,24] and 1y-SR [18,21–24] were available from five studies. Finally, data about toxicity were available from 4 trials [18,19,21,24]. Primary and secondary endpoints were reported in Table 1.

Table 2
Characteristics of the 6 randomized trials included in the meta-analysis.

Trial (reference)	OS months	Chemotherapy regimen	Number of patients	Median age	PS 2 (%)	Squamous histology (%)	Stage IV (%)
Zukin et al. [18]	9.3 5.3 *P:0.001*	Carbo–Pem VS Pem	103 102	65 65	100	2.9 10.8	94.2 95.1
Morabito et al. [19]	5.9 3.0 *P:0.039*	Cis–Gem VS Gem	28 28	63 63	100	36 32	93 93
Kosmidis et al. [24]	6.7 4.8 *P:0.49*	Carbo–Gem VS Gem	43 47	70.5 73	100	30 28	74 64
Reynolds et al. [21]	6.7 5.1 *P:0.24*	Carbo–Gem VS Gem	85 85	72.9 75	100	16.5 25.8	82 94
Lilenbaum et al. [22]	4.7 2.4 *P:0*.016	Carbo–Paclit VS Paclit	49 50	64 63	18	N/A	87 83
Le Chevalier et al. [23]	4.5 4.3 *P: NA*	Cis–Vino/Vind VS Vino	75 46	59 60	20	53 56	52 47

OS indicates overall survival; Carbo, Carboplatin; Cis, Cisplatin; Pem, Pemetrexed; G, gemcitabine; Pacl, paclitaxel; Vino, Vinorelbine; Vind, Vindesine; *P*, *P*-value; PS, Performance status; N/A, not available.



Citation	Arms	Odds Ratio	95% CI
Zukin, JCO 2013	CPm vs Pm	2,71	1,06-6,93
Lilembaum, JCO 2005	CPa vs Pa	2.91	0,94-9,03
Kosmidis, JTO 2007	CG vs G	3.64	0,69-19,15
Reynolds, JCO 2009	CG vs G	3.71	1,29-10,65
Morabito, LC 2013	CisG vs G	5.86	0,63-53,92
Random combined		**3.24**	**1,88-5,58**

Heterogeneity Test

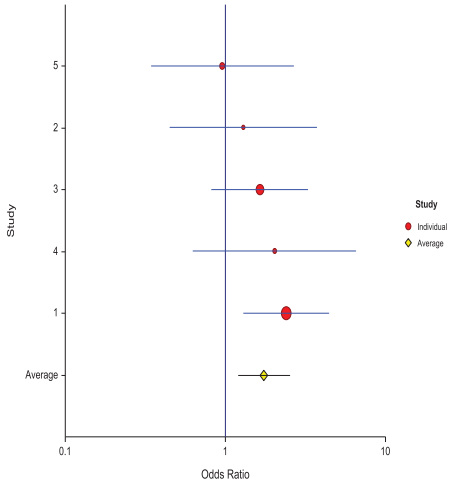
Cochran's Q : 0.52 DF: 4 P-value: 0.97

Fig. 2. Comparison of the Response rate between platinum-doublet arms and single-agent arms of all included trials. 95% CI indicates 95% confidence interval; C, Carboplatin; Cis, Cisplatin; Pm. Pemetrexed; Pa, Paclitaxel; G, Gemcitabine; JCO, Journal of Clinical Oncology; LC, Lung Cancer; DF, degrees of freedom.

Pooled analysis showed a significant improvement in ORR (OR: 3.243; 95% CI: 1.883–5.583] and 1y-SR (OR: 1.743; 95% CI: 1.203–2.525) in favour of platinum-based doublet chemotherapy. The pooled OR for ORR and 1y-SR was calculated using fixed-effect model, because of non-significant heterogeneity between treatment effects (Q-test: P: 0.99 and 0.76, respectively) (Figs. 2 and 3). In terms of toxicity, we analyzed only data on severe haematological toxicities, available for five of six studies included. Pooled OR for grade 3–4 haematological toxicity rate showed a significant increase in patients treated with platinum-based combination: grade 3–4 anaemia (OR: 2.743; 95% CI: 1.359–5.536), grade 3–4 neutropenia (OR: 7.239; 95% CI: 3.725–14.073); grade 3–4 thrombocytopenia (OR: 12.881; 95% CI: 4.901–33.857) (Figs. 4–6). A summary of the Pooled Odds Ratios and 95% CI for each outcome examined is reported in Table 3.

4. Discussion

This meta-analysis included six randomized trials, which compared platinum-based doublets with single-agent chemotherapy in NSCLC patients and specific data for PS 2 patients. The results of these trials suggest that platinum-based combination regimens are superior to single-agent chemotherapy in the first-line treatment of this

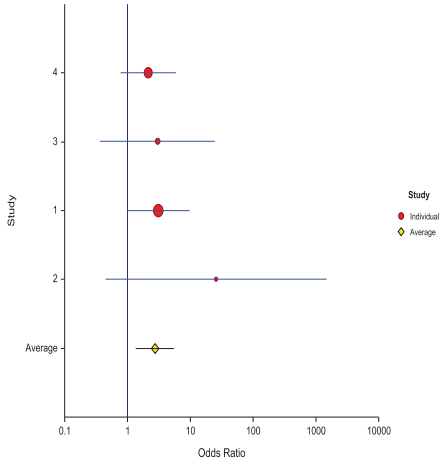


Citation	Arms	Odds Ratio	95% CI
Le Chevalier, The O. 2001	CisV vs V	0.95	0,34-2,67
Kosmidis, JTO 2007	CG vs G	1,29	0,44-3,71
Reynolds, JCO 2009	CG vs G	1,64	0,81-3,28
Lilembaum, JCO 2005	CPa vs Pa	2,02	0,62-6,54
Zukin, JCO 2013	CPm vs Pm	2,4	1,30-4,44
Random combined		**1,74**	**1,20-2,52**

Heterogeneity Test

Cochran's Q : 2.75 DF: P-value: 0.59

Fig. 3. Comparison of the 1-year-survival rate between platinum-doublet arms and single-agent arms of all included trials. 95% CI indicates 95% confidence interval; C, Carboplatin; Cis, Cisplatin; Pm. Pemetrexed; Pa, Paclitaxel; G, Gemcitabine; V,Vinorelbine/Vindesine; JCO, Journal of Clinical Oncology; The O, The Oncologist; DF, degrees of freedom.



Citation	Arms	Odds Ratio	95% CI
Reynolds, JCO 2009	CG vs G	2.12	0,76-5,84
Kosmidis, JTO 2007	CG vs G	2.98	0,36-24,5
Zukin, JCO 2013	CPm vs Pm	3,1	0,99-9,69
Morabito, LC 2013	CisG vs G	25,5	0,44 - 1463,8
Random combined		**2,74**	**1,35-5,53**

Heterogeneity Test
Cochran's Q : 1.46 DF: 3 P-value: 0.69

Fig. 4. Comparison of the Grade 3–4 anemia rate between platinum-doublet arms and single-agent arms of all included trials. 95% CI indicates 95% confidence interval; C, Carboplatin; Cis, Cisplatin; Pm. Pemetrexed; Pa, Paclitaxel; G, Gemcitabine; JCO, Journal of Clinical Oncology; LC, Lung Cancer; DF, degrees of freedom.

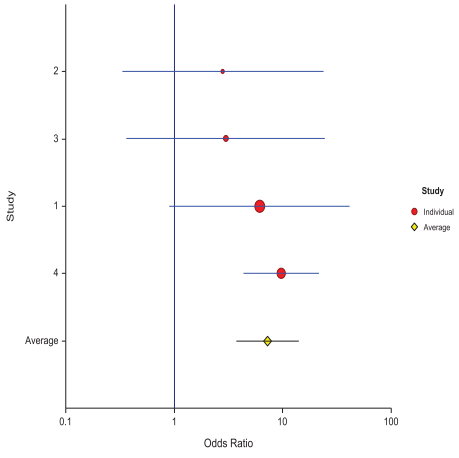
Table 3
Summary of the pooled odds ratios and 95% CI for each outcome examined in all included trials.

Outcomes	Pooled odds ratios	95% CI
ORR	3.24	1.88–5.58
1-year-OS-rate	1.74	1.20–2.52
G3–4 Anemia	2.74	1.35–5.53
G3–4 Neutropenia	7.23	3.72–14.07
G3–4 Thrombocytopenia	12.88	4.9–33.85

1-y-OS-R, 1-year survival rate; ORR, overall response rate; G3–4, grade 3–4.

special population both in terms of ORR and 1y-SR, despite an increase in severe haematological toxicities. This literature-based meta-analysis confirms the results achieved in the randomized trials devoted to PS 2 patients [18,19].

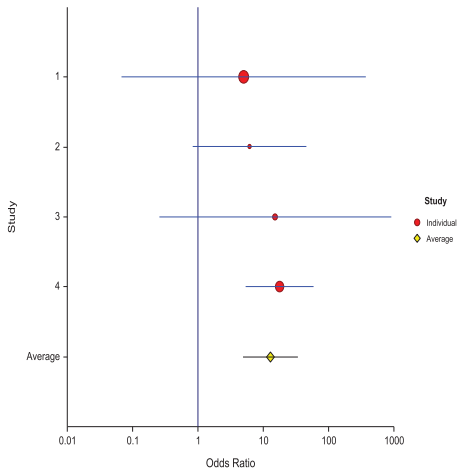
However this meta-analysis has some weaknesses points. Some included studies were specifically devoted to PS2 patients [18,19,21,24], 2 studies were not exclusively devoted to this subset of patients [22,23]. The CALGB trial [22] compared carboplatin-paclitaxel with paclitaxel alone in 584 patients with advanced NSCLC. It showed a significant improvement in ORR and a trend toward improved survival without statistical significance for combination arm in overall population, while subgroup analysis of 105 patients with PS 2 (18%) showed not only a significant improvement of ORR (24% vs 10%), but as well of median OS (4.7 month VS 2.4 month) and 1y-SR (18% vs 10%; hazard ratio [HR]: 0.6; *P*: 0.016), with nearly double survival benefit in favour of platinum-based combination. Unfortunately the authors did not report toxicities in the subgroup of PS2 patients. So this is the only study included in our meta-analysis with



Citation	Arms	Odds Ratio	95% CI
Morabito, LC 2013	CisG vs G	2,80	0,33-23,67
Kosmidis, JTO 2007	CG vs G	2,98	0,36-24,53
Zukin, JCO 2013	CPm vs Pm	6,1	0,89-41,55
Reynolds, JCO 2009	CG vs G	9,71	4,34-21,7
Random combined		**7,23**	**3,72-14,07**

Heterogeneity Test
Cochran's Q : 1.98 DF: 3 P-value: 0,57

Fig. 5. Comparison of the Grade 3–4 neutropenia rate between platinum-doublet arms and single-agent arms of all included trials. 95% CI indicates 95% confidence interval; C, Carboplatin; Cis, Cisplatin; Pm. Pemetrexed; Pa, Paclitaxel; G, Gemcitabine; JCO, Journal of ClinicalOncology; LC, Lung Cancer; DF, degrees of freedom.



Citation	Arms	Odds Ratio	95% CI
Zukin, JCO 2013	CPm vs Pm	5	0,06 - 369,5
Morabito, LC 2013	CisG vs G	6,12	0,82-45,2
Kosmidis, JTO 2007	CG vs G	15,2	0,25 - 911,2
Reynolds, JCO 2009	CG vs G	17,7	5,4-58,3
Random combined		**12,8**	**4,9-33,85**

Heterogeneity Test
Cochran's Q : 1.002 DF: 3 P-value: 0.8

Fig. 6. Comparison of the Grade 3–4 thrombocytopenia rate between platinum-doublet arms and single-agent arms of all included. trials. 95% CI indicates 95% confidence interval; C, Carboplatin; Cis, Cisplatin; Pm. Pemetrexed; Pa, Paclitaxel; G, Gemcitabine; JCO, Journal of Clinical Oncology; LC, Lung Cancer; DF, degrees of freedom.

missing haematological toxicity data. A French study [25] of carboplatin-paclitaxel compared with weekly paclitaxel alone was devoted to elderly patients with advanced NSCLC, but included 123 patients (27.3% of study population) with PS 2. Anyway the extraction of specific outcome measurements and toxicity for PS2 patients is not possible and therefore we had to exclude this study.

Furthermore, most studies included in our meta-analysis did not collect neither reported data on pre-existing patients' comorbidities, while some of these collected them not uniformly. This problem limited the chance of providing clear conclusions about the PS 2 population. In general, the PS 2 represents a heterogeneous and large group of patients, what makes it necessary to better understand the role played by different factors (comorbidities, disease burden and tumour-related symptoms) in compromising PS to select a favourable subgroup of patients who could better tolerate platinum-based doublet chemotherapy. In fact it is conceivable that platinum-based chemotherapy may lead to a clinical and survival benefit in patients whose poor PS is due to tumour burden, whereas those who are relatively asymptomatic for cancer, but are affected from symptomatic concomitant illness may not benefit from an aggressive treatment, which could worsen their clinical situation. In these patients a single-agent treatment with a third-generation drug or BSC could be considered as an alternative. Another point of discussion regards the various treatment regimens in the included studies. In most studies included in our meta-analysis [18,21,22,24] patients received carboplatin-based regimen, while only in two [19,23] cisplatin-based chemotherapy was administered. It is well known that platinum-based regimens represent the standard treatment of advanced NSCLC patients without activating EGFR or ALK mutations [6].

Several trials in the past compared regimens containing cisplatin vs carboplatin with conflicting results [26–33]. In 2007, an individual patient data meta-analysis performed by Ardizzoni et al. [34], including 9 of these trials and comparing cisplatin VS carboplatin-based chemotherapy in 2968 NSCLC patients, showed a significant improvement of ORR in favour of cisplatin arm (30% VS 24%; OR: 1.37, $P < 0.001$), while no significant differences between two arms were observed in survival rate. A subgroup analysis showed a significant increase of mortality rate in favour of carboplatin arm in patients with non-squamous histology and in those treated with a combination of carboplatin and a third generation drug (HR: 1.12, 95% CI: 1.01–1.23 and HR: 1.11, 95% CI: 1.01–1.21, respectively); severe thrombocytopenia was also more frequent with carboplatin regimen, while cisplatin treatment was associated with more severe nausea, vomiting and nephrotoxicity. So the authors concluded that cisplatin-based third-generation regimens should remain the standard references for the treatment of advanced NSCLC. However, a similar more recent meta-analysis [35], including 10 trials with 3973 people, showed no difference between carboplatin-based and cisplatin-based chemotherapy in overall survival (HR: 1.00; 95% CI: 0.51–1.97) and 1y-SR (risk ratio: 0.98; 95% CI: 0.88 to 1.09), but confirmed higher RR in favour of cisplatin arm (RR 0.88; 95% CI 0.79 to 0.99), and also a different toxicity profile between two drugs.

So, based on these conflicting and not conclusive results, we may consider cisplatin and carboplatin as two equal effective options in the treatment of NSCLC population, but it is also clear from these analyses that cisplatin treatment is associated with many serious side effects, including nausea and vomiting, myelosuppression, neurotoxicity and nephrotoxicity and often the need of hospitalization for prolonged hydration. Carbopatin on the other hand is associated with a lower incidence of non-haematological effects compared to cisplatin and does not require prolonged hydration, but produces more profound myelosuppression (especially

thrombocytopenia). Therefore we can conclude that it is easier to administer carboplatin in every day practice The use in combination with a third generation drug should be considered as a favourable option in the treatment of special population such as patients with a PS 2, who are historically considered frail and at higher risk for severe toxicities. Indeed haematological toxicity was more frequent and severe among patients assigned to combination arm.

So, an interesting question in the modern clinical practice for lung cancer management is how much intense should be the treatment of PS 2 patients. Even if contradictory results were reported from prospective randomized trials comparing platinum-based doublets vs single-agent chemotherapy devoted to PS 2 patients, our meta-analysis supports the evidence that platinum-based doublets are superior to single-agent therapy in terms of ORR and survival rate, in spite of an increase of severe haematological toxicities. Additionally, despite the wide range of median OS differences, ranging from 0.2 to 4 months in all included studies, probably due to the heterogeneity of both included patients and investigated treatments, the pooled OR for 1y-SR indicates that those patients receiving platinum-based treatment have a 74% higher probability of being alive after 1 year, with a significant impact for clinical practice.

Even if QoL may not be assessed in our meta-analysis because of the lack of data in the included studies, data available from two included trials that performed a formal QoL assessment [19,24] showed no statistically significant differences between single-agent and platinum-based combination arms. Considering OS and QoL as the two most important endpoints for NSCLC first-line chemotherapy, we suggest that platinum-based combination may be considered as a feasible treatment option in untreated PS 2 patients with EGFR wild-type NSCLC. However this conclusion should not be extended to overall PS 2 population, due to the lack of comorbidity data in the included studies.

Further studies are needed about the comparison of different carboplatin combinations, and also about the comparison between carboplatin- and cisplatin-based combinations, to establish the best treatment of NSCLC PS 2 patients. We agree with the proposal by Zukin et al. about the introduction of a formal comorbidity analysis as a stratification factor, to better select subgroups of patients that may tolerate an aggressive treatment [18].

5. Conclusion

In conclusion this meta-analysis suggests that platinum-based doublets are superior to single-agent therapy in the 1-st line treatment of PS2, NSCLC patients. In particular it supports the evidence that platinum-combination regimens are superior to single-agent both in terms of ORR and survival rate in spite of an increase of severe haematological toxicities. This information could change current treatment of these patients, encouraging the use of platinum as front-line therapy, but this conclusion could not be extended to overall PS 2 population. We endorse here the stratification of PS2 patients according to the reason for their health status worsening (i.e. comorbidity or tumour-related symptoms). We argue that a selection of PS2 patients according with this classification could help to identify those who could better tolerate platinum-based doublets and achieve a greater efficacy from this treatment.

Conflict of interest statement

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

Reviewers

Professor Arnold Ganser, Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation, Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany.

Dr Jacob Rowe, Shaare Zedek Medical Center, Dept. of Hematology12 Shmuel Bayit, Jerusalem, 31096, Israel.

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Biographies

Giuseppe Bronte, MD, PhD, received his MD degree from University Medical School of Palermo (Italy) in 2004. His post-graduate specialty was in Medical Oncology in 2008. He received his PhD degree in Experimental and Clinical Oncology from the same University in 2012. Co-investigator and Data manager in Multicenter Clinical Trials, managed by different Clinical Research Cooperative Groups, according to Good Clinical Practice (ITMO, SICOG, GOIM). He is a member of scientific societies and he is actively involved in the teaching and research of oncology fellows and students. He is author more than 40 publications in top-rated international cancer journals.

Christian Rolfo, MD PhD MBAH (Cordoba, Argentina) is board certified oncologist by University of Milan, Italy, and completed his PhD in Clinical and Experimental Oncology with a thesis on EGFR in NSCLC. He worked in the Spanish Group for Lung Cancer, under the direction of Prof. Rafael Rosell, actively involved in studies of molecular biology and-clinical research in lung cancer. He completed his training in the Phase I program at MDAnderson, Texas, USA, with Prof. David Hong. In 2011, he has been appointed 'visiting professor' in Medical Oncology by the Molecular and Clinical Genetic Oncology Unit at the Interdepartmental Centre of Research in Clinical Oncology, School of Medicine, University ofPalermo (Italy). Since 2012 he is Associate Professor in Oncology and Senior Staff Member, in the Department of Oncology at the University Hospital Antwerp (Belgium). Currently he is head of Phase I - EarlyClinical Trials Unit Director of Clinical Trials Management Program. in Oncology and Director of 'Investigational Cancer Therapeutics Fellowship and Drug Development: Clinical and Experimental' at Antwerp University Hospital in Belgium. His scientific

interests are drug development and resistance, liquid biopsies in lung cancer, more specifically in exosomes isolation and circulating tumour DNA. Since 2013 he has a membership in the Board of IALSC (International Association for the Study of Lung Cancer) and is member of societies including AACR, BACR, EACR, ESMO and ASCO.

Francesco Passiglia, MD, received his M.D. degree from University Medical School of Palermo, Italy, in 2011. He's attending residency school in Medical Oncology at the same University. He is interested in the field of Non-Small Cell Lung Cancer treatment with optimization of targeted drug tolerability. He works at the University Hospital of Palermo and collaborates with other cancer centres in Europe.

Sergio Rizzo MD, PhD, received his M.D. degree from University Medical School of Palermo (Italy) in 2003. His post-graduate specialty was in Medical Oncology. He received his PhD degree in Oncopathology from the same University in 2011. He has been awarded a AIOM Foundation Fellowship and has just spent six months at Lee Moffitt Cancer Center in Tampa, FL (USA). He is author of more than 20 publications in top-rated international cancer journals.

Ignacio Gil Bazo, MD, PhD, Graduated (1999) and was awarded his doctorate (2004) in Medicine and Surgery from the University of Navarra Faculty of Medicine. He is a Medical Oncology Specialist at the Clínica Universidad de Navarra (2004). He completed his training as a Postdoctoral Research Fellow in the Memorial Sloan-Kettering Cancer Center in New York, in the Cancer Biology and Genetics Program. He received a Medical Oncology Certificate in 2012 from the European Society for Medical Oncology (ESMO). He works as a specialist in the Oncology Department at the Clínica Universidad de Navarra. Codirector of the Lung Cancer Area. From 2015 he is Director in the Medical Oncology Department.

Eugenio Fiorentino, MD, PhD is Full Professor of Surgery at University School of Medicine of Palermo, Department of Surgical and Oncological Sciences. He is leading expert in gastroesophageal reflux disease and clinical director of the Esophageal Diseases Clinical Program at University Hospital Policlinico in Palermo. He has authored over 100 scientific publications mainly on gastroesophageal reflux disease and edited one book on acid reflux. Current area of research interest include gastroesophageal reflux, Barrett's esophagus, and esophageal cancer.

Massimo Cajozzo, MD, PhD, is Associate Professor of Thoracic Surgery at University Medical School of Palermo, Department of Surgical, Oncological and Stomatological Sciences (Italy). Since November 2007 is Director of Thoracic Surgery Unit, AOUP "P. Giaccone", Palermo (Italy). He is the author of more than 40 peer-reviewed publications listed on Medline-PubMed.

Jan P. van Meerbeeck, MD PhD was appointed as director of the Thoracic Oncology Program in the Multidisciplinary Oncological Center of Antwerp University Hospital (MOCA), Belgium, as of March 1, 2013. After obtaining his medical degree magna cum laude b from the University of Antwerp in 1980, he completed training to become a board certified specialist in internal medicine and pulmonology. He is a skilled interventional pulmonologist and completed his PhD in 1997 with a dissertation on the presentation of lung cancer in Flanders, Belgium. He is professor of Thoracic Oncology at both Ghent and Antwerp University and practiced as thoracic oncologist from 1986 to 1996 at Antwerp University Hospital, Belgium, and from 1996 to 2003 at Erasmus MC Danielden Hoed Kliniek, Rotterdam, the Netherlands. From 2003 to 2013 he was Chair of the Thoracic Oncology Program at Ghent University Hospital, where he became also Divisional Head and CMO. His translational scientific interests include the molecular diagnosis of mesothelioma and lung cancer and the evaluation of biomarkers of asbestos exposure and mesothelioma. He is or has been the study coordinator or Principal Investigator for numerous international phases II and III studies in thoracic oncology and respiratory medicine. He is promoter of several master thesis students and research fellows, of which 5 successfully completed their PhD. Professor van Meerbeeck has served the Lung Cancer Group of the European Organisation for Research and Treatment of Cancer (EORTC) as secretary, chairman and currently as board member. He is a full member of the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) and the International Association for the Study of Lung Cancer (IASLC), currently as part of its Staging and Ethical Committees and previously as a member of its Scientific Advisory Committee. He is external expert at the Belgian Knowledge Center KCE, where he coordinates the working party on the organisation of care of mesothelioma. Professor vanMeerbeeck has an extensive presentation and publication track, with more than 200 peer-reviewed articles in oncology and pulmonology journals and textbooks. He also serves in the review and editorial boards of several international journals, and has organised several national and international meetings.

Cosimo Lequaglie, MD, PhD. Role: Surgeon. Subspecialty(ies) Peripheral Vascular Surgery & General Thoracic Surgery Background University La Sapienza of Roma, Italy (M.D. 1982) Istituto Nazionale Tumori, Milano, Italy, Oncologic Thoracic Surgery, Fellowship (1986–1988) European School of Oncology Fellowship (1987) Istituto Nazionale Tumori, Milano, Italy, Oncologic Thoracic Surgery, Consultant Surgeon (1989–2004) Department of Cardiovascular Surgery Monzino's Foundation of Milano, Italy, Residency (1999–2000) University of Milano, Professor of Human Anatomy (2001–2002) University of L'Aquila, Professor of Thoracic Surgery (2007-) Consultant Reviewer for CHEST (2001-) Chief Dept. Thoracic Surgery, IRCCS National

Cancer Institute Rionero in V. (2004-) Membership of EACTS, IASCL, ACCP, SICT, STS, ESTS, SICO, SIC, AIOT, ACOI, ISID, ECMM

Interests

Large Demolitions and Repairs of Sternum, Chest Wall, Diaphragm and Pericardium in Cancer patients Tumor Markers and Biologic Variables in Lung Cancer Extended Surgery for Lung, Esophageal, Pleural and Mediastinal Tumors Pulmonary Metastases in Sarcoma Patients Integration of surgery and medical treatments in Oncology.

Daniele Santini MD, PhD: Expertise: Design and conduction of phase II-III clinical trials in solid tumors; chemotherapy in gastrointestinal tumors; molecular mechanisms on tumor progression; molecular prognostic and predictive factors in gastrointestinal tumors; role of bisphosphonates and emerging target theraphies in Osteoncology.

Work experience: 1996–1999 Department of Internal Medicine, Policlinico Universitario "Campus Bio-Medico", Roma. Employed In charge of complex professional activities in Department of Interna Medicine, Policlinico Universitario "Campus Bio-Medico", Roma.1999–2005 Department of Medical Oncology, Policlinico Universitario "Campus Bio-Medico", Roma. Assistant Doctor in charge of complex professional activities in Department of Medical Oncology, Policlinico Universitario "Campus Bio-Medico", Roma. 2001–2010 Università "Campus Bio-medico", Roma. Research Associate on General Pathology.2009-today Department of Medical Oncology, Policlinico Universitario "Campus Bio-Medico", Roma. Chief of Medical oncology day hospital of Trigoria, Università Campus Bio-Medico di Roma.2011-today Università "Campus Bio-medico", Roma. Associate Professor in General Pathology MED/04. Education and training: 1990 University "La Sapienza", Rome, Italy. Graduated cum laude Medicine and Surgery degree.

1994 University "La Sapienza", Rome, Italy. Graduated cum laude Resident-Specialty in Medical Oncology.2001 University of Palermo, Palermo, Italy, PhD in Immunopharmacology.2008-today Coordinator of the National Guidelines on "Bone metastasestreatment" for the Italian Association of Medical Oncology (AIOM). 2009:Consultant of Health Ministry for guidelines of bisphosphonates-related osteonecrosis of the jaw. 2010-today: Coordinator of the National Guidelines on "Lung Bone metastases treatment" for the Italian Association of Thoracic Oncology (AIOT). 2010-today: Co-author of the National Guidelines on "Prostate bone metastases treatment" for the Italian Society of Urology (SIU). Editorial activity:Reviewer of scientific paper(Oncology and General Pathology) on request of the Editors of several International Scientific Journals (New England Journal of Medicine; Journal interferon and cytokine Research; Annals of Oncology; Journal of Cinical Oncology; Journal of biological regulators and homeostatic agents; Cancer Letters; Cancer Treatment Reviews; Br J Cancer; Clin Cancer Res; Cancer; Pharmacogenomics). Member of the Editorial Board of several International Scientific Journals: Journal of Bone and Mineral Research; Cancer Biology and Therapy; Expert Opinion on Therapeutic Targets; Expert Opinion on Biological Therapy; Expert Opinion on Emerging Drugs; Pharmacogenomics; Journal of Experimental and Clinical Cancer Research; Women's Health; Medic; Recent Patents on Anti -Cancer Drug Discovery; Therapy; Internet Journal of Oncology; Journal clinical medicine: oncology; World Journal Clinical Oncology; OncoTargets and Therapy; Journal of Chemotherapy. Publications: 270 publications on International journalswith impact factor.

Patrick Pauwels, MD, PhD, is the former head of the Department of Pathology ND currently Head of Molecular Pathology Unit at Antwerp University Hospital Belgium, and an Professor at the Antwerp University, Belgium.

He is a recognised leader in the field of ALK testing in lung cancer, and his laboratory has screened more than 5000 lung cancer samples for ALK rearrangement. In recognition of his considerable experience, he was appointed to European External Quality Committee, which is submitting guidelines for ALK testing in Europe and organizing quality control rounds for ALK testing. He is involved in several research lines in translational oncology, including new biomarkers discovery, liquid biopsies in lung Cancer and drug resistance.

He is author of several publication in the field of Lung cancer and a recognized national and international speaker.

Antonio Russo, M.D., PhD, is Professor of Medical Oncology at University Medical School of Palermo, Department of Surgical, Oncological and Stomatological Sciences (Italy). From 2004 to July 2011 he has been an Adjunct Associate Professor and since August 2011 Adjunct Full Professor at Temple University's College of Science and Technology, Philadelphia (USA). Since February 2012 is Director of Medical Oncology Unit and Director of Regional Reference Center for Prevention, Diagnosis and Treatment of Rare Tumors and Heredo-familial Solid Tumors in Adults, AOUP "P. Giaccone", Palermo (Italy). Since April 2012 is Director of the Specialization School in Medical Oncology, University of Palermo, School of Medicine, Palermo, Italy. Since November 2013 Medical Oncology Unit directed by Prof A Russo has been recognized as a 2013 ESMO Designated Centres of Integrated Oncology and Palliative Care.

Since 2001 he has been a coordinator with Prof D. Kerr (University of Oxford, UK) and Prof B. Iacopetta (Western Australia University) of the "CRCP53 International Collaborative Study". Since 2003 he has been an expert member of INSERM (Institut National de la Santèet de la RechercheMèdical, France), since 2007 of Scientific Committee INCA (Institut National du Cancer, France) and of NWCRF (North West Cancer Research Fund, UK). He is member of Editorial board of Journal of Carcinogenesis &

Mutagenesis (since 2011) and World Journal of Gastrointestinal Oncology and World Journal of Clinical Oncology (since 2012). Since 2013 is Associate Editor of Journal of Solid Tumors.

Since 2008 he has been Guest Editor of Annals of Oncology (2006, 2007). The central theme of his studies is translational research, meaning the application of molecular genetics in cancer management. He is PI in several national and international clinical trials. He is the author of more than 300 peer-reviewed publications listed on Medline-PubMed.