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

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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.

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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 fragility 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).

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

<table>
<thead>
<tr>
<th>Trial (reference)</th>
<th>1y-SR n* (%)</th>
<th>ORR n. (%)</th>
<th>G3–4 Anaemia n. (%)</th>
<th>G3–4 Neutropenia n. (%)</th>
<th>G3–4 Thrombocytopenia n. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zukin et al. [18]</td>
<td>41/103(40)</td>
<td>197/199(24)</td>
<td>3/125 (2.4)</td>
<td>3/103 (3.8)</td>
<td>3/103 (3.8)</td>
</tr>
<tr>
<td>Morabito et al. [19]</td>
<td>22/102(21.9)</td>
<td>7/176(10.5)</td>
<td>4/102 (3.9)</td>
<td>1/102 (1)</td>
<td>0/102 (0)</td>
</tr>
<tr>
<td>Kosmidis et al. [24]</td>
<td>9/43(20)</td>
<td>6/43(14)</td>
<td>1/28 (4)</td>
<td>3/14 (7)</td>
<td>1/28 (7)</td>
</tr>
<tr>
<td>Reynolds et al. [21]</td>
<td>26/85(31.3)</td>
<td>16/85(18.8)</td>
<td>12/85 (14)</td>
<td>46/85 (54)</td>
<td>38/85 (41)</td>
</tr>
<tr>
<td>Lilenbaum et al. [22]</td>
<td>18/85(21.2)</td>
<td>5/85(5.9)</td>
<td>6/85 (7)</td>
<td>9/85 (10.5)</td>
<td>3/85 (3.5)</td>
</tr>
<tr>
<td>Le Chevalier et al. [23]</td>
<td>11/75(14.7)</td>
<td>5/75(6.7)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Trial (reference)</th>
<th>OS months</th>
<th>Chemotherapy regimen</th>
<th>Number of patients</th>
<th>Median age</th>
<th>PS 2 (%)</th>
<th>Squamous histology (%)</th>
<th>Stage IV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zukin et al. [18]</td>
<td>9.3</td>
<td>Carbo–Pem</td>
<td>103</td>
<td>65</td>
<td>100</td>
<td>2.9</td>
<td>94.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VS Pem</td>
<td>102</td>
<td>65</td>
<td>100</td>
<td>10.8</td>
<td>95.1</td>
</tr>
<tr>
<td>Morabito et al. [19]</td>
<td>5.9</td>
<td>Cis–Gem</td>
<td>28</td>
<td>63</td>
<td>100</td>
<td>36</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VS Gem</td>
<td>28</td>
<td>63</td>
<td>100</td>
<td>32</td>
<td>93</td>
</tr>
<tr>
<td>Kosmidis et al. [24]</td>
<td>6.7</td>
<td>Carbo–Gem</td>
<td>43</td>
<td>70.5</td>
<td>100</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VS Gem</td>
<td>47</td>
<td>73</td>
<td>100</td>
<td>28</td>
<td>64</td>
</tr>
<tr>
<td>Reynolds et al. [21]</td>
<td>6.7</td>
<td>Carbo–Gem</td>
<td>85</td>
<td>72.9</td>
<td>100</td>
<td>16.5</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VS Gem</td>
<td>85</td>
<td>75</td>
<td>100</td>
<td>25.8</td>
<td>94</td>
</tr>
<tr>
<td>Lilenbaum et al. [22]</td>
<td>4.7</td>
<td>Carbo–Paclit</td>
<td>49</td>
<td>64</td>
<td>18</td>
<td>N/A</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VS Paclit</td>
<td>50</td>
<td>63</td>
<td>18</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Le Chevalier et al. [23]</td>
<td>4.5</td>
<td>Cis–Vino/Vind</td>
<td>75</td>
<td>59</td>
<td>20</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VS Vino</td>
<td>46</td>
<td>60</td>
<td>20</td>
<td>56</td>
<td>47</td>
</tr>
</tbody>
</table>

OS indicates overall survival; Carbo, Carboplatin; Cis, Cisplatin; Pem, Pemetrexed; G, gemcitabine; Pacl, paclitaxel; Vino, Vinorelbine; Vind, Vindesine; P, P-value; OS, Overall survival; NA, not available.
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 (P-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
This literature-based meta-analysis confirms the results achieved in the randomized trials devoted to PS2 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 special population both in terms of ORR and 1y-SR, despite an increase in severe haematological toxicities.

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Pooled odds ratios</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>3.24</td>
<td>1.88–5.58</td>
</tr>
<tr>
<td>1-year-OS-rate</td>
<td>1.74</td>
<td>1.20–2.52</td>
</tr>
<tr>
<td>G3–4 Anemia</td>
<td>2.74</td>
<td>1.35–5.53</td>
</tr>
<tr>
<td>G3–4 Neutropenia</td>
<td>7.23</td>
<td>3.72–14.07</td>
</tr>
<tr>
<td>G3–4 Thrombocytopenia</td>
<td>12.88</td>
<td>4.9–33.85</td>
</tr>
</tbody>
</table>

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

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.

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 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 patients, 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. Carboplatin 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

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**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.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Arms</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zukin, JCO 2013</td>
<td>CPr vs Prm</td>
<td>5</td>
<td>0.06 - 369.5</td>
</tr>
<tr>
<td>Morabito, LC 2013</td>
<td>CisG vs G</td>
<td>6.12</td>
<td>0.82-45,2</td>
</tr>
<tr>
<td>Kosmidis, JTO 2007</td>
<td>CG vs G</td>
<td>15.2</td>
<td>0.25 - 911.2</td>
</tr>
<tr>
<td>Reynolds, JCO 2009</td>
<td>CG vs G</td>
<td>17.7</td>
<td>5.4-58.3</td>
</tr>
<tr>
<td>Random combined</td>
<td></td>
<td>12.8</td>
<td>4.9-33.85</td>
</tr>
</tbody>
</table>

**Heterogeneity Test**

Cochran’s Q: 1.002  DF: 3  P-value: 0.8
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 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.

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References


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Interests
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