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Review

Platinum-based chemotherapy in advanced non-small-cell lung cancer: optimal number of treatment cycles

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Abstract

Platinum-based chemotherapy remains the standard-of-care for most patients affected by advanced non-small cell lung cancer (NSCLC). The platinum compounds currently used in NSCLC are cisplatin and carboplatin. The availability of new generation drugs has led to the adoption of schedules with lower doses of platinum compounds leading to increased tolerability. Several data suggest that third generation cisplatin-based regimens are slightly superior to carboplatin-based chemotherapy, with a different safety profile, and so cisplatin should remain the standard reference for the treatment of selected patients with advanced NSCLC. Recent evidence emphasized that the optimal number of first-line platinum cycles should be four for any NSCLC histology. New platinum compounds and the use of functional genomics to deliver platinum drugs as personalised medicine, are being investigated. Here we review the current status of cisplatin and carboplatin regimens looking to the future role of platinum compounds in advanced NSCLC patients.

Keywords: carboplatin, chemotherapy, cisplatin, first-line, metastatic, non-small-cell lung cancer, NSCLC, treatment

INTRODUCTION

Cisplatin, or cis-diamminedichloroplatinum (II), was the first platinum compound approved for use in 1978. Since then several platinum drugs have entered clinical trials, with two, carboplatin, or cis-diammine-cyclobutanedicarboxylato platinum (II), and oxaliplatin, or 1,2-diaminocyclohexaneoxalato platinum (II), approved for cancer therapy worldwide. Platinum drugs are used to treat a wide variety of cancers, including non-small-cell lung cancer (NSCLC). The cytotoxic effects of platinum drugs are induced by targeting nuclear DNA. They form adducts preferentially with the N7 atom on guanine and adenosine bases. Such binding stops DNA replication and transcription, which then initiates cellular apoptosis [1].

NSCLC accounts for about 85% of all new lung cancer diagnoses which are around 1,8 million worldwide every year [2]. Since most patients with NSCLC have advanced disease at diagnosis, chemotherapy is the mainstay of management. In clinical practice, platinum-based regimens are the most widely used in the treatment of advanced NSCLC since meta-analyses showed a median overall survival (OS) improvement for cisplatin-based chemotherapy versus best supportive care [3, 4], or versus single-agent [5], in this setting. Another meta-analysis investigated the role of adding a third agent to platinum-based doublets and showed that triplets are associated with an increase in objective response rate (ORR) which does not translate in a better progression-free survival (PFS) or OS rate but with an increased toxicity [6].

Living in the era of personalised medicine, the determination of oncogene-addicted NSCLC, mainly due to the presence of epidermal growth factor receptor (*EGFR*) activating mutations or anaplastic lymphoma kinase (*ALK*) and proto-oncogene tyrosine-protein kinase ROS (*ROS1*) translocations, is of paramount importance to select patients who can benefit by the use of correspondent inhibitors. However, the percentage of Caucasian patients with advanced NSCLC harbouring these alterations is as high as 20%, meaning that in the most of cases platinum-doublets represent the standard-of-care of the first-line therapy.

In this paper, we review the current status of cisplatin and carboplatin regimens which are those used in the clinical practice for the management of NSCLC patients.

CONCERNS IN THE USE OF CISPLATIN AND CARBOPLATIN

Platinum compounds attack, indiscriminately, all rapidly dividing cells leading to severe side effects and inducing the ability of cancers to develop drug resistance [1]. Common side effects of cisplatin and carboplatin include nausea and vomiting, myelosuppression, neuropathy, ototoxicity, hepatotoxicity and nephrotoxicity.

Cisplatin is one of the most emetogenic drugs used, with considerable variability between individuals. Systematic use of a three-drug combination of a neurokinin 1 receptor antagonist, a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, and dexamethasone improves control of acute emesis, but control of delayed emesis is often suboptimal [7]. Anemia can also occur during treatment with cisplatin. Several mechanisms can led to anemia, including depletion of intrinsic erythropoietin production (caused by peritubular renal cell depletion), reduced bone marrow stem cell activity and the absence of the stem cell reaction to administered erythropoietin [8-10]. The use of erythropoiesis-stimulating agents, when hemoglobin level is less than 10 g/dL, might help but it should be discussed with the patient to evaluate potential risks, such as thromboembolism, and benefits, such as decreased transfusions [11]. Nephrotoxicity may be reduced but not suppressed by hyper-hydration which, however, is not possible in patients with congestive heart failure, a comorbidity often present in patients with NSCLC [12, 13]. Peripheral neurotoxicity is the most common dose-limiting problem associated with modern cisplatin therapy. Cisplatin neurotoxicity, characterized by painful paresthesias and numbness, generally occurs during the first cycles. Loss of vibration sense, paraesthesia and ataxia can become apparent after several treatment cycles. Ototoxicity caused by cisplatin tends to be cumulative and can be irreversible, therefore monitoring by audiograms should be considered. Several therapeutic approaches have been developed and are under investigation to reduce or prevent these effects with very contrasting results [14].

Many of the side effects associated with cisplatin are less common with carboplatin, which is associated with risk of nephrotoxicity only when administered at high doses. However, carboplatin is not free of potentially relevant toxicities, because it causes dose-limiting myelosuppression, and also transient rises in bilirubin levels were observed [14, 15].

In some patients, the side effects associated with the use of cisplatin or carboplatin can be so severe to determine dose reduction. These dose reductions, could increase the chance to develop resistance by cancer cells [16]. However, resistance is frequent also in patients who receive the full dose. A better understanding of the mechanisms associated with platinum resistance could help to improve the prognosis of many cancer patients. To date, four main mechanisms able to induce platinum resistance have been identified, including: (i) reduced cellular uptake of the platinum salt; (ii) increased repair of platinum-induced DNA damage; (iii) degradation and detoxification of the drugs inside the cells by glutathione; and (iv) altered apoptosis [17, 18]. The resistance to platinum drugs has been studied extensively *in vitro* but, the clinical relevance of each of the above listed mechanisms is currently not entirely clear.

The low therapeutic index of both cisplatin and carboplatin, that implies a careful evaluation of the balance between the risk of toxicity and the chance of clinical benefit, should be particularly considered when treating two special groups of NSCLC patients: the elderly subjects and those who are unfit but still eligible for active treatment. Approximately 50% of new lung cancer cases are diagnosed in patients aged more than 70 years, and about 15% in patients aged more than 80 years [19]. Aging may be associated with decreased physiologic reserve, comorbidity and polypharmacy, functional dependence, and inadequate social support, which lead to limited life expectancy with a potential reduced tolerance to cancer chemotherapy [20]. Furthermore, elderly patients are underrepresented in clinical trials and many treatment decisions are based on results of trials conducted in substantially younger individuals [21]. However, according to major international guidelines, age alone should not represent a barrier to best treatment, and fit elderly patients should be considered for standard platinum-based doublets. According to Eastern Cooperative Oncology Group (ECOG) scale, patients with performance status 2 (PS 2) are those who stay in bed, but for less than 50% of their daily time. It is crucial for clinicians to understand the reason why that patient is unfit and limited in daily activities: is it due to cancer symptoms or to comorbidities? Of note, a meta-analysis pooled the data of PS 2 patients coming from 6 randomized trials, for a total of 741 subjects. This pooled analysis showed a significant improvement in ORR (odds ratio [OR] 3.243, 95% confidence interval [CI]: 1.883-5.583) and 1-year OS (OR 1.743, 95% CI: 1.203–2.525) in favour of platinum-

based doublets but, with higher incidence of grade 3-4 hematological toxicities [22]. These results suggest that in selected PS 2 NSCLC patients platinum-combination regimens are superior to single-agent. Thus, in both elderly and unfit subjects, if the patient is considered suitable for standard therapy, the most appropriate platinum-based doublets should be administered.

Overall, the toxicity of platinum compounds depends also by the companion drugs administered in the doublets. To date, third generation drugs, employed in NSCLC, are active and well tolerated. Doses of platinum compounds commonly used are lower than those used some decades ago, and this allows a better safety profile while maintaining a good activity and efficacy.

CISPLATIN VERSUS CARBOPLATIN

The doses at which these agents are administered depend by the drug with which they are being combined and the status of the patient. Cisplatin is usually given at a dose of 50-120 mg/m^2 per cycle. As stated above, with the higher doses have been substantially abandoned with the diffusion of third-generation doublets in the treatment of NSCLC patients. In fact, to date, the dose of cisplatin usually used in doublets is around 75-80 mg/m^2 per cycle every 3 weeks. The dose of carboplatin is usually tailored for each patient using the area under the concentration-time curve (AUC) and renal function of the patient, because this drug is characterized by an extensive renal excretion [23, 24]. Carboplatin is usually given at AUC 4-6 per cycle, recycled every 3 weeks.

The choice of platinum-based doublets is based on histologic subtype of NSCLC. In fact, evidences raised from the availability of pemetrexed and bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), underlined that histology represents an important variable in the decision making. Both drugs are licensed for the use only in non-squamous NSCLC histotype [25].

Based on all previous considerations, international guidelines for the treatment of non-oncogene addicted advanced NSCLC recommend platinum-based third-generation chemotherapy doublets as standard of care

for first-line treatment. The treatment strategy should take into account histology, molecular pathology, age, PS, comorbidities, and patient's preferences [26, 27].

Carboplatin was introduced in the clinical practice as a valid alternative option to cisplatin. However, even if the mechanism of action is similar, the equivalence of cisplatin and carboplatin in terms of clinical efficacy has not been demonstrated for all cancer types. For example, randomized studies on ovarian cancer supported the use of carboplatin instead of cisplatin [28, 29], while cisplatin is considered superior to carboplatin for germ cell and head-neck tumors [30].

Nine trials addressed this relevant issue in patients affected by advanced NSCLC [31-39] (**Table 1**). A meta-analysis of abstracted data from 8 of those trials (2,948 patients) showed that cisplatin-based chemotherapy produced a higher ORR (OR 1.36, 95% CI: 1.15–1.61; $p < 0.001$), but without an OS advantage (hazard ratio [HR] 1.050, 95% CI: 0.907–1.216; $p = 0.515$) when compared with carboplatin-based regimens. Subgroup analysis revealed that combination chemotherapy consisting of cisplatin plus a new agent yields 11% longer OS than carboplatin plus the same new agent (HR 1.106, 95% CI: 1.005–1.218; $p = 0.039$). Patients on cisplatin-based chemotherapy frequently developed nausea and vomiting (OR 2.51, 95% CI: 1.76–3.56), while grade $\geq$ 3 thrombocytopenia was more frequent in patients receiving carboplatin-based treatment (OR 0.58, 95% CI: 0.39–0.87). No significant difference in treatment-related mortality was observed with 54 treatment-related deaths (3.9%) among the 1,380 patients treated with cisplatin-based chemotherapy and 40 (2.9%) among the 1,366 patients treated with carboplatin-based chemotherapy (OR 1.36, 95% CI: 0.89–2.07) [40] (**Table 2**).

An individual patient data meta-analysis included all the 9 randomized trials for a total of 2,968 patients. In detail, seven trials were phase III studies and the remaining two were phase II trials. Third-generation doublets (cisplatin or carboplatin plus paclitaxel or docetaxel or gemcitabine) were administered to 2,330 patients, representing 80% of the total population included in the trials. Overall survival was not significantly different between the two treatment groups. Cisplatin-treated (n = 1,489) patients had a median OS of 9.1 months and a 1-year survival probability of 37%, while carboplatin-treated patients (n = 1,479) had a median OS of 8.4 months and a 1-year survival probability of 34% (HR for carboplatin versus

cisplatin 1.07, 95% CI: 0.99–1.15; p = 0.100). Subgroup analyses showed a statistically significant interaction between the treatment and histology (non-squamous versus squamous NSCLC, p = 0.098) and between treatment and the type of regimen (second-generation versus third-generation regimens p = 0.093). The HRs for mortality in patients with non-squamous and squamous NSCLC were 1.12 (95% CI: 1.01–1.23) and 0.97 (95% CI: 0.85–1.10), respectively. HRs for mortality were 0.94 (95% CI: 0.80–1.11) and 1.11 (95% CI: 1.01–1.21) in the subgroups of patients treated with second- and third-generation regimens, respectively suggesting a significant superiority of cisplatin when used within third-generation regimens. The ORR was 30% for patients treated with cisplatin and 24% for those receiving carboplatin (OR of response with cisplatin compared to carboplatin 1.37, 95% CI: 1.16–1.61; p < 0.001). The result of the interaction test between the treatment and the different variables was statistically significant only for histology (p = 0.046). The OR was 1.58 (95% CI: 1.27–1.97) in the subgroup of the patients with non-squamous histology, and 1.10 (95% CI: 0.85–1.43) in the subgroup with squamous histology. As expected, carboplatin-based chemotherapy was associated with a higher thrombocytopenia when compared with cisplatin doublets (OR 2.27, 95% CI: 1.71–3.01; p < 0.001), while cisplatin-based chemotherapy caused more nausea and vomiting than that showed by carboplatin doublets (OR 0.42, 95% CI: 0.33–0.53; p < 0.001) and renal toxicity (OR 0.37, 95% CI: 0.15–0.88; p = 0.018) [41] (**Table 2**).

Both these meta-analyses showed a statistically significant advantage in terms of OS in favor of cisplatin doublets in patients treated with third-generation chemotherapy. Thus, new generation cisplatin doublets should be considered the preferable choice. However, given the palliative nature of chemotherapy treatment in advanced NSCLC, where the goal is not cure but symptom and disease control, avoiding cisplatin toxicity can be clinically useful, especially considering the little difference in OS compared to the more convenient toxicity associated with carboplatin. Overall, when cisplatin doublets are not recommended due to tolerability concerns, carboplatin doublets are a valid option.

OPTIMAL NUMBER OF CYCLES OF PLATINUM DOUBLETS

In 1997, the American Society of Clinical Oncology (ASCO) guidelines recommended for stage IV NSCLC that platinum-based first-line chemotherapy should be administered for no more than eight cycles [42]. In 2003, ASCO guidelines recommended that chemotherapy should be stopped at four cycles in patients who are not responding to treatment and that no more than six cycles should be administered [43]. These last recommendations were confirmed in 2009, 2011 and 2015 ASCO guideline updates [26, 44, 45]. In 2014, European Society of Medical Oncology (ESMO) metastatic NSCLC guidelines recommend, for most patients, four cycles of chemotherapy, with a maximum of six cycles [27]. To answer to the question concerning the optimal number of treatment cycles to administer in the first-line treatment of advanced NSCLC, several meta-analyses based on abstracted data showed that more than four cycles was associated with a longer PFS, without statistically significant differences in OS but with increased haematological toxicity [46, 47]. However, the results reported by these meta-analyses were difficult to interpret because they included trials with different study designs, and those without platinum-based chemotherapy. Therefore, considering these conflicting data, and in order to provide more solid clinical evidence about the optimal number of cycles of platinum-based induction chemotherapy, an individual patient data meta-analysis including trials comparing six versus fewer planned number of cycles of platinum-based chemotherapy was performed [48]. Five trials addressed this question [49-53] (**Table 3**), but only four studies were included in the analysis because data of the smallest trial were not available [53]. A total of 1,139 eligible patients were eligible, 571 assigned to shorter treatment (three or four cycles of platinum-based chemotherapy), and 568 to six cycles. Median OS, primary endpoint of the analysis, was 8.68 months for patients assigned to shorter treatment, and 9.54 months for patients assigned to six cycles (HR 0.94, 95% CI: 0.83–1.07; p = 0.33), with 1-year survival rate of 37.8% and 41.3%, respectively. There was no evidence of significant heterogeneity according to the number of cycles planned in the shorter treatment (3 or 4, p-value for interaction 0.98), nor according to type of platinum compound (cisplatin or carboplatin, p-value for interaction 0.59). In detail, in the two trials conducted with cisplatin, median OS was equal to 11.3 months in the group receiving 3-4 cycles and 10.9 months in patients receiving 6 cycles (HR 0.97, 95% CI: 0.81-1.17) [49, 51]

(**Figure 1 panel A**). Similarly, in the two trials conducted with carboplatin median OS was equal to 7.0 months in patients receiving 3-4 cycles and 8.2 months in patients receiving 6 cycles (HR 0.91, 95% CI: 0.76–1.08) [50, 52] (**Figure 1 panel B**).

Median PFS was 5.33 and 6.09 months for patients assigned to three-four versus six cycles, respectively (HR 0.79, 95% CI: 0.68–0.90; p = 0.0007), with 1-year PFS of 8.5% and 12%, respectively. The ORR was 36.5% with three-four cycles and 41.3% with six cycles (p = 0.16). Severe anaemia was slightly higher with six cycles (7.8% versus 2.9%, respectively), while there were no significant differences in other toxicities [48] (**Table 4**).

The issue of the optimal number of cycles of first-line platinum-based chemotherapy for the treatment of advanced NSCLC patients became even more relevant when maintenance treatment was developed as a new effective strategy. In fact, in trials demonstrating the efficacy of maintenance treatment for patients without disease progression after the completion of platinum-based chemotherapy, maintenance was started after four cycles. This strategy allowed to avoid two further platinum-based cycles, potentially causing cumulative additional toxicity. However, this is true for non-squamous NSCLC histology, due to the availability of maintenance pemetrexed, but it is not true for patients with squamous tumours, for which no maintenance option is currently available. The availability of maintenance treatment makes easier for physicians to accept that four cycles of platinum-based chemotherapy are enough for patients with a non-squamous tumour. However, the results of this meta-analysis showed that, even in the subgroup of squamous histology, six cycles were associated with only a small benefit in PFS, without significant advantage in OS. Of note, in the short treatment arm, three or four cycles were planned, but there is no single trial prospectively comparing three versus four cycles and this meta-analysis did not produced definitive data. However, as above specified, no significant interaction was reported between OS and the number of cycles planned in the shorter treatment arm.

Overall, based on all these data, four cycles of platinum-based chemotherapy can be considered the optimal duration of first-line treatment for advanced NSCLC both in squamous and non-squamous tumours.

CONCLUSION

Considering that about 20% of Caucasian metastatic NSCLC patients harbours a driver oncogene for which a specific inhibitor is currently in the clinical practice, most of patients are still candidate to chemotherapy. All non-oncogene addicted advanced NSCLC patients suitable for standard treatment should receive the most appropriate platinum doublet. The platinum compounds currently used in NSCLC are cisplatin and carboplatin. Several data suggest that third generation cisplatin-based regimens are slightly superior to carboplatin-based chemotherapy, with a different safety profile, and so it should remain the standard reference for the treatment of selected patients with advanced NSCLC. This treatment became more manageable thanks to the availability of new generation drugs, such as vinorelbine, gemcitabine, taxanes, and pemetrexed, which enable to administer lower doses of platinum compounds and therefore more tolerable. Several evidences underlined that the optimal number of first-line platinum cycles should be four for any NSCLC histology.

EXPERT COMMENTARY

In 1997, when the first ASCO guidelines underlined the role of platinum-based chemotherapy up to a maximum of eight cycles, platinum drugs became the standard of care for first-line management of advanced NSCLC. In the following decades, the advent of new drugs led to the investigation of new platinum doublets, and considering their good activity and tolerability, also non-platinum containing regimens. Moreover, the possibility of using these third-generation drugs led to increased usage of platinum compounds with lower doses rendering them more manageable. Thus, platinum doublets continued to be a standard first-line but up to a maximum of six cycles. The investigation of new approaches, such as maintenance therapy or combination with biological drugs, reinforced the role of platinum doublets also reducing the number of cycles to a maximum of four. However, the definition of the number of cycles was based on few studies or meta-analyses analysing studies with different

characteristics. The issue concerning the optimal number of cycles was clarified by and individual patient data meta-analysis which reported that prolonging treatment to six cycles is not associated with a better outcome. This is true not only in non-squamous histology, which could benefit from maintenance treatment after the completion of four cycles of platinum-based regimen, but also for squamous NSCLC, which still remains an "orphan" histotype. To date, the issue of optimal number of platinum cycles is clear and it does not need further clinical research.

FIVE-YEAR VIEW

Since the time of cisplatin discovery with anticancer potential, more than 50 years ago, around 3,000 platinum derivatives have been synthesised and tested against cancer cells, but only few compounds reached clinical trials. New platinum drugs continue to be developed, and are largely designed to be either more cytotoxic to cancer cells compared with cisplatin and/or to be able to overcome cisplatin drug resistance. In the last years, the research to discover new platinum compounds is also being focused in either prevent drug degradation or better target tumours via passive or active mechanisms [54].

The use of functional genomics is beginning to show promise in delivering platinum drugs as personalised medicine. In fact, the relationship between the excision repair cross-complementation group 1 (ERCC1) expression and either better ORR and OS after platinum-based chemotherapy has already been reported in several retrospective trials addressed to NSCLC. Three meta-analyses [55-57], supported this hypothesis. However, further prospective large randomized trials need to define this predictive role of ERCC1 expression. Other biomarkers, such as ribonucleotide reductase M1 (RRM1), breast cancer 1 (BRCA1), receptor-associated protein 80 (RAP80) and beta-globulin, with potentially predictive role are being studied [58]. About 60% of NSCLC patients have the apoptosis gene p53 mutations supposed to be related to cisplatin resistance [59]. The pharmacogenomics of these agents is being intensively studied to select patients affected by advanced NSCLC who could much benefit by platinum therapy and might impact on therapy choices in the future.

KEY ISSUES

- Cisplatin-based and carboplatin-based doublets represent the standard-of-care of the first-line therapy for non-oncogene addicted advanced NSCLC patients.
- Last generation chemotherapeutics, employed in NSCLC, are active and well tolerated leading to lower dose of platinum compounds to use with a better safety profile while maintaining a good activity and efficacy.
- Third-generation cisplatin doublets should be considered the preferable choice but, when they are not be recommended for safety reasons, carboplatin doublets are a valid option.
- Four cycles of platinum-based chemotherapy can be considered the optimal duration of first-line treatment for advanced NSCLC, both in squamous and in non-squamous cases.
- New platinum compounds and the use of functional genomics to deliver platinum drugs as personalised medicine, are being investigated.

Financial and competing interests disclosure

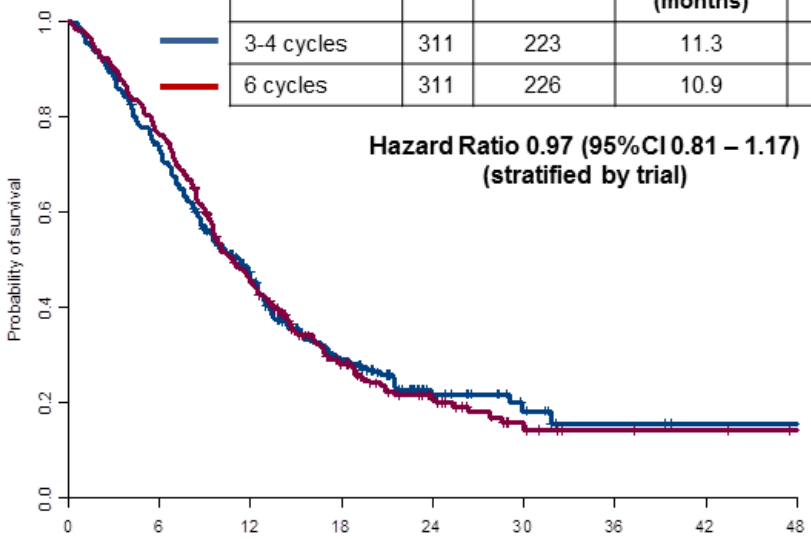
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

LEGEND TO FIGURE

Figure 1. Overall survival curves by treatment arm (6 cycles versus 3-4 cycles) in the two trials conducted with cisplatin-based chemotherapy (panel A) and in the two trials conducted with carboplatin-based chemotherapy (panel B). The curves shown in this figure are obtained from the database used for the individual patient data meta-analysis [48] and have not been published before.

Figure 1. A

	Pts.	Events	Median OS (months)	95% CI
3-4 cycles	311	223	11.3	9.5 - 12.5
6 cycles	311	226	10.9	9.5 – 12.3

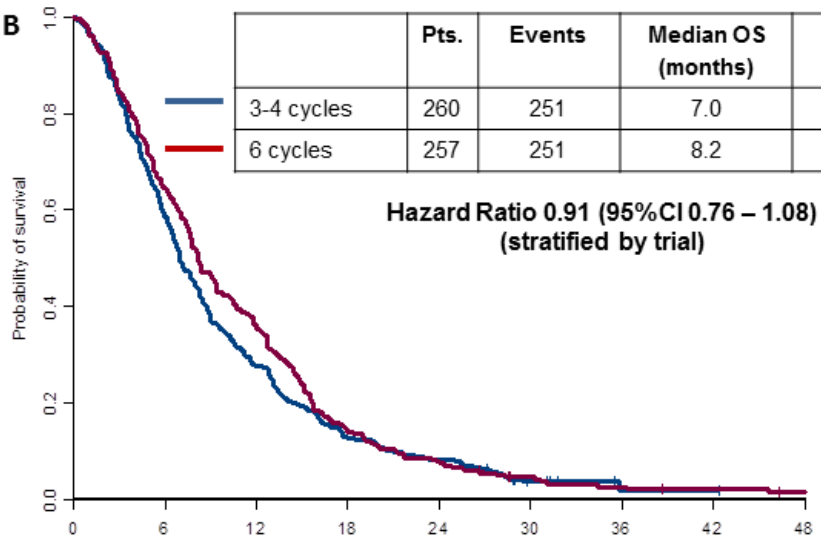


Patients at risk

3-4 cycles	311	225	130	67	21	10	3	1	1
6 cycles	311	234	129	55	27	10	4	3	1

Figure 1. B

	Pts.	Events	Median OS (months)	95% CI
3-4 cycles	260	251	7.0	6.4 – 8.2
6 cycles	257	251	8.2	7.6 – 9.4



Patients at risk

3-4 cycles	260	152	72	34	21	6	2	1	-
6 cycles	257	166	92	36	20	9	5	3	1

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Table 1. Randomized trials comparing CDDP- versus CBDCA-based regimens in advanced NSCLC

Authors	Study phase	Regimens	No.pts	ORR (%)	OR* (95% CI), p	OS (months)	1-year OS	HR* (95% CI), p
Bisset [33]	II	CDDP+TPZ vs CBDCA+TPZ	20 21	25 14	1.95 (0.42-8.95), 0.39	6.3 10.3	21 33	0.55 (0.25.1.22), 0.14
Mazzanti [38]	II	CDDP+GEM vs CBDCA+GEM	62 58	42 31	1.59 (0.76-3.34), 0.21	10.4 11.0	43 43	1.09 (0.75-1.59), 0.65
Klastersky [31]	III	CDDP+ETO vs CBDCA+ETO	114 114	24 14	1.87 (0.97-3.63), 0.063	7.1 6.9	33 22	1.14 (0.87-1.50), 0.33
Jelic [32]	III	CDDP+MMC+VDS vs CBDCA+MMC+VDS	112 104	37 35	1.09 (0.63-1.90), 0.76	7.8 7.9	21 37	0.68 (0.51-0.91), 0.01
Rosell [34]	III	CDDP+PAC vs CBDCA+PAC	309 309	27 25	1.09 (0.76-1.56), 0.64	9.7 8.2	38 32	1.22 (1.03-1.43), 0.19
Schiller [35]	III	CDDP+PAC vs CBDCA+PAC	303 299	21 16	1.40 (0.93-2.11), 0.11	7.9 8.4	7.9 8.4	0.99 (0.84-1.16), 0.85
Zatloukal [36]	III	CDDP+GEM vs CBDCA+GEM	87 89	41 29	1.70 (0.92-3.15), 0.09	8.8 8.0	31 35	0.98 (0.69-1.39), 0.9
Fossella [37]	III	CDDP+DOC vs CBDCA+DOC	408 406	32 24	1.47 (1.08-2.00), 0.01	10.9 9.1	45 37	1.16 (0.99-1.35), 0.06
Paccagnella [39]	III	CDDP+MMC+VBL vs CBDCA+MMC+VBL	74 79	42 35	1.31 (0.68-2.51), 0.41	10.0 7.2	33 25	1.18 (0.84-1.65), 0.34

*expressed as cisplatin-based versus carboplatin-based; NSCLC: non-small-cell lung cancer; CDDP: cisplatin; CBDCA: carboplatin; No.pts: number of patients; ORR: objective response rate; OR: odds ratio; CI: confidence interval; p: p-value; OS: overall survival; HR: hazard ratio; TPZ: tirapazamine; GEM: gemcitabine; ETO: etoposide; MMC: mitomicin C; VDS: vindesine; PAC: paclitaxel; DOC: docetaxel; VBL: vinblastine

Table 2. Results of two meta-analyses comparing CDDP- versus CBDCA-based regimens in advanced NSCLC				
	Hotta [40]		Ardizzoni [41]	
Characteristics	CDDP	CBDCA	CDDP	CBDCA
Data	Abstracted		Individual	
No. Trials	8		9	
Randomized phase II Trials	1		2	
Randomized phase III Trials	7		7	
No. of patients	1,478	1,470	1,489	1,479
ORR (%)	NA		30	24
OR* (95% CI), p-value	1.36 (1.15-1.61), < 0.001		1.37 (1.16-1.61), < 0.001	
Non-squamous: OR* (95% CI), p-value	NA		1.58 (1.27 – 1.97), NA	
Squamous: OR* (95% CI), p-value	NA		1.10 (0.85 – 1.43), NA	
OS (months)	NA		9.1	8.4
HR** (95% CI), p-value	1.05 (0.91-1.22), 0.51		1.07 (0.99-1.15), 0.1	
Non-squamous: HR** (95% CI), p-value	NA		1.12 (1.01-1.23), NA	
Squamous: HR** (95% CI), p-value	NA		0.97 (0.85-1.10), NA	
Second-generation regimens: HR** (95% CI), p-value	NA		0.94 (0.80-1.11), NA	
Third-generation regimens: HR** (95% CI), p-value	1.11 (1.01-1.22), 0.039		1.11 (1.01-1.21), NA	
G $\geq$ 3 Thrombocytopenia: OR* (95% CI)	0.58 (0.39-0.87)		0.44 (0.33-0.58)	
G $\geq$ 3 Leukopenia: OR* (95% CI)	NA		1.04 (0.88-1.23)	
G $\geq$ 3 Neutropenia: OR* (95% CI)	0.94 (0.66-1.35)		1.05 (0.89-1.25)	
G $\geq$ 3 Anemia: OR* (95% CI)	NA		0.91 (0.71-1.15)	
G $\geq$ 3 Nausea/Vomiting: OR* (95% CI)	2.51 (1.76-3.56)		2.38 (1.89-3.03)	
G $\geq$ 3 Renal Toxicity: OR* (95% CI)	2.82 (0.88-9.05)		2.70 (1.14-6.67)	
G $\geq$ 3 Neurotoxicity: OR* (95% CI)	NA		1.04 (0.81-1.33)	
No. Toxic deaths (%)	54 (3.9)	40 (2.9)	NA	

NSCLC: non-small-cell lung cancer; CDDP: cisplatin; CBDCA: carboplatin; ORR: objective response rate; OR: odds ratio; OS: overall survival; HR: hazard ratio; CI: confidence interval; G: grade; NA; not available

*expressed as cisplatin-based versus carboplatin-based. In the original publication by Ardizzoni et al [41] odds ratio of toxicity was expressed as carboplatin-based versus cisplatin-based, in this table it has been inverted for allowing comparison with the other publication by Hotta et al [40].

**expressed as carboplatin-based versus cisplatin-based.

Table 3. Randomized trials comparing six versus fewer cycles of platinum-based chemotherapy in advanced NSCLC

Authors	Regimen	No. cycles	No.pts	ORR (%)	TTP (months)	OS (months)
Smith [49]	CDDP+MMC+VBL	3 vs 6	155 153	31 32	5.0 5.0	6.0 7.0
von Plessen [50]	CBDCA+VNR	3 vs 6	150 147	NA	16*° 21*°	28* 32*
Park [51]	CDDP+PAC or DOC or GEM	4 vs 6	158 156	41.6 47.5	4.6 6.2	15.9 14.9
Barata [52]	CBDCA+GEM	4 vs 6	110 110	43.8 47.3	4.0 5.0	7.0 12.0
Tourani [53]	CDDP+VDS	4 vs 6	81	18.5	NA	5

*weeks; °progression-free survival; NSCLC: non-small-cell lung cancer; No.pts: number of patients; ORR: objective response rate; TTP: time-to-progression; OS: overall survival; CDDP: cisplatin; CBDCA: carboplatin; GEM: gemcitabine; MMC: mitomicin C; VDS: vindesine; PAC: paclitaxel; DOC: docetaxel; VNR: vinorelbine; NA: not available

Table 4. Results of the individual patient data meta-analysis comparing six versus fewer cycles of platinum-based chemotherapy in advanced NSCLC

	Rossi [48]	
Characteristics	Six cycles	Fewer cycles
No. Trials eligible	5	
No. Trials included	4	
No. of patients	571	568
ORR (%)	41.3	36.5
ORR: relative risk* (95%CI), (p-value)	1.13 (0.95-1.34), 0.16	
PFS (months)	6.1	5.3
PFS: HR* (95%CI), p-value	0.79 (0.68-0.90), 0.0007	
OS (months)	9.5	8.7
OS: HR* (95%CI), p-value	0.94 (0.83-1.07), 0.33	
G $\geq$ 3 Thrombocytopenia (%)	1.5	1.2
G $\geq$ 3 Leukopenia (%)	23.3	24.6
G $\geq$ 3 Neutropenia (%)	13.8	10.5
G $\geq$ 3 Anemia (%)	7.8	2.9
G $\geq$ 3 Nausea/Vomiting (%)	2.5	1.9
G $\geq$ 3 Renal Toxicity (%)	0.6	0.0
G $\geq$ 3 Neurotoxicity (%)	1.9	1.9

NSCLC: non-small-cell lung cancer; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; HR: hazard ratio; G: grade

*expressed as 6 cycles versus 3-4 cycles