Effectiveness of adjuvant carboplatin-based chemotherapy compared to cisplatin in non-small cell lung cancer

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Abstract

Background: Cisplatin and vinorelbine given intravenously is a well-established adjuvant chemotherapy regimen after surgery for early non-small cell lung cancer. However, few validated alternatives exist when cisplatin is not indicated or tolerated. Carboplatin is frequently used in this setting. We evaluated the 5-year overall survival, progression-free survival and toxicity in patients treated for stage IB to IIIB resected non-small cell lung cancer receiving adjuvant carboplatin-based chemotherapy compared to cisplatin in association with vinorelbine.

Methods: Single-center retrospective study of patients having received adjuvant chemotherapy between January 2004 and December 2013 at the oncology clinic at Institut Universitaire de Cardiologie et de Pneumologie de Québec (Canada). Three sub-groups, cisplatin/vinorelbine, carboplatin/vinorelbine and the substitution of cisplatin/vinorelbine for carboplatin/vinorelbine (cisplatin/vinorelbine/carboplatin/vinorelbine), were studied during treatment.

Results: One hundred twenty-seven patients were included in this study. The median PFS was not significantly different, with 50.4 months for cisplatin/vinorelbine, 57.3 months for cisplatin/vinorelbine/carboplatin/vinorelbine and not yet achieved for the carboplatin/vinorelbine group ($p = 0.80$). Overall survival also did not differ significantly between the three groups. The 5-year overall survival rates were 66% in cisplatin/vinorelbine group, 55% in carboplatin/vinorelbine group and 70% in cisplatin/vinorelbine/carboplatin/vinorelbine group ($p = 0, 95$). No differences were noted between groups concerning high-grade hematologic toxicity.

Conclusions: Although the effectiveness and hematologic toxicity are comparable between cisplat in and carboplatin in the adjuvant treatment of resected non-small cell lung cancer, the results obtained corroborate the practice used at our oncology clinic. Nevertheless, more prospective studies would be needed to confirm these results.

Introduction

Lung cancer is the second most diagnosed cancer in North America, and the leading cause of death from cancer in both men and women in Canada and in United States.[1,2] Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers.[2] All stages included, patients with NSCLC have a 5-year mean survival of 15%.[3] This poor prognosis is due to the fact that 75% of diagnosed cases are at an advanced or metastatic stage.[4,5] The National Cancer Institute of Canada Clinical Trials Group in JBR-10 trial demonstrated that treatment with cisplatin and vinorelbine is beneficial by significantly improving the 5-year survival rate by 15% in stage II NSCLC.[6] Furthermore, results from a meta-analysis, including five randomized clinical trials, demonstrated that cisplatin-based chemotherapy given after a pulmonary resection produced a beneficial effect on the overall survival (OS) and progression-free survival (PFS).[7] Based on these results, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) consider this regimen as first-line treatment for completely resected early-stage NSCLC.[8,9]

Although its effectiveness has been well established, cisplatin has a notable toxicity profile. It can induce renal, auditory and neurological toxicities that can lead to irreversible complications.[10] Furthermore, its potent emetic effect often decreases the patient's quality of life, limiting its use. Dose reductions or delayed chemotherapy cycles are often necessary to allow patient recovery from these adverse effects. Severe toxicity can lead to premature discontinuation of treatment. Older age, poor tolerance and multiple comorbidities are risk factors for adverse events. Cisplatin can therefore potentially be contraindicated in a large number of patients.[9]

Carboplatin remains the main alternative to cisplatin. Much discussion has taken place regarding the use of carboplatin instead of cisplatin when treating NSCLC. The available data, however, comes from studies in advanced stage and metastatic cancer. In a metaanalysis published in 2004, Hotta et al.[11] observed a superior response rate in favor of cisplatin compared to carboplatin without increasing survival. However, survival became significant when cisplatin was combined with recent third-generation agents such as paclitaxel, docetaxel, gemcitabine and vinorelbine. Two other meta-analyses produced similar results.[3,12] On the other hand, a 2013 Cochrane review including 5017 patients from 10 studies reviewing the effectiveness and safety of carboplatin-based chemotherapy compared to cisplatin in advanced NSCLC did not show increased survival with either molecules.[13] Carboplatin is generally well tolerated and its potential to induce nausea, renal toxicity and neurotoxicity is significantly less than with cisplatin.[14,15] However, the dose of carboplatin can be limited by hematologic toxicity.[11]

When conditions limit the administration of cisplatin, the NCCN recommends combining carboplatin and paclitaxel as an alternative adjuvant treatment in resected NSCLC.[16] This recommendation is based on a study published in 2008 (CALGB 9633) reviewing 344 patients with stage I NSCLC.[17] No survival benefits were demonstrated except for patients who had tumors greater than 4 cm in size. In light of the inconclusive results reported in this study, the absence of significant data for patients in stages II and III, and the higher incidence of neurotoxicity and alopecia associated with the carboplatin-paclitaxel regimen, it was decided at the Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ) to maintain the standard treatment with cisplatin and vinorelbine, but to switch cisplatin to carboplatin in patients who cannot tolerate treatment or have contraindications.

In order to support our practice, we led a retrospective study at our center to evaluate the efficacy and safety of this protocol in an adjuvant setting.

Materials and methods

Study design

We conducted a chart review of all patients with a diagnosis of NSCLC receiving adjuvant cisplatin and vinorelbine or carboplatin and vinorelbine chemotherapy between 1 January 2004 and 31 December 2013 and were analyzed. Patients were identified from a specific database at the oncology clinic.

Patient selection criteria

Patients with completely resected stage IB to IIIB NSCLC (by either pneumonectomy or lobectomy) prior to chemotherapy and receiving all their treatment and follow-up examinations at the IUCPQ oncology clinic were included. Patients receiving neoadjuvant chemotherapy, radiation or undergoing localized pulmonary resection were excluded.

Treatment regimen

Chemotherapy protocols consisted of cisplatin (50 mg/m^2) at days 1 and 8 in association with vinorelbine (25 mg/m^2) at days 1, 8, 15 and 22 or the administration of carboplatin (AUC 3) at days 1 and 8 and of vinorelbine (25 mg/m^2) at days 1, 8, 15 and 22. The cycles were administered every 28 days for a total of four cycles. Three sub-groups were established according to chemotherapy received: the cisplatin-vinorelbine group (CISV), the carboplatin-vinorelbine group (CBV) and finally the combination group which

included patients who started their chemotherapy with cisplatin-vinorelbine but were switched to carboplatin-vinorelbine (CISV/CBV) during treatment.

Measures

The effectiveness of chemotherapy was measured in terms of OS and PFS. The PFS was evaluated according to the time between the date of the first treatment and the date of recurrence or death, whichever came first. Evidence of progression or recurrence was determined from clinical notes made by pulmonologists during chemotherapy and thoracic surgeons during post-chemotherapy follow-up visits. Overall survival was attested using the time between the date of the first treatment and the date of death. Data were analyzed up to the last date of follow-up available but was discarded for patients lost to follow-up. Hematologic toxicity grade was determined using the toxicity scale of the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE).[18]

Statistical analysis

Descriptive statistics (proportions for categorical variables, means and standard deviations, or medians for continuous variables) were used to describe the study population. The percentage of chemotherapy received was calculated as the number of treatments received divided by the total number of protocol-based treatments. Proportions were compared between groups using Fisher's exact tests. For continuous variables, group comparisons according to the chemotherapy received were made using a one-way analysis of variance model. *A posteriori* comparisons were made using the Tukey multiple-comparison method. In addition, we constructed survival curves by considering the date of the first dose of chemotherapy and disease progression or death separately using Kaplan-Meier estimates,

and used the log-rank test for between group comparisons. We also tested the influence of each treatment regimen on the risk of recurrence or death using Cox proportional-hazards models. In all the analyses, statistical significance (*p* value) was set at the 0.05 level.

Results

Patient characteristics

A total of 127 patients were included in this study: 66 patients in the CISV group, 26 patients in the CBV group and 35 patients in the combination treatment (CISV/CBV) group. Study patient characteristics are shown in Table 1. Treatment follow-up ranged from 2.4 to 115.2 months with a median of 36 months for the three treatment groups.

Table 1. Study patient characteristics.

Patient characteristics	CISV (n = 66)	CBV (n = 26)	CISV/CBV (n = 35)	*p* Value
Age[a]	62 (41–77)	67 (52–79)	60 (26–75)	<0.0029[b]
Sex				0.14
Male	36 (54.5)	14 (53.9)	12 (34.3)	
Female	30 (45.5)	12 (46.1)	23 (65.7)	
Comorbidities				
Diabetes	6 (9.1)	2 (7.7)	5 (14.3)	0.73
Heart failure	2 (3.0)	2 (7.7)	1 (2.9)	0.50
Chronic renal failure[c]	2 (3.0)	4 (15.4)	0	0.022
CVD	10 (15.2)	7 (27.0)	6 (17.1)	0.42
COPD	22 (33.3)	10 (38.5)	7 (20.0)	0.24
Performance status (ECOG)				0.57
0	10 (18.5)	5 (22.7)	11 (32.4)	
1	41 (75.9)	15 (68.2)	21 (61.8)	
2	3 (5.6)	2 (9.1)	2 (5.0)	
Histology				0.19
Adenocarcinoma	42 (63.6)	15 (57.7)	24 (68.6)	
Squamous cell	17 (25.8)	11 (42.3)	7 (20.0)	
Large cell	0 (0)	0 (0)	1 (2.9)	
Mixed	7 (10.6)	0 (0)	3 (8.6)	
Pathology stage[d]				0.85
IB	3 (4.6)	1 (11.5)	1 (3.0)	
IIA	8 (12.2)	5 (19.2)	6 (17.7)	
IIB	29 (43.9)	11 (42.3)	13 (38.2)	
IIIA	21 (31.8)	6 (23.1)	11 (32.4)	
IIIB	5 (7.6)	1 (3.9)	3 (8.8)	
Type of resection				0.60
Lobectomy	43 (65.2)	15 (57.7)	22 (62.9)	
Pneumonectomy	19 (28.8)	7 (26.9)	10 (28.6)	
Bilobectomy	2 (3.0)	3 (11.5)	2 (5.7)	
Trisegmentectomy	0 (0)	1 (3.9)	0 (0)	
Lobectomy + trisegmentectomy	2 (3.0)	0 (0)	1 (2.9)	

CISV: cisplatin/vinorelbine; CBV: carboplatin/vinorelbine; CISV/CBV: substitution of cisplatin/vinorelbine for carboplatin/vinorelbine. Data are presented as n (%) and median.

[a]Median (minimal value-maximum value).

[b]Global *p*; *p* adjusted with Tukey-Kramer comparison test: CBV vs CISV/CBV = 0.0026; CBV vs CISV = 0.028; CISV vs CISV/CBV = non-significant.

[c]Defined as creatinine clearance below 60 ml/min.

[d]Based on the 6th edition of the TNM classification of the American Joint Commitee on Cancer.

Adherence to chemotherapy

The number of administered cycles as well as the number of chemotherapy treatments received by each group is shown in Table 2.

Table 2. Number of cycles completed and treatments administered according to chemotherapy received.

Number of cycles and treatments	CISV (n = 66)	CBV (n = 26)	CISV/CBV (n = 35)	*p* Value
Cycles completed[a]				0.14
Day 1 of cycle 1	7 (10.6%)	0 (0%)	0 (0%)	
≥1 cycle(s)	59 (89.4%)	26 (100%)	35 (100%)	
≥2 cycles	51 (77.3%)	24 (92.3%)	33 (94.3%)	
≥3 cycles	41 (62.1%)	18 (69.2%)	28 (80.0%)	
4 cycles	31 (47.0%)	10 (38.5%)	16 (45.7%)	
Number of treatments administered[b,c]				
Platinum and vinorelbine	15 (±7)	14 (±6)	18 (±5)	0.13
	62.9%	60.8%	72.9%	
Platinum	6 (±3)	6 (±2)	7 (±8)	0.28
	71.3%	73.8%	83.8%	
Vinorelbine	9 (±5)	9 (±4)	11 (±3)	0.047[d]
	58.8%	54.4%	67.5%	

Progression-free and overall survival

The 5-year PFS (Figure 1) was estimated at 46% (95% confidence interval [CI]: 33–59) for the CISV group, 60% (95% CI: 37 at 82) for the CBV group and 48% (95% CI: 25–70) for the CISV/CBV group (log-rank p = 0.80). The median PFS was estimated at 50.4 months (95% CI: 31.5-cannot be estimated NE) for the CISV group and 57.3 months (95% CI: 12.2-NE) for the CISV/CBV group. The median PFS could not be calculated for the CBV group as less than 50% of subjects had progressed at the end of the study period. Statistical analysis revealed no significant difference in PFS between CISV vs CBV

(hazard ratio, HR: 1.3 [95% IC: 0.6–2.81]), CISV vs CSV/CBV (HR: 1.02 [95% IC: 0.55–1.87]) and CBV vs CSV/CBV (HR: 0.78 [95% IC: 0.33–1.85]).

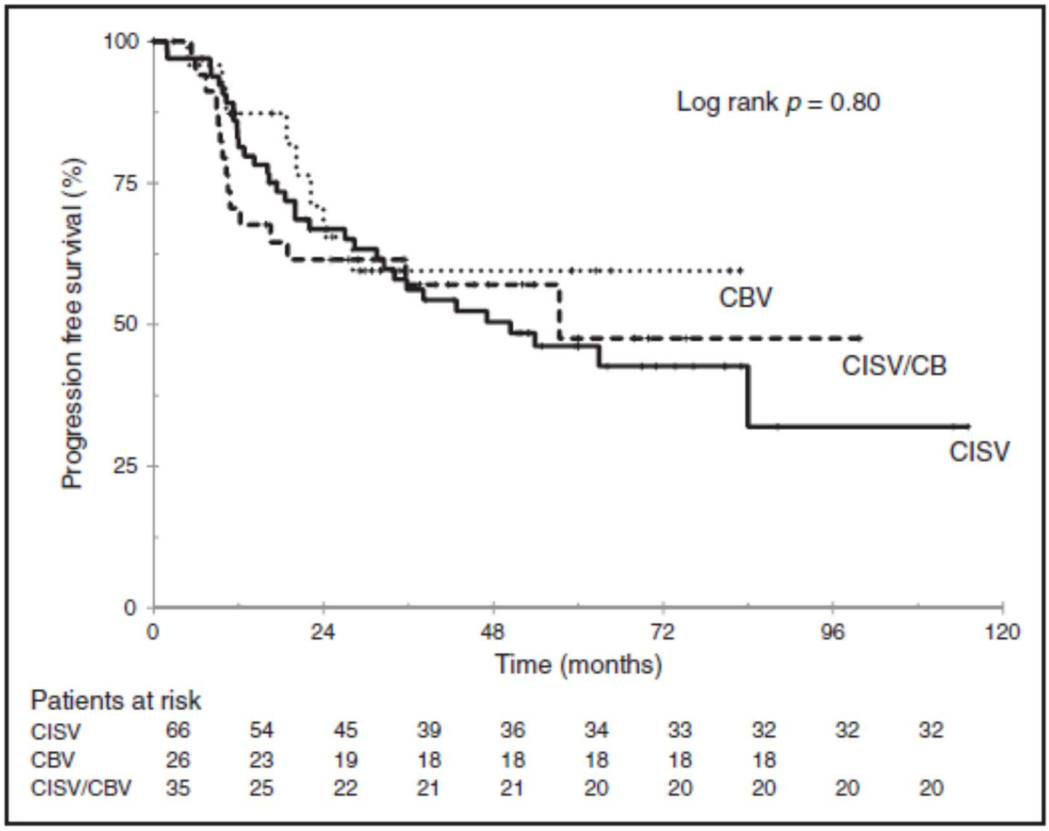

Figure 1. Progression-free survival. CISV: cisplatin/vinorelbine; CBV: carboplatin/vinorelbine; CISV/CBV: substitution of cisplatin/vinorelbine for carboplatin/vinorelbine

The 5-year OS (Figure 2) was respectively 66% (95% CI: 54–79) for the CISV group, 55% (95% CI: 27–83) for the CBV group and 70% (95% CI: 54–86) for the CISV/CBV group. There was no statistically significant difference noted in all three groups (log-rank p =0.95). Statistical analysis revealed no significant difference in OS between CISV vs CBV (HR:

0.97 [95% IC: 0.41–2.26), CISV vs CSV/CBV (HR: 1.11 [95% IC: 0.53–2.31]) and CBV vs CSV/CBV (HR: 1.14 [95% IC: 0.44–3.01]).

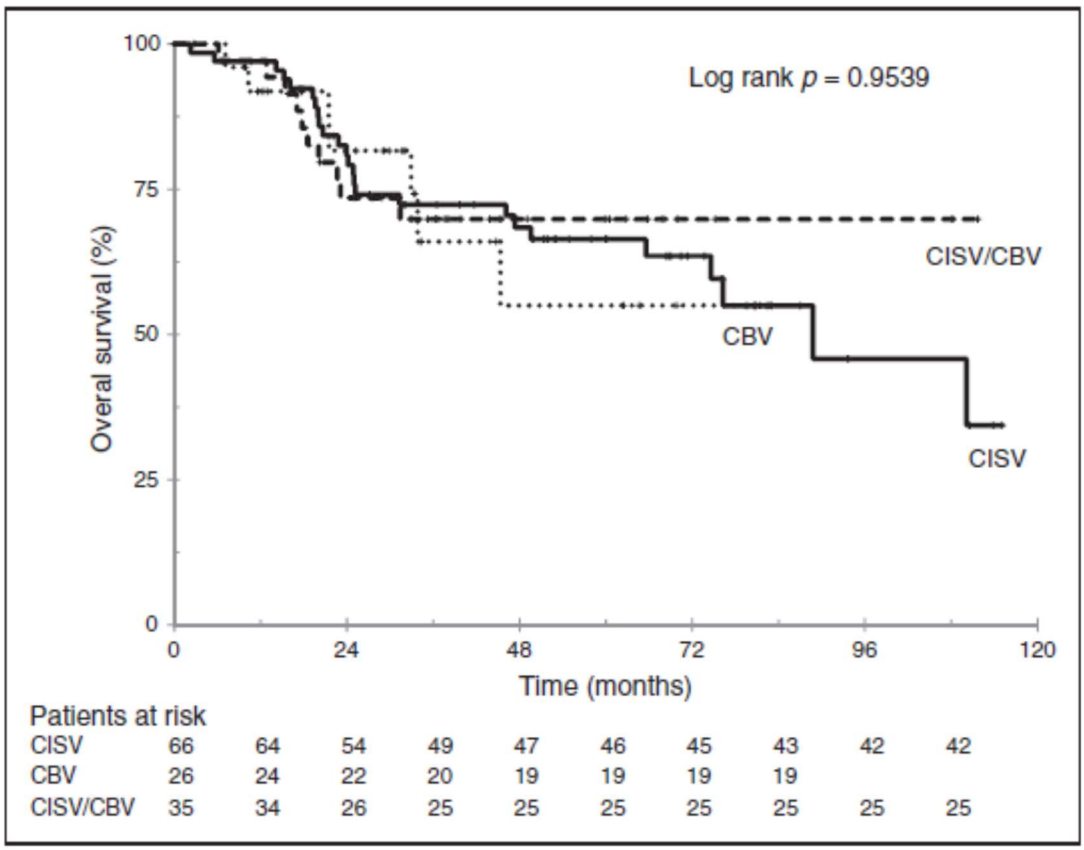

Figure 2. Overall survival. CISV: cisplatin/vinorelbine; CBV: carboplatin/vinorelbine; CISV/CBV: substitution of cisplatin/vinorelbine for carboplatin/vinorelbine.

Toxicity

Grade 3 or 4 hematologic toxicity was compared between the three treatment groups and is reported in Table 3. No significant difference was noted with regard to myelosuppression. Nephrotoxicity was the most reported adverse event (36%) requiring discontinuation of cisplatin. Furthermore, the incidence of nausea and vomiting,

ototoxicity and intolerance (fatigue, loss of appetite, performance status decline) were of 23%, 21% and 18%, respectively, and represented the main reasons for switching cisplatin to carboplatin.

Table 3. Grade 3 or 4 hematological toxicity and the use of support treatment in relation to chemotherapy received.

Hematological toxicities and support treatments	CISV (n = 66)	CBV (n = 26)	CISV/CBV (n = 35)	p Value
Neutropenia[a]				
Grade 3–4	41 (62.1)	18 (69.2)	18 (51.4)	0.057
Anemia[a]				
Grade 3–4	10 (15.2)	2 (7.7)	5 (14.3)	0.62
Thrombocytopenia[a]				
Grade 3–4	0 (0)	0 (0)	0 (0)	1.0
Febrile neutropenia	3 (4.6)	1 (3.9)	2 (5.7)	1.0
support treatments				
Filgrastim (G-CSF)	15 (22.7)	2 (7.7)	14 (40.0)	0.014[c]
Erythropoietin	4 (6.1)	0 (0)	0 (0)	0.25
Unit(s) of blood	17 (25.8)	4 (15.4)	14 (40.0)	0.10

Data are presented as n (%)
[a]The hematological toxicity severity is determined using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale.
[b]Global p; p adjusted using the Tukey-Kramer comparison test: CISV vs CBV = non-significant; CISV vs CISV/CBV = non-significant; CBV vs CISV/CBV = 0.031.
[c]Global p; p adjusted using the Tukey-Kramer comparison test: CISV vs CBV = non-significant (NS) CISV vs CISV/CBV = NS; CBV vs CISV/CBV = 0.0313
CISV: cisplatin/vinorelbine: CBV: carboplatin/vinorelbine; CISV/CBV: substitution of cisplatin/vinorelbine for carboplatin/vinorelbine.

Discussion

This study evaluated the OS, the PFS and hematologic toxicity of patients receiving adjuvant carboplatinbased chemotherapy compared to cisplatin postpulmonary resection in NSCLC at IUCPQ. To our knowledge, no other study had compared cisplatin to

carboplatin in association with vinorelbine in an adjuvant treatment setting. The 5-year OS and PFS results did not show any significant difference between the three groups. Hematologic toxicity was also similar between the treatment regimens.

The CISV population group was similar to the one in the NCIC-JBR-10 study, particularly with regard to age, histology and type of surgery performed.[6] However, a difference was noted in the distribution of pathological stages. The majority of our population consisted of stages II and IIIA in a proportion of 56% and 32%, respectively, compared to 46% in stage IB and 54% in stage II in the NCIC-JBR-10 study. Thus, on average, our patients presented a more advanced disease at the time of diagnosis, indicating a poorer prognosis. Despite this disparity, the 5-year OS obtained in our CSV group was similar to the one found in the NCIC-JBR-10 study (66% and 69%, respectively). As to hematologic toxicity, neutropenia was the most frequently noted adverse event in all three groups. Grade 3 or 4 neutropenia was documented in 62% of the CISV group compared to 73% in the NCIC-JBR-10 study. Forty-seven and 48% of patients completed the four cycles respectively. The results obtained for the cisplatin and vinorelbine group corroborated the results found in the NCICJBR-10 study, which is reassuring regarding the validity and clinical relevance of the data obtained from our study.

The group of patients who received the carboplatin-vinorelbine combination is difficult to compare with other study groups because no other studies evaluated this chemotherapy regimen in early stages of NSCLC. In fact, there is only one controlled randomized trial studying the effectiveness of adjuvant carboplatin in NSCLC combined to paclitaxel instead of vinorelbine and the results were inconclusive.[17] Strauss et al.[17] compared a carboplatin-paclitaxel regimen to observe in patients with stage IB NSCLC. Based on this

study, the NCCN acknowledged the use of this combination as an alternative treatment for NSCLC in the presence of contraindications or intolerance to cisplatin despite a lack of data for patients with resected stages II and III disease.[16] On the other hand, a retrospective study by Chang et al.[19] compared the effectiveness of carboplatin-paclitaxel therapy to the standard cisplatin and vinorelbine in 438 patients with resected stages IB to IIIA NSCLC. Their patient's baseline characteristics were similar to ours with a majority of stage II and IIIA adenocarcinomas and a mean age between 59 and 63 years. The mean PFS was estimated at 63.6 months for the carboplatin-paclitaxel group and 54.8 months for the cisplatin-vinorelbine group ($p = 0.68$). The 5-year OS rate was 73% and 71%, respectively ($p = 0.71$).

There are many other studies that evaluated the effectiveness and safety of carboplatin in combination with other chemotherapy agents such as vinorelbine.[20,21] However, it is not possible to compare the results of our study with them because, in these trials, carboplatin-vinorelbine was given for indications other than adjuvant therapy, mostly in a palliative setting including advanced stages and metastatic NSCLC. Carboplatin is generally better tolerated than cisplatin. However, it is known to induce more severe myelosuppression, which limits dosing.[14,15] In our study, no statistically significant difference was noted regarding hematologic toxicity between the treatment groups, although there was an increased percentage of patients in the CBV group with grade 3 or 4 neutropenia compared to the CISV/CBV group (69.2% vs 51.4%; $p = 0.057$). However, those who received CISV/CBV were, in proportion, prescribed filgrastim more often than those receiving CISV, which could explain this difference. Overall, 24% of patients received filgrastim. The detailed reasons for filgrastim use was not documented in the clinical notes, but we

can assume that the respect of treatment schedule may have been more relevant in the CISV/CBV group, resulting in a higher number of treatment administered. Finally, no cases of grade 3 or 4 thrombocytopenia were reported in the three treatment groups. In light of this data, the carboplatin protocol used at our center appears to be safe, considering the lack of any significant differences between groups in regard to hematologic toxicity.

The results obtained from the CISV/CBV group are difficult to interpret because of its heterogeneity in terms of the platinum received. Even if the majority of patients were switched to carboplatin early in their treatment, they received various doses of carboplatin and cisplatin, which precludes us from drawing clear conclusions in terms of effectiveness and toxicity. Nevertheless, observations are worth noting. Survival rate in the CISV/CBV group was comparable to the two other groups (CISV and CBV), which argues in favor of equivalence between cisplatin and carboplatin. Although not statistically significant, the 11% 5-year survival rate difference between CISV and CBV groups is meaningful. Patients receiving CBV from the beginning were significantly older and had more comorbidities than those in the CISV group. Ultimately, it deprived many of them from completing their four cycles of chemotherapy. Moreover, hematologic toxicity in the CISV/CBV group was lower, which lead to an increase in treatment compliance. Again, the higher use of filgrastim for these patients might explain this difference.

We acknowledge that our study has limitations, the most obvious being its small sample size. Also, treatment allocation was not randomized. Rather, the choice of cisplatin or carboplatin at the start of treatment was at the discretion of the attending physician. For example, patients who received carboplatin as firstline treatment were older or had more comorbidities and were presumably at higher risk of toxicity. However, the patient

characteristics were similar enough between the groups to limit the impact of selection bias.

Conclusion

This study is the first retrospective study comparing the effectiveness of cisplatin versus carboplatin in association with vinorelbine as adjuvant treatment for NSCLC. No significant difference was noted between the three treatment groups, but the small number of patients limited the statistical power of our results. Although we cannot confirm that carboplatin is as effective as cisplatin, the data are reassuring with regard to the practice conducted at IUCPQ. Substituting cisplatin by carboplatin in patients with side effects or a contraindication to cisplatin is a safe and effective alternative to the first-line treatment recommended by the NCCN. A larger, prospective study would be needed to confirm our results.

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