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Effectiveness and toxicity of adjuvant chemotherapy in patients with non-small cell lung cancer

Guilherme Harada[1], Maria Fernanda Batistuzzo Vicentini Neffa[1], Renata Colombo Bonadio[1], Elizabeth Zambrano Mendoza[1], Rafael Caparica[2], Letícia Leone Lauricella[1], Teresa Yae Takagaki[1], Felipe Santa Rosa Roitberg[1], Ricardo Mingarini Terra[1], Gilberto De Castro Jr[1]

1. Instituto do Cancer do Estado de Sao Paulo, Faculdade de Medicina da Universidade de Sao Paulo (SP) Brasil.
2. Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgique.

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Study carrried out at the Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: Adjuvant chemotherapy (AC) improves survival of patients with resected non-small cell lung cancer (NSCLC). However, the cisplatin-vinorelbine regimen has been associated with a significant risk of clinically relevant toxicity. We sought to evaluate the effectiveness, safety, and feasibility of AC for NSCLC patients in a real-world setting. **Methods:** This was a single-center, retrospective cohort study of patients with stage I-III NSCLC undergoing surgery with curative intent between 2009 and 2018. AC was administered at the discretion of physicians. The patients were divided into two groups: AC group and no AC (control) group. Study outcomes included overall survival (OS) and recurrence-free survival (RFS), as well as the safety profile and feasibility of the cisplatin-vinorelbine regimen in a real-world setting. **Results:** The study involved 231 patients, 80 of whom received AC. Of those, 55 patients received the cisplatin-vinorelbine regimen. Survival analyses stratified by tumor stage showed that patients with stage II NSCLC in the AC group had better RFS ($p = 0.036$) and OS ($p = 0.017$) than did those in the no AC group. Among patients with stage III NSCLC in the AC group, RFS was better ($p < 0.001$) and there was a trend toward improved OS ($p = 0.060$) in comparison with controls. Of those who received the cisplatin-vinorelbine regimen, 29% had grade 3-4 febrile neutropenia, and 9% died of toxicity. **Conclusions:** These results support the benefit of AC for NSCLC patients in a real-world setting. However, because the cisplatin-vinorelbine regimen was associated with alarming rates of toxicity, more effective and less toxic alternatives should be investigated.

Keywords: Lung neoplasms; Chemotherapy, adjuvant; Cisplatin/toxicity; Vinorelbine/toxicity.

INTRODUCTION

Lung cancer is one of the most common cancers and the leading cause of cancer-related deaths both in men and women worldwide, with an estimated 1.7 million deaths in 2018.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers.[2] Clinical outcomes and treatment strategies for NSCLC are directly related to stage at diagnosis. Unfortunately, only 25% of the patients with NSCLC have non-metastatic disease at diagnosis, and recurrence rates are often high even when patients are treated with curative intent.[3]

In order to improve patient outcomes, adjuvant cisplatin-based chemotherapy after surgical resection has been extensively studied in the last decades.[4-8] The Adjuvant Navelbine International Trialist Association (ANITA) trial[4] demonstrated that cisplatin and vinorelbine significantly improve five-year survival rates (by 8,6%; p = 0,017) in patients with stage IB-IIIA NSCLC. However, a subgroup analysis indicated that the benefit is mainly seen in patients with stage II or IIIA disease.[4]

The benefit of adjuvant chemotherapy in NSCLC was confirmed in a meta-analysis evaluating more than 4.500 patients in five clinical trials.[5] It showed that platinum-based adjuvant chemotherapy resulted in a 5.4% absolute improvement in overall survival (OS) in patients with stage II or III NSCLC (hazard ratio [HR] = 0.89; 95% CI: 0.82-0.96; p = 0.005).[5] Based on these results, platinum-based adjuvant chemotherapy has become the standard of care for patients with completely resected stage II or IIIA NSCLC, and the most commonly used regimen is a combination of cisplatin and vinorelbine.[4-8]

Although effectiveness of the cisplatin-vinorelbine regimen has been well established, the combination of cisplatin and vinorelbine is associated with clinically relevant toxicity. High rates of grade 3-4 adverse events can compromise treatment adherence, leading to dose reductions and delays, as well as to treatment discontinuation, which is known to be associated with worse outcomes.[4-8] Studies providing real-world data on

Correspondence to:
Guilherme Harada. Instituto do Câncer do Estado de São Paulo, Avenida Dr. Arnaldo, 251, CEP 01246-000, São Paulo, SP, Brasil.
Tel.: 55 11 3893-2000. E-mail: guiarada@hotmail.com
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long-term efficacy and safety of adjuvant chemotherapy in NSCLC are scarce and have heterogeneous methods and outcomes. Therefore, the primary objective of the present study was to evaluate the effectiveness and safety of adjuvant chemotherapy for NSCLC patients in a real-world setting.

METHODS

Study design and participants

In this retrospective cohort study, patients undergoing surgical treatment for localized NSCLC were consecutively evaluated and treated between June of 2009 and January of 2018 at the *Instituto do Câncer do Estado de São Paulo* (ICESP), located in the city of São Paulo, Brazil. The ICESP has a dedicated multidisciplinary thoracic oncology team responsible for evaluating and discussing the cases of patients considered candidates for surgery with curative intent.

We included patients with histologically confirmed NSCLC and TNM stage I-III NSCLC[3] undergoing surgery with curative intent. In accordance with the institutional guidelines, all patients were submitted to pre-operative staging with CT or PET/CT to exclude metastases and with mediastinoscopy or EBUS for mediastinal staging, when indicated. Exclusion criteria included metastatic disease, primary tumor not amenable to complete resection, and a concurrent diagnosis of other malignancies. Data on clinical and demographic characteristics, as well as on treatment received, toxicity, and oncologic outcomes were obtained from electronic medical records. The study was approved by the local research ethics committee (ID 1011/16).

Treatment

The thoracic surgery team defined the type of surgery required to achieve a tumor-free resection margins (lobectomy or pneumonectomy and lymph node dissection) by using an open surgery or video-assisted thoracic surgery, in accordance with the International Association for the Study of Lung Cancer recommendations.[2,3]

Adjuvant chemotherapy, radiation therapy, or both were prescribed at the discretion of the physicians involved, in accordance with institutional guidelines or by tumor board consensus. At our institution during the study period, adjuvant chemotherapy was recommended for patients with completely resected stage II-III NSCLC and was considered on a case-by-case basis in patients with stage IB NSCLC. In addition, patients must have an ECOG performance status of 0-1 and adequate hepatic, renal, and hematological function. Standard adjuvant chemotherapy as defined by institutional guidelines is cisplatin (80 mg/m^2 on day 1) and vinorelbine (30 mg/m^2 on days 1, 8, and 15) every three weeks for four cycles. Alternative platinum-based chemotherapy regimens are allowed in specific settings. Although adjuvant radiation therapy is not part of our routine protocol, it was considered on a case-by-case basis in patients with positive margins or N2 lymph node status.

Statistical analysis

Patient characteristics and treatment-related toxicities were summarized by descriptive statistics. Continuous variables were expressed as median and range, whereas categorical variables were presented as absolute numbers and proportions. Differences in continuous variables between the groups were evaluated by Student's t-test. Categorical variables were compared between groups with the use of Fisher's exact test.

The Kaplan-Meier method was used in order to estimate survival function, and curves were compared by the log-rank test. The primary outcome was OS, defined as the time from the date of surgery to the date of death from any cause or the date of the last medical visit. Recurrence-free survival (RFS) was also analyzed and defined as the time from surgery to disease recurrence or death. Patients presenting with no events of interest were censored at the last follow-up date.

Potential prognostic factors were evaluated by univariate and multivariate analysis with Cox proportional hazards regression, which provided the HR and 95% CI. Prognostic factors evaluated in the univariate analysis included age, gender, TNM stage, lymph node status, histology, and use of adjuvant chemotherapy. For the multivariate model, we included the use of adjuvant chemotherapy and factors showing $p \leq 0.10$ in the univariate analysis as long as they were not associated with each other. The chi-square test was used in order to evaluate the association between variables.

Statistical analyses were conducted with the Stata statistical software package, version 15.1 (StataCorp LP, College Station, TX, USA). The level of significance was set at 5% ($p < 0.05$).

RESULTS

Patient characteristics

The study included 231 consecutive patients who met the eligibility criteria. The median follow-up time was 24 months. Of the 231 patients, 80 patients received adjuvant chemotherapy, and 151 were followed after surgical treatment (controls). Of the 80 patients who received adjuvant chemotherapy, 55 patients (68%) received the cisplatin-vinorelbine regimen. Alternative regimens included carboplatin and paclitaxel (n = 17; 21.2%), cisplatin and gemcitabine (n = 5; 6.2%), cisplatin and paclitaxel (n = 1; 1.2%), and carboplatin and vinorelbine (n = 1; 1.2%). Among the patients who received cisplatin and vinorelbine, the median cumulative dose of cisplatin was 286 mg/m^2 (range:

72-320 mg/m^2), and that of vinorelbine was 292 mg/m^2 (range: 60-360 mg/m^2).

Patients in the adjuvant chemotherapy group were younger than those in the control group (median age: 63.0 years vs. 67.6 years; p < 0.001) and more frequently underwent pneumonectomy (15.0% vs. 7.9%; p < 0.005). The proportion of early stage disease was higher in the control group, with stage I NSCLC in 56.3% (p < 0.001) and negative lymph nodes (N0) in 67.5% (p < 0.001). Of the patients who received adjuvant chemotherapy, only 2.5% had stage I NSCLC, and 31.2% had negative lymph nodes (N0). Table 1 summarizes the characteristics of the study participants.

Effectiveness

In the univariate analysis, factors associated with shorter OS were TNM stage (stage II vs. stage I: HR = 2.57; 95% CI: 1.40-4.71; p = 0.002; and stage III vs. stage I: HR = 3.81; 95% CI: 2.06-7.07; p < 0.001) and lymph node status (N2 vs. N0: HR = 1.82; 95% CI: 1.07-3.11; p = 0.027). Adjuvant chemotherapy use and TNM stage were included in the multivariate model. Lymph node status was not included, because it is part of the TNM stage (p < 0.001).

The multivariate analysis confirmed that TNM stage was a negative prognostic factor for OS (stage II vs. stage I: HR = 3.93; 95% CI: 2.06-7.49; p < 0.001; and stage III vs. stage I: HR = 6.31; 95% CI: 3.23-12.35; p < 0.001), whereas adjuvant chemotherapy use was associated with longer OS in comparison with the control group (HR = 0.43; 95% CI: 0.25-0.72; p = 0.001). The results of univariate and multivariate Cox regression analyses are presented in Table 2.

During the study follow-up period, 97 patients (67%) had disease recurrence or died. Given the discrepancy between the study groups regarding tumor stage and the importance of this factor for oncologic outcomes, survival analyses were carried out according to tumor stage. Among stage II NSCLC patients, those who received adjuvant chemotherapy had longer RFS than did those who did not (median RFS: not reached vs. 25.5 months; HR = 0.50; 95% CI: 0.26-0.95; p = 0.036). Adjuvant chemotherapy was also associated with longer OS. The median OS was not reached in the adjuvant chemotherapy group,

Table 1. Characteristics of the patients included in the study (N = 231).[a]

Characteristic	Group		P
	Adjuvant chemotherapy (n = 80)	No adjuvant chemotherapy (n = 151)	
Age, years	63.0 [45.3-79.1]	68.3 [34.0-87.9]	< 0.001*
Sex			0.388†
Male	36 (45.0)	73 (48.3)	
Female	44 (55.0)	78 (51.7)	
Type of surgery			0.005†
Pneumonectomy	12 (15.0)	12 (7.9)	
Lobectomy	61 (76.2)	134 (88.7)	
Other	7 (8.7)	5 (3.3)	
Histology			0.747†
SCC	21 (26.2)	48 (31.8)	
Adenocarcinoma	53 (66.2)	92 (60.9)	
Other	6 (7.5)	10 (6.6)	
Not available	0 (0)	1 (0.7)	
Stage			< 0.001†
I	2 (2.5)	85 (56.3)	
II	44 (54.9)	41 (27.1)	
III	34 (42.5)	24 (15.9)	
Not available	0 (0)	1 (0.7)	
Lymph node status			< 0.001†
N0	25 (31.2)	102 (67.5)	
N1	27 (33.7)	17 (11.3)	
N2	27 (33.7)	14 (9.3)	
Not available	1 (1.2)	18 (11.9)	
ECOG-PS before chemotherapy	22 (27.5)	-	
0	48 (60.0)	-	
1	1 (1.2)		
2	9 (11.2)		
Not available			
Radiation therapy			
Yes	13 (16.2)	5 (3.3)	

SCC: squamous cell carcinoma; and PS: performance status. [a]Values expressed as median [range] or n (%). *Student's t-test. †Fisher's exact test.

Table 2. Factors associated with overall survival after surgery for resection of non-small cell lung cancer (Cox regression).

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Adjuvant chemotherapy (yes vs. no)	0.97 (0.60-1.55)	0.909	0.43 (0.25-0.72)	0.001
Age (> 60 years vs. ≤ 60 years)	1.26 (0.76-2.08)	0.367		
Sex (male vs. female)	1.44 (0.90-2.29)	0.123		
TNM stage				
I	Reference		Reference	
II	2.57 (1.40-4.71)	0.002	3.93 (2.06-7.49)	< 0.001
III	3.81 (2.06-7.07)	0.000	6.31 (3.23-12.35)	< 0.001
Lymph node status				
N0	Reference			
N1	0.93 (0.48-1.82)	0.854		
N2	1.82 (1.07-3.11)	0.027		
Histology (SCC vs. adenocarcinoma)	1.38 (0.84-2.27)	0.192		

HR: hazard ratio; and SCC: squamous cell carcinoma.

whereas, in the control group, it was 33.8 months (HR = 0.42; 95% CI: 0.21-0.85; p = 0.017). Five-year OS rates were 62.1% (95% CI: 42.5-76.7%) and 12.3% (95% CI: 0.8-39.4%) in the adjuvant chemotherapy and control groups, respectively. The Kaplan-Meier curves for RFS and OS in stage II NSCLC patients are shown in Figure 1.

Patients with stage III NSCLC who received adjuvant chemotherapy had longer RFS than did those in the control group, the absolute difference in the median RFS between the two groups being approximately 30 months (median RFS: 36.5 months vs. 6.9 months; HR = 0.32; 95% CI: 0.16-0.64; p < 0.001). There was a trend toward longer OS in the adjuvant chemotherapy group in comparison with the control group (median OS: 36.5 months vs. 20.5 months; HR = 0.48; 95% CI: 0.22-1.03; p = 0.060). Five-year OS rates were 37.9% (95% CI: 17.0-58.8%) and 31.8% (95% CI: 10.8-55.4%) in the adjuvant chemotherapy and control groups, respectively. Figure 2 presents the RFS and OS curves for patients with stage III NSCLC.

Patients who received adjuvant chemotherapy with cisplatin and vinorelbine were compared with controls, and RFS and OS were found to be similar between the two (Figures S1 and S2 in the supplementary material).

Safety

Because the cisplatin and vinorelbine regimen is considered an acceptable chemotherapy regimen and because it was used by most of the patients who received adjuvant chemotherapy in the present study, the safety profile of this regimen was evaluated. Moreover, previous randomized studies and clinical experience have suggested a high toxicity rate.[4-8]

Of the patients who received adjuvant chemotherapy with cisplatin and vinorelbine, 49 (89%) experienced grade 3-4 toxicities, hospitalization being required in 27 (49%). Sixteen patients (29%) had grade 3-4 febrile neutropenia. In addition, 5 patients (9%) died of treatment toxicity (grade 5 toxicity; Table 3).

Twenty-five patients discontinued the adjuvant cisplatin and vinorelbine regimen, treatment toxicity being the main reason for treatment discontinuation (in 68%). Table 4 summarizes the safety profile of adjuvant cisplatin and vinorelbine regimen in comparison with the safety results of the pivotal ANITA trial.[4]

DISCUSSION

Our findings reinforce the survival benefit of adjuvant chemotherapy in patients with NSCLC, both in terms of OS and RFS. A meaningful OS benefit was observed in patients with stage II or III NSCLC. The benefit of adjuvant chemotherapy in NSCLC patients has already been demonstrated in various randomized phase III trials.[4,6-8] In addition, a meta-analysis evaluating 5,584 patients of five clinical trials showed a 5.4% absolute OS gain with cisplatin-based chemotherapy. Among different chemotherapy regimens, cisplatin plus vinorelbine was marginally better than other drug combinations. Furthermore, the cisplatin-vinorelbine combination was the most commonly used regimen, being the largest (41%) and most homogenous study subgroup.[5] When this regimen was separately analyzed, a significant survival benefit was found (absolute benefit, 8.9% at five years; HR = 0.80; 95% CI: 0.70-0.91; p < 0.001).[9] However, among 6,430 patients of 16 clinical trials included in another meta-analysis,[10] which evaluated the role of adjuvant cisplatin-based chemotherapy in NSCLC patients, an increased risk of non-lung cancer-related deaths was observed in those receiving chemotherapy (relative risk = 1.3, p = 0.002).

More recently, Kenmotsu et al.[11] evaluated adjuvant cisplatin-pemetrexed vs. cisplatin-vinorelbine in the NSCLC setting, and, although the superiority of the pemetrexed-containing regimen over the vinorelbine-containing regimen was not demonstrated, both regimens had similar RFS and OS, pemetrexed showing better tolerability and less toxicity. Therefore, the benefits and risks associated with cisplatin-based adjuvant chemotherapy should be taken into account. Although predictive biomarkers of OS benefits from adjuvant treatments (chemotherapy and, possibly in the future, immunotherapy and targeted therapies)

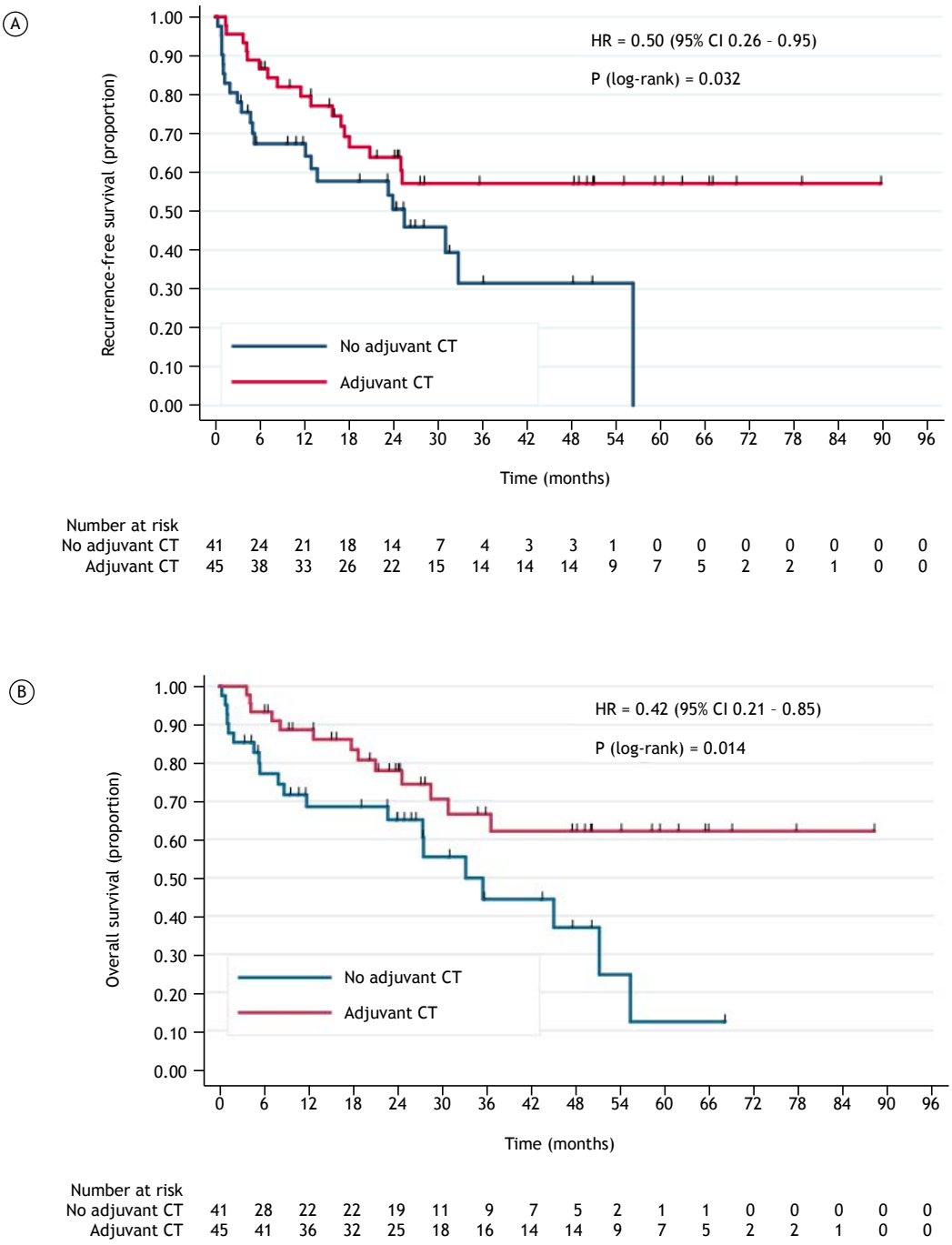

Figure 1. Recurrence-free survival (A) and overall survival (B) curves in patients with stage II non-small cell lung cancer, comparing those who received adjuvant chemotherapy with those who did not (controls). HR: hazard ratio; and CT: chemotherapy.

are of utmost importance for patient selection, they have yet to be identified and validated.

Notably, randomized phase III trials generally enroll a carefully selected population; only a small number of elderly patients are included, with few comorbidities and good performance status, and this does not represent a real-world setting. Therefore, studies addressing real-world evidence are required to evaluate the benefits and risks of the interventions used in clinical trials.[12]. Kolek et al.[13] reported better survival with adjuvant treatment in this setting, with the longest survival in the cisplatin-vinorelbine cohort. Morgensztern et al.[14] presented the results of 19,691 patients with NSCLC and showed a 4.2% treatment-related mortality rate in six months, reinforcing the importance of and need for real-world data.

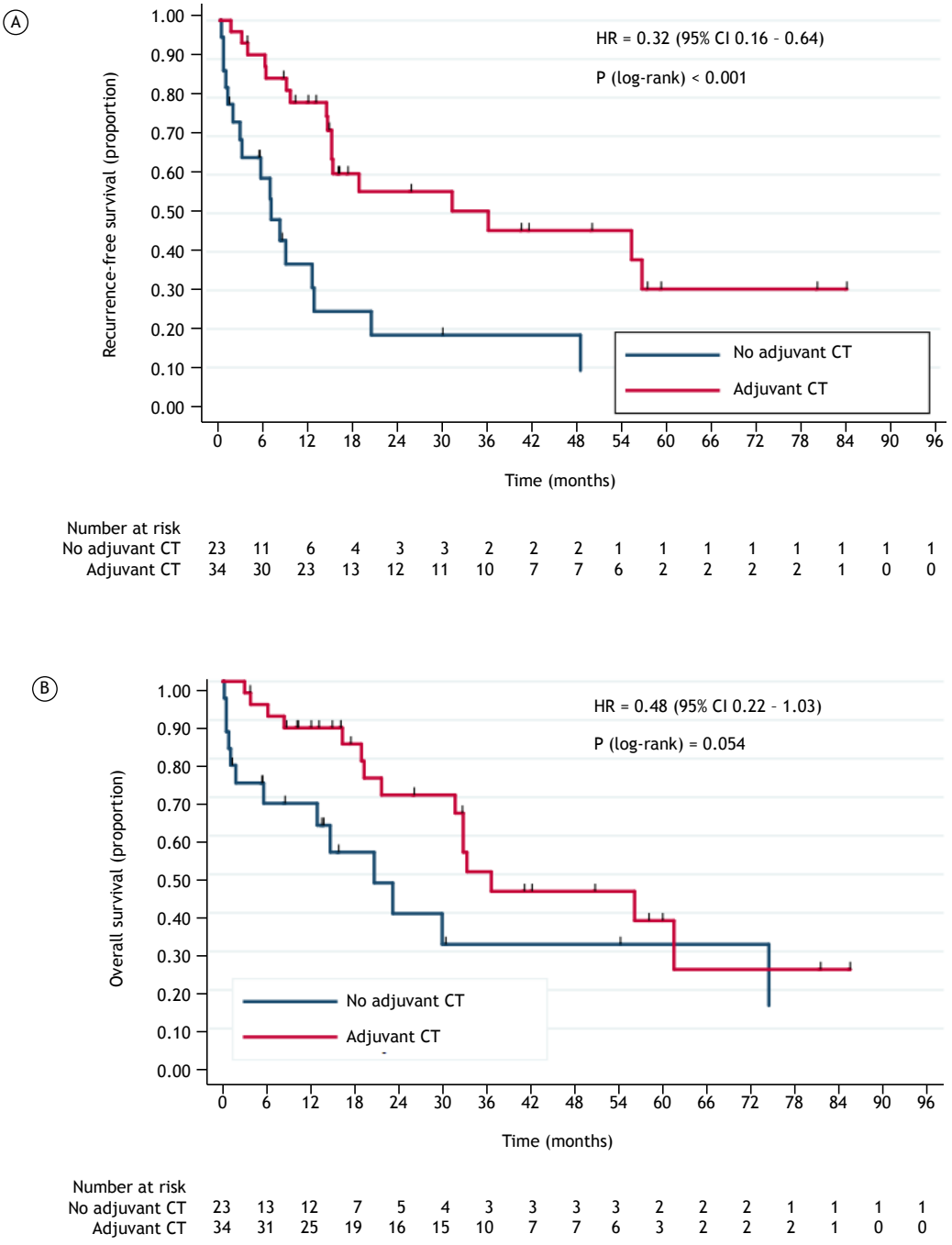

Figure 2. Recurrence-free survival (A) and overall survival (B) curves in patients with stage III non-small cell lung cancer, comparing those who received adjuvant chemotherapy with those who did not (controls). HR: hazard ratio; and CT: chemotherapy.

Another important issue to be discussed is that, although effectiveness was similar, the incidence of toxicity and hospital admissions was consistently higher in the patients treated with the cisplatin-vinorelbine combination. The outcomes in real-world studies should be carefully analyzed. In the ANITA trial,[4] 9% of the patients presented with grade 3-4 febrile neutropenia, and 2% died of treatment-related toxicity, in contrast to a 29% incidence of febrile neutropenia and a 9% mortality rate in our study, which were excessively high for an adjuvant treatment setting. Given that the aim of adjuvant treatment is to improve OS, the difference in the mortality rate between the two studies is noteworthy and potentially exceeds the OS benefit yielded by this treatment. It is of note that 60% of our patients had an ECOG performance

Table 3. Characteristics of the patients who died of adjuvant treatment toxicity.

Patient	Sex	Age, years	ECOG-PS	Staging	Chemotherapy regimen	Toxicity
1	Male	71	1	IIIA	cisplatin + vinorelbine	FN
2	Female	61	0	IIA	cisplatin + vinorelbine	FN + AKI
3	Male	70	1	IIIA	cisplatin + vinorelbine	FN + AKI
4	Male	72	1	IIB	cisplatin + vinorelbine	FN + AKI
5	Male	63	1	IIB	cisplatin + vinorelbine	FN + AKI

PS: performance status; FN: febrile neutropenia; and AKI: acute kidney injury.

Table 4. Safety profile of adjuvant chemotherapy with cisplatin and vinorelbine in patients with non-small cell lung cancer after surgery.

Profile	Present study	ANITA trial[a]
Grade 3-4 toxicity	89%	N/A
Grade 5 toxicity	9%	2%
Grade 3-4 febrile neutropenia	29%	9%
Toxicity as reason for chemotherapy discontinuation	68%	34%
Hospitalization due to toxicity	49%	N/A

[a]Results based on Douillard et al.[4] ANITA: Adjuvant Navelbine International Trialist Association.

status of 1, whereas, in the ANITA trial, 47% had an ECOG performance status of 1,[4] a difference that could explain the higher toxicity observed in our study.

Given the retrospective nature of the present study, selection bias cannot be ruled out. Chemotherapy was prescribed at the discretion of the physicians involved, and the patients who did not receive adjuvant chemotherapy after surgery could have had a worse prognosis a priori. Nevertheless, an indirect comparison reveals that chemotherapy-treated patients show median OS similar to that seen in historical controls.[4-8] Despite the retrospective design and the small sample size, which is prone to treatment bias, our analysis has important strengths. The median cumulative doses of cisplatin and vinorelbine in our study were very similar to those in the ANITA trial.[4] Moreover, our patients were treated at a large cancer center by skilled thoracic oncologists, following standard guidelines and tumor board discussion. These high standards were maintained in patient selection, with 90% of the patients receiving chemotherapy having an ECOG performance status of 0-1. In addition, real-world evidence can validate and extend the results of randomized prospective studies to determine whether they are generalizable. Even regulatory agencies, such as the U.S. Food and Drug Administration, are progressively becoming more interested in data based on real-world evidence.[15]

In conclusion, our study shows that adjuvant chemotherapy improves both OS and RFS in patients with NSCLC in a real-world setting. However, the cisplatin-vinorelbine regimen was not only associated with alarming rates of treatment-related grade 3-4 toxicity but also with a remarkably high risk of treatment-related deaths. Our results endorse the relevance of real-world data to current daily practices and public health policies in patients with NSCLC, especially for treatment with curative intent.

AUTHOR CONTRIBUTIONS

MFVN, RCB, GH, EZM, RC, LLL, TYT, RMT, FSRR, and GCJ: study design and research. MFVN, RCB, GH, EZM, RC, LLL, TYT, RMT, FSRR, and GCJ: data analysis. MFVN, RCB, GH, FSRR, and GCJ: drafting of the manuscript. MFVN, RCB, GH, EZM, RC, LLL, TYT, RMT, FSRR, and GCJ: critical revision of the manuscript for important intellectual content and approval of the final version.

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