

Overuse and Misuse of Adjuvant Chemotherapy for Stages I and II Non-Small Cell Lung Cancer Chemotherapy: Empirical Findings from a Privately Insured Population

Hrushesky WJM^{1,2,3}, Huff DFQ^{1,2}, Shimp WS¹, Bennett CL³, Baranwal A¹, Knopf K¹, Bobolts LR¹, Armitage M¹, and Fishman M¹

¹Oncology Analytics, Inc., Plantation, Florida

²South Carolina Center of Economic Excellence for Medication Safety, South Carolina College of Pharmacy, University of South Carolina, South Carolina

³South Carolina College of Pharmacy and Arnold School of Public Health, Columbia, South Carolina and Hollings Cancer Center, Charleston, South Carolina

*Corresponding author: Hrushesky WJM, MD, FACP, Oncology Analytics, Inc. 8751 W. Broward Blvd., Suite 500, Plantation, Florida 33324, E-mail: whrushesky@oncologyanalytics.com

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Abstract

Background: Among persons with early stage non-small cell lung cancer (NSCLC) resected for cure, appropriate use of adjuvant chemotherapy is an important additional determinant of survival. Oncology quality improvement initiatives focus on reducing overuse, underuse, and misuse. Prior studies identify high rates of overuse and misuse of medical care among patients with cancer in the United States. For patients with resectable NSCLC, adjuvant chemotherapy with cisplatin, but not carboplatin, regimens is supported by phase III clinical trial data and meta-analyses. Adjuvant chemotherapy is not supported for stage I patients by either phase III clinical trial data or meta-analyses. We identified the rates of overuse of adjuvant chemotherapy for stage I, and misuse of carboplatin-based, rather than cisplatin-based, chemotherapy for stage II NSCLC patients in the United States.

Methods: We reviewed all adjuvant NSCLC stage I and II chemotherapy requests and claims submitted by oncologists to Oncology Analytics (OA) for prior authorization from April 2009 through December 2013.

Results: Overall, 24% (54 of 227) of adjuvant chemotherapy requests were for stage I NSCLC patients (overuse). 73% (165 of 227) adjuvant therapy requests for patients with NSCLC stages I and II, were for carboplatin-based regimens (misuse).

Conclusion: High misuse and overuse rates of adjuvant chemotherapy for stage I and II patients with NSCLC characterize the practice of these US oncologists. Quality improvement initiatives in this patient population are needed.

Keywords: Non-small Cell Lung Cancer; Adjuvant Chemotherapy; Cisplatin; Carboplatin; Oncologist

Abbreviations: ECOG PS - Eastern Cooperative Oncology Group Performance status; EGFR - Epidermal growth factor receptor; OS - Overall survival; NCCN - National Comprehensive Cancer Network; NSCLC - Non-small cell lung cancer

Introduction

Adjuvant chemotherapy is standard of care for cancer patients with resected early stage non-small cell lung cancer (NSCLC), based on survival benefit reported in phase III trials. These studies identified survival benefit with cisplatin- (but not carboplatin-) containing regimens in the post-surgical adjuvant setting for NSCLC Stages II and IIIA. Carboplatin-containing regimens are not supported in these studies. No evidence-based reviews or guidelines support post-surgical use of adjuvant chemotherapy for stage I NSCLC (Table 1).

In the current era, high rates of overuse and misuse of resources have been noted among privately insured patients with cancer [1-5]. Herein, we review patterns of utilization of various chemotherapy regimens administered to a cohort of patients with stages I and II NSCLC in the US markets served by Oncology Analytics (OA) over a consecutive 57-month span. We addressed two questions: 1) among a cohort of persons with stage I NSCLC, how many are over-treated with chemotherapy following the surgical resection, and 2) among persons with stage II cancer, most of whom are appropriate candidates for adjuvant chemotherapy, how many are inappropriately treated with carboplatin-, rather than cisplatin-containing regimens. We excluded persons with stage III NSCLC from this analysis because of high rates of under-staging, as many of these individuals actually have stage IV disease at diagnosis.

Methods

Literature Review

A systematic meta-analysis of adjuvant NSCLC trials reported in in 1995 [6] did not identify a survival advantage with adjuvant chemotherapy (p = 0.08); however, subset analyses suggested a “trend” toward improved survival with cisplatin-based chemotherapy for persons with stage II or III NSCLC. We performed a PubMed literature search using the following MeSH terms: “adjuvant chemotherapy” and “non-small cell lung cancer”, with a publication dates within a 01/01/1995 to 12/31/2014 time span (Figure 1). We excluded Phase I and II trials, non-human studies, non-English publications, studies on patients 18-years-old and younger, as well as those studies not using overall survival (OS) as the primary outcome measure. We found eleven cisplatin-based, two carboplatin-based, and four non-platinum-based phase III, randomized, controlled clinical trials that evaluated OS as a primary outcome for adjuvant chemotherapy in post-surgical persons with stage II or III NSCLC.

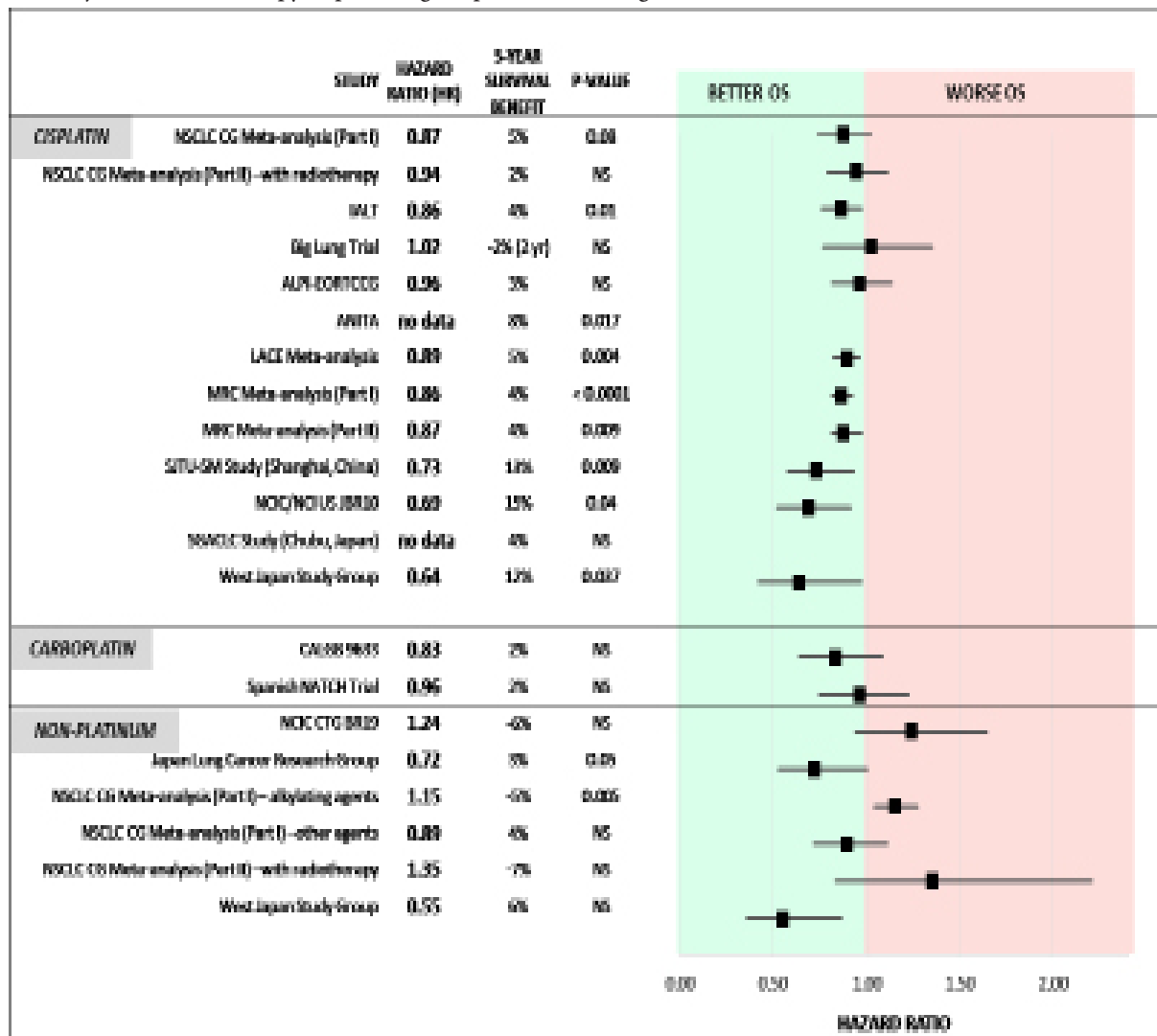


Figure 1: Effect of adjuvant chemotherapy on 5-year overall survival of NSCLC patients in randomized clinical trials and large meta-analyses performed between 1994 and 2013

Cisplatin trials

The International Adjuvant Lung Trial (IALT) randomized 1867 post-surgery patients with stages I, II and IIIA to chemotherapy versus observation. Agents combined with cisplatin were etoposide (56.5%), vinorelbine (26.8%), vinblastine (11.0%), and vindesine (5.8%). Cisplatin-based adjuvant therapy showed a beneficial effect after a median follow-up of 7.5 years (P = 0.10). At five years, patients assigned to chemotherapy had a significantly higher survival rate than those assigned to observation (44.5% vs. 40.4%; P < 0.03) [7].

Big Lung Trial (BLT) randomized 381 patients with resected NSCLC to cisplatin-based chemotherapy versus observation [8]. Although BLT showed no benefit to the use of postoperative adjuvant chemotherapy, the trial is considered underpowered to detect small clinically meaningful survival differences.

Adjuvant Lung Project Italy (ALPI) Trial randomized 1209 patients with stage I, II, or IIIA NSCLC, after complete resection, to receive mitomycin C/vindesine/cisplatin (MVP) every 3 weeks for three cycles versus observation. After a median follow-up of 64.5 months, there was no statistically significant OS difference between the groups [9]. Of concern, a large proportion of patients also received adjuvant radiation. Some discussants suggest that this might have had a confounding effect on the results of this trial [10].

Adjuvant Navelbine International Trialist Association (ANITA) Trial randomized 840 patients with resected stage IB-III A NSCLC to cisplatin/vinorelbine or observation [11]. At a median follow-up of 76 months, there was a significant OS improvement in the treatment arm, from 43.7 months to 65.7 months ($p = 0.017$). 232 (28%) patients enrolled in the study had adjuvant radiotherapy. More patients in the observation arm (144, 33%) than the chemotherapy arm (88, 22%) had adjuvant radiotherapy ($p = 0.0002$). The OS benefit at 5 years was an absolute improvement of 8.6%, which was maintained at 7 years (8.4%). In a subgroup analysis, benefit was limited to patients with stage II and IIIA disease.

The NCIC-CTG-JBR 10 Trial included 482 patients who underwent randomization to cisplatin/vinorelbine or observation. The study included stage IB and II patients with good performance status [12]. Adjuvant chemotherapy significantly improved overall survival (94 vs. 73 months; $P = 0.04$) and five-year survival (69% vs. 54%; $P = 0.03$). In an updated survival analysis, the adjuvant chemotherapy showed benefit after a median follow-up of 9.3 years (hazard ratio [HR], 0.78; 95% CI, 0.61 to 0.99; $P = .04$) [13].

The LACE Meta-analysis of all cisplatin adjuvant trials has been undertaken. Individual patient data were collected and pooled from five trials (4,584 patients). The 5-year absolute OS benefit was 5.4% with adjuvant cisplatin-based chemotherapy, with the benefit limited to stage II and IIIA [14]. There was a detrimental effect on survival in stage IA (HR = 1.40), and no effect on survival in stage IB (HR = 0.93). The lack of efficacy in stage IB is compatible with what had been seen in CALGB 9633, a trial which enrolled only stage IB patients and reached the final conclusion that adjuvant chemotherapy should not be considered in patients with stage IB.

NSCLC Collaborative Group Meta-analysis looked at survival data from published and unpublished randomized trials on chemotherapy after curative resection of NSCLC [6]. 9387 patients (7151 deaths) from 52 randomized clinical trials were included in the analysis. Results show that adjuvant chemotherapy with radical radiotherapy and supportive care resulted in a significant improvement in survival. Subgroup analysis showed that cisplatin-containing chemotherapy provided the best survival benefit compared to non-cisplatin-based regimens (OS +5%, HR 0.87, CI 0.74 - 1.0, $p = 0.08$). Trials using long term alkylating agents tended to show a detrimental effect of chemotherapy on overall survival (OS -5.0%, HR 1.15, CI 1.04 - 1.27, $p = 0.005$).

MRC Meta-analysis examined the overall survival benefit of adding adjuvant chemotherapy to surgery (34 trials, 8,447 patients), compared to surgery plus radiotherapy (13 trials, 2660 patients) [15]. Individual patient data were updated in the meta-analysis. There was significant OS benefit of adding chemotherapy after surgery, with and without radiotherapy. The study, however, found no significant variation in the OS effect between the different types of chemotherapy (platinum-based combinations vs. regimens with tegafur and uracil).

SJTU-SM Study (Shanghai, China) aimed to determine OS and disease-free survival (DFS) effect of post-operative chemotherapy with 4 cycles of cisplatin/vinorelbine in 451 Chinese patients with NSCLC at stages I, II, and IIIA [16]. Patients given chemotherapy survived significantly longer than those in the observation group (5-year OS improvement 13.0%, HR = 0.732, 95% CI: 0.579 - 0.926, $P = 0.009$). There was also a DFS improvement of 2.1% at year 4 (HR = 0.327, 95% CI: 0.214 - 0.500, $P < 0.0001$).

West Japan Study Group for Lung Cancer Surgery performed a clinical trial to determine whether postoperative mild chemotherapy, given to maintain the patient's quality of life (QOL) and immunoactivity, could also improve overall survival [17]. 323 patients with completely resected stage I to III NSCLC were randomized into three treatment groups: cisplatin 50 mg/m² plus vindesine 2 - 3 mg/kg for three courses, followed by 1-year oral tegafur (FT) plus uracil (UFT) 400 mg/kg (CVUft group, 115 patients); 1-year oral administration of UFT 400 mg/kg (Uft group, 108 patients); or surgical treatment only (control group, 100 patients). Results show a higher 5-year OS rate in the cisplatin-containing CVUft group (60.6%; $P = .037$, HR 0.64, CI 0.42 to 0.97) as well as in the Uft groups (64.1%; $P = .009$, HR 0.55, CI 0.36 to 0.86) compared with the control group (49.0%).

Study Group of Adjuvant Chemotherapy for Lung Cancer (Chubu, Japan) performed a randomized trial to investigate the benefits of adjuvant chemotherapy in NSCLC patients after curative resection [18]. 309 patients were treated with chemotherapy (cisplatin, doxorubicin, and UFT) for 6 months vs. observation. The 5-year survival rate in the chemotherapy group was 61.8%, and 58.1% in the observation group, but the difference was not significant. After adjustment for the prognostic significance of pathological lymph node metastasis (pN), however, Cox's proportional hazard model showed a significantly higher rate of 5-year survival for the chemotherapy group ($p = 0.044$).

Carboplatin trials

CALGB 9633 randomized 344 patients with completely resected stage IB NSCLC (T = 3-5 cm, N0, M0) to four cycles of carboplatin/paclitaxel or observation [19]. With a median follow-up of 34 months, initial evaluation showed improvement in 4-year OS from 59% to 71%. Unfortunately, the trial was stopped early and a longer follow-up showed no survival difference between the two groups.

ps ($P = 0.12$). In an unplanned exploratory subset analysis, improvement in survival occurred only among those patients who had tumors ≥ 4 cm but < 5 cm in diameter ($P = 0.043$). Significant survival advantage was not observed. The authors appropriately concluded that adjuvant chemotherapy should not be considered standard care in stage IB NSCLC [20].

The Spanish NATCH Trial randomized 624 patients with stage I, II and IIIA NSCLC into three arms of neo-adjuvant carboplatin/paclitaxel followed by surgery versus surgery followed by adjuvant carboplatin/paclitaxel versus surgery alone. DFS and OS rates were not significantly different with neoadjuvant or adjuvant chemotherapy compared to surgery alone [21].

Non-Platinum Trials

NCIC CTG BR19 conducted a phase III trial to determine the OS, DFS and toxicity of postoperative gefitinib 250 mg /day versus placebo in completely resected stage IB, II, or IIIA NSCLC patients [22]. 17% of the patients received chemotherapy in both, gefitinib and placebo, arms. (The study was closed prematurely following publication of the Iressa Survival Evaluation in Lung Cancer (ISEL) Phase III study and the S0023 trial, showing no OS benefit but potential harm from gefitinib). Results from the 503 randomized patients showed no difference in OS between the gefitinib chemotherapy and the observation arms, with or without previous chemotherapy, at 4.7 years median follow-up (HR 1.24; 95% CI, 0.94 to 1.64; $P = .14$), or in DFS (HR, 1.22; 95% CI, 0.93 to 1.61; $P = .15$). Serious adverse events occurred in $\leq 5\%$ of patients, with the exception of infection and pain. Discontinuation of treatment due to toxicity in occurred in 15.3% of gefitinib patients versus 3.3% of patients on placebo.

Japan Lung Cancer Research Group aimed to determine the OS benefit of uracil-tegafur compared to observation in patients with resected stage I NSCLC [23]. Results from 999 patients enrolled showed a statistically significant OS benefit in favor of the uracil-tegafur group ($P = 0.04$).

NSCLC Collaborative Group Meta-analysis As described above, adjuvant NSCLC chemotherapy trials using long term alkylating agents not only failed to show benefit, but imparted a negative effect on OS (-5.0% ; HR 1.15, CI 1.04 - 1.27, $p = 0.005$) compared to observation alone [6].

West Japan Study Group, 4th Study, examined the efficacy of UFT as post-surgical adjuvant therapy for pathologic stage I (pT1) NSCLC. Patients ($n = 332$) were randomized to observation or treatment with UFT 400 mg/m² for 1 year after surgery, after stratification by the histologic types. Overall, there was no significant 5-year and 8-year OS benefit from UFT treatment. Subset analysis of pT1 patients, however, revealed better 5- and 8-year survival rates of the UFT group compared to control (83.6% and 82.1 versus 77.9% and 57.65, $P = 0.036$). This effect was not seen in pT2 patients [24].

Utilization Data

Our aim was to determine rates of overuse of adjuvant chemotherapy regimens for stage I NSCLC and misuse of carboplatin-containing regimens for adjuvant chemotherapy for stage II NSCLC patients in the markets managed by Oncology Analytics (OA), a decision-support company. Staging information was provided by the treating oncologist requesting approval for the chemotherapy regimen. Patients with stage III NSCLC were not included as a distinction between stage IIIA and IIIB could not be determined.

We tabulated and analyzed rates of prior authorization requests for adjuvant NSCLC regimens submitted to OA from April 2009 through December 2013. These requests came from community oncology practices, with the treating oncologists providing the diagnosis, patient age, tumor stage, gender, performance status, and the planned treatment regimen. Histo-pathological NSCLC subtype information was not captured.

Results

During these 57 months, an oncologist of 227 patients with NSCLC stages I and II requested adjuvant chemotherapy following successful surgical resection of the primary tumor. The requests came from 96 oncologists in 41 community oncology practices in the United States.

A majority of adjuvant orders for stage I and II NSCLC consisted of carboplatin doublets (165/227, 73%) (Figure 2A, Table 1) Requests for stage I patients were defined as overuse (no adjuvant therapy is the evidence-based option), and misuse for the stage II patients (cisplatin-containing chemotherapy is the evidence-based option) (Figure 3). Among the carboplatin requests, 65% (108/165) were for the carboplatin/paclitaxel combination (overuse for stage I and misuse for stage II). In contrast, cisplatin-based regimens were requested only 22% of the time (50/227) (misuse for stage I and appropriate use for stage II). The remaining 5% of adjuvant chemotherapy requests (12/227) were for single -agent non-platinum adjuvant therapy (again, overuse for stage I and misuse for stage II). Overall, 24% (54/227) of requests were for stage I adjuvant chemotherapy (overuse) (Figure 2B, Table 1).

We then determined whether the decision to employ adjuvant chemotherapy, or the selection of the planned regimen, was affected by patient age, performance status, or gender. In patients with ECOG PS of 0 and 1, 27% (38/129) received a cisplatin-based regimen for stage I and 16% (5/13) received a cisplatin-based regimen for stage II (overuse for stage I/appropriate use for stage II) (Table 1). An analysis by age revealed that among NSCLC patients ≤ 70 years with stage II cancers, 38% (32/84) received a cisplatin-based regimen and among those > 70 years, 12% (18/143) received a cisplatin-based regimen (appropriate use) (chi-square: 21.3, $P < 0.001$). Gender did not influence the choice of cisplatin versus carboplatin doublets. We did not find variation in rates of overuse and misuse of chemotherapy agents requested over time during the 57 months of observation.

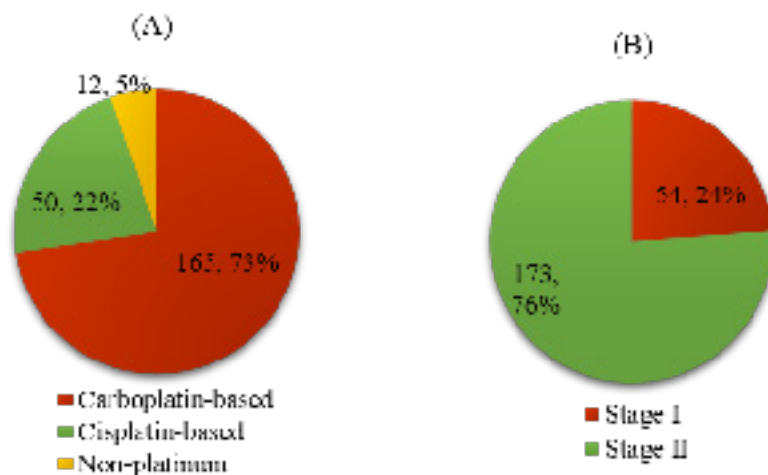


Figure 2: Breakdown of adjuvant chemotherapy authorization requests by chemotherapy regimen (A) and disease stage (B) from 41 community practices in United States

PATIENT CHARACTERISTICS		CHEMOTHERAPY (n, %)						CHI-SQUARE (P-VALUE)
		CARBOPLATIN-BASED		CISPLATIN-BASED		NON-PLATINUM		
Over all		165	73%	50	22%	12	5%	-
Gender (n = 227)	Female	84	68%	31	25%	8	7%	0.26NS
	Male	81	78%	19	18%	4	4%	
Age (n = 227)	≤ 70y	51	61%	32	38%	1	1%	< 0.001
	> 70y	114	80%	18	12.6%	11	7.4%	
ECOG PS score (n = 178*)	0	92	66%	38	27%	9	6%	0.46NS
	1	27	84%	5	16%	0	0%	
	2	1	100%	0	0%	0	0%	
	3	4	67%	2	33%	0	0%	
Stage	I	44	25%	9	5%	1	1%	0.20NS
	II	121	70%	41	24%	11	6%	

*ECOG PS data not available for 49 requests

Table 1: Breakdown by chemotherapy type based on patient characteristics

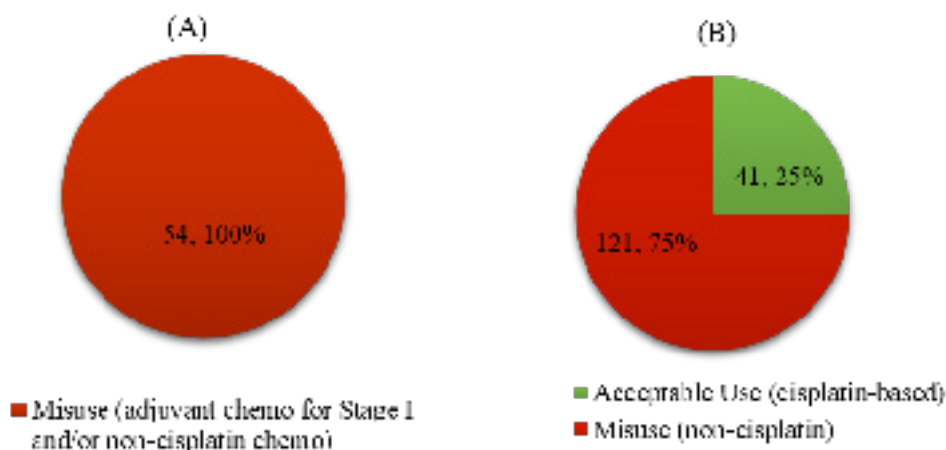


Figure 3: Breakdown of adjuvant chemotherapy misuse in NSCLC stage I (A) and stage II (B) patients from 41 Community Practices in the United States

Discussion

In our series, one in four adjuvant chemotherapy orders among privately insured patients was for persons with stage I NSCLC. The four most universally employed international guidelines (ASCO, NCCN, UK and ESMO), each recommend against adjuvant chemotherapy for patients with resected stage I NSCLC (Table 2). While a recent exploratory analysis of a subgroup of stage IB patients (T ≥ 4 cm) has identified potential survival benefit with adjuvant chemotherapy [15], we must await *a priori* testing of this hypothesis; *a posteriori* analysis does not support use of adjuvant chemotherapy among persons with stage I NSCLC, as these individuals already have a high likelihood of surgical cure.

Guidelines	Stage IA	STAGE IB
NCCN [25]	Adjuvant chemotherapy is not recommended.	Chemotherapy can be considered only for patients with high risk features (poorly differentiated tumors, vascular invasion, wedge resection, tumors > 4cm, visceral pleura involvement, incomplete lymph node sampling).
ASCO [26]	Adjuvant chemotherapy is not recommended.	Adjuvant cisplatin-based chemotherapy is not recommended for routine use.
ESMO [27]	Adjuvant chemotherapy is not recommended.	Adjuvant chemotherapy can be considered with primary tumor > 4cm.
NICE UK [28]	Adjuvant chemotherapy is not recommended.	Adjuvant chemotherapy can be considered with primary tumor > 4cm.

Table 2: Chemotherapy guidelines for early-stage lung cancer

Similarly, overuse of carboplatin (rather than appropriate use of cisplatin) among stage II NSCLC patients was common. It is conceivable that the National Comprehensive Cancer Network (NCCN) guidelines assigning a level 2A recommendation to carboplatin/paclitaxel (if cisplatin-based regimens are not feasible) provides justification, despite absent clinical trials or meta-analysis evidentiary support [25]. Significantly less chair time, higher patient throughput, and lower toxicities with carboplatin may account in part for this practice pattern. Finally, the widespread but variably supported belief that carboplatin and cisplatin have identical efficacy across different stages of NSCLC, as contained in non-evidentiary NCCN opinions, may figure in to the choice of carboplatin.

From the perspective of a health utilization company for privately insured persons with NSCLC, a conundrum exists for adjuvant therapy for stage II tumors. By convention and agreement, requests for carboplatin/paclitaxel adjuvant chemotherapy are not denied, as these common regimens are listed as category 2A recommendation by NCCN -- despite lack of survival advantage in the available peer-reviewed phase III trial and meta-analysis literature. *Primum non nocere* would demand that overall survival be the only reasonable endpoint from which to judge adjuvant treatment to be advantageous. If a patient with resected stage II NSCLC is unable to tolerate cisplatin-based adjuvant chemotherapy, consideration should be given to observation or enrollment in a clinical trial, rather than treatment with ineffective or unproven (but easier to administer and less toxic) carboplatin-containing regimens.

Limitations of our study include our relatively small sample size (227) of adjuvant chemotherapy orders from 96 oncologists in 41 geographically specific medical oncology practices, ranging in size from one to 150 oncologists. Also, NSCLC stage sub-classification into stage IA and IB (tumor size ≥ 4 cm), was not available to us; hence treatment analysis by subgroup was not possible. Data on patient comorbidities, which might explain the use of carboplatin-based chemotherapy, was also not available. We only received requests for authorization of chemotherapy, and the number of early-stage lung cancer patients undergoing observation after the surgery could not be assessed.

Conclusion

Over a concurrent 57-month span in the Southeastern United States, more than three-quarters of 227 consecutive requests for adjuvant NSCLC chemotherapy were for carboplatin doublets, which have not been shown to prolong survival in the adjuvant setting. A quarter of the requests for adjuvant therapy were received for patients with stage I disease, for which there is clear evidence of no benefit and likely harm. We believe action is required.

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