Original Article

Characteristics of toxicity occurrence patterns in concurrent chemoradiotherapy after induction chemotherapy for patients with locally advanced non-small cell lung cancer: a pooled analysis based on individual patient data of CALGB/Alliance trials

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Background: For patients with locally advanced non-small cell lung cancer (NSCLC), concurrent chemoradiotherapy is the foundational treatment strategy. Adding induction chemotherapy did not achieve a superior efficacy but increased the burden from toxicity. Accordingly, we retrospectively investigated the toxicity patterns through pooling individual patient data of the Cancer and Leukemia Group B (CALGB)/Alliance trials.

Methods: We included a total of 637 patients with unresectable stage III NSCLC who received induction chemotherapy with a platinum doublet and concurrent chemoradiotherapy and experienced at least one adverse event (AE) in CALGB 9130, 9431, 9534, 30105, 30106 and 39801 trials. The following toxicity occurrence patterns were evaluated: top 10 most frequent AEs, AE distribution by grade, rate of treatment discontinuation due to AEs, associations of AE occurrence with patient characteristics and treatment phase, the time to the first grade ≥3 AE occurrence and its associations with patient characteristics and treatment phase.

Results: The occurrence of AEs was the main reason accounting for treatment discontinuation (60 of 637 among all patients; 18 of 112 patients who experienced the induction phase only; 42 of 525 patients who experienced both phases). All patients experienced a total of 11,786 AEs (grade ≥3: 1,049 of 5,538 in induction phase, 1,382 of 6,248 in concurrent phase). Lymphocytes and white blood count were of top 3 grade ≥3 AEs that patients experienced the most in the either phase. Multivariable analysis found AE occurrence was associated with age ≥65 [any grade: odds ratio (OR) =1.44, 95% confidence interval (CI): 1.12–1.86] and the concurrent phase (grade ≥3: OR =1.86, 95% CI: 1.41–2.47; any grade: OR =1.47, 95% CI: 1.19–1.81). Patients in the concurrent phase were more likely and earlier to develop grade ≥3 AEs than

those in the induction phase [hazard ratio (HR) =4.37, 95% CI: 2.52–7.59].

Conclusions: The report provides a better understanding regarding the toxicity occurrence patterns in concurrent chemoradiotherapy after induction chemotherapy.

Keywords: Lung neoplasms; chemoradiotherapy; adverse effects

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Introduction

Lung cancer remains the most common cause of cancer-related deaths worldwide (1). Non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancer, and over half of lung cancer patients lose curable treatment opportunities due to a later stage at diagnosis, including locally advanced (stage III) NSCLC (2). Specifically, even though the goal of treatment for patients with stage III NSCLC is cure, most patients relapse and optimal treatment is still unclear. To improve their survival, however, several therapeutic approaches were successively proposed and evaluated. Among them, concurrent chemoradiotherapy has been the established standard treatment for decades, with the median overall survival (OS) ranging 20 to 30 months, and the 5-year survival rate of nearly 30% (3-5).

Based on the encouraging results seen with concurrent chemoradiotherapy, improved patient outcomes have been expected with additional therapy such as induction or consolidation chemotherapy. However, several trials comparing induction chemotherapy and concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone did not reveal an improvement in OS (6-15). As reported in the trials, a contributing factor to the lack of survival benefit could be treatment-related toxicity. Accordingly, we conduct this pooled analysis based on the individual patient data of the trials, investigating the characteristics of the toxicity occurrence patterns among locally advanced NSCLC patients who received induction chemotherapy followed by concurrent chemoradiotherapy. Specifically, we evaluate: top 10 most frequent adverse events (AEs), AE distribution by grade, rate of treatment discontinuation due to AEs, associations of AE occurrence with patient characteristics and treatment phase, the time to the first grade ≥3 AE occurrence and its associations with patient characteristics and treatment phase. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2006/rc).

Methods

This is a pooled analysis conducted by using the individual patient data in the randomized controlled trials of the Cancer and Leukemia Group B (CALGB, currently, the Alliance) (6-15). The inclusion criteria for trials were: (I) locally advanced NSCLC (stages IIIA, IIIB or IIIC); (II) having both treatment phases, induction chemotherapy and concurrent chemoradiotherapy clearly specified in the study protocol; (III) having an identifiable and valid time variable in the dataset for the two phases; (IV) having the record of AEs in the two treatment phases. If a trial had multiple arms but only one arm had both the induction and concurrent treatment phases, we only included the arm with both phases. Patients without any AE reported were excluded in analysis. Accordingly, we included six trials: CALGB 9130 (6,7), 9431 (8,9), 9534 (10), 30105 (11,12), 30106 (13) and 39801 (14,15) (*Table 1*). In the trials, the chemotherapy regimens included cisplatin, vinblastine, carboplatin, gemcitabine, paclitaxel and vinorelbine. All trials used an induction chemotherapy of platinum-based doublet agent chemotherapy. The dose of radiotherapy ranged from 60 to 74 Gy (6-15). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Duke University Institutional Review Board (No. Pro00046684-CR-9.1) and informed consent was taken from all individual participants.

According to the NCI Common Terminology Criteria for Adverse Events (CTCAE), all types of AEs were recorded as mild AE (grade 1), moderate AE (grade 2), severe AE (grade 3), life-threatening AE (grade 4) and death related to AE (grade 5). With the pooled trial data, this study demonstrated the AE occurrence patterns in the both induction chemotherapy and concurrent chemoradiotherapy phases. The data extracted included

Table 1 Characteristics of included CALBG/Alliance trials

Trial	Phase	Patients (enrolled)	Arm	Induction chemotherapy	Time between two phases	Concurrent chemoradiotherapy	Included in the study?
CALGB 9130 (6,7)	III	283	1	Cisplatin + vinblastine	42 days	Radiotherapy (60 Gy) + carboplatin	Yes
			2	Cisplatin + vinblastine		Radiotherapy (60 Gy)	No
CALGB 9431 (8,9)	II	187	1	Cisplatin + gemcitabine	42 days	Radiotherapy (66 Gy) + gemcitabine	Yes
			2	Cisplatin + paclitaxel		Radiotherapy (66 Gy) + paclitaxel	Yes
			3	Cisplatin + vinorelbine		Radiotherapy (66 Gy) + vinorelbine	Yes
CALGB 9534 (10)	II	41	1	Carboplatin + paclitaxel	42 days	Radiotherapy (66 Gy) + carboplatin + paclitaxel	Yes
CALGB 30105 (11,12)	II	69	1	Carboplatin + paclitaxel	42 days	Radiotherapy (74 Gy) + carboplatin + paclitaxel	Yes
			2	Carboplatin + gemcitabine		Radiotherapy (74 Gy) + gemcitabine	Yes
CALGB 30106 (13)	II	63	1	Carboplatin + paclitaxel + gefitinib	42 days	Radiotherapy (66 Gy) + gefitinib + carboplatin + paclitaxel	Yes
			2	Carboplatin + paclitaxel + gefitinib		Radiotherapy (66 Gy) + gefitinib	No
CALGB 39801 (14,15)	III	366	1	Carboplatin + paclitaxel	42 days	Radiotherapy (66 Gy) + carboplatin + paclitaxel	Yes
			2	–		Radiotherapy (66 Gy) + carboplatin + paclitaxel	No

The time between two phases was from the end of induction chemotherapy to the start of concurrent chemoradiotherapy. CALGB, the Cancer and Leukemia Group B.

the top 10 most frequent AEs as well as AE's distribution by the grade level. In addition, the study evaluated the rate of treatment discontinuation due to AEs, the association of the AE occurrence with the treatment phase as well as with patients' characteristics, including age, sex, race, insurance, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, prior history of chemotherapy, radiotherapy and surgery, histopathological type, off protocol treatment reason, and cause of death. Lastly, the study investigated the time to the occurrence of the first grade ≥3 AE, and its associations with the treatment phase as well as with patients' characteristics.

Statistical analysis

The association of patient characteristics with AEs (grade ≥3 AEs *vs.* grade <3 AEs) was examined via univariate analyses, using the Chi-square test or Fisher's exact test where appropriate for categorical variables and the Kruskal-Wallis test for continuous variables. The proportional odds model was used to evaluate the association between treatment phase (induction chemotherapy *vs.* concurrent chemoradiotherapy) and the occurrence of all grade AE as an ordinal outcome, adjusting for patient characteristics including age, sex, race, BMI, ECOG PS score, prior history of surgery and histopathological type. We used the empirical plot method to ensure that the proportional odds assumption was met for each covariate in the model (16). The generalized estimating equations (GEE) with a cumulative logit link was used to fit the model. In addition, the association of grade ≥3 AE, analyzed as a binary outcome, with treatment phase was evaluated using GEE with a logit link, controlling for the same set of patient characteristics above. Since AEs were measured repeatedly for each individual, the within-subject correlation was accounted for in the GEE models by using an appropriate working correlation matrix. The time from chemotherapy administration in the induction phase to the first grade ≥3 AE occurrence was demonstrated by using the Kaplan-Meier method in time-to-event analysis. Patients who never developed grade 3+ AE during the follow-up period were censored. The comparisons of the time to the first grade ≥3 AE between treatment phases (induction *vs.* concurrent

phases) as well as between patient characteristics (age, sex, race, BMI, ECOG PS score, prior history of surgery, histopathological type) were evaluated by using the Cox proportional hazards model. All P values were two-sided and the level of statistical significance was defined as P<0.05 without adjusting for multiple comparisons. The above statistical analyses were conducted in SAS (version 9.4; SAS Institute, Cary, NC, USA) software.

Results

A total of 637 locally advanced NSCLC patients who initially received induction chemotherapy and subsequent concurrent chemoradiotherapy were included in our study (*Table 2*). In the trials, the majority of patients were: male (range, 61.1% to 74.6%), White (range, 77.8% to 91.5%), with insurance (range, 90.9% to 97.5%), ECOG PS score of 0 or 1 (range, 86.4% to 100%), no prior chemotherapy (range, 98.8% to 100%) and surgery (range, 51.3% to 89.5%), and death due to the disease (79.2% to 92.3%). Among all patients enrolled in the trials, 32.7% had adenocarcinoma and 34.5% had squamous-cell carcinoma. The mean age ranged from 60 to 64.7 years; the mean of BMI ranged from 25.7 to 27.2. Among 601 of the 637 patients with records of treatment completed or off protocol, 177 (29.5%) discontinued protocol treatment (*Table 2*). AE was the main reason of off protocol treatment, involving 60 (10%) patients, followed by disease progression/relapse (8%), patient refusal for further treatment (2.8%), death during treatment (2.3%), treatment never started (1%), no response to therapy (0.3%), developing other disease (0.3%) and other (4.7%).

Table 3 demonstrates patient characteristics in those who only experienced induction chemotherapy (and may experience both phases but only have records for the induction phase; n=112) and those who experienced both phases (n=525), respectively. A higher percentage (67.0%) of off-protocol patients were found in the induction phase only, rather than both phases (21.4%). Due to AE, specifically, more patients who discontinued were in the induction phase only (17.0%) than both phases (8.5%).

The whole study population of 637 patients experienced a total of 11,786 AEs (*Tables 4,5*). Among the events, 2,431 (20.6%) were grade ≥3 AEs, occurring in 568 (89.2%) patients. In the induction phase, 18.9% (1,049/5,538) are grade ≥3 AEs, in 443 of 637 patients. In the concurrent phase, 22.1% (1,382/6,248) are grade ≥3 AEs, in 422 of 525 patients. Both *Tables 4,5* also present the top 10 of any grade and grade ≥3 AEs ranked by the total frequency in both phases, based on patient and event levels, respectively.

In the univariate analysis, a higher age was associated with occurring grade ≥3 AEs. No statistically significant difference was found in other patient characteristics with grade ≥3 AEs, including sex, race, insurance, BMI, ECOG PS score, prior history of chemotherapy, radiotherapy and surgery, NSCLC histopathological type, cancer histology, off protocol treatment reason, and cause of death (*Table 6*).

Table 7 demonstrates the association between treatment phase and AE occurrence from the GEE models. Compared to the induction phase, patients in the concurrent phase were more likely to develop AEs {grade ≥3: odds ratio (OR) =1.86 [95% confidence interval (CI): 1.41–2.47], P<0.001; any grade: OR =1.47 (95% CI: 1.19–1.81), P<0.001}. In addition, patient characteristics significantly associated with any grade AE included age ≥65 [OR =1.44 (95% CI: 1.12–1.86); P=0.005].

Figure 1 demonstrates the time to the occurrence of the first grade ≥3 AE. As indicated, 70.2% (443/637) had experienced the first grade ≥3 AE in the induction phase, within 42 days before the patients received concurrent chemoradiotherapy. When considering each of the two phases as an independent variable, patients in the concurrent phase were more likely and earlier to have grade ≥3 AE compared to the induction phase [hazard ratio (HR) =4.37 (95% CI: 2.52–7.59), P<0.001]. None of the other covariates were found to be statistically significant (*Table 8*).

Discussion

As shown in previous trials (6-15) and our pooled analysis based on the trial data, toxicity was the main reason accounting for off protocol treatment of induction chemotherapy and concurrent chemoradiotherapy. Accordingly, in this study we demonstrated the toxicity patterns, including the top 10 most frequent AEs, AE distribution by grade, associations of AE occurrence with patient characteristics and treatment phase, the time to the occurrence of the first grade ≥3 AE, and the comparisons of the time between treatment phases as well as between patient characteristics. Specifically, lymphocytes and white blood count were of top 3 grade ≥3 AEs that patients experienced the most in the either phase. Regardless of any grade or grade ≥3 AEs, the occurrence was associated with concurrent chemoradiation. Age ≥65 was another risk factor for any grade AE. Patients in the concurrent phase were more likely and earlier to develop grade ≥3 AEs than those

Table 2 Characteristics of patients

Characteristics	CALGB 9130 (N=151)	CALGB 9431 (N=158)	CALGB 9534 (N=36)	CALGB 30105 (N=67)	CALGB 30106 (N=59)	CALGB 39801 (N=166)	Total (N=637)
Age, years							
Mean (SD)	61.2 (9.8)	60.0 (9.6)	60.8 (8.9)	60.1 (10.0)	64.7 (9.1)	62.5 (9.1)	61.4 (9.6)
Median	63.0	61.0	60.0	60.0	66.0	63.0	62.0
Q1, Q3	55.0, 69.0	54.0, 68.0	56.5, 67.0	55.0, 68.0	59.0, 70.0	56.0, 69.0	55.0, 69.0
Range	(38.0–78.0)	(30.0–81.0)	(35.0–76.0)	(38.0–79.0)	(40.0–86.0)	(38.0–80.0)	(30.0–86.0)
Sex, n (%)							
Female	53 (35.1)	48 (30.4)	14 (38.9)	17 (25.4)	16 (27.1)	60 (36.1)	208 (32.7)
Male	98 (64.9)	110 (69.6)	22 (61.1)	50 (74.6)	43 (72.9)	106 (63.9)	429 (67.3)
Race, n (%)							
White	135 (89.4)	135 (85.4)	28 (77.8)	59 (88.1)	54 (91.5)	139 (83.7)	550 (86.3)
Non-White	16 (10.6)	23 (14.6)	8 (22.2)	8 (11.9)	5 (8.5)	27 (16.3)	87 (13.7)
Insurance							
Missing	69	5	0	1	0	4	79
No, n (%)	5 (6.1)	9 (5.9)	1 (2.8)	6 (9.1)	2 (3.4)	4 (2.5)	27 (4.8)
Yes, n (%)	77 (93.9)	144 (94.1)	35 (97.2)	60 (90.9)	57 (96.6)	158 (97.5)	531 (95.2)
Body mass index, kg/m^2							
Missing	22	5	0	14	9	4	54
Mean (SD)	25.8 (4.6)	26.6 (4.7)	25.7 (5.3)	26.9 (5.1)	27.2 (5.8)	26.7 (5.8)	26.4 (5.2)
Median	25.1	26.0	25.4	26.4	25.2	26.1	25.7
Q1, Q3	22.4, 28.1	23.5, 29.4	22.4, 27.7	23.8, 29.9	23.7, 31.1	22.6, 30.1	22.7, 29.4
Range	(18.3–42.1)	(15.8–41.1)	(16.4–46.0)	(15.0–40.2)	(17.7–45.5)	(13.8–52.6)	(13.8–52.6)
ECOG performance status score, n (%)							
0	75 (49.7)	81 (51.3)	21 (58.3)	29 (43.3)	18 (30.5)	75 (45.2)	299 (46.9)
1	76 (50.3)	75 (47.5)	14 (38.9)	38 (56.7)	33 (55.9)	91 (54.8)	327 (51.3)
2	0 (0.0)	2 (1.3)	1 (2.8)	0 (0.0)	8 (13.6)	0 (0.0)	11 (1.7)
Prior chemotherapy							
Missing	22	5	1	1	2	5	36
No, n (%)	129 (100.0)	152 (99.3)	35 (100.0)	66 (100.0)	57 (100.0)	159 (98.8)	598 (99.5)
Yes, n (%)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	3 (0.5)
Prior radiotherapy							
Missing	151	157	36	67	59	162	632
Yes, n (%)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)	5 (100.0)

Table 2 (*continued*)

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Characteristics	CALGB 9130 (N=151)	CALGB 9431 (N=158)	CALGB 9534 (N=36)	CALGB 30105 (N=67)	CALGB 30106 (N=59)	CALGB 39801 (N=166)	Total (N=637)
Prior surgery							
Missing	23	13	1	2	2	6	47
No, n (%)	69 (53.9)	76 (52.4)	22 (62.9)	55 (84.6)	51 (89.5)	82 (51.3)	355 (60.2)
Yes, n (%)	59 (46.1)	69 (47.6)	13 (37.1)	10 (15.4)	6 (10.5)	78 (48.8)	235 (39.8)
Histopathological type, n (%)							
Adenocarcinoma	43 (28.5)	57 (36.1)	15 (41.7)	24 (35.8)	20 (33.9)	49 (29.5)	208 (32.7)
Squamous-cell carcinoma	43 (28.5)	53 (33.5)	11 (30.6)	23 (34.3)	25 (42.4)	65 (39.2)	220 (34.5)
Other	65 (43.0)	48 (30.4)	10 (27.8)	20 (29.9)	14 (23.7)	52 (31.3)	209 (32.8)
Treatment completed and off protocol treatment reasons							
Missing	23	7	1	1	0	4	36
Treatment completed per protocol, n (%)	103 (80.5)	128 (84.8)	24 (68.6)	49 (74.2)	8 (13.6)	112 (69.1)	424 (70.5)
Disease progression/relapse, n (%)	12 (9.4)	8 (5.3)	4 (11.4)	0 (0.0)	15 (25.4)	9 (5.6)	48 (8.0)
No response to therapy, n (%)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Adverse event, n (%)	7 (5.5)	5 (3.3)	3 (8.6)	9 (13.6)	11 (18.6)	25 (15.4)	60 (10.0)
Death during treatment, n (%)	1 (0.8)	4 (2.6)	1 (2.9)	1 (1.5)	3 (5.1)	4 (2.5)	14 (2.3)
Patient refusal for further treatment, n (%)	2 (1.6)	4 (2.6)	1 (2.9)	0 (0.0)	5 (8.5)	5 (3.1)	17 (2.8)
Development of other disease, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.7)	0 (0.0)	2 (0.3)
Treatment never started, n (%)	1 (0.8)	2 (1.3)	2 (5.7)	1 (1.5)	0 (0.0)	0 (0.0)	6 (1.0)
Other, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	5 (7.6)	16 (27.1)	7 (4.3)	28 (4.7)
Cause of death							
Missing	51	24	10	10	6	25	126
Due to protocol treatment, n (%)	2 (2.0)	4 (3.0)	0 (0.0)	4 (7.0)	3 (5.7)	6 (4.3)	19 (3.7)
Due to this disease, n (%)	92 (92.0)	119 (88.8)	24 (92.3)	48 (84.2)	42 (79.2)	122 (86.5)	447 (87.5)
Other cause, n (%)	6 (6.0)	11 (8.2)	2 (7.7)	5 (8.8)	8 (15.1)	13 (9.2)	45 (8.8)

CALGB, the Cancer and Leukemia Group B; SD, standard deviation; ECOG, the Eastern Cooperative Oncology Group.

in the induction phase.

Regarding the combination treatment strategies based on concurrent chemoradiotherapy, toxicity has been a main concern, especially in the real-world setting (17). As shown in this study, AE was the main reason for treatment discontinuation in the strategy of induction chemotherapy and concurrent chemoradiotherapy (10% of total patients, 33.9% of all patients who discontinued the treatment). In the PACIFIC trial, which has shown superior efficacy of another combination strategy—concurrent chemoradiotherapy and consolidation durvalumab [a programmed death ligand 1 (PD-L1) inhibitor]—to concurrent chemoradiotherapy (18-21), AE was also a main reason for treatment discontinuation (following disease progression). In the trial, AE accounted for 15.4% of total patients and 30.3% of all patients who discontinued durvalumab, in the group of concurrent chemoradiotherapy and consolidation durvalumab (18,22). As reported in our study, grade ≥3 AEs occurred in 89.3% of all the patients with any grade AEs. In the PACIFIC trial, the proportion was 35.4% (163/460) in the durvalumab group, numerically higher than the proportion in concurrent

Table 3 Patient demographics by treatment phase

Patient characteristics	Induction only (N=112)	Both phases (N=525)	Total (N=637)
Age, years			
Mean (SD)	61.1 (11.2)	61.5 (9.2)	61.4 (9.6)
Median	62.0	62.0	62.0
Q1, Q3	55.0, 69.0	56.0, 69.0	55.0, 69.0
Range	(30.0–86.0)	(35.0–81.0)	(30.0–86.0)
Sex, n (%)			
Female	31 (27.7)	177 (33.7)	208 (32.7)
Male	81 (72.3)	348 (66.3)	429 (67.3)
Race, n (%)			
White	96 (85.7)	454 (86.5)	550 (86.3)
Non-White	16 (14.3)	71 (13.5)	87 (13.7)
Insurance			
Missing	16	63	79
No, n (%)	8 (8.3)	19 (4.1)	27 (4.8)
Yes, n (%)	88 (91.7)	443 (95.9)	531 (95.2)
Body mass index, kg/m^2			
Missing	6	48	54
Mean (SD)	26.1 (5.4)	26.5 (5.2)	26.4 (5.2)
Median	25.1	25.8	25.7
Q1, Q3	22.4, 29.4	22.9, 29.4	22.7, 29.4
Range	(15.6–42.1)	(13.8–52.6)	(13.8–52.6)
ECOG performance status score, n (%)			
0	48 (42.9)	251 (47.8)	299 (46.9)
1	63 (56.3)	264 (50.3)	327 (51.3)
2	1 (0.9)	10 (1.9)	11 (1.7)
Prior chemotherapy			
Missing	4	32	36
No, n (%)	107 (99.1)	491 (99.6)	598 (99.5)
Yes, n (%)	1 (0.9)	2 (0.4)	3 (0.5)
Prior radiotherapy			
Missing	111	521	632
Yes, n (%)	1 (100.0)	4 (100.0)	5 (100.0)
Prior surgery			
Missing	8	39	47
No, n (%)	61 (58.7)	294 (60.5)	355 (60.2)
Yes, n (%)	43 (41.3)	192 (39.5)	235 (39.8)

Table 3 (*continued*)

Table 3 (*continued*)

Patient characteristics	Induction only (N=112)	Both phases (N=525)	Total (N=637)
Histopathological type, n (%)			
Adenocarcinoma	47 (42.0)	161 (30.7)	208 (32.7)
Squamous-cell carcinoma	37 (33.0)	183 (34.9)	220 (34.5)
Other	28 (25.0)	181 (34.5)	209 (32.8)
Treatment completed and off protocol treatment reasons			
Missing	6	30	36
Treatment completed per protocol, n (%)	35 (33.0)	389 (78.6)	424 (70.5)
Disease progression/relapse, n (%)	21 (19.8)	27 (5.5)	48 (8.0)
No response to therapy, n (%)	2 (1.9)	0	2 (0.3)
Adverse event, n (%)	18 (17.0)	42 (8.5)	60 (10.0)
Death during treatment, n (%)	10 (9.4)	4 (0.8)	14 (2.3)
Patient refusal for further treatment, n (%)	4 (3.8)	13 (2.6)	17 (2.8)
Development of other disease, n (%)	0	2 (0.4)	2 (0.3)
Treatment never started, n (%)	5 (4.7)	1 (0.2)	6 (1.0)
Other, n (%)	11 (10.4)	17 (3.4)	28 (4.7)

The patients in the induction phase (n=112) included those who only experience induction chemotherapy and those who may experience both phases of induction chemotherapy and concurrent chemoradiotherapy but have records for the induction phase only. SD, standard deviation; ECOG, the Eastern Cooperative Oncology Group.

chemoradiotherapy + placebo group (33.3%; 73/222) (18). Of note, the report of toxicity in the PACIFIC trial did not include the AEs during the concurrent treatment phase; this means that the patients would have experienced more AEs in total (18). Among the AEs in our study, most were hematologic toxicity regardless of any grade or grade ≥3; other most frequent grade ≥3 AEs were nausea, vomiting, anorexia, pain, dysphagia and esophagitis. These should be well understood by oncologists and other practitioners who manage patients in the real-world setting, reducing the risk and impact of AEs, to improve quality of life and even potentially survival.

Given the toxicity, managing treatment strategies for elderly patients with locally advanced NSCLC is a big challenge. Of note, elderly patients are the majority in lung cancer (2), but under-represented in clinical trials (23,24) and with limited treatment options due to frailty and comorbidities (25). Our previous pooled study based on trials on concurrent chemoradiotherapy has supported that patients aged ≥70 years old are more likely to discontinue the treatment due to AEs (20% *vs.* 13%; P<0.01), refuse further treatment (5.8% *vs.* 3.9%; P=0.02), and have a higher risk of grade ≥3 AEs [OR =1.38 (95% CI: 1.10–1.74)] and death during treatment (7.8% *vs.* 2.9%; P<0.01), compared to patients aged <70 years old (26). This ultimately resulted in a worse OS [HR =1.17 (95% CI: 1.07–1.29)] (26). In concurrent chemoradiotherapy with the addition of induction chemotherapy, this pooled study further supports that elderly patients are more likely to develop AEs including grade ≥3 AEs. In concurrent chemoradiotherapy and consolidation durvalumab, even though the PACIFIC trial has not provided a robust statistical analysis on AEs between age groups yet, the trial has reported that more grade ≥3 AEs were observed in patients aged ≥70 years old (grade 3/4 AEs: 41.6%; grade 5 AEs: 42.6%) compared to patients aged <70 years old (grade 3/4 AEs: 30.2%; grade 5 AEs: 25.4%) in the durvalumab group (27). Also, patients aged ≥70 years old were more likely to discontinue the treatment of durvalumab due to AEs, compared to patients aged <70 years old (21.8% *vs.* 13.6%). Most importantly, the superiority of durvalumab to placebo among the elderly patients was not noted in terms of OS [among patients aged ≥70: HR =0.78 (95% CI: 0.50–1.22); among patients aged ≥65: HR =0.77 (95% CI:

Table 4 Characteristics of adverse events (patient-level)

Characteristics	Induction		Concurrent	
	AE	Value (N=637), n (%)	AE	Value (N=525), n (%)
Grade				
	Mild AE (grade 1)	40 (6.3)	Mild AE (grade 1)	16 (3.0)
	Moderate AE (grade 2)	154 (24.2)	Moderate AE (grade 2)	87 (16.6)
	Severe AE (grade 3)	223 (35.0)	Severe AE (grade 3)	225 (42.9)
	Life-threatening or disabling AE (grade 4 & 5)	220 (34.5)	Life-threatening or disabling AE (grade 4 & 5)	197 (37.5)
Top 10 of any grade AE				
	Nausea	347 (54.5)	Hemoglobin	364 (69.3)
	Hemoglobin	320 (50.2)	Nausea	272 (51.8)
	Granulocytes/bands	267 (41.9)	White blood count	236 (45.0)
	White blood count	264 (41.4)	Platelets	225 (42.9)
	Pain	228 (35.8)	Anorexia	219 (41.7)
	Lymphocytes	224 (35.2)	Lymphocytes	201 (38.3)
	Vomiting	201 (31.6)	Fatigue (asthenia, lethargy, malaise)	192 (36.6)
	Neutrophils/granulocytes (ANC/AGC)	184 (28.9)	Esophagitis/dysphagia	191 (36.4)
	Anorexia	178 (27.9)	Leukocytes	170 (32.4)
	Alopecia	164 (25.7)	Vomiting	166 (31.6
Top 10 grade ≥3 AE				
	Granulocytes/bands	195 (44.0)	Lymphocytes	179 (42.4)
	Lymphocytes	115 (26.0)	Lymphopenia	93 (22.0)
	White blood count	113 (25.5)	White blood count	89 (21.1)
	Neutrophils/granulocytes (ANC/AGC)	105 (23.7)	Leukocytes	75 (17.8)
	Nausea	56 (12.6)	Granulocytes/bands	72 (17.1)
	Vomiting	47 (10.6)	Dysphagia-esophageal related to radiation	59 (14.0)
	Leukocytes	26 (5.9)	Neutrophils/granulocytes (ANC/AGC)	58 (13.7)
	Platelets	26 (5.9)	Esophagitis/dysphagia	57 (13.5)
	Pain	21 (4.7)	Platelets	54 (12.8)
	Anorexia	20 (4.5)	Hemoglobin	49 (11.6)
	Total number of patients with grade ≥3 AE	n=443		n=422

There were two patients who experienced grade 5 AEs (both in the induction phase, with infection), so we combined the results on grade 4 and grade 5 AEs. AE, adverse event; ANC, absolute neutrophil count; AGC, absolute granulocyte count.

Table 5 Characteristics of adverse events (event-level)

Characteristics	Induction		Concurrent	
	AE	Value (N=5,538), n (%)	AE	Value (N=6,248), n (%)
Grade				
	Mild AE (grade 1)	2,787 (50.3)	Mild AE (grade 1)	2,758 (44.1)
	Moderate AE (grade 2)	1,702 (30.7)	Moderate AE (grade 2)	2,108 (33.7)
	Severe AE (grade 3)	718 (13.0)	Severe AE (grade 3)	1,090 (17.4)
	Life-threatening or disabling AE (grade 4 & 5)	331 (6.0)	Life-threatening or disabling AE (grade 4 & 5)	292 (4.7)
Top 10 of any grade AE				
	Nausea	347 (6.3)	Hemoglobin	369 (5.9)
	Hemoglobin	320 (5.8)	Nausea	275 (4.4)
	Pain	293 (5.3)	White blood count	236 (3.8)
	Granulocytes/bands	267 (4.8)	Platelets	231 (3.7)
	White blood count	264 (4.8)	Anorexia	223 (3.6)
	Lymphocytes	224 (4.0)	Pain	207 (3.3)
	Vomiting	201 (3.6)	Fatigue (asthenia, lethargy, malaise)	206 (3.3)
	Neutrophils/granulocytes (ANC/AGC)	184 (3.3)	Lymphocytes	201 (3.2)
	Anorexia	178 (3.2)	Esophagitis/dysphagia	191 (3.1)
	Alopecia	164 (3.0)	Leukocytes (total white blood count)	187 (3.0)
Top 10 grade ≥3 AE				
	Granulocytes/bands	195 (18.6)	Lymphocytes	179 (13)
	Lymphocytes	115 (11.0)	Lymphopenia	95 (6.9)
	White blood count	113 (10.8)	White blood count	89 (6.4)
	Neutrophils/granulocytes (ANC/AGC)	105 (10.0)	Leukocytes (total white blood count)	77 (5.6)
	Nausea	56 (5.3)	Granulocytes/bands	72 (5.2)
	Vomiting	47 (4.5)	Dysphagia-esophageal related to radiation	61 (4.4)
	Leukocytes (total white blood count)	26 (2.5)	Neutrophils/granulocytes (ANC/AGC)	58 (4.2)
	Platelets	26 (2.5)	Esophagitis/dysphagia	57 (4.1)
	Pain	25 (2.4)	Platelets	54 (3.9)
	Anorexia	20 (1.9)	Anorexia	49 (3.5)
	Total of grade ≥3 AE	n=1,049		n=1,382

There were two patients who experienced grade 5 AEs (both in the induction phase, with infection), so we combined the results on grade 4 and grade 5 AEs. AE, adverse event; ANC, absolute neutrophil count; AGC, absolute granulocyte count.

Table 6 Patient characteristics by grade ≥3 adverse events

Patient characteristics	Grade ≥3 (n=568)	Grade <3 (n=69)	Total (n=637)
Age*, years			
Mean (SD)	61.7 (9.5)	58.8 (9.6)	61.4 (9.6)
Median	62.0	61.0	62.0
Q1, Q3	56.0, 69.0	52.0, 66.0	55.0, 69.0
Range	(30.0–86.0)	(38.0–75.0)	(30.0–86.0)
Sex, n (%)			
Female	191 (33.6)	17 (24.6)	208 (32.7)
Male	377 (66.4)	52 (75.4)	429 (67.3)
Race, n (%)			
White	493 (86.8)	57 (82.6)	550 (86.3)
Non-White	75 (13.2)	12 (17.4)	87 (13.7)
Insurance			
Missing	74	5	79
No, n (%)	22 (4.5)	5 (7.8)	27 (4.8)
Yes, n (%)	472 (95.5)	59 (92.2)	531 (95.2)
Body mass index, kg/m^2			
Missing	51	3	54
Mean (SD)	26.4 (5.2)	26.6 (5.0)	26.4 (5.2)
Median	25.7	25.6	25.7
Q1, Q3	22.8, 29.4	22.6, 30.2	22.7, 29.4
Range	(13.8–52.6)	(15.6–42.1)	(13.8–52.6)
ECOG performance status score, n (%)			
0	266 (46.8)	33 (47.8)	299 (46.9)
1	294 (51.8)	33 (47.8)	327 (51.3)
2	8 (1.4)	3 (4.3)	11 (1.7)
Prior chemotherapy			
Missing	35	1	36
No, n (%)	530 (99.4)	68 (100.0)	598 (99.5)
Yes, n (%)	3 (0.6)	0 (0.0)	3 (0.5)
Prior surgery			
Missing	45	2	47
No, n (%)	313 (59.8)	42 (62.7)	355 (60.2)
Yes, n (%)	210 (40.2)	25 (37.3)	235 (39.8)
Histopathological type, n (%)			
Adenocarcinoma	185 (32.6)	23 (33.3)	208 (32.7)

Table 6 (*continued*)

Table 6 (*continued*)

Patient characteristics	Grade ≥3 (n=568)	Grade <3 (n=69)	Total (n=637)
Squamous-cell carcinoma	194 (34.2)	26 (37.7)	220 (34.5)
Other	189 (33.3)	20 (29.0)	209 (32.8)
Treatment completed and off protocol treatment reasons			
Missing	35	1	36
Treatment completed per protocol, n (%)	379 (71.1)	45 (66.2)	424 (70.5)
Disease progression/relapse, n (%)	40 (7.5)	8 (11.8)	48 (8.0)
No response to therapy, n (%)	2 (0.4)	0 (0.0)	2 (0.3)
Adverse event, n (%)	57 (10.7)	3 (4.4)	60 (10.0)
Death during treatment, n (%)	12 (2.3)	2 (2.9)	14 (2.3)
Patient refusal for further treatment, n (%)	14 (2.6)	3 (4.4)	17 (2.8)
Development of other disease, n (%)	2 (0.4)	0 (0.0)	2 (0.3)
Treatment never started, n (%)	6 (1.1)	0 (0.0)	6 (1.0)
Other, n (%)	21 (3.9)	7 (10.3)	28 (4.7)
Cause of death			
Missing	111	15	126
Due to protocol treatment, n (%)	18 (3.9)	1 (1.9)	19 (3.7)
Due to this disease, n (%)	399 (87.3)	48 (88.9)	447 (87.5)
Other cause, n (%)	40 (8.8)	5 (9.3)	45 (8.8)

*, P<0.05. SD, standard deviation; ECOG, the Eastern Cooperative Oncology Group.

0.58–1.03)] and time to distant metastasis (TTDM) [among patients aged ≥70: HR =0.66 (95% CI: 0.39–1.13)] (19,27). Accordingly, careful management of the elderly patients is crucial; for that, established approaches in clinical practice and potential treatments being tested in trials have been well discussed in literatures (25,26,28). Promising strategies such as geriatric assessment-driven intervention (GAIN) for chemotherapy (29), and genomic-adjusted radiation dose (GARD) for radiotherapy (30) have been tested as effective to reduce toxicity and improve survival, respectively; monitoring based on technology and patient-reported outcomes has been found feasible to detect and treat AEs (31,32).

Another potential management strategy is to understand the timing of AE occurrence. In this study, we developed the time-to-event model based on the occurrence of the first grade ≥3 AE. As presented in the study, 69.5% of patients had experienced the first grade ≥3 AE in the induction phase, and they developed grade ≥3 AEs even more quickly during the concurrent phase rather than the induction phase. Similar examples regarding the occurrence time of AE can be found in other studies (33,34). The detailed occurrence patterns including the time to occurrence and the associations of patient characteristics with the timing and occurrence rate deserve to be specifically investigated for those common and fatal AEs (34,35). The results could allow practitioners to predict and intervene the AE as early as possible and take prophylactic steps with the goal of minimizing the complications associated with the AEs, ultimately improving patients' quality of life and even survival.

A strength of this study is using a large sample size by pooling individual patient data from clinical trials with the prospective nature. Limitations include the retrospective nature of this study. Even through the combination of induction chemotherapy and concurrent radiotherapy is not the standard of care, reporting the characteristics and the occurrence patterns of AEs is necessary, especially considering the occasional use of this strategy in the real-

Table 7 Association between patient characteristics and occurrence of adverse events

Patient characteristics	Odds ratio	95% confidence interval	P value
Grade ≥3			
Treatment phase: concurrent phase	1.86	(1.41, 2.47)	<0.001
Age ≥65, years	1.32	(0.97, 1.8)	0.078
Sex: male	1.06	(0.78, 1.44)	0.720
Race: White	1.38	(0.92, 2.09)	0.124
Body mass index, kg/m^2	0.99	(0.97, 1.02)	0.600
ECOG performance status score ≥1	1.15	(0.85, 1.56)	0.354
Prior history of surgery	1.21	(0.89, 1.63)	0.220
Histopathological type			
Adenocarcinoma	1.00	–	–
Squamous-cell carcinoma	0.95	(0.66, 1.38)	0.795
Other	1.03	(0.71, 1.51)	0.861
Any grade			
Treatment phase: concurrent phase	1.47	(1.19, 1.81)	<0.001
Age ≥65, years	1.44	(1.12, 1.86)	0.005
Sex: male	1.11	(0.85, 1.44)	0.442
Race: White	1.36	(0.96, 1.93)	0.086
Body mass index, kg/m^2	0.98	(0.96, 1)	0.051
ECOG performance status score ≥1	0.99	(0.77, 1.27)	0.950
Prior history of surgery	1.11	(0.87, 1.41)	0.421
Histopathological type			
Adenocarcinoma	1.00	–	–
Squamous-cell carcinoma	1.02	(0.75, 1.39)	0.891
Other	1.07	(0.79, 1.46)	0.662

ECOG, the Eastern Cooperative Oncology Group.

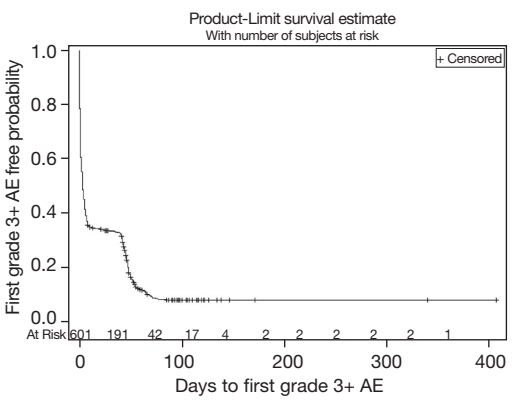

Figure 1 Time to first grade ≥3 adverse event. AE, adverse event.

world setting. Another limitation is that we did not consider treatment characteristics such as specific treatment type, dose and radiotherapy targeting strategy in this study, given that the diversity of combined strategies from included trials could lead to more complex analysis and lack of statistical power. Specifically, since the treatment strategies in trials are so different that each trial could represent a unique treatment strategy, regression results including the treatment strategies could be confounded, because it would be hard to tell whether the effect could be really due to the treatment strategies or due to the trial as a whole. However, for the treatment type, the toxicity patterns have been well

Table 8 Association between patient characteristics and time to first grade ≥3 adverse event

Patient characteristics	Hazard ratio	95% confidence interval	P value
Treatment phase: concurrent phase	4.37	(2.52, 7.59)	<0.0001
Age ≥65, years	1.2	(1, 1.45)	0.056
Sex: female	1.06	(0.91, 1.24)	0.466
Race: White	1.25	(1, 1.58)	0.051
Body mass index, kg/m^2	1	(0.98, 1.01)	0.916
ECOG performance status score ≥1	1.02	(0.84, 1.22)	0.872
Prior history of surgery	1.12	(0.93, 1.35)	0.221
Histopathological type			
Adenocarcinoma	1.00	–	–
Squamous-cell carcinoma	0.95	(0.76, 1.19)	0.667
Other	0.98	(0.81, 1.19)	0.855

ECOG, the Eastern Cooperative Oncology Group.

recorded in each of the corresponding trials (6-15); for radiotherapy dose and targeting strategy, their associations with toxicity among locally advanced NSCLC patients have been well reported in another pooled analysis involving the individual patient data used in this study (36).

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2006/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2006/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2006/coif). HP has an NIHU01 grant from the FDA, owns stock from Roche, and received personal fees from Genentech, outside the submitted work. XW holds NIH grants but not related to this work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Duke University Institutional Review Board (No. Pro00046684-CR-9.1) and informed consent was taken from all individual participants.

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