Immune checkpoint inhibitors in neoadjuvant therapy of non-small cell lung cancer: a systematic review and meta-analysis

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Background: Our objective was to explore the safety and feasibility of immune checkpoint inhibitors (ICIs) in the neoadjuvant treatment of non-small cell lung cancer (NSCLC).

Methods: Embase, PubMed and Web of Science were systematically searched from 1st January 2018 to 1st August 2021 for studies with data on the treatment-related adverse reactions (TRAE), immune-related adverse events (irAE), perioperative information, major pathological response (MPR), pathologic complete remission (pCR) and objective response rate (ORR). The QUADAS-2 tool was used to assess the quality of the studies, then the data were transformed for meta-analysis. Review Manager 5.3 (Cochrane) was used for statistical analyses with a P value of <0.05 considered significant.

Results: Thirteen studies with 358 patients were included in this meta-analysis, of which, 218 patients received ICI and chemotherapy-containing regimens and 140 patients received neoadjuvant ICIs only. The 157 (72.0%) patients who received combined neoadjuvant therapy showed a higher incidence of TRAEs, while only 37 (26.4%) patients who received neoadjuvant ICIs experienced TRAEs. Grade 3 or higher irAEs were observed in 92 (25.7%) patients, of which, 81 patients belonged to the neoadjuvant immunochemotherapy subgroup. The surgical resection rate was between 38.5–100%, with only two patients experiencing a delay in surgery. Complication rates were between 3.6–100% in the 8 studies that reported postoperative complications, with more postoperative complications [35 (18.9%)] identified in the neoadjuvant immunochemotherapy subgroup. Of which 176 patients achieved MPR, 126 received ICI and chemotherapy combined neoadjuvant therapy. Seventy-one of 95 patients who had achieved pCR had undergone ICI and chemotherapy. Compared with the neoadjuvant immunotherapy group, patients undergoing ICI and chemotherapy achieved more radiological response [118 (54.1%)] than patients undergoing ICIs [25 (17.9%)] only. The odds ratio (OR) value of the MPR/pCR/ORR rate in the neoadjuvant immunochemotherapy group was higher [OR =0.55/0.32/0.39, 95% confidence interval (CI): 0.44–0.66/0.22–0.44/0.26–0.53, P=0.0004/0.14/<0.0001] after transformation.

Discussion: Neoadjuvant immunotherapy shows lower toxicity and fewer perioperative complications. ICI combined chemotherapy can achieve more pathological relief and clinical benefits in the neoadjuvant treatment of NSCLC but is associated with increased irAE and perioperative complications. However, the small sample size limits the reliability of the research.

Keywords: Lung cancer; immune checkpoint; neoadjuvant; immune-related adverse events (irAE)

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Introduction

Lung cancer currently causes the highest morbidity and mortality worldwide. According to 2020 cancer statistics, there were 220,000 new lung cancer cases and approximately 13,500 deaths in the United States (1). Radical surgery is the mainstay of treatment for early-stage non-small cell lung cancer (NSCLC) (I–IIIA) but there is still a higher risk of long-term recurrence and distant metastasis (2). Therefore, systemic treatment plays an important role in improving the prognosis of lung cancer patients (3).

Systemic treatment of lung cancer includes adjuvant chemotherapy and neoadjuvant chemotherapy as recommended by National Comprehensive Cancer Network (NCCN) guidelines (4). In recent years, inhibitors of programmed cell death receptor-1 (PD-1) and programmed death-ligand 1 (PD-L1) have shown good efficacy in the treatment of advanced NSCLC. Studies had shown that the 5-year overall survival of patients with advanced NSCLC who received immune checkpoint inhibitor therapy is 15–16% (5,6).

Although it is not a part of the standard treatment currently, anti-PD-1/PD-L1 therapy has already been evaluated in clinical trials, due to its proven efficacy in advanced stages and its low toxicity. In 2020, Provencio *et al.* reported an 83% major pathological remission (MPR) rate when nivolumab was used for neoadjuvant treatment of resectable NSCLC (7). However, another study reported that the neoadjuvant treatment regimen that combines chemotherapy and anti-PD-1 resulted in only 27% of MPRs (8). The effect of neoadjuvant ICIs in neoadjuvant therapy of NSCLC is contradictory, therefore, a systematic review and evaluation of neoadjuvant treatments for ICIs are needed. To date, there is only one systematic review showing that ICI therapy may be a viable treatment option for NSCLC patients before surgery. However, since most of the information came from conference abstracts and lacks statistical differences, further work is still needed. Therefore, we conducted a meta-analysis to evaluate the feasibility and safety of ICIs for the neoadjuvant therapy of NSCLC.

We present the following article in accordance with the PRISMA reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1664/rc>).

Methods

Literature search

Embase, PubMed and Web of Science were systematically searched from 1st January 2018 to 1st August 2021 to include proper studies with a search query combining synonyms of lung cancer, neoadjuvant and ICIs as follows: (lung OR non-small cell lung cancer OR squamous OR adenocarcinoma) AND (cancer OR carcinoma OR tumour OR neoplasm) AND (neoadjuvant OR preoperative OR perioperative) AND (ICIs OR “immune checkpoints”). We also searched the “clinicaltrials.gov” site to identify related clinical trials. The articles cited in the papers were screened to increase the quantity of relevant literature.

Study selection

Studies fulfilling the following criteria were included in this meta-analysis: (I) studies with at least one treatment with an ICI were eligible for inclusion; (II) the target population was untreated/ICI-naïve potentially resectable NSCLC patients; (III) at least one of the efficacy results expressed as objective response rate (ORR), MPR, or pathologic complete remission (pCR); (IV) feasibility data including treatment-related adverse reaction (TRAE), immune-related adverse event (irAE) and surgery-related complications had to be provided.

Studies were excluded if one of the following existed: (I) other publications apart from original articles (such as review articles, letters, conference abstracts and editorials); (II) studies focused on other subjects (e.g., the treatment regimen is neoadjuvant immunotherapy but provides information other than safety and feasibility); (III) studies not using ICIs; (IV) studies with overlapping patient populations; (V) studies that did not provide sufficient information to evaluate the safety and feasibility of NSCLC neoadjuvant immunotherapy.

The literature search and study selection were performed by two reviewers, with a third independent

reviewer consulted to reach a consensus in the event of any disagreements.

Data extraction and quality assessment

Raw data were extracted from the selected studies by two reviewers and checked for consensus. When studies adopted different ICIs schemes but no separate data was provided, pooled results were used and when more than two types of ICIs were used, the data were included in the ICIs subgroup. Data were extracted using a standard form: (I) study characteristics: study origin (authors and years), study design (NCT number and study phase); (II) patient characteristics: study population, medium age and range, percentage of males and smoking history; (III) tumour characteristics: tumour stages and percentage of patients with $\geq$ N2 lymph node metastasis; (IV) neoadjuvant characteristics: the specific name of the ICI, neoadjuvant regimen and neoadjuvant cycles.

The quality of the selected studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (9). Quality control and consensus view were also performed by two independent reviewers.

Data synthesis and analysis

All the included studies were single-arm studies and mainly compare the rate of MPR, ORR, pCR, etc., the included data were transformed according to the following formula because they were not normally distributed.

$$P = \ln(\text{odds}) = \ln(X/(n - X)) \quad [1]$$

$$SE(P) = SE(\ln(\text{odds})) = \sqrt{1/X + 1/(n - X)} \quad [2]$$

Where X is the number of occurrences of an event, n is the total number of observed patients. The Higgins I^2 test with inconsistency index was used to assess heterogeneity as follows: 0–40% heterogeneity might not be important; 30–60% moderate heterogeneity; 50–90% substantial heterogeneity and 75–100% considerable heterogeneity (10). Review Manager 5.3 (Cochrane) was used for statistical analyses with a P value of <0.05 indicating statistical significance. The odds ratio (OR) value and 95% confidence interval (CI) were transformed to obtain the final effect index:

$$P_f = OR/(1 + OR) \quad [3]$$

$$LL = LL_{OR}/(1 + LL_{OR}) \quad [4]$$

$$UL = UL_{OR}/(1 + UL_{OR}) \quad [5]$$

Where P_f : rate of the final effect; LL: the lower limit of the 95% CI for the final effect; LL_{OR} : the lower limit of the 95% CI for the OR; UL: the higher limit of the 95% CI for the final effect; UL_{OR} : the higher limit of the 95% CI for the OR.

Results

Literature search

The systematic literature search initially retrieved 5,193 articles and after duplicates were removed, the titles and abstracts of the 102 remaining articles were screened, identifying 19 potential articles. The full-text articles were reviewed and thirteen studies involving 358 patients met the inclusion criteria (7,8,11–21) (Figure 1), with six studies excluded for the following reasons: clinical trial protocol (n=3), inadequate information (n=3).

Study characteristics

The study characteristics are shown in Table 1. There were five retrospective studies and eight prospective studies. Amongst the study population, the medium age ranged from 61 to 67 years, with 47–85% male patients and the smoking history ranged from 73% to 100%. Tumour stages ranged from Ia to IVb, and seven studies reported $\geq$ N2 lymph metastasis. Different ICIs, including anti-PD-1 drugs like nivolumab, pembrolizumab, sintilimab, toripalimab and anti-PD-L1 drugs like atezolizumab, durvalumab and avelumab were utilised in the different studies. The neoadjuvant treatment options in seven studies combined both ICIs and chemotherapy, and the neoadjuvant cycles were between 2 to 6.

Safety

Table 2 shows the perioperative adverse events reported in the studies. The number of patients ranged from 4 to 67, with 218 of the 358 patients receiving ICI and chemotherapy-containing regimens (Table 3) and the other 140 patients included in six studies receiving ICIs only. The 157 [157/218 (72.0%)] patients who received combined neoadjuvant therapy showed a higher incidence of TRAEs, while only 37 (26.4%) patients who received

Figure 1 Flowchart of study selection.

neoadjuvant ICIs only experienced TRAEs. During neoadjuvant immunotherapy, TRAEs ranged from 0 to 100%, while $\geq$ grade 3 irAEs ranged from 0 to 88.1%. Grade 3 or higher irAEs were observed in 92 of 358 (25.7%) patients (7,8,11,12,14–16,19–21). Among the 92 patients, the rate of $\geq$ grade 3 irAEs [81/218 (37.2%)] was observed in the neoadjuvant immunochemotherapy subgroup (7,8,14,20,21) than neoadjuvant ICIs group [11/140 (7.9%)] (11,12,15,16,19).

The surgical resection rate was between 38.5–100%, with only two patients experiencing a delay in surgery (16). Complication rates ranged between 16.7–100% among the eight studies that reported postoperative complications. More postoperative complications [35/185 (18.9%)] were identified in the neoadjuvant immunochemotherapy subgroup, while there was no direct evidence that this was related to the combined application of ICIs and chemotherapy.

Feasibility

All thirteen studies provided pathological efficacy evaluation data, indicating the presence of less than 10% residual viable tumour cells in the resected primary tumour. Of the 176 people who achieved an MPR, 126 received ICI and chemotherapy combined neoadjuvant therapy. The MPR rates of each study ranged from 27.3% to 82.9%. Of all the seven studies on neoadjuvant immunochemotherapy (7,8,13,14,17,20,21), the MPR rates were all higher than 60% except for Tfayli *et al.* (8). Meanwhile, compared to the neoadjuvant immunotherapy group, the OR value of the MPR rate in the neoadjuvant immunochemotherapy group was significantly higher (OR =0.55, 95% CI: 0.44–0.66, $P=0.0004$, after transformation) (Figure 2). The pCR is another useful tool for predicting the efficacy of neoadjuvant therapy, with all but one study providing pCR data (11), with the pCR ranging between 9.1–63.4%. Seventy-one of

Table 1 Characteristics of included studies

Studies	Study characteristics			Patient characteristics			Tumor characteristics		Neoadjuvant characteristics		
	Year	NCT number	Phase	Median age [range] (years)	Male, n [%]	Smoking history, n [%]	Stage	≥ N2, n [%]	ICI regimen	Neoadjuvant regimen	Neoadjuvant cycle
Bott	2019	NCT02259621	I	67 [55–84]	10 [48]	18 [86]	I–IIla	4 [20]	Nivolumab	ICI	2
Cascone	2021	NCT03158129	II	66 [±8.3]	28 [64]	36 [82]	Ia–IIla	7 [16]	Nivolumab+ ipilimumab	ICI	3
Chen T	2021	NR	NR	61 [55–67]	9 [75]	9 [75]	IIla–IIlb	NR	Nivolumab/ pembrolizumab	Chem + ICI	2/4
Chen Y	2021	NR	NR	62 [43–72]	29 [83]	NR	IIla–IIlb	19 [54]	Pembrolizumab	Chem + ICI	2
Forde	2018	NCT02259621	NR	67 [55–84]	10 [48]	18 [86]	I–IIla	NR	Nivolumab	ICI	2
Gao	2020	CHICTR-OIC-17013726	Ib	62 [47–70]	33 [83]	32 [80]	Ia–IIlb	NR	Sintilimab	ICI	2
Liu	2020	NR	NR	63 [NR]	11 [85]	11 [85]	II–III	NR	Pembrolizumab/ toripalimab	Chem + ICI	2
Lücke	2020	NR	NR	67 [55–78]	2 [50]	NR	IIlb–IVb	3 [75]	Pembrolizumab/ atezolizumab	ICI	2–6
Provencio	2020	NCT03081689	II	63 [58–70]	34 [74]	46 [100]	IIla	34 [74]	Nivolumab	Chem + ICI	3
Reuss	2020	NCT02259621	Ib/II	63 [48–78]	7 [78]	9 [100]	Ib–IIla	NR	Nivolumab + ipilimumab	ICI	3
Shu	2020	NCT02716038	II	67 [62–74]	15 [50]	NR	Ib–IIla	19 [63]	Atezolizumab	Chem + ICI	3
Tfayli	2020	NR	NR	65 [45–80]	7 [47]	11 [73]	Ib–IIla	NR	Avelumab	Chem + ICI	4
Rothschild	2021	NCT02572843	II	61 [41–74]	35 [53]	64 [95.5]	IIla	67 [100]	Durvalumab	Chem + ICI	3

NR, not related; ICI, immune checkpoint inhibitor; Chem, chemotherapy; NR, not related.

the 95 patients who achieved pCR had undergone ICI and chemotherapy. Consistent with this finding, the OR value of the pCR rate in the neoadjuvant immunochemotherapy group was higher (OR =0.32, 95% CI: 0.22–0.44, $P=0.14$, after transformation) (Figure 3). Although the P value (0.14) >0.05, there are differences in trends and the Higgins I^2 is 53.9%, which suggests that there is moderate heterogeneity between the two subgroups.

Another important piece of evidence to measure feasibility is the ORR based on the RECIST 1.1 criteria (22). Patients who achieved partial response (PR) and complete response (CR) were considered radiological responders and the ORR ranged between 9.1% and 75%. Patients undergoing ICI and chemotherapy achieved more radiological response [118/218 (54.1%)] than patients undergoing ICIs [25/140 (17.9%)] only, with the OR value of the ORR also showing a significant difference between

the two groups (OR =0.39, 95% CI: 0.26–0.53, $P<0.0001$, after transformation) (Figure 4).

Discussion

Based on the previous excellent performance of ICIs in the treatment of advanced lung cancer (5,6), the application of ICIs in neoadjuvant treatment of NSCLC is currently being explored. For the exploration of perioperative immunotherapy, the results of a phase IB study and a phase II study respectively showed that in melanoma and glioma, compared with adjuvant therapy, neoadjuvant immunotherapy could bring more obvious overall survival benefit (23,24). In 2018, Forde *et al.* first reported the efficacy and feasibility of neoadjuvant immunotherapy for NSCLC (CheckMate159 study), then finding that neoadjuvant immunotherapy could achieve 43% MPR (15).

Table 2 Safety and feasibility data of different studies in patients with NSCLC

Studies	Year	No. of patients	TRAEs, n (%)	3–4 irAEs, n (%)	Resectable patients, n (%)	Surgery delay, n (%)	Complications, n (%)	MPR, n (%)	pCR, n (%)	ORR, n (%)
Bott	2019	22	2 (9.1)	1 (4.5)	20 (90.9)	0 (0)	10 (50.0)	9 (45.0)	NR	2 (9.1)
Cascone	2021	44	3 (6.8)	2 (4.5)	39 (88.6)	NR	NR	13 (33.3)	8 (20.5)	9 (20.5)
Chen T	2021	12	4 (33.3)	0 (0)	12 (100.0)	0 (0)	3 (25.0)	9 (75.0)	5 (41.7)	6 (50.0)
Chen Y	2021	35	1 (2.9)	1 (2.9)	35 (100.0)	0 (0)	0 (0)	26 (74.3)	18 (51.4)	17 (48.6)
Forde	2018	21	5 (23.8)	1 (4.8)	20 (95.2)	0 (0)	NR	9 (45.0)	3 (15.0)	2 (9.5)
Gao	2020	40	21 (52.5)	4 (10.0)	37 (92.5)	2 (5.4)	4 (10.8)	15 (40.5)	9 (24.3)	8 (21.6)
Liu	2020	13	12 (92.3)	0 (0)	5 (38.5)	0 (0)	5 (100.0)	3 (60.0)	1 (20.0)	8 (61.5)
Lücke	2020	4	0 (0)	0 (0)	4 (100.0)	0 (0)	0 (0)	2 (50.0)	2 (50.0)	3 (75.0)
Provencio	2020	46	43 (93.5)	14 (30.4)	41 (89.1)	0 (0)	12 (29.3)	34 (82.9)	26 (63.4)	35 (76.1)
Reuss	2020	9	6 (66.7)	3 (33.3)	6 (66.7)	0 (0)	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)
Shu	2020	30	26 (86.7)	3 (10.0)	26 (86.7)	0 (0)	13 (50.0)	17 (65.4)	10 (38.5)	19 (63.3)
Tfayli	2020	15	4 (26.7)	4 (26.7)	11 (73.3)	0 (0)	0 (0)	3 (27.3)	1 (9.1)	4 (26.7)
Rothschild	2021	67	67 (100.0)	59 (88.1)	55 (82.1)	NR	2 (3.6)	34 (61.8)	10 (18.2)	29 (43.3)

NSCLC, non-small-cell lung cancer; No., number; TRAEs, treatment-related adverse events; irAEs, immune-related adverse events; MPR, major pathologic response; pCR, pathological complete response; ORR, objective response rate; NR, not related.

Table 3 Safety and feasibility data of different neoadjuvant regimen in NSCLC

Neoadjuvant regimen	No. of patients	TRAEs, n (%)	3–4 irAEs, n (%)	Resectable patients, n (%)	Surgery delay, n (%)	Complications, n (%)	MPR, n (%)	pCR, n (%)	ORR, n (%)
ICI	140	37 (26.4)	11 (7.9)	126 (90.0)	2 (1.6)	15 (11.9)	50 (39.7)	24 (19.0)	25 (17.8)
Chem + ICI	218	157 (72.0)	81 (37.2)	185 (84.9)	0 (0)	35 (18.9)	126 (68.1)	71 (38.4)	118 (54.1)

NSCLC, non-small-cell lung cancer; No., number of; TRAEs, treatment-related adverse events; irAEs, immune-related adverse events; MPR, major pathologic response; pCR, pathological complete response; ORR, objective response rate; ICI, immune checkpoint inhibitor; Chem, chemotherapy.

In the present study, we found that compared to neoadjuvant chemotherapy, ICIs neoadjuvant therapy alone showed a lower incidence of TRAE (25–27), which was similar to the results of previous adjuvant therapy for advanced NSCLC (28,29). Furthermore, the incidence of immune-related adverse reactions above grade 3 is low, mainly immune pneumonia and adrenal insufficiency. Few fatal irAE were reported in our study, mainly caused by immune pneumonia (16). The results of the phase II single-arm study (LCMC3 study) showed that using atezolizumab for neoadjuvant treatment of stage IB–IIIA or resectable stage IIIB NSCLC resulted in only 5.9% (6/101) of patients $\geq$ grade 3 TRAEs (30). Also, more TRAE occurred in patients undergoing ICI and chemotherapy. Apart from

the possibility of chemotherapy-related AEs, we also observed more grade 3 or higher irAEs in the neoadjuvant immunochemotherapy group, suggesting that, in addition to the adverse reactions caused by chemotherapy, the combination therapy may increase the adverse events induced by ICIs.

In terms of surgical resection rate, all but one study showed a surgical resection rate higher than 65% (17), which was not significantly different from the results of neoadjuvant chemotherapy (27); 3 studies showed a 100% surgical resection rate (13,14,18). Concerning surgical delay, only 2/358 patients experienced a surgical delay, mainly due to one case of grade 2 alanine transaminase and aspartate transaminase elevation and a case of grade 1

Figure 2 Forest plots for outcomes: an odds ratio for MPR in the intention to treat population. SE, standard error; CI, confidence interval; ICIs, immune checkpoint inhibitors; MPR, major pathological response.

Figure 3 Forest plots for outcomes: an odds ratio for pCR in the intention to treat population. SE, standard error; CI, confidence interval; ICIs, immune checkpoint inhibitors; pCR, pathological complete response.

Figure 4 Forest plots for outcomes: an odds ratio for ORR in the intention to treat population. SE, standard error; CI, confidence interval; ICIs, immune checkpoint inhibitors; ORR, objective response rate.

hyperthyroidism (16). In contrast, a previous article (31) reported that the surgical delay rate during neoadjuvant chemotherapy was relatively high. Although there is no statistically significant difference, it still suggests the advantages of neoadjuvant immunotherapy. We also observed that compared to the neoadjuvant ICI treatment group, more postoperative complications occurred in the ICI combined immunotherapy group (18.9%), with rare fatal complications. Combined with the published literature reporting that the incidence of severe postoperative complications caused by neoadjuvant chemotherapy is about 1–7% (32), we believe that compared to chemotherapy, ICI therapy is safer and has greater advantages in terms of postoperative complications.

Our study reported that in the neoadjuvant immunochemotherapy group, the MPR (68.1%) of the patients were significantly higher than those in the neoadjuvant immunotherapy group alone. Similarly, concerning the RECIST1.1 assessment, the patient's radiological response rate also showed the same trend. Whereas excluding a study with a small sample size (18), the MRP and pCR rate of the ICI neoadjuvant therapy group were only 15–35%, and the ORR was only 9–20%. Taken

together, this suggests that chemotherapy combined with immunotherapy has a greater advantage in the neoadjuvant treatment of NSCLC.

This study is a meta-analysis that evaluated the safety and feasibility of ICIs in neoadjuvant therapy of NSCLC. The previous systemic review of Zhao *et al.* (32), mainly involved conference abstracts. Given the current high treatment efficiency of ICI combined with chemotherapy, we believe that more efforts should be put into neoadjuvant immunochemotherapy. In addition, through the transformation of the data format, we conducted a meta-analysis of the included single-arm studies for more reliable data.

However, there are some limitations. First, the small sample size limits the reliability of the research. The P value (0.14) in pCR was greater than 0.05, which could not be considered significant. Although there are differences in trends between the two subgroups ($I^2=53.9\%$), further high-quality studies are needed. As the included studies were mostly open single-arm clinical trials, the lack of double-blind comparative studies may also increase the risk of bias. Finally, the study lacks follow-up data, so it is difficult to judge the benefits for the long-term survival of patients.

Conclusions

Neoadjuvant immunotherapy of resectable NSCLC shows better clinical application prospects due to its lower toxicity and fewer perioperative complications. Meanwhile, ICI combined chemotherapy can achieve more pathological relief and clinical benefits in the neoadjuvant treatment of NSCLC, but correspondingly, it will increase irAE and perioperative complications, thus more clinical studies are needed to determine the optimal neoadjuvant treatment plan.

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Footnote

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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.

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