Five-year survival rate analysis: the combination of fortnightly-administration of endostar and concurrent chemoradiotherapy versus concurrent chemoradiotherapy in the treatment of inoperable locally advanced non-small cell lung cancer

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Background: A prospective phase II study showed that Endostar combined with concurrent chemoradiotherapy (CCRT) can improve overall survival (OS) in patients with inoperable locally advanced non-small cell lung cancer (NSCLC). This study aimed to retrospectively compare the 5-year survival rates of patients with inoperable locally advanced NSCLC who received a combination of Endostar and CCRT to that of patients receiving CCRT.

Methods: Treatment-naive patients with inoperable locally advanced NSCLC who had long-term follow-up data were included in this study. Patients in CCRT + Endostar group were treated with Endostar plus radical CCRT, and patients in CCRT group received radical CCRT. For patients with a radiation dose ≥60 Gy, Kaplan-Meier method was used for survival analysis, and Cox proportional-hazards regression model was used for univariate analysis.

Results: A total of 104 participants were included in the CCRT + Endostar group with 89 participants included in the CCRT group. There were 88 (84.6%) and 74 (83.1%) male patients, respectively. The median follow-up times of two groups were 73.6 (95% CI: 65.6 to 81.7 months) and 66.3 months (95% CI: 52.7 to 79.9 months), respectively. The median overall survival (OS) was 29.7 (95% CI: 22.8 to 36.6 months) and 21.3 months (95% CI: 15.9 to 26.7 months), respectively.

Conclusions: This study showed that the 5-year survival of those patients who received the combination treatment of Endostar and radical CCRT was significantly superior to those who received radical CCRT.

Keywords: Non-small cell lung cancer (NSCLC); endostatin; Endostar; fortnightly administration; concurrent chemoradiotherapy (CCRT)

Ann Palliat Med 2021;10(7):7560-7570 | https://dx.doi.org/10.21037/apm-21-1092

Introduction

A meta-analysis in 2010 showed that for patients with inoperable locally advanced non-small cell lung cancer (NSCLC), concurrent chemoradiotherapy (CCRT) was superior to the sequential chemoradiotherapy (SCRT) (1), making CCRT the standard treatment for inoperable locally advanced NSCLC. However, how to optimize the two treatment methods and further improve their efficacy remained to be explored (2-8). The PACIFIC study (9,10) made CCRT plus durvalumab consolidation immunotherapy the new standard treatment for locally advanced NSCLC. However, the PACIFIC study conducted a high-standard screening among the participants. The enrolled patients were those who had no disease progression after CCRT, and some who were resistant to CCRT were dropped from the study. Therefore, challenges remain in how to overcome the resistance of patients with lung cancer to chemoradiotherapy and improve the efficacy of CCRT.

Tumors are obviously resistant to radiation during hypoxia, leading to failure of local tumor growth control (11,12). In the past 10 years, researchers have been trying to reduce tumor radiation resistance by improving tumor blood supply. Pre-clinical models have shown that anti-angiogenesis therapy can temporarily "normalize" the tumor vasculature, allowing it to supply oxygen more effectively, and increasing its sensitivity to radiotherapy (13). Endostar is a broad-spectrum angiogenesis inhibitor, which is known to inhibit the signal pathway through vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) to regulate the survival, proliferation, and migration of endothelial cells (14).

After a series of clinical studies, Yang *et al*. (15-18) determined the dosage and mode of administration of Endostar combined with chemotherapy in the treatment of advanced NSCLC. However, the same mode of administration combined with CCRT did not show an improvement in efficacy in the treatment of locally advanced NSCLC, while toxic side effects were increased (19). Taken that mode of administration of Endostar combined with radiotherapy may affect the efficacy and toxic side effects in the treatment of locally advanced NSCLC, our research team conducted an animal study, which showed that the tumor blood vessels were normalized after 5–7 days of treatment with Endostar, the hypoxic environment was improved, and the best tumor suppression effects were achieved under combination with radiotherapy (20,21). Based on *in vitro* evidences, a Phase II clinical study was designed to explore the optimal mode of the combination of fortnightly-administered Endostar and CCRT in the treatment of inoperable locally advanced NSCLC, and the initial therapeutic effects were satisfactory (22,23).

In this study, long-term follow-up visits were paid to participants in pre-liminary studies, and the data was compared with patients who received only CCRT during the same time. The objective aimed to evaluate the mechanisms of how anti-angiogenesis therapy can temporarily "normalize" the tumor vasculature, as well as whether the fortnightly-administration of Endostar combined with CCRT can improve the 5-year survival rate for patients with locally advanced NSCLC. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1092).

Methods

The sources of the patients and the inclusion criteria

From 2009 to 2015, our research team carried out two prospective phase II clinical studies (ClinicalTrials.gov, No. NCT01218594 and No. NCT01733589), using fortnightly administration of Endostar combined with CCRT to treat locally advanced NSCLC patients (CCRT + Endostar group). A total of 227 patients with treatment-naive inoperable locally advanced NSCLC who had the data of long-term follow-up visits in the same period were included retrospectively, and received radical CCRT (CCRT group). Three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) was applied in both groups, and the regimens of both groups were platinum-based 2-drug regimens. Excluding patients with a radiotherapy dose of <60 Gy, 193 patients were finally included in the analysis, with 104 cases in the CCRT + Endostar group and 89 cases in the CCRT group. The patients in this study was strictly included according to the inclusion and exclusion criteria from two clinical studies (ClinicalTrials.gov, No. NCT01218594 and No. NCT01733589) to achieve a relatively balanced exposure groups at baseline was used in this study to reduce selective bias. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) (No. ZJZLYY-2012-10-24). Individual consent for this retrospective analysis was waived.
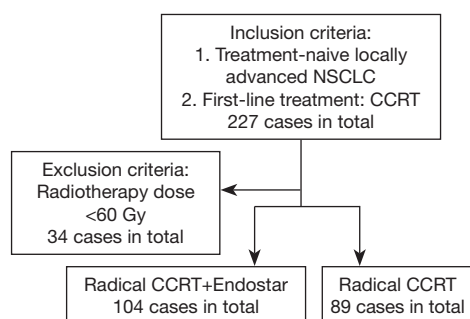
Figure 1 STROBE diagram of flowchart of patient inclusion. NSCLC, non-small cell lung cancer; CCRT, concurrent chemoradiotherapy.

Treatment

Radiotherapy

Either 3D-CRT or IMRT was applied in both groups, and the dose of radical radiotherapy was given, conventional fractionated 2 Gy/F, once a day, 5 times a week.

Chemotherapy

Participants received concurrent platinum-based 2-drug CCRT, including EP regimen (etoposide 50 mg/m^2, D1–D5; cisplatin 50 mg/m^2, D1 and D8, repeated every 4 weeks), DP/C regimen [docetaxel 65 mg/m^2, D1; cisplatin 65 mg/m^2 or carboplatin area under the curve (AUC) =5, D1, repeated every 4 weeks], or TP/C regimen (paclitaxel 135–175 mg/m^2, D1; cisplatin 65 mg/m^2 or carboplatin AUC =5, D1, repeated every 4 weeks), NP regimen (vinorelbine 60 mg/m^2, D1 and D8; cisplatin 65 mg/m^2, D1, repeated every 4 weeks), AP regimen (pemetrexed 500 mg/m^2, D1; cisplatin 65 mg/m^2, D1, repeated every 4 weeks), and GP regimen (gemcitabine 1,000 mg/m^2, D1 and D8; cisplatin 65 mg/m^2, D1, repeated every 4 weeks).

Endostar

In the CCRT + Endostar group, the dose of Endostar was 7.5 mg/m^2 per day with 5–7 days of continuous administration. The administration of Endostar was given 5–7 days before radiotherapy, and fortnightly during radiotherapy. The cycle was repeated every 2 weeks to a total of 4 cycles.

Statistical analysis

The OS calculation was as follows: the duration from the start of treatment to death due to any cause. In the case of survival, the OS was recorded to the time point of the last

follow-up visit. Local progression-free survival (LPFS) was calculated as follows: duration from the start of treatment to local tumor progression, including the relapse time of the primary lesion and regional lymph nodes (including relapse both in- and out of the irradiation field). Distant metastasis-free survival (DMFS) was calculated as follows: duration from the start of treatment to the first appearance of distant metastasis. The software SPSS 24.0 (IBM Inc., Armonk, NY, USA) was employed for statistical analysis. The chi-square test was used to compare participant characteristics and treatment-related factors. The Kaplan-Meier estimator was used for survival analysis, and log-rank test was used for OS inter-group comparison. The hazard ratio (HR) and 95% confidence interval (95% CI) for Cox-model were used to perform univariate survival analysis for variables which may have affected the results, and the Cox proportional-hazards regression model was used for multivariate survival analysis for statistically significant univariate factors. All statistical tests used a 2-sided hypothesis test with type I error. P<0.05 was deemed statistically significant.

Results

The comparison of baseline characteristics between two groups

Two hundred twenty seven patients with treatment-naive inoperable locally advanced NSCLC from two prospective phase II clinical studies (ClinicalTrials.gov, No. NCT01218594 and No. NCT01733589) conducted from 2009 to 2015 were screened and among them, 34 patients were excluded due to Radiotherapy dose of <60 Gy. A total of 193 patients were enrolled in this study, including 104 patients in the CCRT + Endostar group and 89 patients in the CCRT group (*Figure 1*). Baseline characteristics of the Endostar + CCRT and CCRT groups were as follows: median age: 58 and 56 years, respectively; there were 88 (84.6%) and 74 (83.1%) male participants, and 16 (15.4%) and 15 (16.9%) females, respectively. There were 63 cases (60.6%) and 40 cases (44.9%) of squamous cell carcinoma, respectively. The stage IIIA and stage IIIB were 33.7% and 66.3% in CCRT + Endostar group and 28.1% and 71.9% in CCRT group. The regimens of CCRT in the CCRT + Endostar group were EP regimen (61.5%) and DP regimen (38.5%), while a variety of platinum-based 2-drug chemotherapy regimens were used in the CCRT group, with the TP/C regimen in the majority (53.9%), 20 cases of DP regimen

(22.5%), 3 cases of EP regimen (3.4%), and 18 cases (20.2%) of other regimens. Baseline characteristics and treatment condition of participants in two groups were displayed, and the two groups of patients were comparable in terms of baseline demographics and clinical data in *Table 1*.

Survival analysis

The median follow-up times of the CCRT + Endostar group and CCRT group were 73.6 months (95% CI: 65.6 to 81.7 months) and 66.3 months (95% CI: 52.7 to 79.9 months), respectively. A total of 72 participants died in the CCRT + Endostar group, of which 64 cases died of lung cancer progression, 5 died of other diseases, 2 died of treatment complications, and 1 case died of unknown cause; in the CCRT group 62 participants died, of which 60 cases died of lung cancer progression, and 2 of other diseases. The median survival times of two groups were 29.7 months (95% CI: 22.8 to 36.6 months) and 21.3 months (95% CI: 15.9 to 26.7 months), the 5-year survival rates were 34.7% and 23.6%, respectively (P=0.038). The OS curves were shown in *Figure 2*. According to the univariate analysis, the differences in the effects of gender, age stratification, Eastern Cooperative Oncology Group (ECOG) score, pathological type, Union for International Cancer Control (UICC) staging, radiotherapy technology, and whether EP regimen was used in concurrent chemotherapy on OS were statistically significant (*Table 2*).

Late-stage adverse reactions

The records of late-stage adverse reactions mainly included late-stage lung injury and esophageal injury. Late-stage lung injury and esophageal injury after radiotherapy were evaluated according to standards of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). No grade 4–5 late-stage lung injury occurred in the CCRT + Endostar group or CCRT group. A single case of grade 3 lung injury was observed in the CCRT + Endostar group. The incidence rates of grade 1 and grade 2 lung injury in the CCRT group were significantly higher than that in the CCRT + Endostar group, which were 33.7% and 14.4%, 9.1% and 3.8%, respectively (P=0.002). The incidence rate of late-stage esophageal injury was low in both groups, which were 5.6% and 1.0% respectively (P=0.188). The late-stage adverse reactions are shown in *Table 3*.

Discussion

In this study, long-term follow-up visits were paid to participants in pre-clinical studies, and the data were retrospectively compared with those who received only CCRT at the same time, elucidating the mechanisms of how anti-angiogenesis therapy can temporarily "normalize" the tumor vasculature, and that fortnightly administration of Endostar combined with CCRT can improve the 5-year survival rate for patients with locally advanced NSCLC. In this study, the median follow-up time of the CCRT + Endostar group and CCRT group was 73.6 months (95% CI: 65.6 to 81.7 months) and 66.3 months (95% CI: 52.7 to 79.9 months), respectively. The median follow-up time of the two groups both exceeded 5 years. The median OS and 5-year OS rate of the CCRT + Endostar group were significantly better than those of the CCRT group (29.7 *vs.* 21.3 months, 34.7% *vs.* 23.6%, respectively, P=0.038).

In the study of locally advanced NSCLC with longer follow-up period, the median follow-up time reported by Southwest Oncology Group (SWOG) 9019 was 52 months, the median OS was 15 months, and the 3- and 5-year OS rates were 17% and 15%, respectively (3). In a study using cetuximab combined with CCRT to treat patients with stage III NSCLC, the median follow-up time was 32 months, and the median OS was 25.2 months (5). The RTOG 0617 (2) study compared the efficacy of CCRT with different radiotherapy doses of 60 and 74 Gy in the treatment of locally advanced NSCLC. The median follow-up time was up to 5.1 years, median survival time was 28.7 and 20.3 months, and the 5-year OS rate was 32.1% and 23%, respectively. In that study, 69% of patients had stage-IIIA disease; while in this study participants with stage-IIIB disease accounted for 66.3% and 71.9% in two groups. The OS of the CCRT group was not as good as the that of the 60 Gy group in the RTOG 0617 study, but the outcome of participants in the CCRT + Endostar group was comparable to that of the 60 Gy group in the RTOG 0617 study (median OS was 29.7 and 28.7, and 5-year OS rate was 34.7% and 32.1%, respectively).

The PACIFIC study (10) had achieved great success as it conducted durvalumab consolidation immunotherapy after CCRT in the treatment of inoperable locally advanced NSCLC. Survival data were updated in 2017 (9): the median follow-up time was 25.2 months, median OS was not reached (95% CI: 34.7 to NR), which was significantly

Table 1 Baseline characteristics and treatment conditions in two groups

Characteristics	CCRT + Endostar (n=104)		CCRT (n=89)		P value
	n	%	n	%	
Gender					0.782
Male	88	84.6	74	83.1	
Female	16	15.4	15	16.9	
Median age (range), years	58 [31–71]		56 [33–73]		0.411
ECOG score					0.312
0	27	26.0	29	32.6	
1	77	74.0	60	67.4	
Primary lesion					0.412
Upper lobe of left lung	35	33.7	23	25.8	
Lower lobe of left lung	14	13.5	9	10.1	
Upper lobe of right lung	35	33.7	40	44.9	
Middle lobe of right lung	7	6.7	8	9.0	
Lower lobe of right lung	11	10.6	9	10.1	
Mediastinum-typed	2	1.9	0	0	
Pathological type					0.083
Squamous cell carcinoma	63	60.6	40	44.9	
Adenocarcinoma	32	30.8	43	48.3	
Large cell carcinoma	1	1.0	0	0	
Adenosquamous carcinoma	0	0	1	1.1	
Unclassified	8	7.7	5	5.6	
UICC staging					0.405
Stage IIIA	35	33.7	25	28.1	
Stage IIIB	69	66.3	64	71.9	
Radiotherapy technology					0.000
3D-CRT	40	38.5	89	100	
IMRT	64	61.5	0	0	
Chemotherapy regimen					0.000
EP	64	61.5	3	3.4	
Other regimens	40	38.5	86	96.6	
DP/C	40	38.5	20	22.5	
TP/C	0	0	48	53.9	
NP	0	0	9	10.1	
AP	0	0	5	5.6	
GP	0	0	4	4.5	

EP, etoposide, cisplatin; DP/C, docetaxel, cisplatin or carboplatin; TP/C, paclitaxel, cisplatin or carboplatin; NP, vinorelbine, cisplatin; AP, pemetrexed, cisplatin; GP, gemcitabine, cisplatin; ECOG, Eastern Cooperative Oncology Group; UICC, Union for International Caner Control; 3D-CRT, three-dimensional conformal radiation therapy.
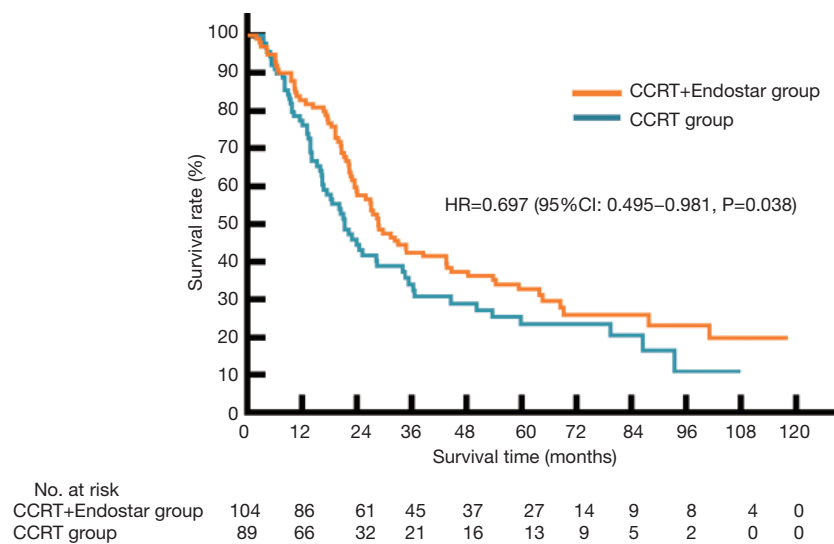
Figure 2 The OS curves of two groups. CCRT, concurrent chemoradiotherapy; OS, overall survival.

Table 2 Univariate analysis

Factors	HR (95% CI)	P value
Treatment plan (CCRT + Endostar/CCRT)	0.697 (0.495–0.981)	0.038
Gender (male/female)	1.222 (0.766–1.949)	0.400
Age stratification (<60/≥60 years old)	0.855 (0.605–1.207)	0.372
ECOG score (0/1)	0.889 (0.603–1.309)	0.550
Pathological type (squamous cell carcinoma/non-squamous cell carcinoma)	1.044 (0.652–1.673)	0.858
UICC staging (IIIA/IIIB)	0.868 (0.602–1.252)	0.449
Radiotherapy technology (3D-CRT/IMRT)	1.304 (0.900–1.889)	0.160
Chemotherapy regimen (EP regimen/non-EP regimen)	0.869 (0.604–1.250)	0.449

CCRT, concurrent chemoradiotherapy; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; UICC, Union for International Caner Control; 3D-CRT/IMRT, three-dimensional conformal radiation therapy or intensity-modulated radiation therapy; EP, etoposide, cisplatin.

superior to that of the CCRT group (28.7 months, 95% CI: 22.9 to NR), (P=0.0025). For this reason, durvalumab consolidation immunotherapy after CCRT has become the new standard treatment for locally advanced NSCLC in 2018. Based on this, we did not further carry out a prospective RCT to compare the combination of Endostar and CCRT with CCRT alone. However, the PACIFIC study conducted a high-standard screening of its patients. The participants were those who had no disease progression after CCRT, and some who had shown resistance to CCRT were dropped. Therefore, challenges remain in how to overcome the resistance of patients with lung cancer to

chemoradiotherapy and improve the efficacy of CCRT.

Increasingly, studies have also shown that appropriate anti-angiogenic drugs can promote the normalization of tumor blood vessels within a certain time window, which can directly alleviate hypoxia and make the tumor immune environment change from an immunosuppressive state to an immune-supportive one (24). The mechanism is mainly manifested in the following aspects (25): (I) promote T cell infiltration; (II) reduce hypoxia, preferentially induce the polarization of tumor-associated macrophages (TAMs) to M1 phenotype; (III) blood vessel normalization reduces the recruitments of regulatory T cells (Treg) and myeloid-

Table 3 The late-stage adverse reactions in two groups

Late-stage adverse reactions	CCRT + Endostar (n=104)		CCRT (n=89)		P value
	n	%	n	%	
Late-stage lung injury					0.002
Grade 1	15	14.4	30	33.7	
Grade 2	4	3.8	8	9.10	
Grade 3	1	1.0	0	0	
Total	20	19.2	38	42.8	
Late-stage esophageal injury					0.188
Grade 1	0	0	1	1.1	
Grade 2	0	0	3	3.4	
Grade 3	1	1.0	1	1.1	
Total	1	1.0	5	5.6	

CCRT, concurrent chemoradiotherapy.

derived suppressor cells (MDSC); (IV) block the inhibiting signals of the differentiation of dendritic cells (DC); (V) immunosuppressive signals such as programmed death-ligand 1 (PD-L1) induced by hypoxia can be down-regulated by improving perfusion. Various mechanisms suggest that anti-tumor angiogenesis therapy and immunotherapy can promote compensate for each other, achieving a synergistic interaction. At present, many ongoing studies to explore the combination of anti-angiogenesis therapy and immunotherapy have been registered in ClinicalTrials.gov.

The combination of anti-angiogenic drugs and immunotherapy has become a new direction of exploration; concurrently, the toxic and side effects have also become a special concern of researchers. Endostar showed a better safety profile than other antiangiogenic drugs, and the side effect of Endostar less than that of other antiangiogenic drugs might be related to its own structure and biological characteristics. Recombinant human endostatin (rhE, Endostar), a C-terminal fragment naturally derived from type XVIII collagen could maintain good structural stability and specifically inhibit the activity of vascular endothelial growth factor to block angiogenesis as well as induce cancer cell apoptosis, which could better simulate the roles of endostatin in tumor suppression *in vivo* than other antiangiogenic drugs with less side effect (23). However, more researches and clinical trials remained to be conducted for further verification of the link between less side effect of Endostar and its lower dosage.

Among the currently available anti-angiogenic drugs, Endostar, bevacizumab and Anlotinib were the most applied in the treatment of various cancer types. Based on previously reported evidences, the advantages of Endostar over two other antiangiogenic drugs could summarized as follows, better suitability for treatment of more extensive pathologic types, wider patient coverage than other antiangiogenic drugs, a better safety profile and less toxic side effects, capability of being used in combination with radiotherapy (23,26-30). Among other anti-angiogenic drugs, the reported toxic and side effects mainly include vascular events, cardiovascular toxicity, proteinuria, delayed wound healing, intestinal perforation, and esophagotracheal fistula. A phase II RCT of bevacizumab combined with carboplatin and paclitaxel in the first-line treatment of advanced NSCLC showed that the increase in pulmonary hemorrhage was related to the mass or cavity of the central part, and 4/6 of the patients had squamous cell carcinoma. The risk of pulmonary hemorrhage for squamous cell carcinoma was 31%, and the risk of pulmonary hemorrhage for other pathological subtypes was 4% (31). Therefore, in the subsequent phase III clinical study (ECOG 4599), the efficacy of paclitaxel plus carboplatin combined with bevacizumab in the treatment of recurrent or advanced NSCLC was evaluated and compared with the efficacy of the chemotherapy. Patients with squamous cell carcinoma and hemoptysis were excluded (32). The SWOG S0533 study (33) aimed to evaluate the feasibility of using bevacizumab combined with CCRT for stage III NSCLC. The study was terminated due to the occurrence of severe esophagotracheal fistula. The Food and Drug Administration (FDA) also issued a warning: there is a risk of esophagotracheal fistula when lung cancer patients receive bevacizumab combined with chemoradiotherapy, and the corresponding warnings should be made clear on the drug insert. Therefore, in the combination use of anti-angiogenic drugs and radiotherapy, clinical studies were difficult to be carried out due to the concerns about fistulas, hemorrhage, and other serious toxic and side effects, especially in patients with squamous cell carcinoma. At present, tumor vascular inhibitors used in China include anlotinib and apatinib, both of which were used for the monotherapy or the combination with chemotherapy in the second-line and third-line treatment studies, and there is a lack of safety data for their combination with radiotherapy.

Endostar is administered fortnightly, and it was shown to be tolerated well in the prospective phase II clinical study of

our research team. Except for 1 case of grade 5 hemoptysis due to the great vessels involved by the tumor, no serious anti-angiogenesis drugs-related bleeding adverse reactions occurred. The most common acute toxicity can be attributed to the toxic and side effects of chemoradiotherapy, including blood toxicity, esophagitis, and pneumonia. The incidence rate was lower than or similar to the results reported in previous studies using CCRT for NSCLC (5,34,35). With the advent of the age of immunotherapy, the possible lung injury caused by the combination use of chest radiotherapy and immunotherapy has also become the special concern of researchers. In our phase II study of the combination use of Endostar and CCRT for locally advanced NSCLC, the incidence rate of grade 3–5 acute radiation pneumonitis was 6.8%, which was still lower than the that reported by Cancer and Leukemia Group B (CALGB) 30407 (12%) (5). Due to the poor therapeutic effects on lung cancer and short survival period, reports of late-stage radiation injury were rarely seen. In this study, except for 1 case of grade 3 late-stage lung injury in the CCRT + Endostar group, the lung injuries were mainly grade 1–2 in two groups. The incidence rate of CCRT + Endostar group was significantly lower than that of the CCRT group (19.2% *vs*. 42.8%, respectively). In this study, 4 participants in the CCRT group received GP regimen in concurrent chemotherapy despite studies having shown that the combined use of radiotherapy and concurrent GP regimen (gemcitabine + cisplatin) can increase the incidence rate of symptomatic radiation pneumonitis (36), in which 2 patients developed grade 1 late-stage lung injury, 1 developed grade 2 lung injury, no patient developed ≥ grade 3 lung injury, and the incidence rate of late-stage radiation-induced lung injury was not higher than other chemotherapy regimens (Table S1). The pathological features of radiation-induced lung injury mainly include inflammatory cell infiltration, type I alveolar cell injury, increased capillary permeability, alveolar interstitial edema, and thickened alveolar septum, resulting in the occlusion of residual alveoli and capillary cavities, and finally leading to pulmonary fibrosis. From the perspective of pathophysiology, a series of pro-inflammatory factors and growth factors are involved in the process of radiation-induced lung injury (37). Jackson *et al*. (38) demonstrated that radiation damage was related to the increase of macrophage infiltration induced by hypoxia and the production of transforming growth factor beta (TGF-β) and VEGF. According to a report by Tanabe *et al*. (39), endostatin can significantly inhibit the expression of VEGF-A, alpha-smooth muscle actin (α-SMA) and

the pro-fibrotic factor TGF-β1 in a mouse model, and inhibit peritoneal fibrosis in a dose-dependent manner. An experimental study found that compared with the animals exposed to radiation but not treated with Endostar, those animals treated with Endostar were relatively mild in pulmonary alveolitis, pulmonary edema, and fibrosis degree, and lower in TGF-β1 expression, suggesting that Endostar can relieve the degree of radiation-induced pulmonary lesions (40). In this study, the CCRT + Endostar group adopted a fortnightly-administration mode, using anti-angiogenic drugs to "normalize" tumor blood vessels in the window period and combining with chemoradiotherapy. On the one hand, previous reports revealed that Endostar increased the safety and efficacy of chemoradiotherapy in several cancers (41,42). On the other hand, pre-clinical results showed that Endostar may reduce the incidence rates of acute radiation-induced lung injury (RILI) by inhibiting the expression of inflammatory factors related to RILI (40). Besides, previous study revealed that Endostar was involved in the regulation of both metabolism and tumor microenvironment hypoxia, which may be responsible for enhanced antitumor effects of Endostar combined with radiotherapy (43). For inoperable locally advanced NSCLC, further exploration and research into whether the addition of Endostar on the basis of the new standard of CCRT plus consolidation immunotherapy can further improve the therapeutic effects and also play a role in radiological protection is warranted.

The limitations in this study should never be neglected. For one thing, this was a retrospective study with a small sample size, and prospective clinical randomized controlled trials (RCTs) will be conducted in the future for further verification of the efficacy and safety of Endostar combined with CCRT in the treatment of inoperable locally advanced non-small cell lung cancer. For another, heterogeneity of patients enrolled in clinical trials should be further considered in the future to reduce potential selective bias. Furthermore, the optimal dosage, frequency and course of treatment of Endostar in combination with CCRT in the treatment of inoperable locally advanced non-small cell lung cancer should be further investigated and explored for better validation.

Conclusions

The combined use of radical CCRT and fortnightly-administered endostatin (Endostar) significantly improved the median OS and 5-year survival rate for patients with

inoperable locally advanced NSCLC, and the toxic and side effects were significantly lower than those of patients received CCRT. In the age of immunotherapy, CCRT plus consolidation immunotherapy has become the new treatment standard for locally advanced NSCLC. The effectiveness and safety of anti-angiogenic drugs, immunotherapy, and CCRT in the treatment of inoperable locally advanced NSCLC should be further explored.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1092

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-1092

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1092). The 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) (No. ZJZLYY-2012-10-24). Individual consent for this retrospective analysis was waived.

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Table S1 Late-stage lung injury under different chemotherapy regimens

Chemotherapy regimens (n=193)	Grade 1		Grade 2		Grade 3		Total	
	n	%	n	%	n	%	n	%
EP [67]	15	7.8	3	1.6	1	0.5	19	34.7
DP/C [60]	5	2.6	3	1.6	0	0	8	31.1
TP/C [48]	17	8.8	5	2.6	0	0	22	24.9
NP [9]	4	2.1	0	0	0	0	4	4.7
AP [5]	2	1.0	0	0	0	0	2	2.6
GP [4]	2	1.0	1	0.5	0	0	3	2.1
Total	45	23.3	12	6.2	1	0.5	58	

EP, etoposide, cisplatin; DP/C, docetaxel, cisplatin, or carboplatin; TP/C, paclitaxel, cisplatin, or carboplatin; NP, vinorelbine, cisplatin; AP, pemetrexed, cisplatin; GP, gemcitabine, cisplatin.