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ORIGINAL ARTICLE

Different administration routes of recombinant human endostatin combined with concurrent chemoradiotherapy might lead to different efficacy and safety profile in unresectable stage III non-small cell lung cancer: Updated follow-up results from two phase II trials

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Keywords
Concurrent chemoradiotherapy; continuous intravenous pumping; intravenous injection; non-small cell lung cancer; recombinant human endostatin.

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Abstract

Background: There are two main choices of administration route of recombinant human endostatin (Endostar) available and the treatment options of concurrent chemoradiotherapy (CCRT) have changed over time. The aim of this study was to observe the long-term efficacy and safety of different administration routes of Endostar combined with CCRT.

Methods: Patients with unresectable stage III non-small cell lung cancer (NSCLC) from two phase II trials were included as two cohorts. Both were treated with Endostar combined with CCRT. Endostar was administrated by intravenous injection (7.5 mg/m^2/day, seven days) in the IV arm and by continuous intravenous pumping (7.5 mg/m^2/24 hours, 120 hours) in the CIV arm.

Results: A total of 48 patients were included in the IV arm and 67 patients in the CIV arm. The median progression-free survival (PFS), overall survival (OS), local recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) in the IV arm and CIV arm were 9.9 months versus 15.4 months (HR = 0.751, 95% CI 0.487–1.160, P = 0.200), 24.0 months versus 38.5 months (HR = 0.746, 95% CI 0.473–1.178, P = 0.209), 32.3 months versus 27.1 months (HR = 1.193, 95% CI 0.673–2.115, P = 0.546), 20.1 months versus 49.7 months (HR = 0.603, 95% CI 0.351–1.036, P = 0.067). The one, three, five-year PFS in the IV arm and CIV arm was 45.8% versus 52.9%, 18.3% versus 31.4%, and 18.3% versus 27.7% and the one, three, five-year OS was 81.2% versus 82.1%, 31.1% versus 50.3%, and 31.1% versus 41%, respectively. Incidence of hematological adverse reactions were numerically lower in the CIV arm than the IV arm.

Conclusions: Endostar delivered by CIV with CCRT may be a better option than IV in terms of potential survival and safety for unresectable stage III NSCLC.

Key points

Significant findings of the study

Endostar delivered by continuous intravenous pumping might achieve more favorable survival over intravenous injection and reduce adverse hematological reactions in patients with unresectable stage III NSCLC treated with Endostar combined with CCRT.

What this study adds

The administration route of recombinant human endostatin is also one key factor for survival and safety to consider when treating patients with unresectable stage III NSCLC.

Introduction

Concurrent chemoradiotherapy (CCRT) is still the standard treatment for locally advanced unresectable non-small cell lung cancer (NSCLC), although its five-year survival rate is only 15%–20%.[1,2] Recombinant human endostatin (Endostar) was approved by the Chinese Food and Drug Administration in 2005 and has been shown to be effective and safe when combined with chemotherapy or radiotherapy in the treatment of NSCLC.[3–5] Preclinical models have shown that Endostar may transiently normalize the tumor vasculature and oxygen delivery, thereby providing a window of opportunity to enhance the sensitivity to radiation treatment.[6] Thus, physicians commenced treatment with Endostar combined with CCRT in unresectable NSCLC. In 2009, we initiated a prospective phase II clinical study applying an intravenous injection (IV) of Endostar with CCRT for patients with locally advanced NSCLC which showed promising survival and local control rates.[7] Based on preclinical data[8,9] the inhibition effect of Endostar on tumor cells is time-dependent.[10] Continuous intravenous pumping (CIV) is considered a better administration route to maintain a steady blood concentration and might improve efficacy. In addition, since continuous intravenous pumping is more convenient for patients, it can also enhance treatment compliance. Several trials have proved its safety and efficacy.[11,12] Thus, since 2012, Endostar delivered IV has been gradually replaced by CIV in NSCLC. In 2012, we initiated another phase II study (named HELPER) of Endostar CIV combined with CCRT for patients with locally advanced NSCLC and achieved preferable overall survival (OS), promising two-year progression-free survival (PFS) and favorable distant metastasis-free survival (DMFS) with acceptable toxicities.[10] However, whether Endostar CIV is superior to IV in addition to CCRT for patient with unresectable NSCLC remains unclear because until now direct comparisons of the two administration routes have mostly been performed in advanced NSCLC or ovarian cancer patients treated with chemotherapy and the study design of the only study carried out in patients treated with Endostar combined with chemoradiotherapy was poor as it included all kinds of advanced malignant tumors and the chemoradiotherapy was not fixed.[12] Therefore, we prolonged the follow-up of our two studies as mentioned above and attempted to provide evidence for different administration routes of Endostar combined with CCRT in patients with unresectable stage III NSCLC. Here, we report the efficacy and safety results of the study.

Methods

Patients and treatments

Participants in the study were from two prospective clinical trials of unresectable stage III NSCLC treated with Endostar combined with CCRT. A total of 48 patients who received intravenous injection of Endostar (IV arm) were from our study initiated in 2009 (ClinicalTrials.gov, number NCT01218594) as historical controls,[7] and 67 patients who received continuous intravenous pumping of Endostar (CIV arm) were from the HELPER study initiated in 2012 (ClinicalTrials.gov, number NCT01733589).[13] The treatment procedure is shown in Fig. 1.

Recombinant human endostatin (Endostar): In the IV arm, intravenous Endostar (7.5 mg/m^2/day) was administered over four hours each day for seven days, while in the CIV arm, continuous intravenous pumping of Endostar (7.5 mg/m^2/24 hours) was administered over 120 hours. Endostar was administered a week before the beginning of radiotherapy, and then repeated every two weeks for four cycles in both arms. Electrocardiogram monitoring was performed during the first delivery of Endostar.

Chemotherapy: Patients in the IV arm received docetaxel (65 mg/m^2) and cisplatin (65 mg/m^2) on days one and 29. In the CIV arm, patients received etoposide (50mg/m^2, on days 1–5, 29–33) combined with cisplatin (50 mg/m^2, on days one, eight, 29, 35). Chemotherapy began on the same day as radiotherapy in both arms.

Radiotherapy: All the patients were fixed with vacuum bags or body covers, and enhanced computed tomography (CT) or 4D-CT simulation was performed. The targets were contoured in accordance with the International Commission on Radiation Units and Measurements (ICRU 62) guidelines. Primary and mediastinal lymph nodes were all irradiated in the target area, but no prophylactic irradiation was given to lymph nodes. Patients in the IV arm received 3D conformal radiotherapy (3D-CRT) with a linear accelerator using 8-MV photons. A total dose of 60–66 Gray (Gy) was delivered in 30–33 fractions over 6–7 weeks;

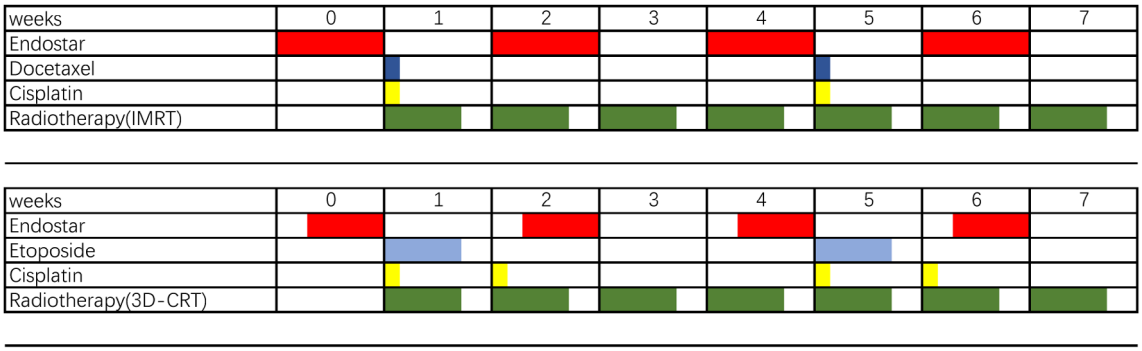

Figure 1 The treatment procedure. Two cohorts of patients with unresectable stage III non-small cell lung cancer treated with Endostar combined with CCRT were included. Endostar was administered a week before the beginning of radiotherapy, and then repeated every two weeks for four cycles in both arms. In the IV arm, intravenous Endostar (7.5 mg/m^2/day) was administered over four hours each day for seven days, while in the CIV arm, continuous intravenous pumping of Endostar (7.5 mg/m/24 hours) was administered over 120 hours. CCRT in the IV arm (■) Endostar, 7.5 mg/m^2/d, intravenous injection (IV), (■) Docetaxel, 65 mg/m^2/d, (■) Cisplastin, 65 mg/m^2/d, and (■) Radiotherapy (IMRT) and the CIV arm were DP regimen plus IMRT and EP regimen plus 3D-CRT, respectively (■) Endostar, 7.5 mg/m^2/24h*120h, continuous intravenous pumping (CIV), (■) Etoposide, 50 mg/m^2/d, (■) Cisplastin, 50 mg/m^2/d, and (■) Radiotherapy (3D-CRT). CCRT, concurrent chemoradiotherapy; continuous intravenous pumping; IV, intravenous injection; CIV.

2 Gy × 20 fractions to an initial target volume including PTV, followed by 2 Gy× (10–13) fractions to a boost volume including GTV-T and GTV-N with a margin of 1–1.5 cm. Patients in the CIV arm received intensity modulated radiotherapy (IMRT) with a linear accelerator using 6-MV photons. A total dose of 60–66 Gy was delivered in 30–33 fractions covering 95% PTV, 2 Gy per fraction, five fractions per week.

Follow-up evaluation

Chest and abdominal CTs, and cervical lymph node ultrasonography were assessed at the end of treatment, one month after treatment, and every three months for the first two years and thereafter every six months for three years (or earlier if clinically indicated). Other imaging examinations were obtained when suspicious recurrence occurred. The treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. In-field failure was defined as progressive consolidation on CT within the radiation site (PTV). Out-field failure was defined as progressive out of the PTV including recurrence in regional of thorax and distal metastasis. Local regional failure included in-field and regional failure. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCICTC), version 3.0. Radiation Therapy Oncology Group/ European Organization for Research and Treatment Cancer (RTOG/ EORTC) criteria was used for the evaluation of late pulmonary adverse reactions in three to four months after radiotherapy.

Statistical analysis

Progression-free survival (PFS) was defined as the time from the beginning of treatment to the date of the patient's first local or distant progression or death from any cause. If there was no progression or the patient survived, PFS was defined as the date of confirmation of no progression. OS was defined as the time from the beginning of the treatment to the date of death of any cause or the nearest follow-up. Local recurrence-free survival (LRFS) was calculated from the beginning of treatment to the date of local regional failure. Distant metastasis-free survival (DMFS) was calculated from the beginning of the treatment to the date of distant metastasis. Survival rates were estimated using the Kaplan-Meier method and the difference between the two arms was estimated using the method described by Hajime *et al.*[14] Hazard ratios (HR) were estimated using Cox proportional hazards models. A two-sided $P < 0.05$ was considered statistically significant. All the analyses were done using the SPSS software package (version 17.0, SPSS, Inc.).

Results

A total of 115 patients were included, of which 48 patients were in the IV arm (enrolled from March 2009 to January 2012) and 67 patients in the CIV arm (enrolled from November 2012 to June 2015). A total of 60.9% of the patients had squamous cell carcinoma and 67.8% of the patients had stage IIIB disease. Most of the baseline characteristics were well balanced in the two groups, except for

the stage. The percentages of patients with stage IIIB disease in the IV arm and the CIV arm were 83.3% and 56.7% (P = 0.003), respectively and the percentages of patients with N3 disease in the IV arm and the CIV arm were 66.0% and 35.8% (P = 0.002), respectively. The demographics and characteristics of patients in the two arms are listed in Table 1.

In the IV arm and CIV arm, 43 (89.6%) and 62 (92.5%) patients completed four cycles of Endostar, respectively; 45 (93.8%) and 64 (95.5%) patients completed two cycles of adequate doses of chemotherapy, respectively; 47 (97.9%) and 66 (98.5%) patients received radiation for at least 56 Gy, respectively. Treatments details were all well balanced in the two groups (Table 2). In total, 36 (75%) and 59 (88.1%) patients in the IV arm and CIV arm completed the full course of the planned therapy of Endostar and CCRT treatment, respectively (P = 0.068).

In the IV arm and CIV arm, five (10.4%) and eight (11.9%) patients showed complete response (CR); 32 (66.7%) and 43 (64.2%) patients had partial response (PR); three (6.3%) and 12 (17.9%) patients had stable disease (SD); five (10.4%) and four (6.0%) patients had progressive disease (PD).

By the end of December 2018, the median follow-up was 28.4 months for overall patients. In the IV arm, it was 24.5 months (range: 0.2 to 110.2 months) and in the CIV arm, it was 34.8 months (range: 2.7 to 68.3 months). At the last follow-up, 37 of 48 patients (77.1%) died and 10 (20.8%) were still alive in the IV arm, and 40 of 67 patients (59.7%) died and 26 (38.8%) were still alive in the CIV arm, (P = 0.122). One patient in both groups was

Table 2 Treatment details

Treatment	IV arm (n = 48)	CIV arm (n = 67)	P-value
Radiotherapy (Gray)			0.811
≥56	97.9%	98.5%	
<56	2.1%	1.5%	
Chemotherapy cycles			0.673
1	6.2%	4.5%	
2	93.8%	95.5%	
Endostar cycles			0.686
1	2.1%	0.0%	
2	2.1%	1.5%	
3	6.2%	6.0%	
4	89.6%	92.5%	

Table 1 Demographic and baseline clinical characteristics

Patients' characteristics	Total (n = 115)	IV arm (n = 48)	CIV arm (n = 67)	P-value
Sex				0.745
Male	82.6%	81.2%	83.6%	
Female	17.4%	18.8%	16.4%	
Age				0.624
<60 years	55.7%	58.3%	53.7%	
≥60 years	44.3%	41.7%	46.3%	
ECOG performance status				0.375
0–1	97.4%	95.8%	98.5%	
2	2.6%	4.2%	1.5%	
Pathology				0.316
Squamous	60.9%	54.2%	65.7%	
Adenocarcinoma	31.3%	35.4%	28.4%	
Other	7.8%	10.4%	5.9%	
Tumor stage				0.288
T0	0.9%	0.0%	1.5%	
T1	9.6%	6.4%	12.0%	
T2	24.6%	25.5%	23.9%	
T3	25.4%	17.0%	31.3%	
T4	39.5%	51.1%	31.3%	
Nodal stage				0.002
N0	3.5%	6.4%	1.5%	
N1	5.3%	4.3%	6.0%	
N2	43.0%	23.4%	56.7%	
N3	48.2%	65.9%	35.8%	
AJCC stage				0.003
IIIA	32.2%	16.7%	43.3%	
IIIB	67.8%	83.3%	56.7%	

AJCC, American Joint Committee on Cancer; ECOG, The Eastern Cooperative Oncology Group.

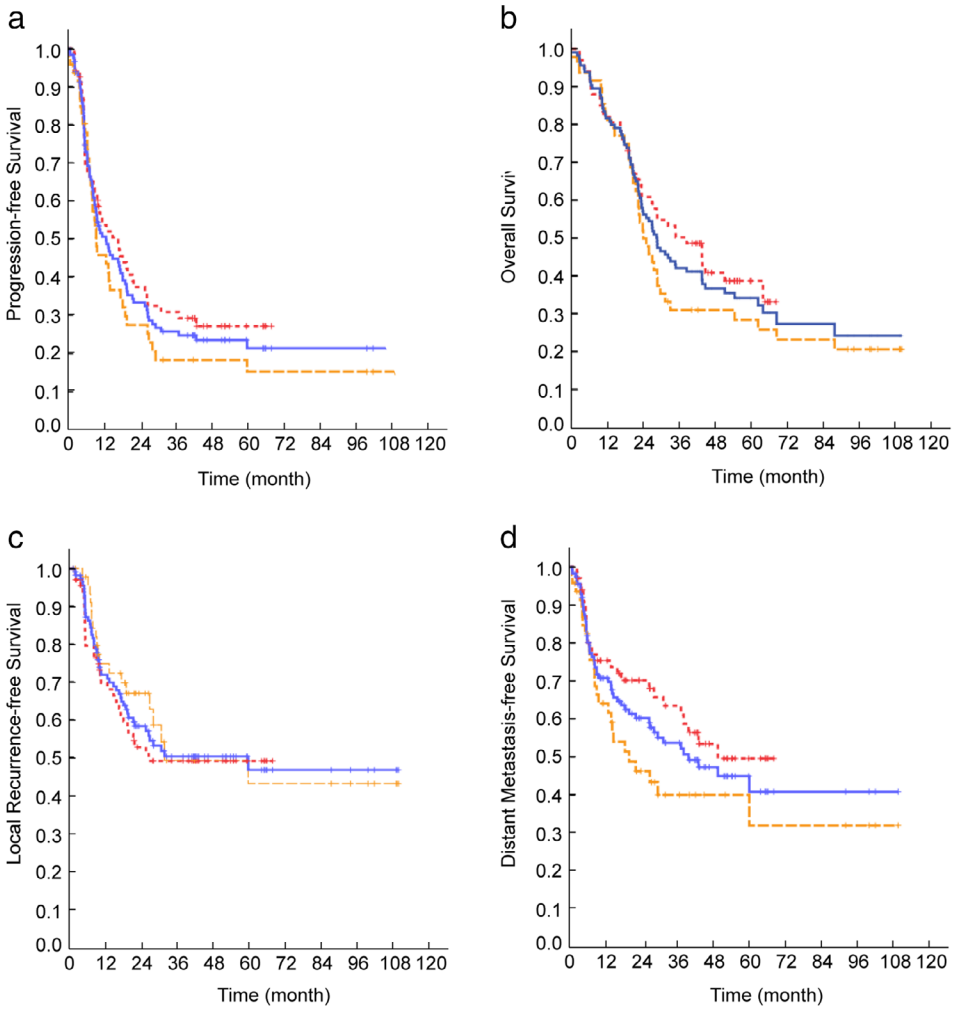

Figure 2 Kaplan-Meier survival curves of PFS, OS, LRFS and DMFS. No significant difference in median PFS, OS, LRFS and DMFS between two groups was seen. PFS, OS, LRFS and DMFS were 9.9 months versus 15.4 months (HR = 0.751, 95% confidence interval [CI], 0.487 to 1.160, P = 0.200), 24.0 months versus 38.5 months (HR = 0.746, 95% CI, 0.473 to 1.178, P = 0.209), 32.3 months versus 27.1 months (HR = 1.193, 95% CI, 0.673 to 2.115, P = 0.546), 20.1 months versus 49.7 months (HR = 0.603, 95% CI, 0.351 to 1.036, P = 0.067), respectively. (a) (-----) CIV arm, (- - - -) IV arm, (——) Overall patients; (b) (-----) CIV arm, (- - - -) IV arm, (——) Overall patients; (c) (-----) CIV arm, (- - - -) IV arm, (——) Overall patients; (d) (-----) CIV arm, (- - - -) IV arm, (——) Overall patients

lost to follow-up. The causes of death were directly related to NSCLC in 32 and 33 patients in the IV arm and CIV arm, respectively, and the number of cases of treatment-related complications were 2 in both arms. A total of 37 patients (77.1%) in the IV arm and 46 patients (68.7%) in CIV arm developed disease progression (P = 0.320). Local-regional recurrence was observed in 19 (39.6%) and 31 (46.3%) patients, (P = 0.476) and distal metastasis was observed in 26 (54.2%) and 27 (40.3%) patients in the IV arm and CIV arm, respectively (P = 0.141). The patterns of first failure were not statistically significantly different between the two arms.

In overall patients, the median PFS, OS were 13.2 months, 28.6 months; the one, three, five-year PFS were 50.1%, 26.0% and 23.7%; the one, three, five-year OS were 81.7%, 42.1%, 36.5%. In the IV arm and CIV arm, the median PFS was 9.9 months versus 15.4 months (HR = 0.751, 95% confidence interval [CI] 0.487–1.160, P = 0.200); the median OS was 24.0 months versus 38.5 months (HR = 0.746, 95% CI 0.473–1.178, P = 0.209); the median LRFS was 32.3 months versus 27.1 months (HR = 1.193, 95% CI 0.673–2.115, P = 0.546); the median DMFS was 20.1 months versus 49.7 months (HR = 0.603, 95% CI 0.351–1.036, P = 0.067). In the IV arm and CIV arm, the one, three, five-year PFS was 45.8% versus 52.9%, 18.3% versus 31.4%, and 18.3% versus 27.7%, respectively; the one, three, five-year OS was 81.2% versus 82.1%, 31.1% versus 50.3%, and 31.1% versus 41.0%, respectively; the one, three, five-year LRFS was 74.8% versus 69.7%, 49.1% versus 49.0%, and 49.1% versus 49.0%, respectively; and the one, three, five-year DMFS was 64.1% versus 75.4%, 40.1% versus 63.5%, and 40.1% versus 49.7%, respectively. Kaplan-Meier survival curves are shown in Fig. 2.

The incidences of nonhematological adverse reactions including nausea (87.6% versus 59.8%, P = 0.003), hair loss (91.7% versus 74.6%, P = 0.001) and dermatitis (97.9% versus 76.2%, P = 0.006) were higher in the CIV arm than in the IV arm while the incidence of decreased neutrophils

Table 3 Incidence of adverse events

	IV arm (n = 48)	CIV arm (n = 67)	P-value
Nausea	59.8%	87.6%	0.003
Grade 1	46.3%	68.8%	
Grade 2	9.0%	18.8%	
Grade 3	4.5%	0.0%	
Grade 4	0.0%	0.0%	
Grade 5	0.0%	0.0%	
Vomiting	41.9%	41.7%	0.263
Grade 1	29.9%	22.9%	
Grade 2	9.0%	18.8%	
Grade 3	3.0%	0.0%	
Grade 4	0.0%	0.0%	
Grade 5	0.0%	0.0%	
Hair loss	74.6%	91.7%	0.001
Grade 1	71.6%	68.8%	
Grade 2	1.5%	22.9%	
Grade 3	1.5%	0.0%	
Grade 4	0.0%	0.0%	
Grade 5	0.0%	0.0%	
Dermatitis	76.2%	97.9%	0.006
Grade 1	67.2%	89.6%	
Grade 2	9.0%	6.2%	
Grade 3	0.0%	2.1%	
Grade 4	0.0%	0.0%	
Grade 5	0.0%	0.0%	
Esophagitis	92.5%	97.8%	0.113
Grade 1	0.0%	6.2%	
Grade 2	79.1%	81.2%	
Grade 3	13.4%	10.4%	
Grade 4	0.0%	0.0%	
Grade 5	0.0%	0.0%	
RIP	22.4%	41.7%	0.202
Grade 1	10.4%	18.8%	
Grade 2	7.5%	12.5%	
Grade 3	3.0%	8.3%	
Grade 4	0.0%	2.1%	
Grade 5	1.5%	0.0%	
Decreased WBC	95.5%	95.8%	0.415
Grade 1	13.4%	8.3%	
Grade 2	37.3%	29.2%	
Grade 3	28.4%	27.1%	
Grade 4	16.4%	31.2%	
Grade 5	0.0%	0.0%	
Decreased neutrophils	89.5%	81.3%	0.010
Grade 1	17.9%	14.6%	
Grade 2	34.3%	18.8%	
Grade 3	26.9%	14.6%	
Grade 4	10.4%	33.3%	
Grade 5	0.0%	0.0%	
Decreased lymphocytes	98.6%	95.8%	0.644
Grade 1	4.5%	10.4%	
Grade 2	19.4%	18.8%	
Grade 3	49.3%	45.8%	
Grade 4	25.4%	20.8%	
Grade 5	0.0%	0.0%	
Decreased hemoglobin	76.1%	64.5%	0.441
Grade 1	29.9%	35.4%	
Grade 2	31.3%	20.8%	
Grade 3	11.9%	6.2%	
Grade 4	3.0%	2.1%	
Grade 5	0.0%	0.0%	
Decreased platelets	46.2%	31.2%	0.248
Grade 1	14.9%	12.5%	
Grade 2	14.9%	12.5%	
Grade 3	11.9%	6.2%	
Grade 4	4.5%	0.0%	
Grade 5	0.0%	0.0%	
SAE	6.0%	0.0%	0.085

RIP, radiation induced pneumonitis; SAE, severe adverse events; WBC, White blood cells.

(81.3% versus 89.5%, P = 0.010) was lower in the CIV arm than the IV arm. Incidence of most other hematological adverse reactions such as decreased WBC, decreased lymphocytes, decreased hemoglobin, decreased platelets were also numerically lower in the CIV arm than in the IV arm, although they were not statistically significant. Incidence of late pulmonary adverse reactions including radiation induced pneumonitis and esophagitis were similar between the two arms. The incidence of SAE was also numerically lower in the CIV arm than the IV arm, but the difference was not significant (Table 3).

Discussion

Results from our study in patients with locally advanced NSCLC (LA-NSCLC) treated with Endostar combined with CCRT indicated a prolonged median OS (28.6 months) compared with previous reports treated with CCRT alone (15 months to 18.9 months) and three-year OS was also superior to previous studies.[1,15,16] Moreover, in our study, the CIV arm achieved a much longer median OS (>14.5 months) than the IV arm. Although not statistically significant, a trend could be concluded. As seen in the OS rates, the survival benefit mainly came from the later phase (three-year OS 50.3% vs. 31.1%). In terms of safety, the CIV arm showed a different safety profile from the IV group which indicated that the CIV arm might have a trend of improving hematological adverse reactions. Since there were several differences between the two arms besides the administration routes of Endostar, that is disease stage, regimen of chemotherapy and way of radiotherapy, the benefits seen in the CIV arm might be attributed to multiple factors. For example, later disease stage might result in poorer prognosis and this might also be one of

the important factors for patients in the IV arm to present a shorter survival than the CIV arm. Herein, we discuss these potential influencing factors below.

The half-life of Endostar in vivo is only 10 hours.[17] In the IV arm, Endostar was delivered for four hours every day, so the drug concentration would be in a pulse form which might limit its efficacy. Evidence has shown that under normal conditions, the physical and chemical properties of Endostar is quite stable in vitro, so CIV might be an acceptable method of administration. In the CIV arm of our study, Endostar was continuously delivered for 120 hours using a miniosmotic pump, which maintained a stable and effective concentration. Previous studies in other fields have shown favorable feasibility of CIV Endostar. In the report by Li *et al.*[18] advanced NSCLC treated with CIV Endostar combined with chemotherapy showed a significantly higher disease control rate (86.2% vs. 70.7%, $P < 0.01$), longer median PFS (six months vs. four months, $P = 0.037$) and median OS (17.5 months vs. 13.5 months, $P = 0.034$) compared with IV Endostar combined with chemotherapy. The trend seen in the single-center retrospective study by Cheng *et al.*19 was similar to that in the report by Li *et al.* Yao *et al.*[20] retrospectively compared the efficacy of CIV Endostar to IV Endostar in advanced or metastatic lung squamous cell carcinoma, both combined with gemcitabine/cisplatin chemotherapy (GP regimen). The median OS in the CIV group appeared to be longer compared with the IV group (22.9 months vs. 14.3 months). Other small sample studies in advanced NSCLC treated with specific chemotherapy regimens such as GP regimen,[21,22] NP regimen (vinorelbine/cisplatin)[23] and TC regimen (paclitaxel/carboplatin)[24] also reported similar results and they found CIV Endostar could reduce cardiovascular toxicity and bone marrow suppression. Other studies comparing CIV Endostar and IV Endostar were mainly done in ovarian cancer patients treated with chemotherapy and the results were also similar. Based on clinical and preclinical data,[8,25] the sustained delivery of Endostar might be crucial to PFS and OS in the CIV arm.

The optimal chemotherapy regimen in CCRT remains unclear because there have been few large, randomized trials. Etoposide-cisplatin (EP) is one of the most commonly used concurrent regimens and is the recommended standard regimen in CCRT for LA-NSCLC by NCCN guideline. Therefore, we chose EP in the CIV arm. Sen *et al.*[26] compared the outcome of patients treated with either EP (etoposide 50 mg/m^2 on days 1–5 and 29–33 and cisplatin 50 mg/m^2 on days 1, 8, 29, and 36) or weekly DP (docetaxel and cisplatin each 20 mg/m^2) in curative CCRT. The results indicated that EP provided more favorable outcomes than DP. Ozcelik *et al.*[27] compared the efficacy and toxicities of EP (etoposide, 50 mg/m^2, on days 1 to 5 and 29 to 33 plus cisplatin, 50 mg/m^2, on days 1, 8, 29, and 36), DP (docetaxel, 20 mg/m^2, on day 1 plus cisplatin, 20 mg/m^2, on day 1, every week), and PC (paclitaxel, 45 mg/m^2, on day 1, every week plus carboplatin, AUC = 2) regimens delivered concurrently with radiotherapy for inoperable LA-NSCLC. Although the results did not prove a statistically significant difference in OS among the groups (37 months, 27 months and 23 months, respectively. $P = 0.098$), PFS was significantly prolonged in the EP group (21 months, 15 months and 10 months, respectively. $P = 0.01$). Another study showed weekly DP with reduced dose intensity may decrease the efficacy.[28] There is no prospective evidence comparing EP with DP for which combination might be more effective. The most accepted and commonly used chemotherapy regimen for concomitant treatment used is EP and PC. In the study by Liang *et al.*[29] median OS was 23.3 months in the EP arm and 20.7 months in the PC arm. In our study, it is worth noting that the median OS (38.5 months) and OS rate (one year: 82.1%, three years: 50.3%, five years: 41%) in the CIV arm were far superior to the historical studies of treatment of stage III NSCLC that used concurrent EP plus radiotherapy.[1,2,15,29,30]

In our study, the patients received 3D-CRT in the IV arm and IMRT in the CIV arm. Modern techniques such as IMRT have improved target coverage using optimized modulated fields (typically 6–12). IMRT might bring substantial benefits in prognosis compared to 3D-CRT. So far, there is a lack of prospective, randomized trial results which directly compare the efficacy and toxicity of 3D-CRT versus IMRT for lung cancer. Some retrospective studies have shown that IMRT has better normal-tissue sparing compared with 3D-CRT and IMRT is always being used to treat patients with larger volume tumors. However, there were no significant differences in survival time compared with IMRT and 3D-CRT. In RTOG 0617[31,32] which compared IMRT with 3D-CRT in 482 patients, researchers found two-year OS, PFS, local failure, and DMFS of IMRT were similar to 3D-CRT, but the IMRT group had lower rates of severe pneumonitis and cardiac doses. In the study by Shrimali *et al.* [33] there was also no significant difference in survival between IMRT and 3D-CRT (two-year OS: 49.9% vs. 51.3%). Appel *et al.*[34] retrospectively reviewed LA-NSCLC patients treated with a trimodality strategy consisting of concomitant chemoradiation to 60 Gy followed by completion surgery. They found that for NSCLC, 3D-CRT and IMRT techniques resulted in similar pathologic response, negative margins, local control, disease free survival and OS.

Our study also had limitations. First, due to different administration routes of Endostar, chemotherapy regimens, radiotherapy techniques and baseline characteristics, our analysis results could be potentially biased. It is still uncertain whether the favorable survivals seen in the CIV arm were mainly due to the different administration routes. Second, the median OS in the CIV arm was much longer

than that in the IV arm, but without statistical significance. This could be because the number of patients was limited. Furthermore, the PACIFIC study[35] showed that the median time to death or distant metastasis was 23.2 months with durvalumab after chemoradiotherapy in stage III NSCLC, which established a new standard treatment strategy in 2018. We did not combine immunotherapy in our trials because we had already finished the trials prior to 2018. Patients in the CIV arm in our study achieved a more favorable median DMFS of 41.7 months. Appropriate low-dose antiangiogenic therapy induced vascular normalization has been reported to improve immunotherapy.[36,37] Immunotherapy combined with antiangiogenic therapy may be considered in a subsequent study. Since the treatment of CCRT has developed rapidly over several years, including the choice of treatment regimens and radiotherapy techniques, the bias caused by the long time span in our study is unavoidable. Nevertheless, our study is still valuable because it is the first study that has reported CIV Endostar and IV Endostar combined with CCRT in patients with unresectable stage III NSCLC.

In conclusion, the addition of Endostar to CCRT has been shown to have a promising effect for the treatment of patients with unresectable stage III NSCLC. Endostar delivered as continuous intravenous pumping might have preferable OS, promising three-year PFS compared with that of delivery via intravenous injection. Further randomized II/III clinical trials are needed and have been planned for future studies.

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Disclosure

The authors declare that they have no competing interests.

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