# The Evaluation of Durative Transfusion of Endostar Combined with Chemotherapy in Patients with Advanced Non-small Cell Lung Cancer

Xiaoqin Li[a]，Guomin Gu[a]，Faris Soliman[b,c]，Andrew J Sanders[b]，Xiuli Wang[a]，Chunling Liu[a]

[a] Affiliated Tumor Hospital of Xinjiang Medical University, Urumqi, 830011,China; [b] Cardiff China Medical Research Collaborative, Cardiff　University School of Medicine, Cardiff, UK

[c] Cardiff and Vale University Health Board, University Hospital Wales, Cardiff, UK

## Keywords

Non-small Cell Lung Cancer·Endostar·Durative Transfusion·chemotherapy

**Abstract**

Background: The overall survival in Non-Small Cell Lung Cancer (NSCLC) is poor, with median overall survival of advanced NSCLC with standard systemic chemotherapy being reported at 13.6 months and the 5-year survival rate was less than 15%. Therefore, the aim of this study was to evaluate the endostar combined with chemotherapy in patients with advanced NSCLC. Methods: 116 cases of the histological pathology diagnosed stage IIIB-IV NSCLC were retrospectively collected. The control group was treated with chemotherapy combined with intravenous infusion of Endostar while the test group was durative transfusion of Endostar. The short-term therapeutic effects including overall response rate (ORR), disease control rate (DCR) and safety were evaluated in the both groups. In the follow-up, progressive free survival (PFS) and overall survival (OS) were also analysed. Results: In the test group, the ORR is 53.4%, which is similar to the control group (44.8%) ($p>0.05$). However, the DCR in the test group (86.2%) is significantly higher than the control group (70.7%) ($p<0.01$). The median time to progression in the test group (6 months) is also significantly longer than the control group (4 months). Importantly, the median OS in the test group (17.5 months) was improved compared to the control group (13.5 months). The one-year survival rate in the test and control groups was 9.7% and 15.8%. There was no significant difference in the side effects including thrombocytopenia, leucopenia，nausea and vomiting between the two groups. Conclusions: Endostar durative transfusion combined with chemotherapy showed a higher DCR, longer PFS, OS time and well tolerated in patients with advanced NSCLC.

## Background

Lung cancer is the most common malignancy and cause of cancer-related deaths worldwide,

particularly non-small cell lung cancer (NSCLC). This may be due to approximately 57% of all lung cancers being found at an advanced stage at diagnosis [1,2]. The accepted standard duel regimen chemotherapy consisting of paclitaxel and a platinum agent which demonstrates consistent objective responses [3]. However, the 5-year survival rate is still low [4] and treatment efficacy needs to be improved.

Solid tumour growth requires both nutrients and oxygen, which is facilitated by vessel angiogenesis to enable energetic tumour cell proliferation [5]. Therefore, anti-angiogenesis has represented a new approach for targeted cancer therapy [6]. Recent, clinical studies have demonstrated patients with advanced non-small cell lung cancers (NSCLCs) benefitting further from anti-angiogenic therapy, when combined with chemotherapeutic regimes [7, 8].

Endostatin is an endogenous angiogenesis inhibitor with strong anti-angiogenic activity that can inhibit the growth of various tumours and prevent the progression of metastasis [9]. Endostar, a novel recombinant human endostatin with an additional nine-amino acid sequence (MGGSHHHHH) at the N terminus, increased heat stability and proteolytic resistance compared to endogenous endostatin [10]. It has been reported that Endostar, as an angiogenesis inhibitor, strongly inhibits the growth of a variety of murine and xenotransplanted human tumours [11]. The clinical studies show that Endostar combined with first-line chemotherapy (vinorelbine-cisplatin or paclitaxel-carboplatin) in patients with advanced NSCLC significantly improved the progression-free survival (PFS) time and overall survival (OS) time [12].

Endostar is recommended to be administered by intravenous infusion once per day for four hours, nevertheless, its half-life *in vivo* is only 10 h, and thus the efficacy of endostar is limited. The mini-osmotic pump is a modality of delivering a continuous infusion, which is able to deliver a variety of solutions or suspensions at a constant rate for days and even up to several weeks. Thereby enabling an effective concentration of drug to be maintained and the efficacy of the drug enhanced. Here, we investigated whether the durative transfusion of Endostar combined with chemotherapy could enhance the efficacy in advanced NSCLC compared to

intravenous infusion once a day combined with chemotherapy for 10 days.

## Materials and Methods

### Eligibility/Inclusion Criteria

A retrospective review of all consecutive patients with pathologically confirmed stage IIIB-IV NSCLC were collected and analysed, over five- year period**.** These patients were staged according to American Joint Committee on Cancer Staging System. All patients were required to have at least one measurable tumour, which was not amenable to surgical excision. Further eligibility criteria required patients older than 18-years, the Karnofsky performance status (KPS) is more than 70 points, and life expectancy being greater than three-months. Finally, all patients' blood routine, liver and kidney function, and electrocardiogram (ECG) were identified as normal before the trial.

Patients were split into two groups where patients undergoing standard intravenous chemotherapy were defined as the control group and patients undergoing treatment durative pump chemotherapy, were defined as the treatment group.

Due to the nature of a retrospective review of approved treatment regimens, which were not experimental trials, submission and approval to a formal ethics committee was not required.

### Therapy schedule

The control group received intravenous infusion of Endostar once per day combined with chemotherapy, whilst the test group was treated with durative transfusion of Endostar for 10 days in each chemotherapy cycle. The chemotherapeutics for both groups were mainly docetaxel, gemcitabine, Pemetrexed, cisplatin and Nedaplatin. For the intravenous infusion, Endostar was given daily at the dose of 15 mg in 500 ml saline for 4 hours from day 1 to day 14 and repeated 7 days later. For the durative transfusion, Endostar was continuously pumped at the rate of 5 ml/h (210 mg in 279 ml saline) by the mini-osmotic pump (DBB-I-I type, Love's scientific instrument co., LTD, China) from day 1 to day 10.

During administration of Endostar, patient heart rate, blood pressure, pulse oxygen saturation and electrocardiogram were continuously monitored using an intelliVue MP20 patient monitor (Royal Philips Electronics, the Netherlands).

#### Evaluation of efficacy

The clinical symptoms and signs, side effects, and blood routine were examined every week. Blood chemistry and ECG were performed in every cycle. Efficacy was evaluated by CT scan in each cycle according to the Response Evaluation Criteria in Solid Tumours (RECIST) including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The disease control rate (DCR) was defined as the percentage of patients with CR, PR or SD. The overall response rate (ORR) was defined as the percentage of patients with CR or PR. OS was defined as the time from first treatment to death while PFS was considered as the time from randomization to tumour progression or death from any cause.

#### Statistical analysis

Statistical analysis was performed using the SPSS 18.0 statistical package. The short-term efficacy between the two groups were analysed by $\chi^2$ test. The differences in KPS were analysed by *t* test. Survival curves were drawn by Kaplan-meier method using the GraphPad prism software. Log-rank test was used to compare the survival rates of the two groups. A value of $p < 0.05$ was considered to be statistically significant.

## Results

#### Patient characteristics

A total of 116 patients were enrolled in the study, with an even split of 58 patients in both the control and treatment group. Characteristics of patients were summarized in Table 1. Of the control group there were 37 males and 21 females. The age range was 45- 70 years. Whereas, the treatment group consisted of 40 male and 18 female patients. The age range was 41-67years. There was no statistically significant difference in age, gender, clinical stage, smoking status, Karnofsky performance status, epidermal growth factor receptor (EGFR) status and Histology

between the two groups.

#### Response to therapy

Following treatment, we observed that the control group had 1 case of CR, 13 cases of PR and 16 cases of SD. The test group had 0 case of CR, 22 cases of PR and 14 cases of SD. The overall response rate (CR+PR) between the two groups was similar. However, the DCR of the test group was significantly improved, when compared to the control group (Table 2) ($p<0.01$). Importantly, the median PFS was significantly improved from 4 months in the control group, to 6 months in the test group (p=0.037) (Fig. 1a). The median OS time was also seen to be extended from 13.5 months in the control group to 17.5 months in the test group (p=0.034) (Fig. 1b). Finally, the one-year survival rate of the test group and the control group was seen to be 9.7% and 15.8%, respectively.

#### Safety

Patients were carefully monitored for significant, unintended and unwanted side effects. Mild to moderate side effects such as fatigue, vomiting, diarrhoea, and myelosuppression were tolerated well by all patients (Table 3). There were no significant differences in the side effects between the two groups. Only one case in the test group had grade IV myelosuppression and recovered after the injection of recombinant human granulocyte colony-stimulating factor and recombinant human interleukin-11. There were no treatment-related deaths.

## Discussion

In the treatment of non-small cell lung cancer, the efficacy of first-line platinum-containing regimen of duel regimen therapy has reached a bottleneck. The addition of anti-angiogenic drugs can improve efficacy and prolong survival. These have been confirmed previously by ECOG4599 and Beyond clinical trials. Endostar is a vascular endothelial inhibitor, which was developed by China independently and its mechanism is different from bevacizumab (anti-VEGF receptor monoclonal antibody).

Phase IV clinical trials showed that applying Endostar both in first-line and second-line chemotherapy in the treatment of non-small cell lung cancer could increase ORR and 1-year survival rate[13]. Therefore, this study changes the mode of administration, using a continuous infusion method, to maintain a stable blood concentration. Compared to traditional intravenous infusion for four hours per day, the continuous infusion mode is safer and can improve patients' compliance, shorten the time in hospital and cut costs.

Previously, a number of studies have demonstrated the Endostar can maintain the stability of physical and chemical properties under normal conditions at high concentration *in vitro*.

Endostatin, an endogenous angiogenic inhibitor, has been shown to inhibit VEGF, metalloproteinases, integrins, c-myc, cyclin D1, and even the Wnt signaling pathway [14]. *In vitro*, Endostar (the recombination human endostatin) can inhibit the growth of human lung adenocarcinoma cell line SPC-A4, the migration of human umbilical vein endothelial cell (HUVEC), and the angiogenesis of Chorio Allantioc Membrane [15]. Furthermore, Endostar can suppress tumour growth in mouse models (S180 sarcoma, H22 liver cancer) and human xenograft models (SPC-A4 lung adenocarcinoma, SGC7901 gastric cancer, HeLa cervical cancer, SMMC-7721 and Bel7402 liver cancer). It has been reported that Endostar can suppress not only the angiogenesis but also lymph node metastasis [16,17]. The addition of Endostar results in significant improvement in RR, median time to tumour progression, and clinical benefit rate in patients with advanced NSCLC [12,18-20]. From 2007, Endostar could be used as a first line agent together with chemotherapy in the treatment of NSCLC [21]. No death related to Endostar has been reported. In I ~ III period clinical study, heart reaction is the main adverse event in dose limited toxicity of Endostar and arrhythmia is the most common case [22, 23].

Our results showed that the durative transfusion of Endostar significantly improved the DCR and PFS compared to the intravenous infusion, although the ORR had no significant difference between the two groups. Importantly, the OS in test group was significantly extended compared to the control group. Within the literature, a randomized, double-blind,

placebo-controlled study demonstrated that Endostar plus chemotherapy caused only grade 1 and grade 2 cardiac ischemia in patients, but no significant difference was noted in OS and PFS between the treatment and control groups [24]. The different timing, sequence or dose of the anti-angiogenic drugs in combination with cytotoxic chemotherapy drugs might be resulted in the distinct clinical efficacy, but we thought that the different injection methods might be the major reason. The mini-osmotic pump was used to do the durative transfusion of Endostar in our study, which can maintain stable and effective blood drug concentration. Therefore, the efficacy of Endostar was improved. Furthermore, manageable side effects were observed in our study and there was no significant difference in the two groups. Previously, in a determination of Endostar concentration test, to exclude the effects of residual drug released from the osmotic pump 24 h after termination of pump flow, the concentrations of Endostar in serum of the control and test groups were tested at that time point, only nanogram amounts of drug were detected in the serum of the two groups and there was no difference, indicating that the difference between the two groups was not due to the residual Endostar in the pump [25].

In conclusion, the continuous administration of Endostar combined with chemotherapy for advanced NSCLC results in a higher DCR and longer PFS, with tolerable adverse effects. Further work would include prospective randomisation studies to further evaluate treatment response.

**Acknowledgements**

This work was supported by grants from the international medical foundation special fund of anti-tumour treatment (CIMF-F-H001-279). The authors declared no conflict of interest.

**References**

[1]. American Cancer Society. Cancer Facts & Figures, 2009. American Cancer Society, Inc.: Atlanta, GA, 2009.

[2]. Juergens R, Brahmer J. Targeting the epidermal growth factor receptor in non-small-cell lung cancer: who, which, when, and how? Curr Oncol Rep 2007; 9:255–64.

[3]. Stinchcombe TE, Socinski MA. Current treatments for advanced stage non-small cell lung cancer. Proc Am Thorac Soc 2009; 6:233–41.

[4] Hiroaki A, Keita M, Tateaki N, Hisao O, Takehito S, Tetsuhiko T et al. Progression-free survival at 2 years is a reliable surrogate marker for the 5-year survival rate in patients with locally advanced non-small cell lung cancer treated with chemoradiotherapy. BMC Cancer 2014; 14: 18.

[5] Poyil P, Amit B, Young-Ok S, Xin W, Zhuo Z, Songze D et al. Quercetin inhibits angiogenesis mediated human prostate tumor growth by targeting VEGFR- 2 regulated AKT/mTOR/P70S6K signaling pathways. Plos one 2012; e47516

[6]. Kaya M, Wada T, Nagoya S, Yamashita T. Prevention of postoperative progression of pulmonary metastases in osteosarcoma by antiangiogenic therapy using endostatin. J Orthop Sci 2007;12: 562-7.

[7]. Sheng J, Yang Y, Ma Y. The efficacy of combining antiangiogenic agents with chemotherapy for patients with advanced non-small cell lung cancer who failed first-line chemotherapy: a systematic review and meta-analysis. 2015; e0127306.

[8]. Aristea K, Anastasios K, Dora H, Maria T, Emmanouel K, Efstathios S et al. Clinical outcome of patients with non-small cell lung cancer receiving front-line chemotherapy according to EGFR and K-RAS mutation status. Lung Cancer 2010; 110-15

[9]. Olsson AK, Johansson I, Akerud H, Einarsson B, Christofferson, Sasaki T. The minimal active domain of endostatin is a heparin-binding motif that mediates inhibition of tumor vascularization. Cancer Res 2004; 64: 9012-17.

[10]. Jia H, Kling J. China offers alternative gateway for experimental drugs. Nat Biotechnol 2006; 24: 117–118.

[11]. Hongmei W, Shukui Q, Xiaojin Y et al. Endostar, a modified endostatin inhibits aseites formation, prolonging survival in mice tumor ascites model. 9th international Con of the Asian Clin Oncol Soc 2010; 388-01.

[12]. Wang JW, Sun Y, Liu YY, Yu QT, Zhang YP, Li K et al. Results of randomized, multicentre, double-blind phase III trial of rh-endostatin (YH-16) in treatment of advanced non-small cell lung cancer patients. Zhongguo Fei Ai Za Zhi 2005; 8: 283–90.

[13] Wang J, Sun Y, Quin S, Endstar phase IV Study Group. 2010. Results of phase IV clinical trial of combining endosctar with chemotherapy for treatment of advanced non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 28 (Suppl.15):7598-7598.

[14]. Abdollahi A, Hlatky L, Huber PE. Endostatin: the logic of antiangiogenic therapy. Drug Resist Updat 2005;8: 59–74

[15]. Thompson G, Mills SJ, Coope DJ. Imaging biomarkers of angiogenesis and the microvascular environment in cerebral tumors. Brit J Radi 2011; 84:127-44

[16]. Jia Y, Liu M, Huang W, Wang Z, He Y, Wu J et al. Recombinant human endostatin endostar inhibits tumor growth and metastasis in a mouse xenograft model of colon cancer. Pathol Oncol Res 2012;18: 315-23.

[17]. Ke QH, Zhou SQ, Huang M, Lei Y, Du W, Yang JY. Early efficacy of Endostar combined with chemoradiotherapy for advanced cervical cancers. Asian Pac J Cancer Prev 2012;13: 923-26.

[18]. Eder JP, Supko J, Clark JW, Puchalski TA, Garcia-Carbonero R, Ryan D et al. Phase I clinical trial of recombinant human endostatin administered as a short intravenous infusion repeated daily. J Clin Oncol 2002;20:3772–84.

[19]. Herbst RS, Hess KR, Tran HT, Tseng JE, Mullani NA, Charnsangavej C et al.

Phase I study of recombinant human endostatin in patients with advanced solid tumors. J Clin Oncol 2002;20:3792–03.

[20]. Thomas JP, Arzoomanian RZ, Alberti D, Marnocha R, Lee F, Friedl A et al. Phase I pharmacokinetic and pharmacodynamic study of recombinant human endostatin in patients with advanced solid tumors. J Clin Oncol 2003;21:223–31.

[21]. Zhu H, Zhang GW, Wang HJ, Yan XT, Wang QM, Li P et al. Endostar combined with NP or GP as first-line treatment options in advanced non-small cell lung cancer. J Med Forum 2011; 32:59-63

[22]. Yang I, Wang JW, Tang ZM, Liu XW, Huang J, Li ST et al. A phase I clinical trial for recombinant human endostatin. Chin J New Drugs 2011;13:548-53.

[23]. Yang I, Wang JW, Cui CX, Huang J, Zhang HP, Li ST et al. Rh-endostatin (YH-16) in combination with vinorelbine and cisplatin for advanced non-small-cell lung cancer: a muhicenter phase II trial. Chin J New Drugs 2005;14: 204-7.

[24]. Han B, Xiu Q, Wang H, Shen J, Gu A, Luo Y, Bai C, Guo S, Liu W, Zhuang Z, Zhang Y, Zhao Y, Jiang L, Zhou J, Jin X. 2011. A Multicentre, Randominzed, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Paclitaxel-Carboplatin Alon or with Endostar for Advanced Non-small Cell Lung Cancer. Journal of Thoracic Oncology. Vol 6 (6):1104-1109

[25]. Huang R, Zhan Q, Zhou X, Chu ZH, Jiang JW, Liang XH. Continuous administration of recombinant human endostatin (Endostar): A pre-clinical safety study. 2012;3:1018-22

Table 1. Baseline characteristics of the patients

| Characteristic | Control group (n=58, %) Intravenous infusion | Test group (n=58, %) Durative transfusion | $\chi^2$ | *P* |
|---|---|---|---|---|
| Number of case | 58(50.0) | 58(50.0) | | |
| sex | | | | |
| female | 21 | 18 | 0.56 | 0.41 |
| male | 37 | 40 | | |
| Age range | 45-70 | 41-67 | | |
| median age | 60 | 57 | | |
| Clinical stage | | | | |
| IIIB | 15 | 19 | 1.18 | 0.28 |
| IV | 43 | 39 | | |
| Smoking status | | | | |
| Never smoker | 30 | 32 | 0.38 | 0.67 |
| Current smoker | 28 | 26 | | |
| Karnofsky | | | | |
| 70-80 | 4 | 5 | 0.47 | 0.31 |
| 80-90 | 54 | 53 | | |
| EGFR status | | | | |
| M(+) | 18 | 20 | 0.29 | 0.79 |
| M(-) | 22 | 22 | | |
| NE | 18 | 16 | | |
| Histology | | | | |
| Adenocarcinoma | 14 | 24 | 0.77 | 0.68 |
| Squamous cell carcinoma | 22 | 22 | | |
| Large cell Undifferentiated carcinoma | 1 | 0 | | |

Table 2 Comparison of efficacy between control group and test group

| Response evaluation | Control group (%) | Test group (%) | *P* |
|---|---|---|---|
| CR | 1(1.7) | 0(0) | >0.05 |
| PR | 25(43.1) | 31(53.4) | >0.05 |
| SD | 15(25.9) | 19(32.8) | >0.05 |
| ORR | 26(44.8) | 31(53.4) | >0.05 |
| DCR | 41(70.7) | 50(86.2) | <0.01 |

*Table 3 Comparison of adverse reactions between two groups (n = 116)*

| Toxicity | Control group | | Test group | | |
|---|---|---|---|---|---|
| | Ⅰ~Ⅱ | Ⅲ~Ⅳ | Ⅰ~Ⅱ | Ⅲ~Ⅳ | P value |
| Neutropenia | 30 | 16 | 30 | 17 | 0.963 |
| anemia | 16 | 2 | 19 | 2 | 0.904 |
| thrombocytopenia | 9 | 1 | 9 | 1 | 0.999 |
| hemorrhage | 0 | 0 | 0 | 0 | 1.000 |
| Nausea/vomiting | 31 | 4 | 29 | 5 | 0.980 |
| mucositis | 0 | 0 | 1 | 0 | 0.422 |
| diarrhea | 3 | 1 | 2 | 0 | 0.553 |
| constipation | 13 | 1 | 10 | 0 | 0.822 |
| Transaminase increase | 3 | 0 | 4 | 0 | 0.860 |
| Total bilirubin increase | 0 | 0 | 1 | 0 | 0.423 |
| Serum creatine increase | 0 | 0 | 0 | 0 | 1.000 |
| Fever | 0 | 0 | 1 | 0 | 0.423 |
| Skin rash | 1 | 0 | 0 | 0 | 0.423 |
| Fatiaue | 21 | 1 | 19 | 2 | 0.973 |
| Pain | 6 | 1 | 7 | 0 | 0.999 |
| Allergy | 0 | 0 | 1 | 0 | 0.423 |
| Peripheral nerve toxicity | 2 | 0 | 1 | 0 | 0.698 |
| Alopecia | 8 | 1 | 7 | 0 | 0.858 |
| Arrhythniia | 2 | 0 | 4 | 0 | 0.698 |

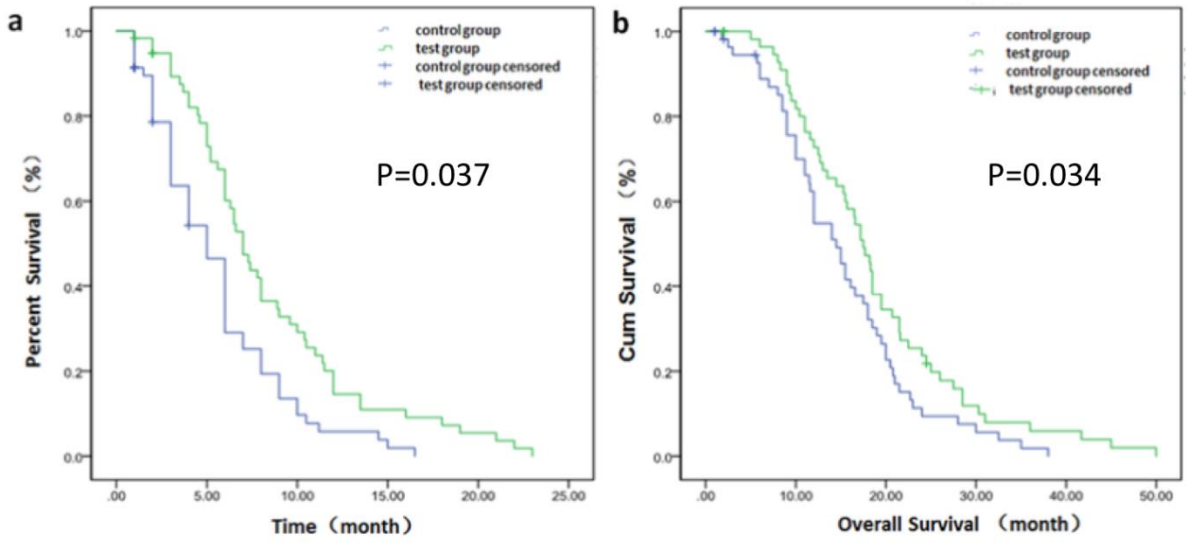


Fig.1 Kaplan－Meier estimated survival for all patients by treatment groups. (a) progression-free survival and (b) overall survival for all patients.