RESEARCH ARTICLE

Thalidomide Combined with Chemotherapy in Treating Patients with Advanced lung Cancer

Li Li, Xin-En Huang*

Abstract

Objectives: To evaluate efficacy and toxicity in patients with advanced lung cancer, including non-small cell and small cell variants (NSCLC and SCLC), treated with thalidomide plus chemotherapy. Methods: Fourteen patients with advanced lung cancer were scheduled to receive chemotherapy combined with thalidomide. All patients in this study received thalidomide (100 mg orally per night before sleeping, produced by Changzhou Pharmaceutical Factory Co.Ltd) after the start of chemotherapy for at least 14 days. Chemotherapy was administered according to the condition of patients. After at least 14 days of treatment, efficacy and toxicity were evaluated. Results: There were 6 female and 8 male patients with advanced lung cancer recruited into this study, including 2 with SCLC and 12 with NSCLC. The median age was 56.7 (44-65) years. Progressive disease was observed in 12 patients (12/14), and stable disease in 2 (2/14). Grade 1 to 2 myelosuppression was observed in 4/14 patients, and Grade 1 to 2 elevation of hepatic enzymes was recorded in 5/14 patients. Adverse effects on the gastrointestinal tract were documented in 2/14 patients, all beingGrade 1. No Grade 3-4 toxicity was recorded. No treatment related deaths occurred. Conclusions: Our results demonstrate that thalidomide combined with chemotherapy is mildly effective and safe for treating patients with advanced lung cancer. However, further evaluation of this combination is warranted.

Keywords: Advanced lung cancer - thalidomide - chemotherapy - combined treatment

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Introduction

The pathologic classification of lung cancer mainly includes non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC represents 75%-80% of lung cancer cases and accounts for approximately 1.2 million new cases worldwide each year (Jemal et al., 2005). The survival of patients with SCLC, which accounts for 15% - 20% of lung cancers, has improved only marginally in the past 25 years (Govindan et al., 2006). In non-squamous cell subtype of advanced NSCLC, cisplatin/pemetrexed provides similar efficacy with better tolerability and more convenient administration than cisplatin/gemcitabine (Ji et al., 2014; Cui et al., 2015; Li et al., 2015; Huang et al., 2015; Huang et al., 2015; Shi et al., 2015; Wu et al., 2015).

In advanced SCLC, first-line chemotherapy regimen is still etoposide plus carboplatin. In recent years, several large studies show that irinotecan combined with nedaplatin or carboplatin could achieve superior effect, wild similar hematological toxicity. And on the other way chemotherapy could be associated with better prognosis for patients with advanced lung cancer.

However, for patients with both NSCLC and SCLC, 5 year survival rate and rate of disease progression were relatively poor. Therefore, we need more efforts to develop more effective, lower toxic therapy. Several lines of evidence suggest that angiogenesis plays an important role in carcinogenesis (Hanahan et al., 2000). Thalidomide was given concurrently with chemotherapy to decrease tumor vascular permeability and interstitial fluid pressure and thus improve chemotherapy delivery (Jain et al., 2001; Ansiaux et al., 2005; Jain et al., 2005; Segers et al., 2006). Thalidomide is postulated to have a synergistic effect with platinum-based chemotherapy (Vasvari al., 2007). Long-term survival of a patient with SCLC following treatment with thalidomide and combination chemotherapy has been reported (Mall et al., 2006).

Given the above evidence, we hypothesize that thalidomide could be effective when combined with chemotherapy in treating patients with advanced lung cancer.

Materials and Methods

Eligibility criteria

Eligibility criteria for recruiting patients histologically or cytologically confirmed advanced lung cancer in Jiangsu

*Department of Chemotherapy, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, Nanjing, China *For correspondence: huangxinen06@163.com*

Table 1. Characteristic of Recruited Patients with Advanced Colorectal Cancer

Hospital registration number	Gender Male/Female	Age (year)	Chemotherapy with thalidomide	Response
239582	F	58	PEM+CPT-11+LBP	SD
212715	M	57	E-ADM+GEM+VP-16	PD
254891	F	48	PEM+DOC+DDP	PD
261998	M	52	PEM+CBP	SD
262219	M	64	PEM+CBP	SD
265816	F	58	PEM+CBP	PD
262435	M	62	CPT-11+NDP	PD
259865	M	52	GEM+NDP+CPT-11	PD
263321	M	65	GEM+NDP	PD
241749	F	63	PEM+DOC+OXA	PD
269320	F	55	GEM+PTX+CBP	PD
263356	M	61	DOC+IFO+LBP	PD
270024	M	55	PEM+LBP	PD
228987	F	44	PEM+DOC+CBP	PD

PR, partial response; PD, progressed disease; SD, stable disease

Cancer Hospital & Research Institute (from Sept 2015 to March 2016) to sign a consent of chemotherapy before treatment, to have a score of karnofsky performance status (KPS) ≥ 60, with an expectancy life span for more than 3 months; without contraindications for chemotherapy; to have a routine blood test performed 0 to 3 days before chemotherapy and with normal hematopoietic function as evidenced by white blood cell and platelet count for no less than the upper limit of normal, normal hepatic (aspartate amino transaminase and alanine aminotransferase less than 1.5 times of the upper limit of normal values), and renal function test (serum total bilirubin<1.5mg/dl and creatinine<1.5mg/dl). Exclusion criteria included history of alcoholic intoxication, diabetes, and patients who were pregnant or nursing. Chemotherapy was administered according to NCCN guideline. Thalidomide (produced by CHANGZHOU PHARMACEUTICAL FACTORY CO.LTD) was orally administered at a dosage of 50mg/day to 150mg/day before sleeping for at least 14 days. After at least 14 days of treatment, safety and side effects were evaluated.

Toxicity Evaluation

The incidence rates of toxicity in this study were assessed at baseline and respectively after treatment, the grade of toxicities was determined according to The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3).

Results

There were 6 female and 8 male pretreated patients with advanced cancer recruited into this study, including 2patients with SCLC, 12 patients with NSCLC. The median age of patients was 56.7 (44-65) years. Progressed disease was observed in 12 patients (12/14), and stable disease in 2 patients (2/14). Incidences of Grade 1 to 2 myelosuppression was observed in 4/14 patients, and Grade 1 to 2 elevation of hepatic enzyme was recorded in 5/14 patients. Adverse effects on the gastrointestinal tract were documented in 2/14 patients, and were Grade 1. No Grade 3-4 toxicities were diagnosed. No treatment related death was found.

Discussion

Thalidomide is a potent teratogen, also with anti-inflammatory and anti-angiogenic activity and was newly applied in treating patients with cancer (D'Amato et al., 1994). The mechanism of thalidomide in this setting involving immunomodulatory activity which is considered to inhibit the production of TNF-α, IL-1β, IL-6, IL-12, and granulocyte macrophage colony-stimulating factor. Previous studies suggested that thalidomide could induce an IL-2-mediated proliferation and increases IFN-γ production (Bartlett et al., 2004; Haslett et al., 1998), and inhibit NF-κB, a critical regulator of inflammatory processes (Keifer et al., 2001). Moreover, thalidomide is reported to inhibits IL-1β-induced IL-8 production, nuclear translocation of NF-κB, degradation of Iκ-Bα (Jin et al., 2002), and LPS-induced COX-2 (Fujita et al., 2001). Another mechanism is considered to involve in tumor angiogenesis of thalidomide (Folkman et al., 1995), that plays a key physiological role in wound healing while also playing a pathophysiological role in tumor growth, diabetic retinopathy, atherosclerosis, and chronic inflammation (Folkman et al., 1995). Angiogenesis is regulated through a balance of positive and negative regulatory mediators. VEGF is one of the most important positive angiogenic factors (Battegay et al., 1995; Veikkola et al., 2000). VEGF plays an essential role in endothelial proliferation and angiogenesis during embryogenesis as well as the menstrual cycle, and tumogenosis (Carmeliet et al., 1996; Gerber et al., 1999). Enhanced expression of VEGF may contribute to pathological mechanisms in adenocarcinoma, and chronic inflammation (Folkman et al., 1995). The importance of angiogenesis in the disease processes has been demonstrated by the success of antiangiogenic therapeutic trials, which are approved for the treatment of advanced colorectal adenocarcinoma (Prat et al., 2007). VEGF plays a key role in tumor neovascularization (Ferrara et al., 1999; Plate et al., 1992; Shweiki et al., 1992). And, it was hypothesized that the mechanism of anti-angiogenesis of thalidomide could be due to suppression through an induction of cell surface adhesion molecules in human umbilical veinendothelial cells (Geitz et al., 1996). In this study, our purpose is to assess the safety and effectiveness of thalidomide combined with chemotherapy in treating patients with advanced lung cancer. We recruited 6 female and 8 male patients with advanced cancer recruited into this study, including 2 patients with SCLC, 12 patients with NSCLC. The median age of patients was 56.7 (44-65) years. progressed disease was observed in 12 patients (12/14), and stable disease in 2 patients (2/14). Incidences of Grade 1 to 2 myelosuppression was observed in 4/14 patients, and Grade 1 to 2 elevation of hepatic enzyme was recorded in 5/14 patients. Adverse effects on the gastrointestinal tract were documented in 2/14 patients, and were Grade 1. No Grade 3-4 toxicities were diagnosed. No treatment related death was found. In conclusion, our current study suggested that thalidomide combined with chemotherapy was safe and mildly effective in treating

patients with advanced lung cancer. However, further study should be conducted to clarify the effectiveness and the best combination of thalidomide with chemotherapy.

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References

Ansiaux R , Baudelet C, Jordon BF , et al (2005). Thalidomide radiosensitises tumors through early changes in the tumor microenviroment. *Clin Cancer Res*, 11, 743-50 .

Bartlett JB, Dredge K, Dalgleish AG et al (2004). The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat Rev Cancer*, 4, 314-22.

Battegay EJ (1995). Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects. *J Mol Med (Berl)*, **73**, 333-46.

Carmeliet P, Ferreira V, Breier G, et al (1996). Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. *Nature*, **380**, 435-9.

Cui L, Liu XX, Jiang Y, et al (2014). Phase II study on dose escalating schedule of paclitaxel concurrent with radiotherapy in treating patients with locally advanced non-small cell lung cancer. *Asian Pac J Cancer Prev,* **15**, 1699-702.

D'Amato RJ, Loughnan MS, Flynn E, et al (1994). Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA,* **91**, 4082-5.

Ferrara N (1999). Molecular and biological properties of vascular endothelial growth factor. *J Mol Med,* **77**, 527-43.

Folkman J (1995). Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med*, **1**, 27-31.

Fujita J, Mestre JR, Zeldis JB, et al (2001). Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of -2. *Clin Cancer Res*, **7**, 3349-55.

Geitz H, Handt S, Zwingenberger K (1996). Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacology*, **31**, 213-21.

Gerber HP, Hillan KJ, Ryan AM, et al (1999). VEGF is required for growth and survival in neonatal mice. *Development*, **126**, 1149-59.

Govindan R, Page N , Morgensztern D, et al (2006). Changing epidemiology of small-cell lung cancer in the United States over the last 30years:analysisoftheSurveillance, Epidemiologic, and End Results database. *J Clin Oncol,* **24**, 4539-44.

Hanahan D, Weinberg RA (2000).The hallmarks of cancer. *Cell*, **100**, 57-70.

Haslett PA, Corral LG, Albert M, et al (1998). Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. *J Exp Med*, **187**, 1885-92.

Huang XE, Wang L, Ji ZQ, et al (2015). Safety of Lienal Polypeptide Injection Combined with Chemotherapy in Treating Patients with Advanced Cancer. *Asian Pac J Cancer Prev,* **16**, 7837-41.

Huang XE, Tian GY, Cao J, et al (2014). Pemetrexed as a component of first-, second- and third- line chemotherapy in treating patients with metastatic lung adenocarcinoma. *Asian Pac J Cancer Prev,* **14**, 6663-7.

Jain RK (2001) .Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med*, **7**, 987-9.

Jain RK (2005). Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*, **307**, 58-62.

Jemal A, MurrayT, WardE, et al (2005). Cancer statistics. *CA Cancer J Clin*, **55**, 10-30.

Ji ZQ, Huang XE, Wu XY, et al (2014). Safety of Brucea javanica and cantharidin combined with chemotherapy for treatment of NSCLC patients. *Asian Pac J Cancer Prev,* **15**, 8603-5.

Jin SH, Kim TI, Han DS, et al (2002). Thalidomide suppresses the interleukin 1beta-induced NFkappaB signaling pathway in colon cancer cells. *Ann NY Acad Sci*, **973**, 414-8.

Keifer JA, Guttridge DC, Ashburner BP, et al (2001). Inhibition of NF-kappa B activity by thalidomidethrough suppression of IkappaB kinase activity. *J Biol Chem*, **276**, 22382-7.

Li Y, Huang XE (2015). A Pooled Analysis on Crizotinib in Treating Chinese Patients with EML4-ALK Positive Non-small-cell Lung Cancer. *Asian Pac J Cancer Prev,* **16**, 4797-800.

Mall JW, Philipp AW, Mall W, Pollmann C (2002). Long-term survival of a patient with small-cell lung cancer :SCLC: following treatment with thalidomide and combination chemotherapy. *Angiogenesis*, 5, 11-3.

Prat A, Casado E, Cortes J (2007). New approaches in angiogenic targeting for colorectal cancer. *World J Gastroenterol*, 13, 5857-66.

Plate KH, Breier G, Weich HA, et al (1992). Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. *Nature*, **359**, 845-8.

Segers J, Fazio VD , Ansiaux R, et al (2006). Potentiation of cyclophosphamide chemotherapy using the anti-angiogenic agent thalidomide:importance of optimal scheduling to exploit the 'normalization 'window of the tumor vasculature. *Cancer Lett,* **244**, 129-35 .

Shi B, Zhang XB, Xu J, et al (2015). Systematic Analysis of Icotinib Treatment for Patients with Non-Small Cell Lung Cancer. *Asian Pac J Cancer Prev,* **16**, 5521-4.

Shweiki D, Itin A, Soffer D, et al (1992). Vascular endothelial growth factor induced by hypoxia may mediate hypoxiainitiated angiogenesis. *Nature*, **359**, 843-5.

Vasvari GP , Dyckhoff G , Kashfi F , et al (2007). Combination of thalidomide and cisplatin in an head and neck squamous cell carcinomas model results in an enhanced antiangiogenic activity in vitro and in vivo. *Int J Cancer,* **121**, 1697-704.

Veikkola T, Karkkainen M, Claesson-Welsh L, et al (2000). Regulation of angiogenesis via vascular endothelial growth 7870 Asian Pacific Journal of Cancer Prevention, Vol 16, 2015 factor receptors. *Cancer Res*, **60**, 203-12.

Wu XY, Huang XE (2015). Screening for patients with non-small cell lung cancer who could survive long term chemotherapy. *Asian Pac J Cancer Prev,* **16**, 647-52.