Thalidomide Combined with Chemotherapy in Treating Patients with Advanced Colorectal Cancer

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Abstract

Objective: To assess the safety and effectiveness of thalidomide (produced by CHANGZHOU PHARMACEUTICAL FACTORY CO.LTD) combined with chemotherapy in treating patients with advanced colorectal cancer. Method: A consecutive cohort of pretreated patients with advanced colorectal cancer were treated with thalidomide combined with chemotherapy. And chemotherapy for patients with advanced colorectal cancer were administered according to the condition of patients. Thalidomide 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. Results: There were 12 female and 3 male patients with advanced cancer recruited into this study, including 9 patients with colon, 6 patients with rectal cancer. The median age of patients was 57(41-82) years. Partial response was observed in 2 patients (2/15), and stable disease in 3 patients (3/15). Incidences of Grade 1 to 2 myelosuppression was observed in 1/15 patients, and Grade 1 to 2 elevation of hepatic enzyme was recorded in 1/15 patients. Adverse effects on the gastrointestinal tract were documented in 1/15 patients, and were Grade 1. No Grade 3-4 toxicities were diagnosed. No treatment related death was found. Conclusions: Thalidomide combined with chemotherapy was safe and mildly effective in treating patients with advanced colorectal cancer. However, further study should be conducted to clarify the effectiveness of this combination. Keywords: Thalidomide - chemotherapy - advanced colorectal cancer

Introduction

It was suggested by worldwide investigation that 14.1 million new cancer cases, and 8.2 million cancer-related deaths occurred, as well as 32.6 million people would live with cancer in 2012 (WHO, 2012). And among this, colorectal cancer (CRC) is one of the commonest cancers in both men and women with an estimated annual incidence of 1 million new cases (Ferlay et al., 2010), and the third most commonly diagnosed cancer and the third leading cause of cancer death worldwide (Jemal et al., 2011). Chemotherapy is an important component for patients with CRC, especially for those with advanced or metastatic disease. However, within these decades, the standard chemotherapeutic agent for advanced or metastatic CRC is still considered to be 5-FU or 5-FU combinations. Response rates to 5-FU alone are less than 20% and a combination regimen with biochemical modulating agents (i.e., leucovorin) seems improved response rate, while survival has not been affected. Now, multiple other agents are available for treatment of metastatic CRC. These agents include UFT, capecitabine, CPT-11, oxaliplatin and raltitrexed. All have predictable toxicities with very similar response rates and survival. Based on phase II data, UFT gave a response rate of 30% (95% CI: 14%-46%) with a median time to progression of 7.4 months and a median survival time of 14.2 months (Nogu et al., 1996). Capecitabine had very similar response rates with 7 of 36 patients on continuous treatment, 9 of 32 on intermittent treatment and 8 of 33 patients on intermittent treatment with leucovorin. Median times to progression were 17, 30 and 24 weeks, respectively. A good safety profile was also noted (Findlay et al., 1997). How to improve the treatment efficacy and to reduce side effects are the topics of clinical studies.

Previous reorts suggested that thalidomide could be active against a variety of cancers eg., myeloma, renal cell carcinoma, Kaposi’s sarcoma, and colorectal cancer (Rajkumar et al., 2000). The combination of thalidomide and irinotecan has been used in treating patients with metastatic colon cancer. Phase I-II study demonstrated that irinotecan at a dose of 300-350 mg/m2every 3 weeks and thalidomide at a dose of 400 mg/day could be safe (Govindarajan R et al., 2002). In animal models, the concomitant treatment with irinotecan and thalidomide did not significantly alter plasma pharmacokinetics of

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irinotecan (Yang et al., 2005), and in the treatment of advanced or metastatic cancer, thalidomide was modest active when combined with cytotoxic agents (Fine HA et al., 2003).

On this background, we hypothesize that thalidomide combined with chemotherapy could be established as an optimal schedule in treating Chinese patients with advanced or metastatic colorectal cancer.

Materials and Methods

Eligibility criteria

Patients recruited in this study were required to be pathologically/ cytologically diagnosed with colorectal cancer in Jiangsu Cancer Hospital & Research Institute; to sign an informed consent before treatment; to expose to long term chemotherapy or supportive care; to have a score of karnofsky performance status (KPS) ≥ 60 with expectancy life span more than 3 moths; to be classified with no contraindications for chemotherapy; to have a routine blood test performed 0 to 3 days before chemotherapy and normal hematopoietic function as evidenced by white blood cell count 3000/ul and platelet count 100000/ul, normal hepatic function test (aspartate aminotransaminase and alanine aminotransferase less than 1.5 times of the upper limit of normal values), renal function test (serum total bilirubin<1.5mg/dl and creatinine<1.1mg/dl). Exclusion criteria included history of alcoholic intoxication, diabetes, and patients who were pregnant or nursing. Chemotherapy was administered according to NCCN guideline. Thalidomide was orally administered at a dosage of 50mg/day to 150mg/day according to NCCN guideline. Thalidomide was modest active when combined with cytotoxic agents (Fine HA et al., 2003). In this study, 17 patients who had failed the standard chemotherapy were entered. Patients were treated with thalidomide at a dose of 200 mg/day with an increased dose of 200 mg/day every 2 weeks until a final daily dose of 800 mg/day was achieved. One patient was removed from the study due to toxicities. There were no objective responses or stable disease. Median OS was 3.6 months. In this study, our purpose is to assess the safety and effectiveness of thalidomide (produced by CHANGZHOU PHARMACEUTICAL...

Discussion

Thalidomide is a potent teratogen, also with anti-inflammatory and antiangiogenic activity and was newly applied in treating patients with cancer (D’Amato RJ et al., 1994). The mechanism of thalidomide in treating cancer patients 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. In primary human T cells, and thalidomide induces an IL-2-mediated proliferation and increases IFN-γ production (Bartlett JB et al., 2004; Haslett PA et al., 1998). Thalidomide also inhibits NF-κB, a critical regulator of inflammatory processes (Keifer JA et al., 2001). Moreover, thalidomide inhibits IL-1β-induced IL-8 production, nuclear translocation of NF-κB, degradation of Iκ-Bα (Jin SH et al., 2002), and LPS-induced COX-2 (Fujita J et al., 2001). In addition to effects on classic immune cell populations, the effect of thalidomide on tissue-specific microvascular endothelial populations, specifically the gut microvascular endothelium, during carcinogenesis and inflammatory remains a topic of research. Microvascular endothelial cells are a critical cell population in carcinogenesis, inflammation, wound healing, and inflammatory response. Angiogenesis, the growth of new microvessels, plays a key physiological role in wound healing while also playing a pathophysiological role in tumor growth, diabetic retinopathy, atherosclerosis, and chronic inflammation (Folkman J 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 EJ et al., 1995; Veikkola T et al., 2000). VEGF plays an essential role in endothelial proliferation and angio genesis during embryogenesis as well as the menstrual cycle, and tumogenesis (Carmeliet P et al., 1996; Gerber HP et al., 1999). Enhanced expression of VEGF may contribute to pathological mechanisms in adenocarcinoma, and chronic inflammation (Folkman J 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 A et al., 2007). VEGF plays a key role in tumor neovascularization (Ferrara N et al., 1999; Plate KH et al., 1992; Shweiiki D et al., 1992). And, it was hypothesized that the mechanism of anti-angiogenesis could be due to suppression of thalidomide through an induction of cell surface adhesion molecules in human umbilical vein endothelial cells (Geitz H et al., 1996).

Clinical investigation on thalidomide in treating patients with gastrointestinal cancer is limited. A previous study exploring the effects of thalidomide in refractory progressing metastatic colorectal cancer was published in 2003 (Lago LD et al., 2003). In this study, 17 patients who had failed the standard chemotherapy were entered. Patients were treated with thalidomide at a dose of 200 mg/day with an increased dose of 200 mg/day every 2 weeks until a final daily dose of 800 mg/day was achieved. One patient was removed from the study due to toxicities. There were no objective responses or stable disease. Median OS was 3.6 months. In this study, our purpose is to assess the safety and effectiveness of thalidomide (produced by CHANGZHOU PHARMACEUTICAL...

FACTORY CO.LTD) combined with chemotherapy in treating patients with advanced colorectal cancer. We recruited 12 female and 3 male patients with advanced cancer recruited into this study, including 9 patients with colon, 6 patients with rectal cancer. The median age of patients was 57 (41-82) years. All patients were treated with thalidomide combined with chemotherapy. And chemotherapy for patients with advanced colorectal cancer were administered according to the condition of patients. Thalidomide was orally administered at a dosage of 50mg/day to 150mg/day before sleeping for at least 14 days. Partial response was observed in 2 patients (2/15), and stable disease in 3 patients (3/15). Incidences of Grade 1 to 2 myelosuppression was observed in 1/15 patients, and Grade 1 to 2 elevation of hepatic enzyme was recorded in 1/15 patients. Adverse effects on the gastrointestinal tract were documented in 1/15 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 colorectal cancer. However, further study should be conducted to clarify the effectiveness and the best combination of thalidomide with chemotherapy.

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References


