

RESEARCH ARTICLE

Leucogen Tablets at 60 mg Three Times per Day are Safe and Effective to Control Febrile Neutropenia

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Abstract

Purpose: To investigate whether it is safe to use leucogen tablets 60 mg three times per day (180 mg for a day) and whether this regimen could reduce the incidence of febrile neutropenia caused by chemotherapy. **Methods:** This prospectively designed study focused on the safety and effectiveness of leucogen tablets 60mg three times per day for a group of cancer patients during chemotherapy for mainly lung or gastric cancers. The tablets were administered from 5 days before until the termination of chemotherapy. Neutropenia and other healthcare encounters were defined as events and occurrence was estimated for comparison. **Results:** We identified 39 patients receiving leucogen tablets 60mg three times per day, including 11 with gastric, 12 with lung and 16 with other sites of cancer. The mean age was 65 (29-75) years and there were 27 male and 12 female patients. The mean duration of leucogen tablets intake was 59 days. Eighteen patients were treated with taxane-based, 4 with irinotecan-based and 17 with other chemotherapy. The incidence of febrile neutropenia was 0%. Twelve patients were found severe neutropenia (grade III/IV), and the duration of severe neutropenia (grade III/IV) was 5 days. Treatment-emergent adverse events were attributable to complications of myelosuppressive chemotherapy or the primary disease (i.e., alopecia, nausea, asthenia, neutropenia, and severe hepatic renal dysfunction). No chemotherapy was delayed and no treatment related death was observed. **Conclusions:** This study suggested that leucogen tablets 60mg three times per day (180mg for a day) are safe and could be effective for preventing febrile neutropenia in patients with chemotherapy.

Keywords: Leucogen tablets - cancer patients - chemotherapy - febrile neutropenia

Asian Pac J Cancer Prev, 15 (19), 8495-8497

Introduction

Granulocyte colony stimulating factor (G-CSF) is recommended to be administered until neutrophil recovery occurs after the expected chemotherapy-induced nadir for patients who are receiving myelosuppressive chemotherapy and who are at risk of developing febrile neutropenia, a major dose-limiting toxicity of systemic chemotherapy associated with hospitalization, use of intravenous antibiotics, and mortality (Lyman et al., 1998; Lyman et al., 2002; Crawford et al., 2004; Caggiano et al., 2005; Lyman et al., 2005; Kuderer et al., 2006; Weycker et al., 2007; Schilling et al., 2011; Kozma et al., 2012). But the short circulating half-life (~3.5 hours) of G-CSF necessitates that it should be given daily. The efficacy of G-CSF also depends on the number of days it is administered. In clinical practice, if G-CSF is often administered for fewer than 10-11 days and may be associated with reduced efficacy (Weycker et al., 2006).

And one important use of G-CSF is to prevent febrile neutropenia (FN), for which hospitalization is

necessary. A previous review suggested that the risk of hospitalization was approximately one-third higher with filgrastim compared with pegfilgrastim (Morrison et al., 2007). Retrospective study showed that prophylactic use of G-CSF was associated with a one-third to two-thirds reduction in the risk of hospitalization for FN (Weycker et al., 2009). Two more recent studies on comparative effectiveness of G-CSF prophylaxis reported similar findings (Tan et al., 2010; Weycker et al., 2011). Thus, cost increase of cancer care following chemotherapy is significant. During 1989-2007, the number of neutropenia-related hospitalizations among cancer patients in the United States was estimated to be approximately 57,000-103,000 per year (Kozma et al., 2012). In another study, the average cost per hospitalization due to FN was reported to be \$12,372 for breast cancer patients, \$18,437 for lymphoma patients, and \$38,583 for leukemia patients (Kuderer et al., 2006). And further study found that mean hospitalization costs were \$18,042 for cancer patients with neutropenia, \$22,839 for those with neutropenia plus infection or fever (Schilling et al., 2011). That is,

FN in patients receiving chemotherapy pose a significant medical and financial burden. And notably, the side effects of G-CSF is obvious, eg., bone pain related symptoms, stomatitis grade , liver enzyme disturbance grade 2-3, cutaneous reactions, subclavian vein thrombosis, and decline in LVEF, etc.

On this background, we conduct this study to test if oral administration of prophylaxis use of leucogen tablets (Likejun) 60 mg three times per day (180 mg for a day), instead of currently dose schedule (20 mg three times per day, 60 mg for a day) or G-CSF, could be associated with a reduction of neutropenia and FN caused by chemotherapy.

The primary objective of the current study was to determine whether leucogen tablets 60 mg three times per day (180 mg for a day) is safe. The second objective of this study was to observe if this regimen could reduce the incidence of FN caused by chemotherapy.

Materials and Methods

Patient eligibility

All patients were required to be pathologically/cytologically diagnosed with cancer and received chemotherapy in Jiangsu Cancer Hospital & Research Institute from September 2013 to September 2014. Eligibility criteria before chemotherapy were as follows: 1. to have a score of karnofsky performance status (KPS) ≥ 70 ; 2. to be 25 to 75 years of age; 3. to sign an informed consent before treatment; . 5. Blood test results meet the following requirements: white blood cell count $> 4.0 \times 10^9$ and platelet count $> 150 \times 10^9$, bilirubin and transaminases < 1.5 times the upper normal limit and creatinine level < 1.5 times the upper normal limit. Patients were excluded from this study: 1.failed to complete two cycles of chemotherapy; 2.with any serious medical or psychiatric condition; 3 suffer from other malignancies at the same time; 4.pregnant or lactating women.

Treatment method

Eligible patients were provided with Likejun (leucogen tablets) 60 mg three times per day (totally 180 mg a day) 5 days before and till the termination of chemotherapy. Leucogen tablets (Likejun) were produced by Jiangsu Jibeier Pharmaceutical Co., Ltd. Each patient received chemotherapy. Patients were assessed and graded for toxicity according to WHO criteria (Miller et al., 1981).

Statistical analysis

SPSS13.0 statistical software was used for data input. If comparison was conducted, statistically significant difference was set at $p < 0.05$. We have enough experience in conducting medical research into adjuvant agents to counter effects of chemotherapy (Li et al., 2012; Liu et al., 2013; Yan et al., 2013). Follow-up examination was performed after three cycles of chemotherapy. All examinations were reviewed by two medical oncologists.

Blood assessments

Blood samples were collected for ANC determination 3 days before and after chemotherapy and then weekly after each cycle of chemotherapy until an ANC of $\geq 2.0 \times$

$10^9/L$ was reached. Safety assessments (blood sampling for determination of antibodies, physical examinations, vital signs) were performed within 24 hours if an ANC $< 1.5 \times 10^9/L$ and at the end of the study. Patients recorded their oral body temperature twice daily until day 15 or until ANC reached $\geq 2.0 \times 10^9/L$, and they were monitored for adverse events (AEs) and concomitant medication use throughout the study.

Results

We identified 39 patients receiving leucogen tablets 60 mg three times per day, including 11 patients with gastric, 12 with lung and 16 with other sites of cancer (none Hodgkin's lymphoma, esophageal, colorectal, cervical, and ovary cancer etc.). All patients were inpatient of Department of Chemotherapy, Jiangsu Cancer Hospital. The mean age of patients was 65 (29-75) years of age. There are 27 male and 12 female patients. The mean duration of leucogen tablets intake was 59 days. Eighteen patients were treated with taxanes based (mainly for patients with gastric, esophageal, cervical and ovary cancer), 4 with irinotecan based (mainly for patients with colorectal cancer) and 17 with other chemotherapy. No patients were found with FN, thus the incidence of FN was 0%. Twenty three patients were documented with neutropenia (grade I/II), and 12 were found severe neutropenia (grade III/IV). Patients with severe neutropenia (grade III/IV) were treated with a combination therapy consisting leucogen tablets 60 mg three times per day and G-CSF. The median duration of severe neutropenia (grade III/IV) was 5 days. Bone-pain-related symptoms, eg., bone pain, myalgia and arthralgia were reported only when G-CSF was used.

Discussion

G-CSF is an effective therapy for reducing the duration and incidence of chemotherapy-induced neutropenia and FN in cancer patients (Weycker et al., 2007; Schilling et al., 2011). Placebo-controlled clinical studies have shown significant reductions in the incidence of FN in patients treated with G-CSF (Kuderer et al., 2006; Schilling et al., 2011). However, the side effects of G-CSF are also obvious, eg., stomatitis grade , liver enzyme disturbance grade 2-3, cutaneous reactions, subclavian vein thrombosis, and decline in LVEF, etc. Therefore, it is necessary to develop medications with more convenience and low toxicities.

Oral administrated leucogen tablet is a derivative of L-cysteine. L-cysteine is associated with an effect to boost bone marrow hematopoietic function, but could be oxidized to cystine, and is not stable in vivo. Therefore L-cysteine is not applicable in clinical use. Oral administrated leucogen tablet is stable than its derivative and is widely used in clinical practice. However, the conventional dose is 20 mg three times per day (60 mg for a day), and is not an effective treatment for neutropenia. In this prospective designed study, 18 patients were treated with taxanes based, 4 with irinotecan based and 17 with other chemotherapy, all chemotherapeutic regimens with high myelosuppression. We found that at a mean duration

of leucogen tablets for 59 days, when leucogen tablets was administered at 60 mg three times per day, 5 days before and till the termination of chemotherapy, 12 patients were found severe neutropenia (grade III/IV), and the duration of severe neutropenia (grade III/IV) was 5 days. Incidence of febrile neutropenia was 0%. No ongoing chemotherapy was delayed and no treatment related death was observed. And, the treatment cost of leucogen tablet is low.

There are several bias and limitations inherent in the study design that could influence interpretation of these results. As this was a phase II study, patients were in the 29-75 year age range. Thus, the effects of leucogen tablet on outcomes in the population of patients aged 75 years or above were not fully captured. Secondly, the data are dependent on a small sample size without comparative group and hence contain errors or omissions when confounding factors exist, eg., variability of chemotherapeutic regimes, sites of cancer, general performance of patients, complications of treatment, social-economic condition of patients, and gender, etc. Likewise, our categorization of certain cycles as containing highly myelosuppressive chemotherapy based on the presence of individual agents used in that cycle may not adequately capture the various factors that affect the myelosuppressive effects of a chemotherapy regimen, such as combination chemotherapy and doses of specific agents. Thirdly, although the rate of FN is reported to be 0%, this study did not adequately capture the various known patient, disease, and treatment characteristics that are risk factors for developing FN, eg., comorbidities, recent history of anemia, history of radiation, and number of previously use of myelosuppressive agents (Lyman et al., 2005; et al., NCCN 2014). To reduce the effect of possible selection bias, randomized data should be collected to adjust these covariates. Thus, we should recommend to conduct further comparative studies to verify our results.

So, in conclusion, we suggest in current status that leucogen tablets (Likejun) 60 mg three times per day (totally, 180 mg for a day) is safe and could be effective for preventing FN in patients with chemotherapy, and this conclusion should be confirmed by randomized phase III studies.

Acknowledgements

Dr. Xin-En Huang is supported in part by the project of science and technology of Nanjing science committee. (Grant 201303046) and Jiangsu Provincial Special Program of Medical Science (BL2014092).

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