Use of Chinese Herbal Medicine Improves Chemotherapy-Induced Thrombocytopenia among Gynecological Cancer Patients: An Observational Study

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Background. Chemotherapy-induced thrombocytopenia (CIT) is a serious complication among patients with gynecological malignancies, yet management options are limited. This study aimed at reporting the potential of the Chang Gung platelet elevating formula (CGPEF), a prescription with a fixed proportion of Chinese herbs, for improving CIT among gynecologic cancer patients.

Materials. From 1/1/2007 to 31/12/2009, a total of 23 patients with two consecutive CIT episodes (≤100 × 10^3/μL) (last cycle: C0; index cycle: C1) received the CGPEF from the nadir of platelet count of C1 and through the subsequent chemotherapy cycles (C2 and beyond). The CGPEF was taken orally four times a day. The evolution of platelet counts of 18 patients after administration of CGPEF was analyzed (2 patients had different chemotherapy regimens after CGPEF, two patients discontinued CGPEF due to the flavor and the amount of CGPEF, and one patient had no further chemotherapy). Results. Most of the patients had recurrent ovarian cancer (11/18, 61%) with a median of 2.5 previous chemotherapy regimens, and carboplatin-based regimens were the most commonly used for these patients (13/18, 72%). The trend of successive CIT could be reversed after taking CGPEF. Also, the platelet nadir was higher after CGPEF treatment (16.5×10^3/μL versus 32×10^3/μL, before and after CGPEF treatment, resp., p = 0.002). Moreover, the chemotherapy interval decreased from 30.5 days to 24 days. No thrombocytosis, clinical bleeding, thromboembolism, or other adverse events were found among these patients. Conclusions. The CGPEF is worthy of further large-scale, well-designed clinical trials for CIT among gynecological cancer patients.

1. Introduction

Thrombocytopenia is one of the most severe complications of chemotherapy, and more than one-fifth of adult patients receiving chemotherapy ever experience thrombocytopenia [1, 2]. In addition to increased bleeding risks, CIT may force physicians to reduce chemotherapy dose, change the chemotherapy regimen, and postpone the chemotherapy schedule, although the treatment is effective [3–5]. These events may prolong hospitalization course, increase medical cost, lower quality of life, and even influence disease outcome [3, 4]. In addition to cisplatin-based chemotherapy, regimens
2. Methods

2.1. Study Design. From 1/1/2007 to 31/12/2009, patients with gynecological malignancies who suffered from two successive episodes of CIT were referred to TCM doctor for the CGPEF treatment. The patients’ eligibility was assessed by two gynecologic oncologists (Dr. Chyong-Huey Lai and Jian-Tai Qiu) in the Chang Gung Memorial Hospital (CGMH) once CIT was noted after two successive chemotherapy cycles, while CIT was defined as the platelet count lower than 100×10^3/μL after chemotherapy. The decision about eligibility was mainly based on gynecologic oncologists’ clinical experiences and patients’ preference. If CIT had occurred in the previous chemotherapy cycle (C0) and CIT recur at the subsequent course (C1), the intervention of CGPEF would be suggested and administered from the nadir of platelet count of C1 and through the subsequent chemotherapy cycles (C2 and beyond) if patients agreed (Figure 1).

2.2. The Chang Gung Platelet Elevating Formula (CGPEF) for CIT. The CGPEF is a prescription composed of 24 kinds of CHMs from 4 classic formulas: Ren-Shen-Yang-Ying-Tang, Gui-Pi-Tang, Gui-Lu-Er-Xian-Jiao, and Hu-Qian-Wan. These formulas have same ingredients recorded in the TCM textbooks, except tiger bone in Hu-Qian-Wan, because it is strictly prohibited in Taiwan. All CHMs have been commonly used for hundreds of years and were often used by TCM doctors to treat qi, blood, and kidney deficiency, which are thought to be the main cause of CIT on TCM’s viewpoint [24, 27]. The composition of the CGPEF is summarized in Table 1. All these herbs are produced by the Chuang Song-Zong Pharmaceutical Factory with good manufacturing practice during the entire observation time and are examined in detail for possible heavy metal, pesticide, or toxin. Every patient was given one pack of CGPEF, weighted 18 gm for adult weighing more than 60 kg, four times a day. The content of CGPEF, safety issues, and possible effectiveness were well explained to these patients in detail after the eligibility was confirmed. Patients were free to choose to take the CGPEF or not or discontinue the CGPEF at any time.

2.3. Ethical Consideration. The Institutional Review Board at Chang Gung Memorial Foundation approved this study (No. 99-1241B, 102-0721C).

2.4. Outcome Assessment. The changes in platelet counts after taking the CGPEF were the primary outcome of this study, while the lab data of each patient was collected retrospectively. The timing to collect blood samples was between days 7 and 14 of the cycle of chemotherapy in C1 and the first day of next cycle (C2) with 3-5 days’ intervals, depending on the severity of thrombocytopenia. Outcome parameters were compared between C1 and C2 (Figure 1). The secondary outcome parameters included duration of platelet counts less than 25×10^3/μL, 50×10^3/μL, and 75×10^3/μL after chemotherapy, platelet recovery time to 50×10^3/μL and 75×10^3/μL, and the interval between chemotherapies. Moreover, the need for blood transfusion was recorded as transfusion frequency and amount.
Patients with gynecologic malignancies who suffered from Chemotherapy-induced thrombocytopenia

CGEP treatment 23 subjects

Final analysis 18 subjects

Subjects excluded in final analysis:
1. changed chemotherapy regimen
2. could not tolerate amount and flavor of CGEP
3. stopped chemotherapy after taking CGEP

Figure 1: Diagram of enrollment and investigation of subjects in this study.

2.5. Statistical Analysis. Wilcoxon signed-rank test was used to compare platelet counts, durations, and days for recovery of C1 and C2, presenting the condition of CIT before and after CGEP treatment. All statistical calculation is done by the SPSS software and the results with p value less than 0.05 were thought to be statistically significant.

3. Results

A total of 23 patients ever received CGEP for their CIT, and 18 of them are included in the final analysis. Among the excluded patients, two patients could not tolerate CGEP due to drug amount and flavor; two patients received different chemotherapy regiments when taking CGEP and one patient did not receive further chemotherapy after CGEP treatment (Figure 2). The characteristics of enrolled patients are listed in Table 2. These patients aged 58.06 years on average. More than 60% of patients had ovarian cancer, followed by cervical cancer (27.78%). These patients had no other severe comorbidities, and only one patient had well-controlled hypertension. These patients had regionally or distantly advanced malignancies and had received at least two courses with different chemotherapy regimens for palliative intention (2.72 courses in average). Carboplatin was the most commonly used chemotherapy among these patients, about 72.2% of all patients.

The interval in chemotherapy initiation date extended to 31 days in average (median value: 30.5 days). The nadir of platelet count was about 24.1×10³/µL (median count: 16.5×10³/µL) (Table 3). After CGEP treatment, the interval of chemotherapy cycles was about nine days shorter than a previous cycle (30.5 versus 24 days in median value, p = 0.109). Additionally, the nadir of platelet count was also higher after treatment (16.5×10³/µL versus 32.0×10³/µL) in median value, p = 0.002). However, duration of nadir and recovery time did not differ significantly, although the durations were all shorter after CGEP treatment (Table 3). Overall, the trends of thrombocytopenia after chemotherapy seemed reversible after CGEP treatment (Figures 3 and 4), in which median value was 53×10³/µL. 62.5% of patients could have nadir higher than 25×10³/µL after chemotherapy during CGEP treatment.

Generally, the CGEP was well tolerated for the patients, except the intolerance to CGEP amount and smells. Sometimes patients complained about minor abdominal fullness.
When taking CGPEF but it recovered soon after adjusting the medication time. As for chemotherapy, hematologic disorders were the most concerned complications after chemotherapy. For leukocytopenia, one patient had grade IV, five patients had grade III, and seven patients had grade I-II leukopenia, without fever episodes. Additionally, for anemia, one had grade III, and seven patients had grade I-II leukopenia, according to the Common Terminology Criteria for Adverse Events v3.0.

**4. Discussion**

CGPEF may be a potentially effective alternative treatment for CIT with the significantly higher nadir of platelet count after/before CGPEF among patients with advanced gynecological malignancies. Also, CGPEF seems beneficial to improve delays in subsequent chemotherapy with marginally statistical significance. The benefit of CHM has been proposed for treating chemotherapy-related side effects; however, the evidence is still lacking, especially for CIT patients with gynecological malignancies [22]. Thrombocytopenia is one of the most important factors to postpone patient’s subsequent chemotherapy since carboplatin is commonly used among these patients, as our case series [28]. Delayed chemotherapy, especially with a reduced dose, could decrease overall survival rate [8–10]. Additionally, thrombocytopenia may increase risks of gastrointestinal bleeding and even hemorrhagic stroke [1]. It is difficult in reversing the trend of CIT if chemotherapy is ongoing without any intervention in clinical practice. CGPEF appeared to reverse the trend of CIT even if chemotherapy was kept without a reduced dose and prolonged interval (Figure 3). The interval between chemotherapies could be shortened to near 21 days, which is the modest interval of chemotherapy, and the median platelet nadir became higher than 30×10³/μL, (C2) which is associated with much lower risks for spontaneous bleeding compared to 16.5×10³/μL in previous chemotherapy course (C1).

Also, to reverse the trend of CIT, the benefit of CGPEF seems comparable to current medical treatment. IL-11, the only drug for CIT which is approved by the Food and Drug Administration in the United States, can elevate nadir of platelet count from 40×10³/μL to 60×10³/μL, while rhuTPOs have been reported to elevate nadir (from 20×10³/μL to 44×10³/μL) and shorten the duration of thrombocytopenia [II, 29, 30]. Moreover, through stimulating megakaryocyte, platelet transfusion can be reduced by using IL-11 without a reduction in chemotherapy dose [II, 31]. In our case series, the tendency for the duration of and transfusion rate of CIT to decrease can also be found, although not statistically significant (Table 3). The duration of platelet counts less than 50×10³/μL and 75×10³/μL can be shortened 2-3 days, and it takes 1-2 days shorter to recover to a safe level of thrombocytopenia. This trend may be more prominent if CGPEF starts on the first day of the C2 cycle but not in the late period of the C1 cycle, which may improve recovery of CIT in C1 cycle. Nevertheless, the larger study population is still needed to stress the difference in duration and recovery rate of CIT.

Furthermore, CGPEF treatment was quite tolerable among these patients, and only two patients stopped taking CGPEF due to its flavor and amount (72 gm/day). In clinical settings, CGPEF is unfavorable for CIT patients with adhesion ileus or massive ascites. For IL-11, although effective, the drug-related adverse events rate is as high as 30-50%, including edema, fever, hepatitis, coagulopathy, fatigue, and arthralgia [32, 33]. On the other hand, TPO receptor agonists

Table 1: Composition of Chang Gung platelet elevating formula (CGPEF).

<table>
<thead>
<tr>
<th>Chinese herbal products</th>
<th>Weight (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervus nippon Temminck</td>
<td>1.8</td>
</tr>
<tr>
<td>Trionyx sinensis (Wiegmann)</td>
<td>1.6</td>
</tr>
<tr>
<td>Phellodendron chinense Schneid.</td>
<td>0.7</td>
</tr>
<tr>
<td>Angelica sinensis (Oliv.) Diels.</td>
<td>0.7</td>
</tr>
<tr>
<td>Panax ginseng C. A. Meyer</td>
<td>0.7</td>
</tr>
<tr>
<td>Paeonia lactiflora Pall.</td>
<td>0.7</td>
</tr>
<tr>
<td>Achyranthes bidentata Blume</td>
<td>0.6</td>
</tr>
<tr>
<td>Zingiber officinale Rosc.</td>
<td>0.6</td>
</tr>
<tr>
<td>Rehmannia glutinosa (Gaertn.) Libosch.</td>
<td>0.5</td>
</tr>
<tr>
<td>Astragalus membranaceus (Fisch.) Bunge</td>
<td>0.5</td>
</tr>
<tr>
<td>Atractylodes macrocephala Koidz.</td>
<td>0.5</td>
</tr>
<tr>
<td>Poria cocos (Schw.) Wolf</td>
<td>0.5</td>
</tr>
<tr>
<td>Polygala tenuifolia Willd.</td>
<td>0.4</td>
</tr>
<tr>
<td>Glycyrrhiza uralensis Fisch.</td>
<td>0.4</td>
</tr>
<tr>
<td>Citrus reticulata Blanco</td>
<td>0.4</td>
</tr>
<tr>
<td>Anemarrhena asphodeloides Bunge</td>
<td>0.4</td>
</tr>
<tr>
<td>Zizyphus jujuba Mill.</td>
<td>0.3</td>
</tr>
<tr>
<td>Euphoria longan (Lour.) Steud.</td>
<td>0.3</td>
</tr>
<tr>
<td>Zizyphus jujuba Mill.</td>
<td>0.3</td>
</tr>
<tr>
<td>Cinnamomum cassia Blume</td>
<td>0.2</td>
</tr>
<tr>
<td>Lycium barbarum L.</td>
<td>0.2</td>
</tr>
<tr>
<td>Schisandra chinensis (Turcz.) Baill.</td>
<td>0.2</td>
</tr>
<tr>
<td>Gynecomorium sanguinum Rupr.</td>
<td>0.2</td>
</tr>
<tr>
<td>Aucklandia lappa Decene.</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Each CGPEF contains 24 Chinese herbs (12.7 gm) and 5.3 gm starch, totally 18 gm; daily dose: 72 gm.

Figure 3: The distribution of nadir platelet count after chemotherapy (C0: the first cycle of nadir platelet count ≤ 100×10³/μL; C1: the successive cycle with nadir platelet count ≤ 100×10³/μL; C2: the first chemotherapy course completely treated by CGPEF).
Table 2: Characteristics of the patients treated with Chinese herbal medicine formula: Chang-Gung platelet elevating formula (CGPEF).

<table>
<thead>
<tr>
<th>Count (%)</th>
<th>Median (Q1; Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>59.63 (49.11;64.75)</td>
</tr>
</tbody>
</table>

**Cancer type**

- Cervical cancer: 5 (27.8)
- Ovarian cancer: 11 (61.1)
- Endometrial cancer: 2 (11.1)

**Comorbidities**

- Hypertension: 1 (5.6)
- Diabetes mellitus: 0 (0)
- Ischemic heart disease: 0 (0)
- Cerebral vascular disease: 0 (0)
- Coagulopathy/bleeding disorder: 0 (0)
- Other malignancies: 0 (0)

**Preceding chemotherapy regimens**

- 2.5 (1.0;4.0)

**Chemotherapy regimens for CGPEF treatment**

- Cisplatin-based: 2 (11.1)
- Carboplatin-based: 13 (72.2)
- Taxane alone: 1 (5.6)
- Others: 2 (11.1)

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Table 3: Comparisons of presentations of CIT before and after using CGPEF (n = 18).

<table>
<thead>
<tr>
<th>Before CGPEF</th>
<th>Median</th>
<th>Q1; Q3</th>
<th>After CGPEF</th>
<th>Median</th>
<th>Q1; Q3</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy interval (days)</td>
<td>30.5</td>
<td>21.75;41.25</td>
<td>24</td>
<td>15.5;30.0</td>
<td>0.109</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>Times (per cycle)</td>
<td>0</td>
<td>0;0</td>
<td>0</td>
<td>0;0</td>
<td>0.564</td>
</tr>
<tr>
<td></td>
<td>Amount (units per cycle)</td>
<td>0</td>
<td>0;0</td>
<td>0</td>
<td>0;0</td>
<td>0.999</td>
</tr>
<tr>
<td>Platelet counts</td>
<td>Nadir (10^3/μL)</td>
<td>16.5</td>
<td>8.75;33.75</td>
<td>32</td>
<td>18.5;83.0</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>&lt; 25x10^3/μL duration (days)</td>
<td>4</td>
<td>0;7.5</td>
<td>0</td>
<td>0;8</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>&lt; 50x10^3/μL duration (days)</td>
<td>8.5</td>
<td>4.0;13.0</td>
<td>8</td>
<td>0;14.5</td>
<td>0.211</td>
</tr>
<tr>
<td></td>
<td>&lt; 75x10^3/μL duration (days)</td>
<td>14</td>
<td>8.5;28.0</td>
<td>10.5</td>
<td>0.5;19.75</td>
<td>0.279</td>
</tr>
<tr>
<td></td>
<td>Recover to 50x10^3/μL (days)</td>
<td>9</td>
<td>5.5;11.5</td>
<td>10</td>
<td>0;13.0</td>
<td>0.232</td>
</tr>
<tr>
<td></td>
<td>Recover to 75x10^3/μL (days)</td>
<td>10.5</td>
<td>6.75;13.5</td>
<td>10.5</td>
<td>0.5;14.5</td>
<td>0.629</td>
</tr>
<tr>
<td></td>
<td>Recover to 100x10^3/μL (days)</td>
<td>11.5</td>
<td>9.88;19.5</td>
<td>16.25</td>
<td>10.25;24.17</td>
<td>0.050*</td>
</tr>
</tbody>
</table>

* indicates p value < 0.05.

CIT: chemotherapy-induced thrombocytopenia.

with potential effects on CIT, such as eltrombopag and romiplostim, are reported to increase the risk of cerebral and portal vein thrombosis, abnormal liver function and, most seriously, myelofibrosis [34–36]. Thrombocytosis associated with the use of TPO receptor agonist became another potential drawback, since thrombocytosis may be related to poor prognosis of malignancies [37,38]. In the light of significantly higher serum TPO level among CIT patients [39, 40], medical treatment other than recombinant TPO and TPO receptor agonist may be needed to recover thrombocytopenia without causing possible thrombosis, myelofibrosis, and even thrombocytosis [7].

CGPEF with potential effects on CIT may be related to megakaryocyte stimulation and stem cell proliferation/differentiation [41]. The precise mechanism may be different from TPO agonist. In TCM theory, a patient with fatigue, nausea, and bone marrow suppression after chemotherapy is often diagnosed as qi and blood deficiency [27]. CGPEF was composed of 24 CHM to supplement qi and blood. *Panax ginseng*, one of the major ingredients of CGPEF, was usually used to supplement qi and its extract, panaxadiol saponins, was able to stimulate megakaryocytic maturation [42]. Moreover, *Astragalus membranaceus* and *Angelica sinensis* radix were reported to improve bone marrow stem cell...
proliferation [43]. In addition to improvements on thrombocytopenia, the anticancer and immunomodulation effects of *Angelica sinensis* [44], *Panax ginseng* [45–47], and *Astragalus membranaceus* [48, 49] in bench studies may imply the valuable role as adjuvant therapy in patients with gynecological malignancies and CIT.

In this observational study, we demonstrated the potential efficacy of CGPEF in treating CIT. However, there are still limitations. First, the post hoc power analysis showed that the $\beta$-error probability was about 0.23 by using Lehmann equation [50], and therefore the conclusion may be more solid if the case number could be higher. However, the important information about medication dose and duration, follow-up duration, examination scheme, and even endpoints provided in this study is crucial for further large-scale, randomized clinical trials, which are still lacking so far [12]. Second, since this is a pilot retrospective study, the differences in hemogram check-up timing may inevitably cause some errors in recording the timing and the platelet nadir count. However, because gynecologists often check hemogram earlier and more frequently once thrombocytopenia occurs, as two consecutive episodes of platelet count lower than $100\times10^3/\mu\text{L}$ in C0 and C1 in this study, the error should be minimal.

Third, since this is an observation study, we cannot completely exclude the possibility that CIT recovered by nature course. However, since only patients with two successive CIT episodes were included in this study and CIT is highly associated with courses of chemotherapy [1], the spontaneous recovery of CIT seemed less possible.

5. Conclusion

In this study, we demonstrated that CGPEF is a potentially effective treatment for CIT. Although this study is relatively small without untreated control, we demonstrated that the median platelet nadir count after CGPEF treatment (C2) was significantly higher than before (C1). Further well-designed, double-blind, placebo-controlled clinical trial with a larger number of subjects can be done based on these preliminary results.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.
Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References


Evidence-Based Complementary and Alternative Medicine


