Flexible Granulocyte Colony-Stimulating Factor Dosing in Ovarian Cancer Patients Who Receive Dose-Intense Taxol Therapy

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As is emerging with other chemotherapeutic agents, evidence is emerging to suggest that increased taxol dose intensity is associated with improved therapeutic efficacy. Granulocyte colony-stimulating factor (G-CSF) effectively protects the bone marrow from taxol-induced neutropenia and allows for higher taxol dose administration. This report addresses the optimal use of G-CSF as a supportive agent for dose-intense taxol therapy. Forty-seven patients were evaluated. Each ovarian cancer patient received taxol with G-CSF support, with starting doses of 250 mg/m² per 21 days and 10 µg/kg/d, respectively. Five patients were treated with the same dose of G-CSF for multiple cycles. Forty-two patients were given "flexible" G-CSF dosing. Instead of reducing taxol dose after a cycle of therapy complicated by febrile neutropenia (F + N +), the G-CSF dose was increased. Only after a second episode of F + N + was the taxol dose reduced. The initial 5 patients who developed F + N + after taxol (250 mg/m²) and G-CSF (10 µg/kg/d) were retreated at the same doses of both drugs: subsequently, 4 of 5 patients had another episode of F + N +. With flexible G-CSF dosing, taxol dose intensity could be maintained at the target level in 34 of 42 patients (81% of the cohort). Sixteen of these patients (38% of the cohort) would have required taxol dose reductions for F + N + if flexible G-CSF dosing had not been used. By increasing the G-CSF dose when indicated, patients at high risk for recurrence of F + N +, because they had already experienced one episode, appeared to have a lower risk of developing a recurrent episode. These data suggest that flexible G-CSF dosing may have merit and may allow the administration of more dose-intensive taxol. A prospective, randomized, controlled clinical trial of flexible G-CSF dosing versus fixed-dose G-CSF appears warranted. This is a US government work. There are no restrictions on its use.

CYTOTOXIC CHEMOTHERAPY regimens used in cancer therapy are often associated with substantial hematopoietic toxicity. Fever and neutropenia (F+N+) are major morbidities that result, and the patient suffers an increased risk of life-threatening infection and prolonged hospitalization. In addition, neutropenia can limit the doses of effective therapy administered. Shortening the length and severity of neutropenia can have major benefits to patients by reducing the risk of infection and perhaps by increasing the amount of chemotherapy that can be administered per unit time. The advent of recombinant DNA technology has allowed the cloning and production of a number of colony-stimulating factors for clinical use that can potentially ameliorate much of the hematopoietic toxicity associated with cytotoxic therapy.

In humans, granulocyte colony-stimulating factor (G-CSF) stimulates the production of functional neutrophils that are protective against infection, and it is safe and effective when administered by either intravenous or subcutaneous routes. G-CSF, in conjunction with anticancer chemotherapy, is effective in stimulating granulopoiesis and decreasing the frequency of episodes of F+N+. G-CSF was used as an adjuvant with methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) chemotherapy for remission therapy is associated with improved survival. In patients with non-Hodgkin's lymphoma, retrospective analyses have suggested that increased dose intensity may have resulted in an increased disease response rate. Also, increased dose intensity of cisplatin, studied by meta-analysis, correlated with an improved response rate in ovarian cancer patients. In patients with acute myeloid leukemia who are less than 60 years of age, dose-intensive postremission therapy is associated with improved survival. Thus, a wide range of results in a number of different cancer types supports the theory of dose intensity.

Taxol is a novel chemotherapeutic agent that is active against recurrent ovarian cancer. The dose-limiting toxicity of taxol without G-CSF support is usually neutropenia, which can be readily treated with G-CSF. We recently developed a higher-dose taxol regimen for patients with advanced epithelial ovarian cancer whose disease is platinum-refractory. This report summarizes our efforts to use flexible G-CSF dosing to maintain taxol dose intensity.

MATERIALS AND METHODS

Patient selection. The analyses presented are from 47 individuals treated on an approved experimental treatment regimen of taxol (250 mg/m² every 21 days) with G-CSF support. Detailed analyses of disease response are presented elsewhere. Patients with histologically confirmed epithelial ovarian cancer who had failed to re-

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FLEXIBLE G-CSF DOSING AND TAXOL

2 Patients (5%) Taxol 250 mg/m² G-CSF 10 µg/kg

14 Patients (33%) Taxol 250 mg/m² G-CSF 20 µg/kg

2 Patients (5%) F(+)N(+)

No Further Therapy

19 Patients (45%) Continue Same Dosage

1 Patient (2%) Taxol 250 mg/m² G-CSF 5 µg/kg

2 Patients (5%) Taxol 200 mg/m² G-CSF 10 µg/kg

F(+)N(+)

1 Patient (2%) Taxol 200 mg/m² G-CSF 20 µg/kg

10 Patients (24%)

Continue Same Dosage

G-CSF Bone Pain

Grade 4 Thrombocytopenia

Grade 3 Peripheral Neuropathy

2 Patients (5%)

F(-)N(+/-)

4 Patients (10%)

Taxol 200 mg/d

10 Patients (24%)

Grade 3

Initial patients. The first 5 patients treated in this study to develop F+N+ were retreated at the same dose of taxol (250 mg/m²) and G-CSF (10 µg/kg/d) on subsequent cycles. Five of five patients (100%) developed subsequent neutropenia and 4 of 5 patients (80%) developed another episode of F+N+, including 1 patient who died from polymicrobial sepsis. Thus patients who had one episode of F+N+ were at high risk for another episode if no dose modifications of taxol or G-CSF were made. This initial experience with a rigid taxol and G-CSF dosing schedule led us to modify our protocol to include flexible G-CSF dosing.

Fig 1. Flow of patients through the protocol algorithm. Forty-two patients were entered onto this study of flexible G-CSF dosing and were treated with an initial dose combination of taxol and G-CSF. Subsequent cycles were administered as indicated. The first episode of febrile neutropenia was managed by increasing the dose of G-CSF for the next cycle. If a second episode of fever and neutropenia occurred, the taxol dose was reduced for subsequent cycles. G-CSF was reduced by 5 µg/kg/d if intolerable bone pain occurred. Grade 4 thrombocytopenia or grade 3 peripheral neuropathy were managed by dose reductions of taxol.
**Table 1. Hematologic Toxicity Seen in Patients Receiving Various Taxol/G-CSF Dose Combinations**

<table>
<thead>
<tr>
<th>G-CSF (μg/kg)</th>
<th>Taxol (mg/m²)</th>
<th>Total Patients*</th>
<th>Total Cycles*</th>
<th>Cycles AGC &lt;5001</th>
<th>Patients F+N+</th>
<th>Cycles F+N+</th>
<th>Patients F+N+</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>250</td>
<td>42 (100%)</td>
<td>165 (84%)</td>
<td>57 (35%)</td>
<td>34 (81%)</td>
<td>18 (11%)</td>
<td>18 (43%)</td>
</tr>
<tr>
<td>20</td>
<td>250</td>
<td>14 (33%)</td>
<td>53 (21%)</td>
<td>25 (10%)</td>
<td>12 (86%)</td>
<td>6 (11%)</td>
<td>4 (23%)</td>
</tr>
<tr>
<td>10</td>
<td>200</td>
<td>4 (10%)</td>
<td>13 (5%)</td>
<td>6 (46%)</td>
<td>3 (75%)</td>
<td>1 (8%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>20</td>
<td>200</td>
<td>5 (12%)</td>
<td>14 (6%)</td>
<td>5 (35%)</td>
<td>3 (60%)</td>
<td>2 (14%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>15</td>
<td>250</td>
<td>2 (6%)</td>
<td>8 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>250</td>
<td>1 (2%)</td>
<td>2 (1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>150</td>
<td>1 (2%)</td>
<td>2 (1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Percentage reflects percent of patients or cycles relative to total number evaluated (total no. of patients, 42; total no. of cycles, 257).
† Percentage reflects percent relative to total number evaluated at that dose combination.

**Patient flow through the protocol.** Figure 1 shows the flow of patients through the G-CSF treatment schema. All 42 patients (100%) started therapy with taxol 250 mg/m² and G-CSF 10 μg/kg/d. Nineteen patients (45%) continued the same dosage combination throughout therapy. Eighteen patients (43%) experienced F+N+. Of these 18 patients, 2 patients did not receive further therapy and 16 patients had their G-CSF dose increased to 15 or 20 μg/kg/d for the next cycle (2 patients were only increased to 15 μg/kg/d because of significant bone pain from G-CSF at 10 μg/kg/d). Of the 16 patients receiving 250 mg/m² taxol and 15 or 20 μg/kg/d G-CSF, 12 patients continued on that dose combination. Four of these 16 individuals had their taxol dosage reduced because of a second episode of F+N+. Four additional patients had taxol dose reductions for thrombocytopenia or peripheral neuropathy (Fig 1). G-CSF was reduced to 10 μg/kg/d in a single patient who experienced severe bone pain secondary to G-CSF during her first cycle.

**Episodes of neutropenia and/or fever.** Table 1 summarizes the results for the combinations of taxol and G-CSF used in this study. All patients received the first cycle of taxol (250 mg/m²) with 10 μg/kg/d G-CSF and 165 cycles were administered with this dose combination. Eighteen patients treated with the initial dose combination had one or more episodes of F+N+ and had their G-CSF dosage increased during the next cycle. A comparison of patients treated with 250 mg/m² taxol and either 10 or 15 to 20 μg/kg/d G-CSF (Table 1) showed 43% of patients treated with 10 μg/kg/d G-CSF had initial episodes of F+N+, whereas at the higher G-CSF dose of 15 to 20 μg/kg/d, 25% of patients had F+N+.

Eighty-one percent of patients receiving 10 μg/kg/d developed neutropaenia, whereas 75% of patients developed neutropaenia while receiving 15 to 20 μg/kg/d of G-CSF. Thus, the occurrences of neutropaenia were similar in the two groups. Because 4 of the first 5 patients with neutropaenia studied at the 10 μg/kg/d G-CSF dose level had repeated episodes of F+N+, we interpret this to suggest that the high-risk group may have been protected by the increases in their G-CSF dose.

A similar conclusion can be reached when data are analyzed in terms of cycles of therapy administered (Table 1). An analysis of all cycles was made of patients treated with 250 mg/m² taxol and either 10 or 15 to 20 μg/kg/d G-CSF. In cycles administered with 10 μg/kg/d G-CSF, 57 of 165 cycles (35%) were associated with neutropaenia and 18 cycles (11%) with F+N+. At the higher G-CSF dose of 15 or 20 μg/kg/d, 25 of 61 cycles (35%) were associated with neutropaenia and 6 cycles (10%) were complicated by F+N+. Thus, the two groups seem to be comparable in outcome.

**Effects on neutrophil counts.** Table 2 shows the analysis of the G-CSF dose effect on neutropaenia for all patients treated with a taxol dose of 250 mg/m² and either 10 or 20 μg/kg/d G-CSF. No significant differences were found in mean neutrophil nadir or day of onset. Note that complete blood counts were obtained on Mondays and Thursdays and were not obtained more frequently unless the patient developed fever. This may have reduced the ability of the study to detect small differences in endpoints. When a patient developed fever, daily counts were obtained until F+N+ resolved. Therefore, a cycle of therapy with docu-

**Table 2. Analysis of G-CSF Effect on WBC Toxicity at the Taxol Dose of 250 mg/m²/3 wk**

<table>
<thead>
<tr>
<th>G-CSF (μg/kg)</th>
<th>Taxol (mg/m²)</th>
<th>No. of Cycles</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>250</td>
<td>130</td>
<td>1,341 ± 1,636</td>
<td>865</td>
<td>0-6,232</td>
</tr>
<tr>
<td>Day of onset of neutropenia in neutropenic cycles</td>
<td></td>
<td>54</td>
<td>7 ± 0.8</td>
<td>7</td>
<td>5-9</td>
</tr>
<tr>
<td>Nadirs in neutropenic cycles</td>
<td></td>
<td>49</td>
<td>178 ± 158</td>
<td>162</td>
<td>0-494</td>
</tr>
<tr>
<td>20</td>
<td>200</td>
<td>42</td>
<td>1,204 ± 1,430</td>
<td>626</td>
<td>0-6,536</td>
</tr>
<tr>
<td>Day of onset of neutropenia in neutropenic cycles</td>
<td></td>
<td>20</td>
<td>7 ± 1.1</td>
<td>7</td>
<td>6-11</td>
</tr>
<tr>
<td>Nadirs in neutropenic cycles</td>
<td></td>
<td>20</td>
<td>200 ± 155</td>
<td>191</td>
<td>0-493</td>
</tr>
</tbody>
</table>

Data are from all cycles in which counts are available. For some patients observed at outlying hospitals, frequent blood counts were not obtained.
mented fever included a carefully documented WBC nadir after the onset of the fever. Our reported severity and duration of neutropenia may be an underestimation in some patients for these reasons. The average duration of neutropenia in patients receiving taxol (250 mg/m²) and G-CSF (10 µg/kg/d) who developed F+N+ was 2.0 ± 1.1 days. Thus, even in patients who developed F+N+, the duration of neutropenia was brief.

G-CSF was administered for an average 7.2 ± 1.6 days for patients who did not develop F+N+, and 7.8 ± 1.8 days for the 18 patients who did. Figure 2 shows the average number of days that G-CSF was administered for each cycle of therapy for patients receiving 10 µg/kg/d (Fig 2A) or 20 µg/kg/d (Fig 2B). No significant differences in length of G-CSF administration were found between different cycles of therapy or between the two G-CSF dose levels. The presence of F+N+ during cycle one did not correlate with the number of prior therapies received, which averaged 2.6 (range, 1 to 6) for the patients studied.

DISCUSSION

Our phase II study using G-CSF support demonstrated an objective response rate of 50% in patients who had failed to respond to platinum-based therapy, suggesting the need for a trial of high- versus low-dose taxol, because prior small phase II trials showed a lower response rate. This trial successfully attempted to test the efficacy of dose-intense taxol. One of the most important obstacles to this trial was the predictable neutropenia that high-dose taxol induces. We therefore used G-CSF for bone marrow support. After we treated 5 patients on this protocol, we realized that the dose intensity we sought would be difficult to maintain. F+N+ was common, and patients who experienced one episode of F+N+ could not be retreated with taxol at the high dose without a grave risk of recurrent F+N+. Consequently, we decided to use flexible G-CSF dosing. This strategy proved to be successful and allowed patients who otherwise may have required dose reductions of taxol to receive continued high-dose therapy. In this study, WBC counts did not differ significantly between the 10 and 20 µg/m²/d doses of G-CSF, suggesting a possible protective effect by the higher G-CSF dose in cycles administered to patients who had already experienced F+N+. Neutrophil function may be responsible in part for the protective effect, because increased function has been observed in vitro with G-CSF administration.

The optimal dose and schedule of G-CSF that is effective as an adjunct in patients treated with chemotherapy is currently under investigation. G-CSF has been administered in a variety of schedules in patients being treated with chemotherapy. In one of the earliest trials of G-CSF with chemotherapy, patients treated with M-VAC for bladder cancer were treated with G-CSF. Doses from 1 to 60 µg/kg/d were administered as an IV infusion over 30 minutes on days 4 through 11 of the protocol. Pretreatment neutrophil counts were increased in a dose-dependent fashion; neutrophil counts increased 1.9-fold with the administration of 1 µg/kg/d for 5 days, and up to 10.2-fold with 60 µg/kg/d. In a randomized, placebo-controlled trial of patients receiving chemotherapy for small cell lung cancer, G-CSF was self-administered subcutaneously in a fixed dosage of 230 µg/m²d starting 24 hours after the completion of chemotherapy from day 4 until day 17. This regimen was well tolerated and led to reductions of F+N+ and of documented infections. A wide variety of schedules of G-CSF were effective whether administered IV (bolus or continuous) or subcutaneously, and a dose-response relationship (peripheral white blood counts) has been routinely observed, although the effect has not yet been studied in detail in patients receiving chemotherapy. The data presented here illustrate one major point. When using a cytotoxic agent in which myelosuppression is the major toxicity, flexible dosing of the appropriate CSF may permit maintained optimal dose intensity.

A G-CSF dose of 5 µg/kg/d has been suggested as an appropriate dose for chemotherapy trials, but the optimal dose is not yet defined. Whereas this may be reasonable for regimens of low or intermediate levels of myelosuppression, more aggressive cytotoxic chemotherapy may require more substantial bone marrow protection. Individualization of therapy with flexible G-CSF doses based on the patient's tol-

![Fig 2](https://example.com/fig2.png)

**Fig 2.** (A) Average number of days that G-CSF was administered per cycle in patients receiving 10 µg/kg/d. No significant differences were found between cycles of therapy. The standard deviations of these measurements ranged from 1.3 to 2.1 days. (B) Average number of days that G-CSF was administered per cycle in patients receiving 20 µg/kg/d. No significant differences were found between cycles of therapy. Note that no patient received G-CSF (20 µg/kg/d) during the first cycle of therapy. The standard deviations of these measurements ranged from 1.3 to 1.7 days.
erance and response to chemotherapy may be a new and useful approach. G-CSF dose escalation may be beneficial in some patients, whereas lower doses or no G-CSF may be sufficient in patients with more tolerant bone marrow. Thus, added drug cost and complications can be avoided. Treatment regimens designed with flexible G-CSF dosing tailored to the individual may also allow for more dose-intense therapy that might in turn improve patient survival. Taxol appears to be an important addition to the treatment armamentarium for ovarian and breast cancer. \(^{11,14,19}\) and possibly other malignancies.\(^{21,22}\) This study suggests the need for a randomized control trial of fixed dose versus flexible dose G-CSF as an adjunct to dose-intensive chemotherapy with taxol in ovarian cancer patients. A phase III intergroup trial has been organized by the Cancer Therapy Evaluation Program of National Cancer Institute that will test these hypotheses.

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**REFERENCES**


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