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The absence of cumulative bone marrow toxicity in patients with recurrent adenocarcinoma of the ovary receiving dose-intense taxol and granulocyte colony stimulating factor

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Forty-eight patients with recurrent adenocarcinoma of the ovary were treated with taxol and granulocyte colony stimulating factor (G-CSF), with a target taxol dose intensity of 250 mg/m^2 every 3 weeks (83.3 mg/m^2/week). We have assessed the patterns of granulocyte and platelet toxicity seen in this cohort. Individual patients received up to nine cycles of therapy. Criteria for entry onto protocol included good end organ function, good performance status and the absence of substantial co-morbid disease. Mean taxol dose intensity was 79.0 mg/m^2/week for the whole cohort and did not diminish with increased duration of therapy. Granulocytopenia and thrombocytopenia were well controlled, with the average duration of platelet and neutropenic nadirs being less than 1 day for all cycles. There was no evidence of cumulative toxicity for granulocytes nor platelets, for up to eight cycles of therapy. We conclude that taxol, when given with G-CSF support, can be safely administered in a dose-intense fashion for multiple cycles of therapy, without cumulative bone marrow toxicity.

Key words: Cumulative toxicity, dose intensity, ovarian cancer, taxol.

Introduction

Platinum-based chemotherapies are considered standard as initial treatment for advanced stage epithelial ovarian carcinomas with surgically documented complete response rates of 30–60%.[1,2] However, duration of response and rates of recurrence are areas of concern. Recurrence rates of 37–62% after a negative second look laparotomy have been reported in patients who received aggressive platinum-based regimens.[1,3] Taxol, a novel antimicrotubule agent derived from the western yew *Taxus brevifolia*, has been found to have significant antitumor activity in advanced recurrent or persistent epithelial ovarian cancer in several phase II trials.[4–6] The most significant dose-limiting toxicity in all of these trials was myelosuppression, with severe neutropenia occurring in 57–70% of the patients. Other significant toxicities included thrombocytopenia, mucositis and peripheral neuropathy.[4–6]

Given the high incidence of hematologic toxicity, a phase I trial of taxol with granulocyte colony stimulating factor (G-CSF) support was undertaken. The use of G-CSF for bone marrow support allowed for the administration of taxol at 83.3 mg/m^2/week without dose-limiting myelosuppression or mucositis.[7] Dose-limiting neurotoxicity was seen at 100 mg/m^2/week. Thus, taxol can be delivered at a dose intensity of 83.3 mg/m^2/week when hematologic support with G-CSF is provided.[7]

There is significant evidence for a dose–response relationship between cisplatin dose intensity and objective disease response in ovarian carcinoma.[8] Thus, a phase II study of taxol with G-CSF support was undertaken to evaluate if dose intensification would lead to an improved disease response rate. Prior studies have shown response rates ranging from 21 to 36% with planned dose intensity values ranging from 33 to 83.3 mg m^2 week. However, it has not been reported whether a substantial number of dose reductions occurred due to hematologic toxicity.[4–6] For this reason, we have examined in detail the neutrophil and platelet toxicity profiles of ovarian cancer patients started at a taxol dose of 250 mg m^2 every 3 weeks, with G-CSF support. Disease response to this regimen is the subject of a

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preliminary report,[9] which will be described in detail in a separate manuscript.

Materials and methods

Forty-eight ovarian cancer patients were included in this analysis. Each patient received taxol on either a phase I or II study of taxol and G-CSF under an approved experimental therapy protocol conducted in the Medicine Branch of the National Cancer Institute (NCI), Bethesda, MD.[7] All patients who entered onto either protocol at the level of 250 mg/m^2/cycle of taxol are included in this analysis.

The starting dose of G-CSF was 10 μg/kg/day and was fixed for six patients included from the phase I study. In the phase II study provisions were made for G-CSF dose escalation and dose reduction. G-CSF dose was escalated to 20 μg/kg/day if a patient experienced an episode of febrile neutropenia. If a second episode of febrile neutropenia was experienced, taxol was dose reduced to 200 mg/m^2/cycle. G-CSF was decreased by 5 μg/kg/day in response to G-CSF related bone pain.

Patients were treated who had epithelial ovarian carcinoma which had recurred after, or progressed during, platinum-based chemotherapy. Eligibility criteria also included age of 18 or over, with no upper age limit. For the six patients from the phase I portion of the study, minimal pre-treatment was required, i.e. only one or two prior therapies. For patients from the phase II study, there was no limit to the number of prior therapies. In both studies, good end-organ function was required, which included liver function studies less than twice the upper limit of normal and a 24 h creatinine clearance value of $\geq$45 ml/min. Also required was a performance status of ECOG (Eastern Cooperative Oncology Group) $\leq$2, and no objective findings on neurologic examination [grade $\leq$1, Cancer Therapy Evaluation Program (CTEP) criteria, see below]. In both studies, patients who had received external beam radiation therapy were excluded. Patients requiring anti-hypertensive medication were eligible for study, but patients who were taking anti-arrhythmic or anti-anginal medication were specifically excluded.

Two hundred cycles of therapy are included in this analysis. Since taxol was administered every 21 days, dose intensity was calculated from the first day of taxol until 21 days after the last dose of taxol. Therefore, a patient who received only one cycle of therapy was calculated to have received 250 mg/m^2/cycle divided by 3 weeks, or 83.3 mg/m^2/week. All statistical analyses were performed using the Cricket Graph Version 1.3 software package on a Macintosh SE computer (Macintosh, Palo Alto, CA).

Taxol and G-CSF were supplied by the Pharmaceutical Resources Branch of the Developmental Therapeutics Program of the NCI. Toxicities were assessed according to the Common Toxicity Criteria of the CTEP of the NCI. Taxol was continued or discontinued based on the occurrence of clinical benefit to the patient. If there was a greater than 30% reduction in tumor mass from the previous assessment or a greater than 50% decline in the CA125 level, the patient was continued on therapy. If neither of these events occurred, taxol was discontinued. Taxol therapy was discontinued in any patient at such time that there was clear clinical evidence of progressive disease.

Results

Administered dose intensity of taxol

Patients ranged in age from 26 to 74 years, with a median of 55. The age distribution of the cohort is shown in Figure 1. Twenty-nine percent of patients (14 of 48) were of age 61 or older and 8% (four patients) were of age 70 or older. In all of our graphical analyses below, we chose to view age as a continuous variable and not group patients by age. Overall, the mean administered dose intensity in this cohort was 79.0 mg/m^2/week, with a median

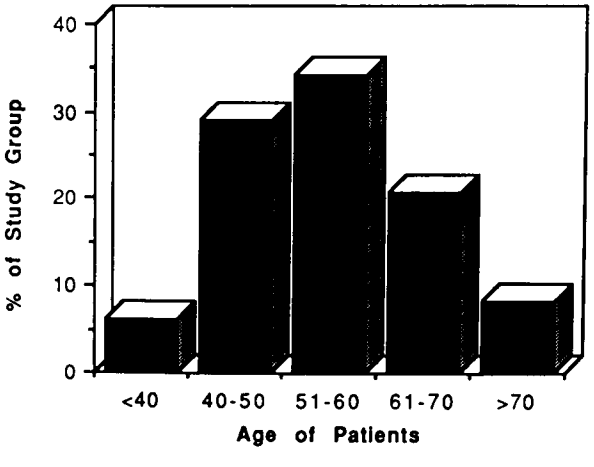

Figure 1. The age distribution of the cohort.

Table 1. Dose intensity was maintained in patients who received multiple cycles of therapy

Number of cycles of taxol administered	No. of patients	Age of patients (mean ± SD)	Administered dose intensity (mean ± SD)	Percent of patients given full dose taxol
1	48	54 ± 10	80.2 ± 6.5	100
2	45	54 ± 10	80.0 ± 6.7	96
3	29	54 ± 10	78.9 ± 7.7	93
4	25	54 ± 10	78.7 ± 7.3	88
5	18	54 ± 10	79.3 ± 6.2	89
6	16	52 ± 10	79.1 ± 6.5	87
7	10	56 ± 11	77.3 ± 6.6	80
8	7	57 ± 12	78.2 ± 6.1	86
9	2	49	77.7	100

of 83.3 (range 56.25–93.75 mg/m^2/week). The target dose intensity was 83.3. In this study, no patient experienced dose reduction below 200 mg/m^2/cycle although several patients experienced dose delays.

The number of cycles of therapy administered to patients in the study are listed in Table 1. All 48 patients received a dose of 250 mg/m^2 in cycle 1. Because of tumor progression, three patients received only one cycle of therapy, resulting in 45 patients receiving a second cycle. Of these 45 patients, 16 were determined to have progressive disease or a minimal decrease (below 50%) in the CA125 level *and* a minimal decrease (below 30%) in tumor bulk after cycle 2, and did not receive further therapy. As shown in Table 1, the number of patients receiving drug gradually declined with seven patients receiving eight cycles of therapy and only two patients receiving nine cycles. Listed in column 3 is the mean age (±2 SD) for all patients who received the respective number of cycles of therapy. For example, 16 patients received cycle 6 of taxol and their average age was 52.3. A similar analysis is performed for administered dose intensity, listed in column 4. As shown, there were no changes in mean age or average dose intensity as the length of therapy increased.

In column 5 of Table 1, the percentage of patients who received full dose taxol (250 mg/m^2/cycle) is listed. Once dose reduced, no patient had their taxol dose re-escalated. Therefore a patient who received full dose on cycle 9 received full doses of drug on each of the previous 8 cycles. As shown, the greatest percentage of dose reduction occurred in cycle 7, in which two of 10 patients received 200 mg/m^2 of drug.

Six of the 48 patients studied were a part of our phase I study of taxol and G-CSF, and had received only one or two treatment regimens prior to receiving taxol.[7] In the 42 other patients included in this analysis, there was no restriction on prior therapy. Table 2 is an analysis of this cohort with respect to dose intensity, toxicity and prior therapy. As listed, 12 patients had received only one regimen prior to receiving taxol; 16 patients had received only two regimens; and two patients had received six treatment regimens prior to receiving taxol. There was no significant variability in administered taxol dose intensity as prior therapy increased (column 3). The total number of serious (CTEP grade 3 or 4) toxicities experienced during treatment also did not vary. Although there appears to be a trend towards a higher number of minor

Table 2. The absence of an impact of the extent of prior treatment on the occurrence of taxol-related toxicities

Number of prior taxol cycles	No. of administered doses		No. of toxicities (mean ± SD)	
	patients	intensity	grade 3 or 4	grade 1 or 2
1	12	80.6 ± 6.8	3.6 ± 1.4	5.8 ± 1.8
2	16	77.7 ± 8.5	3.9 ± 1.7	7.3 ± 3.5
3	8	82.5 ± 2.1	5.3 ± 3.1	7.6 ± 3.2
4	7	81.7 ± 2.9	4.3 ± 1.8	7.2 ± 2.7
5	3	80.5 ± 3.9	5.0 ± 1.0	9.5 ± 0.5
6	2	83.3	4.5	11.5

(CTEP grade 1 or 2) toxicities in the more heavily pretreated patients (column 5), when these data were analyzed by linear regression analysis the suggested trend was not statistically significant (correlation coefficient = 0.102).

Patterns of myelosuppression after cycle 1

Given on an intermittent schedule, Taxol's primary toxicity is leukopenia.[4] We assessed taxol effect on leucocyte and platelet nadirs during cycle 1 of therapy as a function of age (Figure 2A and B). Figure 2(A) shows that the taxol induced leukocyte nadir (under G-CSF influence) did not increase as a function of age although there was a wide range of nadir counts ($0.4–5.7 \times 10^6$ cells/mm^3). In Figure 2(B) a similar relationship was observed with respect to platelets, with the nadir counts ranging from 16 to 235×10^3 cells/mm^3, but having no correlation with age.

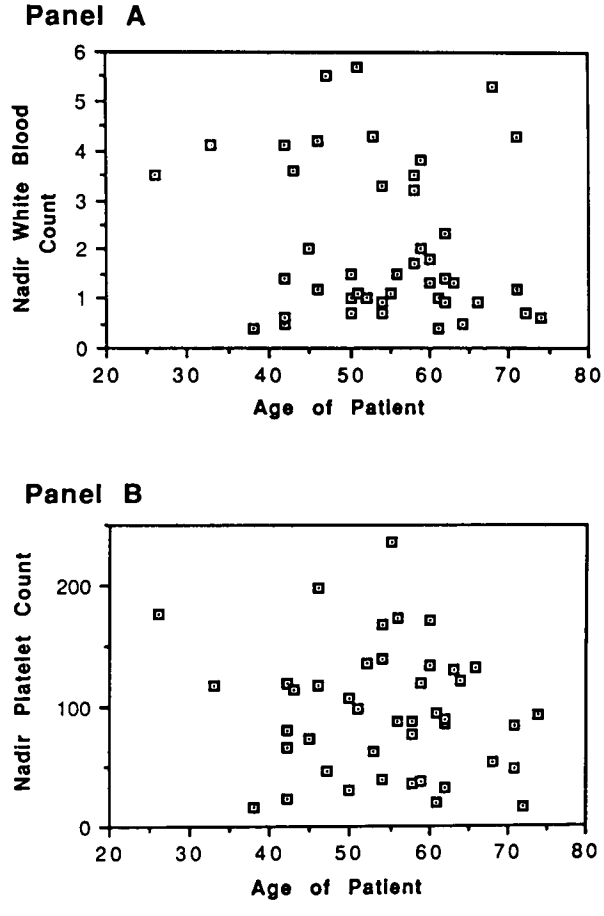

Figure 2. Two measures of myelosuppression assessed relative to patient age. These data are from cycle 1 of therapy for each individual, wherein the taxol dose was 250 mg/m^2 and the G-CSF dose was 10 μg/kg/day. (A) The nadirs for the total white blood cell count. (B) The nadirs for the platelet counts.

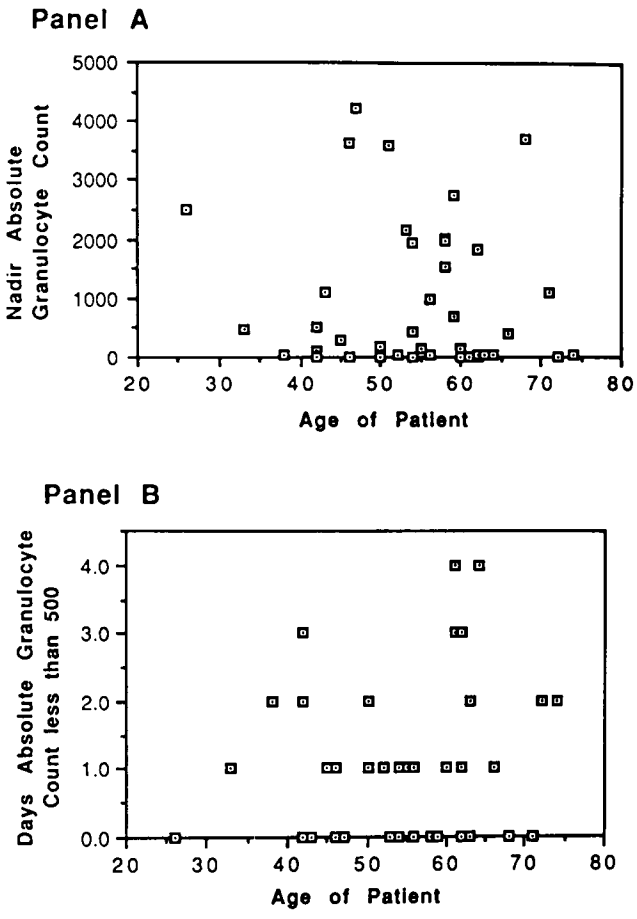

Figure 3. The nature of the granulocytopenic nadirs assessed in greater detail for cycle 1 of therapy for each patient. (A) The magnitude of the AGC nadir. (B) The duration of the AGC count being below 500 cells/mm^3.

To further assess taxol myelotoxicity, we analyzed the depths (Figure 3A) and lengths (Figure 3B) of the nadirs of the absolute granulocyte counts (AGCs) during cycle 1 of therapy. The AGC fell to unmeasurable levels in nine patients ranging in age from 38 to 74 years (Figure 3A). However, 12 patients (25% of the cohort) maintained an AGC above 1500 for the duration of cycle 1. There was no apparent relationship to age for either of these observations. In panel B, the duration of absolute neutropenia (AGC < 500 cells/mm^3) is plotted against age. Again, there was no relationship of this parameter to age. Table 3 lists the hematologic toxicities occurring in cycle 1 relative to arbitrary

Table 3. Taxol-induced hematologic toxicities experienced while receiving G-CSF support: cycle 1 only (taxol dose, 250 mg/m^2; G-CSF dose, 10 μg/kg/day)

Age	Total no. of patients	WBC nadir[a]	Platelet nadir[a]	AGC nadir[a]	Occurrence of neutropenia	
					no. of patients[b] (%)	number of days AGC < 500[c]
<51	17	1.5 (0.4–5.5)	81 (16–199)	280 (0–4235)	10 (58.8)	1 (0–3)
51–60	17	1.6 (0.7–4.3)	109 (36–235)	434 (0–2769)	7 (41.1)	0 (0–1)
>60	14	1.0 (0.4–5.3)	86 (16–133)	29 (0–3712)	8 (57.0)	2 (0–4)

[a] Data given are the medians, with range in parentheses.
[b] Number of patients having AGC < 500 cells/mm^3 for at least 1 day during cycle 1 of therapy.
[c] The median number of days for which AGC < 500 cells/mm^3 during cycle 1 of therapy is listed. The range is given in parentheses.

age divisions and confirms that there is no correlation between these toxicities and age.

Granulocyte and platelet toxicity during therapy

When hematologic toxicity is assessed on cycle 1 of therapy (Table 3 and Figures 2 and 3), such an evaluation is relevant for taxol at 250 mg/m^2 and G-CSF at 10 μg/kg/day for that cycle only. We sought to assess the profile of leukocyte and platelet toxicity for the duration of therapy for the cohort. These data are summarized in Table 4, with further analyses shown in Figures 4 and 5.

Table 4 lists a summary analysis of the grade 4 hematologic events that occurred on the study, as a function of the cycle of therapy administered. During cycle 2 of therapy, for example, data are available for 44 patients who received drug. Fourteen of these (32%) experienced grade 4 neutropenia of average duration of less than 1 day (range 0–3 days). Six of the 44 patients (14%) experienced grade 4 thrombocytopenia of average duration of less than 1 day (range 0–7 days). This pattern of short-lived leukopenia and thrombocytopenia was seen during every cycle of taxol/G-CSF administered, through nine cycles of therapy.

Figure 4 shows graphically the data contained in columns 4 and 6 of Table 4. There appears to be no evidence of cumulative leukocyte or platelet toxicity with taxol/G-CSF, in contrast to what has been reported with high dose carboplatin regimens.[10,11] Figure 5 shows graphically the numerical mean values for the lengths of granulocyte and platelet nadirs for each cycle of therapy. With sequential cycles of treatment the average durations of these nadirs are reduced, but the average lengths of all nadirs are clearly less than 1 day.

Table 4. Granulocyte and platelet toxicity during the course of therapy

Cycle of therapy	Total no. of patients[a]	No. of patients with AGC < 500 on this cycle (%)	Mean length of ACG nadir days (range)	No. of patients with platelets < 50 000 on this cycle (%)	Mean length of platelet nadir days (range)
1	46	23 (50)	<1 (0–3)	12 (26)	<1 (0–6)
2	44	14 (32)	<1 (0–2)	6 (14)	<1 (0–5)
3	29	13 (45)	<1 (0–2)	4 (14)	<1 (0–4)
4	23	8 (35)	<1 (0–2)	5 (22)	<1 (0–7)
5	18	5 (28)	<1 (0–1)	2 (11)	<1 (0–3)
6	15	3 (20)	<1 (0–1)	2 (13)	<1 (0–1)
7	10	1 (10)	<1 (0–1)	0 (0)	<1 (0)
8	7	1 (14)	<1 (0–1)	2 (29)	<1 (0–1)
9	2	0 (0)	<1 (0)	0 (0)	<1 (0)

[a] Patients for which data is available.

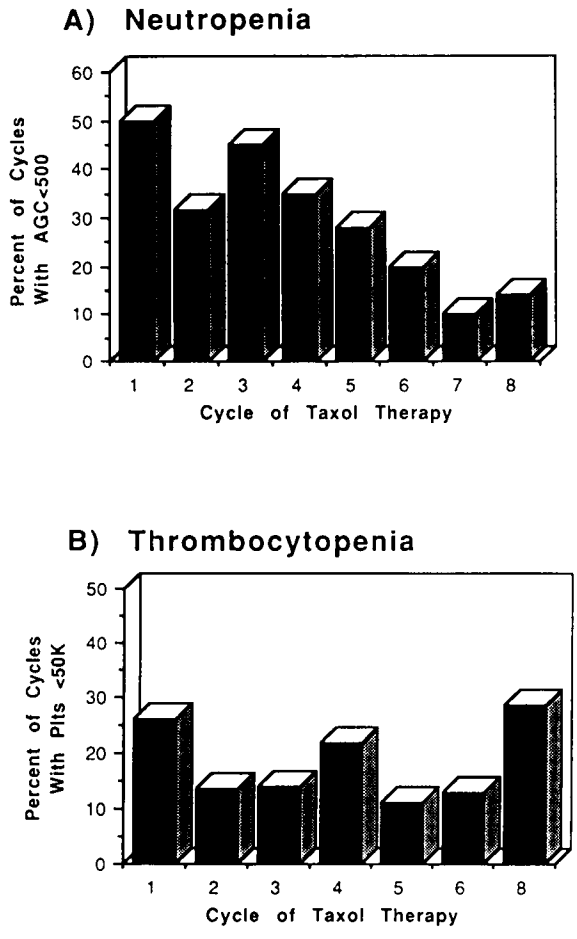

Figure 4. The occurrence of grade 4 hematologic toxicity evaluated relative to the cycle of taxol therapy. (A) The percent of cycles with AGC < 500 cells/mm^3 is depicted for each cycle of taxol therapy. (B) The percent of cycles with a platelet count less than 50 000 for each cycle of taxol therapy is shown.

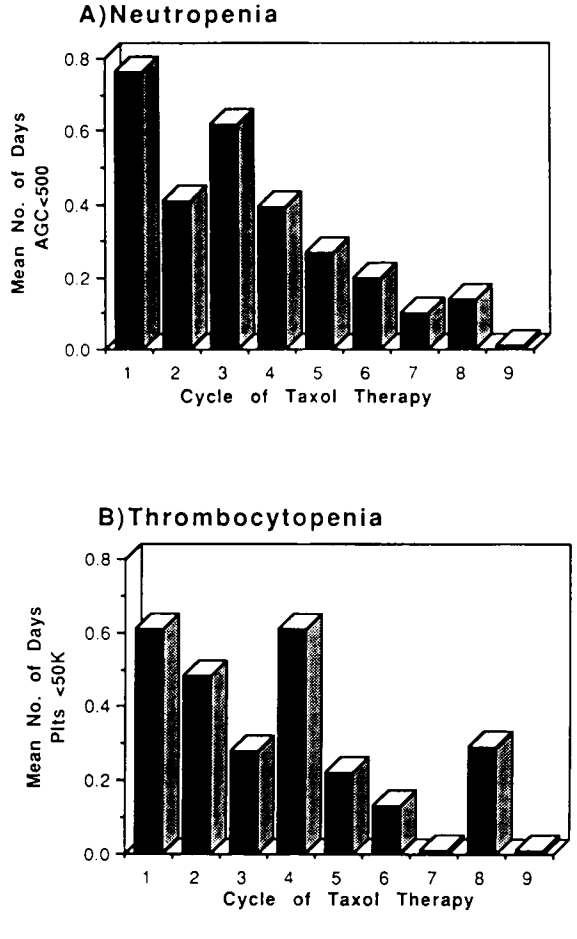

Figure 5. The duration of grade 4 hematologic toxicity evaluated relative to the cycle of taxol therapy. (A) The mean duration of absolute granulocytopenia (AGC < 500 cells/mm^3) is depicted for each cycle of taxol therapy. (B) The mean duration of severe thrombocytopenia (platelet count less than 50 000) is depicted for each cycle of taxol therapy.

Discussion

This is a retrospective analysis of a study designed to administer taxol in a dose-intense fashion to patients with recurrent epithelial ovarian carcinoma. Eligibility criteria included normal or near normal renal and hepatic function, good performance status, and the absence of substantial co-morbid disease. The evaluation reveals that with G-CSF support, dose intensity is able to be maintained through nine cycles of taxol therapy. Despite the maintenance of dose intensity, there was no evidence of cumulative leukocyte or platelet toxicity with increasing duration of taxol therapy. When hematologic toxicity was evaluated relative to patient age, no correlation was noted. With increasing number of prior therapies, no increase in hematologic toxicities was observed. Also, no statistically significant correlation was noted between the number of prior therapies received and major (grade 3 and 4) or minor (grade 1 and 2) toxicities. Thus, in our study we were able to maintain taxol dose intensity with G-CSF support with no increase in toxicity.

It is noteworthy that with prolongation of dose-intense therapy, myelotoxicity did not increase. This finding is both surprising and significant in that the administration of other dose intense chemotherapies is associated with cumulative toxicity. Cisplatin, for example, is associated

with cumulative neurotoxicity, and carboplatin with cumulative hematopoetic toxicity.[10,11] Taxol, which has significant disease response rates in recurrent ovarian carcinoma, does not have cumulative hematopoetic toxicity when delivered in a dose-intense fashion with G-CSF support. Although neurotoxicity is seen with taxol, it has not been found to be cumulative in nature and its incidence does not increase with increasing cycles when given at standard doses.[13] Although we have not studied neurotoxicity in detail, our clinical impression has been consistent with this report by Rowinsky *et al.*[13]

In this study of toxicities related to dose-intense taxol therapy, age was evaluated as a continuous variable. There were no increased toxicities noted with increasing age. A more in-depth analysis of the influence of age on the ability to deliver dose-intense taxol therapy in this cohort of patients is in press as of this writing.[14] It revealed that age does not adversely influence the ability to deliver aggressive taxol therapy.[14] Similar findings have been reported with dose-intense carboplatin[11] as well as with aggressive combination chemothrapy regimens.[15]

Retrospective analyses have shown that chemotherapy dose intensity is an important determinant for disease response in ovarian cancer,[8] breast cancer,[16] Hodgkin's disease,[17] non-Hodgkin's lymphoma[18] and other illnesses. Agents contained in these analyses include DNA damaging agents (such as cisplatin, cyclophosphamide and procarbazine), natural products such as adriamycin, and antimetabolites (5-fluorouracil, methotrexate, etc.).[8,16–18] Our analysis suggests that taxol can be safely dose intensified in ovarian cancer for multiple cycles of therapy, provided that the patients have good end-organ function and good performance status.

The unexpected observation in this study is the lack of correlation between prior therapy and the ability to deliver taxol in a dose-intensive fashion (see Table 2). It is frequently assumed that the more heavily pre-treated the patient, the more difficult it will be to administer cytotoxic agents. Although far from being conclusive, our data suggest that good end-organ function and good performance status may be more important than the amount of prior therapy *per se*. It is noteworthy, however, that our patients did not receive external beam radiation therapy. An analysis is ongoing to assess whether the *type* of prior therapy (specific drug used) may be an important factor in taxol tolerance.

Taxol is the most important new anti-cancer agent to be developed in the past two decades. Its usefulness is proven in recurrent ovarian cancer,[4–6] and preliminary studies suggest similar levels of effectiveness in breast cancer,[19] malignant melanoma[20,21] and possibly other malignancies.[22] Thus, the use of taxol in a dose-intense fashion with G-CSF support is a promising new option for the treatment of recurrent ovarian carcinoma, which may have implications for a variety of illnesses. When used as a single agent, taxol shows no evidence of cumulative myelosuppression.

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