What is the role of interval blood testing in the management of chemotherapy for gynecologic malignancies

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Summary

Purpose: To determine the safety of omitting routine interval laboratory assessments, dietary restrictions, and isolation precautions between cycles of chemotherapy for gynecologic malignancies.

Methods: Data were retrospectively obtained from the records of women receiving chemotherapy for gynecologic cancer from July 1999 - June 2000. Routine nadir determinations were not performed between treatment cycles; social interaction was encouraged, and pathogen-free diet recommendations were not provided.

Results: Eighty women received 449 cycles of chemotherapy. Four (5%) patients developed neutropenic fevers, and one of these women succumbed to sepsis. Eighteen (22.5%) women had 29 cycles delayed due to persistent myelosuppression when the ensuing chemotherapy infusion was to be administered. Hematopoietic growth factors overcame these delays during subsequent cycles in all but two patients.

Conclusion: Omitting scheduled interval laboratory monitoring, dietary restrictions, and isolation precautions between chemotherapy cycles is convenient for patients, likely cost-effective, and does not increase morbidity in the gynecologic oncology population.

Key words: Chemotherapy; Toxicity; Gynecologic oncology; Neutropenia.

Introduction

Consistent guidelines for monitoring patients receiving cytotoxic chemotherapy are not available. Many investigational protocols adjust dosing, alter treatment intervals, and/or provide hematopoietic growth factor support based on hematologic toxicity experienced between treatment cycles, whereas others make no adjustment for uncomplicated nadirs. Infection prophylaxis with isolation or antibiotics during times of severe neutropenia is often recommended despite the absence of data documenting improved outcome with such an approach in the gynecologic oncology population.

No single approach can accommodate all of the patints' needs or account for the many variables important in the safety and efficacy of chemotherapy. We have noted that routine cell counts obtained between treatment cycles in women with gynecologic malignancies rarely result in a management change. Awaiting results of these laboratory tests also leads to significant anxiety for both the patients and physicians. This lack of alteration in treatment plan combined with the typically short nadir duration observed with the chemotherapeutic agents commonly used in gynecologic oncology, has led us to eliminate scheduled weekly (serial) complete blood counts between treatment cycles. We present our experience using this approach over a 12-month period. To our knowledge, this is the first reported series focusing on the role of nadir determinations between cycles of cytotoxic chemotherapy.

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Materials and Methods

We routinely prospectively record data on all of our patients receiving cytotoxic chemotherapy in a treatment database. Specific information is collected relative to patient demographics, type of cancer, previous treatment history, current treatment regimen, and hematopoietic complications (using the Gynecologic Oncology Group toxicity criteria - Table 1). We used these chemotherapy records from patients treated under the direction of two board certified gynecologic oncologists between July 1, 1999 and June 30, 2000 to formulate this report.

Drug dosing and schedules were consistent for all women during their primary treatment relative to the type of cancer. Regimens utilized for recurrent carcinoma were attending physician-dependent but were with standard commercially available chemotherapy agents. Patients were instructed to record their temperature daily and notify the nurse if they experienced a temperature greater than 38°C, unusual fatigue, shortness of breath, chest pain, bleeding, or any other symptoms of illness. There were no specific recommendations given for a pathogen free diet or contact precautions, and social interaction was encouraged.

Table 1. — *Hematologic toxicity criteria of the Gynecologic Oncology Group.*

Hematologic component	Grade				
	0	1	2	3	4
WBC (1000 cells/µl)	≥ 4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
ANC (1000 cells/µl)	≥ 2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
Hgb (g/dl)	NL	10.0-NL	8.0-9.9	6.5-7.9	< 6.5
PLT (1000 cells/µl)	NL	75-NL	50-74	25-49	< 25

WBC: white blood cell; ANC: absolute neutrophil count; Hgb: hemoglobin; PLT: platelet; NL: normal.

A complete blood count, metabolic panel, and tumor markers (where appropriate) were obtained immediately prior to each treatment cycle for every subject. No other scheduled blood tests were performed between treatment cycles. Chemotherapy was administered to patients with a Gynecologic Oncology Group performance status of 0 or 1 when the platelet (PLT) count was greater than 100,000 cells/μl, white blood cell (WBC) count was greater than 2,500 cells/μl, absolute neutrophil count (ANC) was greter than 1,500 cells/μl, and there were no signs of significant hepatic or renal dysfunction. Otherwise treatment was delayed at weekly intervals until these parameters were satisfied.

For subsequent cycles following a treatment delay for persistent grade 2 neutropenia, granulocyte colony stimulating factor (G-CSF) was administered for ten days (without serial monitoring) at 5 mcg/kg starting 24 hours after chemoterapy. Repeated delay for granulocytopenia led to interval blood testing to determine a more precise duration of G-CSF treatment (until the post nadir ANC was greater than 10,000 cells/μl). If further treatment delays were encountered, a 25% dose reduction or an increased treatment interval was incorporated.

A single treatment delay for persistent grade 1 thrombocytopenia did not result in a specific intervention during subsequent cycles. However, repeated delays secondary to thrombocytopenia led to interval PLT counts to determine if there was a role for growth factor support (PLT nadir less than 50,000 cells/μl). When necessary, oprelvekin was administered at 50 μg/kg once daily until the post-nadir PLT count was > 50,000 cells/μl. When patients with repeated delays for thrombocytopenia did not have a PLT nadir that qualified for growth factor support, a 25% dose reduction or an increased treatment interval was incorporated.

Patients with symptomatic anemia or a hemoglobin of less than 9 mg.dl were offered transfusion. The amount of blood transfused was determined by the alleviation of patient symptoms or the volume necessary to achieve a hemoglobin of ≥ 11 g/dl (each unit of blood was assumed to increase hemoglobin by 1 g/dl). Erythropoietin use was not standardized in these patients.

Febrile neutropenia (FN) was defined as a temperature > 38°C with an associated ANC < 1,500 cells/μl. Patients with FN were admitted to the hospital for evaluation and parenteral antibiotic therapy. All women had urine and blood collected for culture. Further search for an infectious etiology was based on the patient's presenting symptoms and clinical findings. No isolation or dietary precautions were utilized. Antibiotic choice was directed at the infectious source, and cefipime was given empirically in the absence of an obvious infectious etiology. Hospitalization with empiric treatment was continued until the patient had clinically improved, had negative cultures x 48 hours, and had a resolving granulocyte nadir (ANC > 1,000 cells/μl). G-CSF was not utilized to enhance the recovery of the neutrophil nadir in these women, but a prophylactic 10-day course was incorporated into subsequent treatment cycles in efforts to prevent repeated episodes of FN.

Patients requiring office visits or hospitalization for other reasons between chemotherapeutic cycles were treated based on their clinical diagnosis. The treating physician judged whether these factors required a change or delay in the patient's chemotherapeutic regimen.

The recorded chemotherapy data and associated complications along with the patients, medical charts were retrospectively reviewed. Women on investigational protocols were excluded. Information was entered into an electronic database and analyzed with SPSS statistical software. The Mann-Whitney U test was used to explore for differences in age and the amount/duration of chemotherapy relative to the development of FN or persistent myelosuppression. Chi square analysis was performed to evaluate the relationship between these same factors and performance status, cancer diagnosis, prior treatment, and the chemotherapeutic agent.

Results

We administered 512 cycles of chemotherapy to 88 women between July 1, 1999 and June 30, 2000. Four hundred forty-nine cycles among 80 patients were not under the direction of an investigational protocol and consisted of cytotoxic drugs. This latter group of patients is the subject of this report. None of these women underwent routine scheduled interval blood testing for nadir

Table 2. — *Cancers treated.*

Cancer	Number of patients
Epithelial ovarian cancer	64
Cervical carcinoma	9
Endometrial carcinoma	2
Uterine sarcoma	1
Gestational trophoblastic disease	3
Vaginal carcinoma	1

Table 3. — *Chemotherapeutic regimens.*

Chemotherapy regimen	Dose	Interval (days)	Patients	Cycles
Paclitaxel (3 hour) Carboplatin	175 mg/m² AUC = 5	21	33	154
Paclitaxel (24 hous) Cisplatin	135 mg/m² 75 mg/m²	21	1	8
Doxorubicin Cisplatin	60 mg/m² 50 mg/m²	21	2	12
Topotecan (d 1-5) Carboplatin (d 1)	0.5 mg/m² AUC = 6	21	1	5
Paclitaxel	175 mg/m²	21	2	7
Docetaxel	75 mg/m²	28	1	5
Paclitaxel	80 mg/m²	7	3	39
Carboplatin	AUC = 5	21	13	57
Cisplatin	75 mg/m²	21	4	13
IP Cisplatin	75 mg/m²	21	2	13
Topotecan (d 1-5)	1.5 mg/m² 1.2 mg/m² 1 mg/m²	21 21 21	2 2 2	9 4 9
Liposomal Doworubicin	40 mg/m²	28	10	35
Etoposide (oral x 21 d)	50 mg/m²	28	9	53
Methotrexate	40 mg/m²	7	2	11
Actinomycin-D	1.25 mg/m²	14	1	1
Etoposide (d1, 2) Methotrexate (d 1, 2) Actinomycin (d 1, 2) Cyclophosphamide (d 8) Vincristine (d 8)	100 mg/m² 100 mg/m² bolus then 200 mg/m² infusion 0.5 mg/m² 1 mg/m² 600 mg/m²	14	1	9
Cisplatin*	40 mg/m²	7	5	23
Cisplatin* (d 1) 5 Flourouracil* (d 1-5)	40 mg/m² 1000 mg/m²	21	1	2

d: days; AUC: area under the curve; IP: intraperitoneal; *: given concomitantly with radiation.

determination. Subjects had a mean age of 58.4 years (median 59, range 28 - 84 years). The specific gynecologic malignancies treated are listed in (Table 2) with the chemotherapeutic regimens in (Table 3).

Thirty-three women (41.3%) had received prior cytotoxic chemotherapy before being treated during the reviewed period for recurrent or persistent disease. These patients had received a median of 1 (mean 1.6, range 1-5) prior chemotherapeutic regimens and a median of 6 (mean 9.2, range 3 - 31) prior treatment cycles.

FN complicated five cycles among four (5%) women. Only one of these patients had been previously treated. Three women had a single episode of FN, whereas one patient required hospitalization on two occasions for FN. G-CSF prevented recurrent FN in all but the latter patient, and she required a 25% dose reduction to complete her treatment regimen. There was one septic mortality. No patient had positive blood cultures. These patients are summarized in (Table 4).

Treatment delays were encountered in 18 (22.5%) women due to persistent grade 2 hematologic toxicity at the time of the next scheduled cycle. No patient on a weekly treatment regimen experienced a treatment delay secondary to persistent myelosuppression. Twenty-two cycles among 15 (18.8%) women were delayed for persistent neutropenia. Six of these patients had been treated previously. The mean ANC at the time of the delayed cycle was 1032 cells/μl (median 1,060, range 410 - 1,260 cells/μl). Ten days of G-CSF prevented repeated delay for neutropenia in ten of the 15 patients. Four of the remaining five experienced no additional treatment delays once interval WBC determinations were obtained, and G-CSF was administered until the ANC was > 10,000 cells/μl. The remaining patient suffered repeated delays in spite of G-CSF and dosing adjustments.

There were no hemorrhagic complications in this series; however, persistent grade 1 thrombocytopenia did result in a treatment delay for five (6.3%) women during nine cycles. Two of these patients also had persistent granuloctopenia when the next scheduled cycle was due and are discussed above. The mean PLT count necessitating treatment delay was 76,667 cells/μl (median 86,000, range 26,000 - 90,000 cells/μl). Three women had more than one thrombocytopenic associated delay, and two of three required and were successfully supported with oprelvekin during subsequent cycles. Two of these five patients had been previously treated. No dose adjustments were necessary based on platelet toxicity.

Overall, six of 33 (18%) women who were previously treated suffered a delay for prolonged hematologic toxicity, representing one-third of those delayed for persistent neutropenia or thrombocytopenia. Delays did not correlate with the amount of previous therapy or with the portion of the current regimen that had been received.

Twenty (25%) women required blood transfusion including three of the four that experienced FN and eight of the 18 who required treatment delays for prolonged grade 2 hematologic toxicity. Blood transfusion was administered after a mean of 5.2 cycles (median 4.5, range 1 - 12). Blood transfusion was associated with a treatment delay of >24 hours in only two women, and both of these delays were for social reasons. Six women were treated with erythropoietin during the study period. The specific reasons for initiating such treatment in these women were not apparent, and all patients who were on erythropoietin also received a blood transfusion.

Six additional women had treatment postponed for an upper respiratory infection (1), complications of a pleural effusion (1), poor performance status (2), and mediport infection (2). Neither FN nor persistent myelosuppression resulting in treatment delay were found to significantly clinically relate to patient age, performance status, type of cancer, the presence or number of prior treatments, or the chemotherapeutic agent in univariate analysis.

Discussion

Hematologic toxicity is common to nearly all chemotherapeutic agents. Such toxicity plays a major role in determining the maximum tolerated dose and thus designing treatment protocols. Subsequent monitoring of hematologic nadirs can lead to significant patient discomfort (repeated blood draws) and potential anxiety as well as considerable increased costs of time for both office staff and patients along with the increased fiscal expenses of office visits and blood testing.

In our gynecologic oncology population, we have observed relatively little myelosuppressive related complications when administering chemotherapy. Generally, severe hematologic toxicity is only for a short duration when it does occur. Large series of women with ovarian cancer, the most common gynecologic malignancy neces-

Table 4. — *Summary of women who suffered febrile neutropenia.*

Pt	Cancer	Regimen	Admit cycle	ANC	Hosp days	Comments
1	EOC	paclitaxel/carboplatin	3	1450	2	No source identified
2	EOC	paclitaxel/carboplatin	1	610	5	Pulmonary *Nocardia* and *Aspergillas*
			2	590	5	No source identified
3	EOC	carboplatin	1	1400	2	No source identified
4	EOC	paclitaxel/carboplatin	2	350	6	Pyelonephritis; died of sepsis

Pt: patient
EOC: epithelial ovarian cancer
ANC: absolute neutrophil count at admission (cells/μl)
Hosp: hospital

sitating chemotherapy, confirm our anecdotal observations [1, 2].

Likewise, FN is not terribly common in our population. Curtin and associates reported a 10% incidence of FN with a 2% mortality among women with ovarian malignancy treated with platinum-based chemotherapy [3]. McMeekin *et al.* identified only 45 episodes of FN among 40 women in a retrospective review of a 4-year treatment period [4]. No comment was made about the overall denominator relative to the total number of patients treated by these authors during the same time interval. They reported a 4% mortality.

Only four (5%) women in this series experienced FN. These results were obtained in the absence of recommendations regarding a pathogen-free diet, contact precautions, prophylactic antibiotics, or routine G-CSF administration. This is not surprising since these approaches have not been found consistently effective in patients with solid tumors. The patient who succumbed to sepsis had not been previously treated, and she presented febrile with grade 4 granulocytopenia only five days after receiving her second cycle of chemotherapy. It is therefore unlikely that this event would have been predicted or in any way prevented with hematologic monitoring.

Carlson and associates randomized women with ovarian cancer being treated with paclitaxel to prophylactic ciprofloxacin or placebo during periods of grade 4 granulocytopenia [5]. They found no difference in the incidence of FN, duration of neutropenia, or lenght of hospital stay for FN between the groups. A recent metanalysis of 19 randomized trials involving 2,112 patients also found that quinolone prophylaxis during periods of severe neutropenia was ineffective in preventing febrile morbidity or infectious mortality [6]. Likewise, a review on preventing neutropenic infections published by Verhoef concluded that strict isolation and gut decontamination have no clinically significant role in patients that experience short periods of granulocytopenia, especially when little time is spent with an ANC < 100 cells/μl [7].

Interestingly, this latter review focused on patients with hematologic malignancies, which are usually treated with more myelotoxic regimens than are typically utilized in gynecologic oncology.

Hartman *et al.* studied the use of G-CSF in chemotherapy induced afebrile neutropenia [8]. These investigators randomized 138 patients with lymphomas or solid tumors who experienced grade 4 granulocytopenia to placebo or G-CSF. They found no difference in the development of FN, need for hospitalization, or infectious complications between the groups. Additionally, G-CSF shortened the recovery time of the nadir by only two days. The use of G-CSF did not alter oncologic outcome.

Alternatively, a multi-center trial reported by Crawford *et al.* showed that propylactic administration of G-CSF reduced FN and infectious complications in patients with small cell lung cancer receiving combination chemotherapy with cyclophosphamide, doxorubicin, and etoposide [9]. This population or treatment regimen was obviously unique since 98% of the patients in the placebo group exprienced grade 4 granulocytopenia, and 57% suffered FN. Of particular interest however is that patients with FN from the placebo group who crossed over to the G-CSF group for subsequent cycles had a significantly shorter nadir duration and fewer episodes of FN. Other authors have reported similar findings relative to the ability of G-CSF to decrease the degree and duration of neutropenia [10, 11]. These results allowed us to anticipate the success of G-CSF support in subsequent cycles (without interval cell count determinations) administered to women that had suffered FN and those that had experienced previous treatment delays for persistent myelotoxicity.

Eighteen (22.5%) of our patients required a treatment delay for prolonged myelotoxicity. G-CSF prevented further delays in all but one of the patients delayed for persistent neutropenia. This patient's repeated delays were attributed to her past treatment with heavy metal compounds for rheumatoid arthritis. Previous cytotoxic chemotherapy was not associated with treatment delay or the success or failure of the prophylactic 10-day regimen of G-CSF. This suggests a possible role for the secondary use of G-CSF to maintain dose intensity. On the other hand, dose modification has not been shown to alter the overall response to therapy.

Our results are consistent with the observations of the sited publications. Combined, they suggest that there is not a role in the gynecologic oncology population for scheduled hematologic monitoring, a pathogen-free diet, special isolation precautions, routine prophylaxis with G-CSF, or prophylactic antibiotics during periods of granulocytopenia in efforts to prevent FN. This is also congruent with the 2,000 American Society of Clinical Oncologists (ASCO) guidelines regarding the use of G-CSF [12]. G-CSF is recommended for use only in patients who have a 40% risk of developing FN or those with special circumstances that may place patients at higher risk for chemotherapy related infectious complications. No variables were found to predict FN or infection in this series.

Sixty percent (3/5) of the women that were delayed for persistent grade 1 thrombocytopenia obtained benefit from oprelvekin administration to prevent repeated delays at subsequent cycles. These patients were all being treated with paclitaxel and carboplatin, and two of the three had received prior chemotherapy. On the contrary, 22 additional women with prior treatment received salvage chemotherapy with paclitaxel/carboplatin, topotecan, or single agent carboplatin, and there were no delays for persistent thrombocytopenia. Thus, we are unable to draw any meaningful conclusions relative to thrombocytopenia on the basis of these five women. The role of oprelvekin is yet to be clearly defined in this patient population where grade 3 and 4 thrombocytopenia is uncommon, especially of any significant duration.

Similarly, the value of erythropoietin in gynecologic oncology is unclear. This series was not standardized relative to eruthropoietin administration, and only six

women received this medication. Intuitively, the complete blood count obtained prior to each chemotherapy cycle could be utilized to judge the potential value and subsequent efficacy of erythropoietin for each patient. Weekly testing between cycles would likely provide no additional clinically relevant information.

Conclusion

Ultimately, 90% of the women in this series received chemotherapy without the need for interval blood testing, and complications attributed to hematologic toxicity were consistent with other published reports. We do not believe it is necessary or justified to subject all patients to the inconvenience and expense of serial blood tests when only a small subset actually require such vigilant monitoring. The only group of women that may obtain benefit from serial blood testing in our patient population are those with repeated treatment delays or recurrent episodes of FN. These women could potentially be found to have prolonged periods of severe neutropenia (ANC < 100 cells/μl) and may possibly benefit from G-CSF or prophylactic antibiotics during subsequent treatment cycles. Even in these few, the true clinical benefit relative to infectious mortality, tumor response, and survival remains to be demonstrated.

The results of this series must be interpreted carefully since women with six different malignancies treated with 20 different chemotherapeutic regimens were included. This is also a retrospective cohort study with no control population. Future direction includes the development of a prospetive randomized trial where costs, oncologic outcome, and quality of life are also evaluated.

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