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A phase I study with an expanded cohort to assess the feasibility of intravenous paclitaxel, intraperitoneal carboplatin and intraperitoneal paclitaxel in patients with untreated ovarian, fallopian tube or primary peritoneal carcinoma: A Gynecologic Oncology Group study☆,,☆☆,,★

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Abstract

Objective—To define the maximum tolerated dose (MTD) and assess the feasibility of intravenous (IV) paclitaxel, intraperitoneal (IP) carboplatin, and IP paclitaxel in women with newly diagnosed Stages II–IV ovarian, fallopian tube, or primary peritoneal carcinoma.

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Conflict of interest statement

The authors wish to report that there are no conflicts of interest with the exception of Dr. Natalie Gould who wishes to disclose that she is on the Speaker's Bureau for Myriad.

Methods—Patients received escalating doses of paclitaxel IV and carboplatin IP on day 1 and paclitaxel IP 60 mg/m^2 on day 8. A standard 3+3 design was used in the escalation phase. A two-stage group sequential design with 20 patients at the MTD was used in the feasibility phase. Patient-reported neurotoxicity was assessed pre and post treatment.

Results—Patients were treated with paclitaxel 175 mg/m^2 IV and carboplatin IP from AUC 5–7 on day 1 and paclitaxel 60 mg/m^2 IP on day 8. The MTD was estimated at carboplatin AUC 6 IP and 25 patients enrolled at this dose level. Within the first 4 cycles, seven (35%) of twenty evaluable patients had dose-limiting toxicities (DLTs) including grade 4 thrombocytopenia (1), grade 3 neutropenic fever (3), >2 week delay due to ANC recovery (1), grade 3 LFT (1), and grade 3 infection (1). De-escalation to paclitaxel 135 mg/m^2 IV was given to improve the safety. After six evaluable patients completed 4 cycles without a DLT, bevacizumab was added and six evaluable patients completed 4 cycles with one DLT (grade 3 hyponatremia).

Conclusions—Paclitaxel at 175 mg/m^2 IV, carboplatin AUC 6 IP day 1 and paclitaxel 60 mg/m^2 IP day 8 yield 18–56% patients with DLTs. The tolerability of the regimen in combination with bevacizumab was indicated in a small cohort.

Keywords

Phase I trial; Intraperitoneal chemotherapy; Carboplatin; Paclitaxel; Ovarian cancer

Introduction

In 2010, approximately 21,880womenwere expected to be diagnosed and 13,850 were expected to die of ovarian cancer [1]. Most are diagnosed with advanced stage disease, requiring a chemotherapy regimen containing a platinum and taxane. While these agents have traditionally been given intravenously, several randomized trials have indicated improved progression-free survival and overall survival for patients treated with a combination of intravenous and intraperitoneal chemotherapy [2,3]. The most recent Phase III intraperitoneal trial, GOG-0172, randomized patients to IV paclitaxel followed by IV cisplatin versus IV paclitaxel followed by IP cisplatin day 2, and IP paclitaxel day 8 for 6 cycles [4]. Median progression-free survival was 18.3months versus 23.8months in favor of the IP arm (p=0.05). Median overall survival was 49.5 months versus 66.9 months in favor of the IP arm (p=0.03). Improved survival with the IP arm came with increased hematological, gastrointestinal, metabolic and neurotoxicities as well as decreased quality of life [5]. This study prompted the publication of a NCI Clinical Announcement recommending that women be counseled about the clinical benefit associated with combined intravenous and intraperitoneal chemotherapy [6].

Phase II trials have also demonstrated that IP carboplatin can produce objective responses in patients with small volume disease [7,8]. Intraperitoneal carboplatin administration provides peak peritoneal fluid levels 18–24 times higher than peak serum levels [7]. In studies where the instilled carboplatin is removed after four hours the MTD is 350–650 mg/m^2, whereas it is 300 mg/m^2 in patients where the infused fluid is not removed [7]. As with IV administration, the DLT is thrombocytopenia. While Markman has suggested superiority of IP cisplatin compared to IP carboplatin, IP carboplatin has not been studied to the extent that cisplatin has [8]. Recent data suggest that doses used in prior studies were too low since they assume equivalency of dose between carboplatin and cisplatin [9].

This Phase I study was performed to evaluate MTD, DLT and the feasibility of intraperitoneal carboplatin in combination with intravenous and intraperitoneal paclitaxel in previously untreated patients with advanced ovarian, fallopian tube or peritoneal carcinoma, in hopes of finding a less toxic alternative to GOG −0172. In addition, a small cohort of

patients was treated with this regimen in combination bevacizumab to assess its tolerability. Patient-reported outcome data were collected as an exploratory study aim to enhance understanding of the development of neurotoxicity, specifically as a potential DLT.

Materials and methods

Eligibility criteria

Patients with a histologic diagnosis of Stages II–IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma were eligible. Patients with a GOG performance status of 0–2 were entered within 12 weeks of surgery. Laboratory criteria included an absolute neutrophil count (ANC)≥1500/mcL, platelet count≥100,000/mcL, white blood count≥3000/mcL, creatinine≤1.5 times upper limit of normal (ULN), bilirubin≤1.5 times ULN, alanine transaminase and aspartate transaminase≤2.5 times ULN, and neuropathy (sensory and motor)≤grade 1 using the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI CTCAE v3).

This study was reviewed and approved by the Cancer Therapy Evaluation Program of the National Cancer Institute. All patients gave written informed consent before study entry in compliance with institutional, state, and federal regulations.

Treatment

On day 1, patients in all dose levels received paclitaxel (135 or 175 mg/m^2) IV as a 3 hour infusion followed by carboplatin (AUC 5 to 7) IP and returned on day 8 to receive paclitaxel (60 mg/m^2) IP (Table 1). In addition, patients in dose level IV received bevacizumab (NCI CTEP supplied agent NSC 704865, IND 7921) 15 mg/kg on day 1 following cycle 1. IP carboplatin or paclitaxel was reconstituted in 1 l of normal saline and infused through the peritoneal catheter as rapidly as possible. It was preferred that patients receive an additional liter of normal saline in the peritoneal cavity afterward. Patients were asked to change position at 15-minute intervals for 2 h to ensure adequate intra-abdominal distribution. Pretreatment steroids, histamine-blocking agents, and antiemetics were recommended. Cycles were repeated every 21 days for 6–8 cycles.

Evaluation of toxicity

Patients underwent weekly laboratory evaluations and toxicity assessments. Toxicities were graded according to the NCI CTCAE v3. Dose-limiting toxicity was defined as: a dose delay>2 weeks due to failure to recover counts, febrile neutropenia, grade 4 neutropenia >7 days, grade 4 thrombocytopenia, clinically significant bleeding with grade 3 thrombocytopenia, grade 3 or 4 non-hematological toxicity (excluding fatigue, hypersensitivity reaction, hypokalemia, abdominal pain, nausea or vomiting), and any drug-related death. Treatment-related neuropathy (Grade 2 or worse) persisting for 2 weeks was considered a DLT. Patients with intraperitoneal port-related complications were considered inevaluable for toxicity and replaced. Patient reported neurotoxicity symptoms were evaluated with the short form (4 items) of the FACT/GOG-Ntx subscale [10]. The four items are ‘I have numbness or tingling in my hands’, ‘I have numbness or tingling in my feet’, ‘I feel discomfort in my hands’, and ‘I feel discomfort in my feet’. Each item is dichotomized to answer Yes or No regarding presence of the stated symptom. This assessment was conducted prior to each cycle and 3, 6, 9, and 12 months post treatment.

Patients received therapy until disease progression, intolerable toxicity, or completion of therapy. Subsequent cycles of treatment did not begin until all toxicities were grade 1 or below, ANC was ≥1500 cells/mcl, platelet count was ≥100,000 cells/mcl and creatinine was <2.0 mg%. Day 8 IP paclitaxel was not held due to low counts.

Statistical design

The first phase, termed the dose escalation phase, identified the MTD using a standard 3+3 design [11]. Dose escalation for each cohort of 3 patients continued until a DLT was observed during the first cycle of therapy. If one patient out of three experienced a DLT, an additional number of three patients were enrolled at that dose level. The MTD was estimated by the maximum dose level at which ≤1 patient (among 6) experienced a DLT. No intra-patient dose escalation occurred.

Following the dose escalation phase, the second phase or feasibility phase began. This assessed treatment toxicities at the MTD over 4 cycles of therapy. The feasibility phase of the trial was carried out in a 2-stage group sequential design. The first stage required 20 patients. If 4 or fewer patients had adverse events, then the study closed early and the regimen was deemed feasible. If 8 or more patients had events, then the study closed and the regimen was declared not feasible. If 5–7 patients experienced adverse events, the study reopened to a second stage, targeting accrual of 40 patients. If 11 or fewer patients had an adverse event, then the regimen was declared feasible. Otherwise, the regimen was declared not feasible.

If the true event rate for this regimen is 40%, the design provided a 90.6% chance of classifying the regimen as not feasible, with a 58.4% chance reaching this conclusion before beginning the second stage. If the event rate is 20%, the design provided a 91.2% chance of classifying the regimen as feasible and a 63.0% chance of reaching this conclusion before beginning the second stage [12,13].

Results

Patient demographics and toxicities

Fifty-seven eligible patients enrolled from May 2004 to December 2009. Demographics are summarized in Table 2. Toxicity during the escalation phase is summarized in Table 3. In the dose escalation phase, three patients enrolled at Dose Level I receiving day 1 paclitaxel 175 mg/m^2 IV and carboplatin AUC 5 IP followed by day 8 paclitaxel IP. As no DLTs occurred, three patients enrolled at Dose Level II (carboplatin AUC 6 IP). One patient was taken off study due to a worsening preexisting condition and was replaced. Given that there were no DLTs in 3 evaluable patients, three patients were enrolled at Dose Level III (carboplatin AUC 7 IP). Two patients had thrombocytopenia (one with asymptomatic Grade 3 thrombocytopenia and one patient with a treatment delay of one week due to thrombocytopenia), though not DLTs by definition, and it was decided to expand this dose level for safety reasons. Of these three additional patients, one experienced a DLT consisting of Clostridia difficile enterocolitis and Klebsiella bacteremia associated with grade 4 neutropenia, thrombocytopenia, hypophosphatemia, fatigue, and grade 3 tinnitus with cycle 1. Given this DLT and the thrombocytopenia noted as this dose level, Dose Level II was re-opened for 3 more patients and there were no further DLTs at this dose level during the first cycle.

Dose Level II was estimated to be the MTD and 25 participants enrolled to assess the feasibility of this regimen. Five were not evaluable due to port failures (4) and non-compliance (1). Twenty evaluable patients remained for toxicity assessment (Table 4). Thirteen completed the required 4 cycles without a DLT. Seven patients (35%) had a DLT within the first 4 treatment cycles. These DLTs were grade 4 thrombocytopenia (1), grade 3 neutropenic fever (3), >2 week delay in therapy for ANC recovery (1), grade 3 LFT abnormalities (1), and grade 3 infection (1). Other toxicity included grade 3–4 neutropenia in 37/75 cycles. Twelve cycles were delayed 7 days due to prolonged neutropenia and 1 cycle was delayed 7 days due to prolonged thrombocytopenia. Grade 2 neuropathy was

noted in 8 cycles (4 patients) but only one patient was dose reduced for persistent grade 2 neuropathy.

The decision rules recommended opening the study to an additional number of 20 patients during a second stage. However, given the nature of the toxicities (35% observed with DLTs and a 90% CI from 18 to 56% for the proportion of DLTs) observed in the first stage, a medical decision was made to treat 6 evaluable patients with a reduction in day 1 paclitaxel to 135 mg/m^2 IV while maintaining day 1 carboplatin AUC 6 IP and day 8 paclitaxel IP (Dose Level −1). One patient did not complete cycle one due to C. difficile infection unrelated to therapy and a seventh was added. Six participants completed 4 cycles without a DLT. Therefore, this dose level was chosen to evaluate the addition of bevacizumab. Nine patients were enrolled in the bevacizumab cohort. Three were unevaluable; one each with prolonged LFT elevation and decline in status not related to protocol therapy, and one due to non-compliance. Six patients completed 4 cycles with one DLT, grade 3 hyponatremia in cycle 1.

Initial investigations with IP carboplatin raised concerns about dose as it was related to body surface area. In order to explore this, doses in this study were converted from AUC to mg/m^2. For the patients enrolled in the feasibility phase with carboplatin at AUC 6, doses ranged from 277 to 544 mg/m^2, with a mean of 385 mg/m^2 for cycle one.

Thirty-six patients participated in the survey of neurotoxicity symptoms. Of these, 29 patients received Dose Level 2 (25 feasibility and 4 dosing) and 7 patients were treated with Dose Level −1. Neurotoxicity symptoms at each assessment time point are presented in Table 5. In the feasibility phase, 8 of 16 patients reported at least one neurotoxic symptom by cycle 6 with 5 (31%) reporting 3 or 4 symptoms. These reported symptoms seemed to be sustained post treatment.

Discussion

Though GOG −0172 demonstrated superior progression-free and overall survival for intraperitoneal chemotherapy, it has not been widely accepted by the oncology community because of the toxicity and the difficulty associated with administering intraperitoneal drugs [4]. Various attempts have been made to optimize intraperitoneal chemotherapy regimens including omitting the IP paclitaxel, reducing the IP cisplatin dose to 75 mg/m^2, administering the IP cisplatin on day 1, changing to a 3 hour infusion of paclitaxel, and evaluating the role of IP carboplatin [14].

Since 1990, studies in Japan using intraperitoneal carboplatin have provided crucial information about its dosing and safety [9,15,16]. Pharmacokinetic data have demonstrated that, while filtered platinum AUC in the intravenous space was similar with IV or IP administration, the mean intraperitoneal space AUC after IP dosing was approximately 17 times higher than after IV dosing [15]. They suggested that if antitumor activity is based on AUC, intraperitoneal carboplatin may be better than intravenous dosing as it can achieve the same IV AUC while providing a much higher IP AUC. Fujiwara et al. retrospectively analyzed toxicity data from 42 patients undergoing intraperitoneal carboplatin administration in combination with paclitaxel 175 mg/m^2 IV [16]. They found grade 3 thrombocytopenia in 31.6 % at carboplatin AUC 6, 44.4 % at AUC 6.5 and 25% at AUC 7. Other toxicities included 85.4% grades 3–4 neutropenia and 14.3% grades 2–3 sensory neuropathy. In our study, grades 3–4 neutropenia occurred in 51% of patients who received IP carboplatin AUC 6 and 30% of patients who received carboplatin AUC 7 in combination with paclitaxel 175 mg/m^2 IV. Grades 3–4 thrombocytopenia was much less common, occurring in only 2 of 141 cycles treated at carboplatin AUC 6. As expected, it was more

common in the patients receiving carboplatin at AUC 7, occurring in 30% of cycles and accounting for dose-limiting toxicities in two of six treated patients.

This trial represents an attempt to evaluate the safety and the feasibility of the combination of IV paclitaxel and IP carboplatin on day 1 followed by IP paclitaxel on day 8 in women with newly diagnosed advanced ovarian, fallopian tube or primary peritoneal carcinoma. We have shown that paclitaxel 175 mg/m^2 IV and carboplatin AUC 6 IP administered on day 1 followed by paclitaxel 60 mg/m^2 IP on day 1 yield a sample proportion of 35% with DLTs and a 2-sided 90% CI for the proportion with DLTS equal to 18%–56%. However, we noted hematologic and non-hematologic toxicities were lessened by decreasing the paclitaxel administered on day 1 to 135 mg/m^2 IV. The importance of day 8 IP paclitaxel as given in GOG−0172 is unknown. Concurrent to this study, Morgan et al. evaluated IP carboplatin at AUC 5–8 along with IV paclitaxel at 175 mg/m^2 [17]. They also found the regimen to be well tolerated over multiple cycles with a high completion rate. The pattern of toxicity in both studies suggests that with more liberal use of growth factors or broader criteria for dose delays, IP carboplatin and IV paclitaxel can be safely administered.

Initial concerns about using carboplatin IP were due to dose as it was related to body surface area. Markman concluded that carboplatin may be inferior to cisplatin when administered intraperitoneally [8]. However, the dose of carboplatin was low (200–300 mg/m^2) when compared to the dose of cisplatin used in the study. Fujiwara et al. has presented long-term follow-up on 165 patients treated with intraperitoneal carboplatin as part of first-line therapy for ovarian carcinoma [18]. Patients could be treated with single agent carboplatin or in combination with intravenous cyclophosphamide or paclitaxel. Median survival for advanced stage patients was 51 months for patients with carboplatin doses at or above 400 mg/m^2 and only 25 months with doses less than 400 mg/m^2. Doses in the current study ranged from 277 to 544 mg/m^2, with a median of 385 mg/m^2 for patients in the feasibility phase. While survival data is not available for this cohort, the doses used are clearly higher than in the Markman study which suggested inferiority for intraperitoneal carboplatin. The current Phase III trial within the Gynecologic Oncology Group (GOG#0252) should provide survival data as related to intraperitoneal carboplatin dosing.

GOG-0172 highlighted that neurotoxicity was a significant and sustained concern in both trial arms, especially in the IP study arm [5]. As a result, it was considered important to continue to examine features of neurotoxicity outside of the Phase III setting. It is recognized that inclusion of patient-reported outcome assessment in Phase I clinical trials is unconventional, and may be of limited value due to trial design and sample size considerations. However, Wagner and colleagues provide a meaningful discussion of the use of PROs in Phase II trials [19]. One might extend this argument to consider cases in which inclusion of PROs in Phase I trials may be justified. For example, as in this study, a case can be made to include PROs in order to further understand the impact of a (presumably) toxic therapy on capacity to endure further treatment. In so doing, future trial development could be informed by descriptive results. In this trial, grade 2 neuropathy was reported at least once by 20% of patients treated at the feasibility doses, which is higher than that reported in the Japanese series [16,18]. Although only two thirds of the patients in the feasibility phase completed the survey on cycles 4, 5, and 6, 50% of them reported one or more symptoms, and roughly 30% reported 2 or more symptoms. Thus, it is reasonable to consider that the patient-reported outcomes (PROs) may indeed be a sensitive, early indicator of developing neurotoxicity

IP catheter issues have been of concern in successful delivery of intraperitoneal drugs. In Armstrong et al. catheter failure was cited in 36% of patients who could not complete all 6 cycles of IP chemotherapy [4]. These included catheter infection, blockage, leaking and

access problems. Fujiwara demonstrated a much lower catheter failure rate of 9.7% [16,18]. We found a catheter failure rate of only 8.3% in the first 4 cycles of chemotherapy. In Morgan et al., when only IP carboplatin was given, the catheter failure rate was even lower at 5.6% [17]. This low rate of catheter failures may be due to the more common placement of catheters at the time of initial surgery using the insertion procedure mandated by the GOG Surgical Manual and the commitment to intraperitoneal therapy by the investigators and staff participating in GOG Phase I trials.

In conclusion, our results indicate that intravenous and intraperitoneal paclitaxel can be safely combined with intraperitoneal carboplatin. In addition, the safety of this combination with bevacizumab was indicated in a small cohort. The judicious use of growth factors or more liberal criteria for dose delay may allow higher doses of paclitaxel to be combined with intraperitoneal carboplatin though chronic neurotoxicity remains a concern with this regimen containing both IV and IP paclitaxel. This was less of a concern in the similar GOG Phase I study administering only IP carboplatin [17]. The safety of intravenous docetaxel with IP carboplatin is being explored as it may allow for a decrease in the neurotoxicity seen in paclitaxel containing regimens.

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Table 1

Schema of dosing levels.

Dose level	Drug	Dose (mg/m^2)	Drug	Dose	Drug	Dose (mg/m^2)
−I	Paclitaxel IV	135	Carboplatin IP	AUC 6	Paclitaxel IP	60
I	Paclitaxel IV	175	Carboplatin IP	AUC 5	Paclitaxel IP	60
II	Paclitaxel IV	175	Carboplatin IP	AUC 6	Paclitaxel IP	60
III	Paclitaxel IV	175	Carboplatin IP	AUC 7	Paclitaxel IP	60
IV[a]	Paclitaxel IV	135	Carboplatin IP	AUC 6	Paclitaxel IP	60

[a]In Dose Level IV, fixed dose bevacizumab 15 mg/kg IV was given cycles 2–6.

Table 2

Demographics.

Characteristic	Category	No.	% Cases
Age	30–39	1	1.8
	40–49	9	15.8
	50–59	18	31.6
	60–69	16	28.1
	70–79	12	21.1
	80–89	1	1.8
Race	American Indian	2	3.5
	White	55	96.5
Site of disease	Ovary	44	77.2
	Fallopian tube	6	10.5
	Peritoneal	7	12.3
Cell type	Adenocarcinoma, unsp.	1	1.8
	Clear cell carcinoma	2	3.5
	Endometrioid adenocarcinoma	5	8.8
	Mixed epithelial carcinoma	1	1.8
	Transitional cell carcinoma	1	1.8
	Serous adenocarcinoma	46	80.7

Table 3

Toxicity in dose escalation phase for cycle 1.

Adverse event	Dose level																			
	Level −I				Level I				Level II				Level III				Level IV			
	N=6				N=3				N=7				N=6				N=7			
Grade of adverse event	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Allergy		1																		
Auditory															1[a]					
Blood/bone marrow																				
Hemoglobin	4	2			2				5	2			3	1			5	1		
Neutrophils		3	2			1		2	1	1		3	1	1		4	3		1	2
Platelets	1								1				1		1	1[a]	1			
Cardiac									1											
Coagulation																				
Constitutional	3	2			1	2			1	2	2		4			1[a]	3	2		
Dermatology	5	1			1				5				3				6	1		
Endocrine		1							2											
Gastrointestinal	3	2				3			2	2	2		3	1	1[a]		6			
Genitourinary									2	1			1				1			
Hemorrhage					1				1				1				1	1		
Hepatobiliary									2											
Infection														1	1[a]			3		
Metabolic	2	1			1					1		1[b]	2			1[a]	3	1	1[c]	
Musculoskeletal																	1			
Neurologic		1							5								1			
Ocular/visual						1			2				1				2			
Pain	2	3			1				3	1			2				1	1		
Pulmonary					1				2				1				1	1		

[a] Dose Level III: DLT with all toxicities occurring in a single patient.

[b] Dose Level II: Grade 3 toxicity in an inevaluable patient taken off study during cycle 1.

[c] Dose Level IV: DLT.

Table 4

Toxicity in feasibility phase for 4 cycles (N=25 patients).

Adverse event					
Grade of adverse event	0	1	2	3	4
Allergy	22	3	0	0	0
Auditory	20	1	4	0	0
Blood/bone marrow					
Hemoglobin	3	10	11	1	0
Neutrophils	2	1	4	5	13[*]
Platelets	8	15	1	0	1[#]
Cardiac	21	3	1	0	0
Coagulation	22	2	0	1[a]	0
Constitutional	7	7	10	1	0
Dermatologic	3	5	17	0	0
Endocrine	21	3	1	0	0
Gastrointestinal	4	10	9	2	0
Genitourinary	23	2	0	0	0
Hemorrhage	22	3	0	0	0
Hepatic	23	1	0	1[$]	0
Infection	14	1	6	4[^,&]	0
Metabolic	8	9	7	1	0
Musculoskeletal	22	2	1	0	0
Neurologic	12	10	3	0	0
Ocular	21	3	1	0	0
Pain	10	7	8	0	0
Pulmonary	14	7	4	0	0
Sexual/reproductive	23	2	0	0	0

DLTs include 1 patient with >2 week delay to recover ANC, [*]1 with grade 4 thrombocytopenia, [#]1 with grade 3 LFT abnormalities, [$]3 with neutropenic fevers and [^]one with pneumonia [&].

[a]Thrombosis related to malignancy.

Table 5

Number of patients who reported neurotoxicity symptoms at each time point.

Assessment time points	Dose Level −I						Dose Level II						Feasibility phase					
	N	No. of Ntx symptoms					N	No. of Ntx symptoms					N	No. of Ntx symptoms				
		0	1	2	3	4		0	1	2	3	4		0	1	2	3	4
Prior to cycle 1	6	6					3	2	1				25	24	1			
Prior to cycle 2	6	4		2			3	2		1			21	17	1	2		1
Prior to cycle 3	6	3	1	2			3	1	1	1			17	9	4	1	1	2
Prior to cycle 4	6	4	2				3	1	1			1	16	8	2	4		2
Prior to cycle 5	6	4	1	1			3		1		1	1	17	11	2	2		2
Prior to cycle 6	6	4	1			1	2					2	16	8	2	1	2	3
3 month post treatment	6	2	2	1	1		3	1		1		1	17	10	2	3		2
6 months post treatment	4	4					3	1	1			1	18	9	3	2	1	3
9 months post treatment	2	1				1	2					2	16	5	5	5	1	
12 months post treatment	3	2				1	3			2		1	14	7	1	4	1	1

N: Number of patients who completed Ntx survey.