Published in final edited form as:
Gynecol Oncol. 2011 February ; 120(2): 224–228. doi:10.1016/j.ygyno.2010.10.018.

Low dose abdominal radiation as a docetaxel chemosensitizer for recurrent epithelial ovarian cancer: A phase I study of the Gynecologic Oncology Group

Charles A. Kunos, MD[1], **Michael W. Sill, PhD**[2], **Thomas E. Buekers, MD**[3], **Joan L. Walker, MD**[4], **Jeanne M. Schilder, MD**[5], **S. Diane Yamada, MD**[6], **Steven E. Waggoner, MD**[7], **Mohammed Mohiuddin**[8,*], and **Paula M. Fracasso, MD, PhD**[9]

[1] Department of Radiation Oncology, University Hospitals Case Medical Center, Cleveland, OH 44106

[2] Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY 14263

[3] Gyn/Onc Division, University of Iowa, Iowa City, IA 52242

[4] Obstetrics & Gynecology, University of Oklahoma, Oklahoma City, Oklahoma 73190

[5] Section of GYN Oncology, Indiana University Medical Center, Indianapolis, IN 46202

[6] Section of Gynecologic Oncology, University of Chicago, Chicago, IL 60637

[7] Department of Obstetrics and Gynecology, University Hospital Case Western Medical Center, Cleveland, OH 44106

[8] Department of Radiation Oncology, University of Kentucky, Lexington, KY 40536

[9] Department of Medicine, University of Virginia, Charlottesville, VA 22908

Abstract

Objectives—To determine the maximum tolerated dose and dose-limiting toxicity (DLT) of whole abdomen radiation as a chemosensitizer of weekly docetaxel for women with recurrent epithelial ovarian fallopian tube, or peritoneal cancers.

Patients and methods—Women were enrolled on one of three dose levels of docetaxel (20, 25, or 30 mg/m^2) administered weekly with concurrent low dose whole abdominal radiation given as 60 cGy bid two days weekly for a total of 6 weeks.

Results—Thirteen women were enrolled and received 70 weekly treatments of docetaxel in combination with radiation therapy. At the first dose level, docetaxel 25 mg/m^2, grade 3 fatigue and thrombocytopenia were observed. At the next dose level, docetaxel 30 mg/m^2, grade 3 febrile neutropenia, grade 4 thrombocytopenia with epistaxis and grade 3 diarrhea were observed. Given

Corresponding author: Paula M. Fracasso, MD, PhD, Department of Medicine, University of Virginia, PO Box 800716, Charlottesville, VA 22908, Phone: 434-243-6143, Fax: 434-982-4199, fracasso@virginia.edu.
*Dr. Mohiuddin's current position is Director of the Oncology Centre at King Faisal Specialist Hospital & Research Center in Saudi Arabia

CONFLICT OF INTEREST STATEMENT
The authors wish to report that there are no conflicts of interest.

these dose-limiting toxicities, a lower dose of docetaxel 20 mg/m^2 was administered and found to be tolerable. No objective responses were observed among the 10 patients with measurable disease; however, the median progression-free survival (PFS) in all patients was 3.3 months, and 3 of the patients with measurable disease were free of tumor progression after 6 months (30%; 90% Confidence Interval 8.7–61%).

Conclusions—Twice weekly low dose whole abdomen radiation during weekly docetaxel 20 mg/m^2 was well-tolerated. Given the PFS demonstrated in these women with resistant ovarian cancer, further study of whole abdominal radiation and concurrent chemotherapy may be warranted.

Keywords

Ovarian cancer; Docetaxel; Abdominal radiation; Chemosensitizer

INTRODUCTION

In 2009, it is estimated that 21,550 women will be diagnosed and 14,600 women will die of epithelial ovarian cancer in the United States [1]. Despite aggressive primary therapy with debulking surgery followed by platinum and taxane chemotherapy, disease recurs in most women [2]. Chemotherapeutic agents administered to treat this recurrence include the semisynthetic taxane, docetaxel. Docetaxel promotes tubulin assembly and stabilizes microtubules, suggesting an antitumor cytotoxic effect during the G_2/M phase of the cell cycle [3,4]. Clinical response rates of docetaxel in women with the persistent or recurrent disease setting are 22 to 28 % [5–8]. The Gynecologic Oncology Group (GOG) noted a 22% clinical response rate to docetaxel in women with paclitaxel-resistant ovarian and peritoneal cancer who had recurrence within 3 months of completion of paclitaxel and carboplatin [8]. As such, docetaxel is active in paclitaxel-resistant ovarian and peritoneal cancer, but whether other therapeutics may improve upon its antitumor drug effect remains uncertain.

Abdominopelvic radiation has been shown to sterilize ovarian and peritoneal cancers, as a consequence of relatively high intrinsic ovarian or peritoneal cell radiosensitivity [9–13]. Despite radiation targeting the whole abdomen (i.e., 2250 to 3000 cGy) and pelvis (i.e., pelvic dose of 4500 to 5000cGy) for treatment of women with suboptimal cytoreductive surgery, intraperitoneal disease persisted in 41 and 44% of women five years after treatment [14,15]. Yet, the use of radiation for intraperitoneal spread of ovarian cancer disease has been limited secondary to radiation-mediated acute toxicities of nausea, emesis, diarrhea, and chronic bowel injury, and treatment delaying myelosuppression [10–15]. Radiation-mediated toxicities are exacerbated if full-dose cisplatin and paclitaxel chemotherapies are added to treatment together or in sequence [10–13].

In preclinical experiments, low-dose radiation (50 cGy X 4 fractions) enhanced p53-mutated colon cancer cytotoxicity as compared to single fraction (200 cGy) radiation [16]. Enhanced cytotoxicity is speculated to occur from first dose fraction arrest of cells in the radiosensitive G_2/M phase of the cell cycle and subsequent low dose fractions resulting in cell cytotoxicity [17]. Given that the cytotoxicity of docetaxel is enhanced in G_2/M phase cells, we hypothesized that fractionated whole abdominal radiation, through its G_2/M phase synchronization, may enhance the sensitivity of ovarian and peritoneal cancers to docetaxel with an acceptable toxicity profile. Therefore, the GOG performed a phase I study using low dose whole abdominal radiotherapy as a docetaxel chemosensitizer in women with persistent or recurrent advanced ovarian, peritoneal, or fallopian tube cancer. In this study, docetaxel was chosen for dose escalation due to its modest anticancer effect upon chemoresistant

ovarian and peritoneal cancers. In GOG-9915, the maximum tolerated dose and dose-limiting toxicities on this regimen were evaluated.

PATIENTS AND METHODS

Eligibility criteria

Patients ≥18 years of age were eligible if they had persistent or recurrent histologically or cytologically confirmed diagnosis of advanced epithelial ovarian carcinoma, peritoneal carcinoma, or fallopian tube carcinoma following first or subsequent relapse after taxane and platinum-based chemotherapy. All patients had a GOG performance status of 0 or 1, and measurable disease was not required. Laboratory criteria for eligibility included an absolute neutrophil count (ANC) ≥ 1,500/mcL, platelet count ≥ 100,000/mcL, white blood count ≥ 3,000/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 2.0 (NCI CTC v2). Patients with ureteral obstruction were eligible if a stent or nephrostomy tube was placed prior to study entry. Women of child bearing potential could not be nursing or pregnant and had to be using an acceptable method of contraception. Patients were ineligible if they received prior radiation to the pelvis or abdomen. All patients gave written informed consent before study entry in compliance with institutional, state, and federal regulations.

Treatment

Patients received docetaxel (Taxotere®, Aventis Pharmaceuticals, Bridgewater, NJ) as a 30-minute intravenous infusion at one of 3 dose levels: 20, 25, 30 mg/m^2 on days 1, 8, 15, 22, 29, 36. The initial docetaxel dose level (25 mg/m^2) was designed to be 50 percent of the phase 1 maximum tolerated dose estimated by Briasoulis and colleagues [18]. Intravenous dexamethasone 10 mg and/or anti-emetic were administered 0.5-1 h prior to each therapy. Low dose whole abdominal radiation therapy (LDWART) was administered during or within one hour after the completion of the docetaxel infusion for each of the six weeks of docetaxel therapy. LDWART was delivered by megavoltage equipment (6–25 MV) at dose rates of 200 to 300 cGy per minute at the midplane with a minimum source to skin distance of 80 cm. Treatment was given at 60 cGy fractions, twice daily for two days, with a minimum of 4 h interfraction interval, starting on day 1 of each chemotherapy cycle. Anterior-posterior and posterior-anterior fields encompassed superiorly one centimeter above the dome of the diaphragm at the patient's maximum comfortable expiration and inferiorly either the inferior border of obturator foramina or 2 cm below the lowest extent of disease.

Evaluation of toxicity, dose modifications, and assessment of response

Patients were eligible to continue treatment unless there was evidence of unacceptable toxicity or progressive disease. Toxicities were graded in accordance with the NCI CTC v2. Dose-limiting toxicities were identified by the highest graded toxicity observed during any of the six treatment cycles or within four weeks following completion of treatment. Dose-limiting toxicities (DLT) were defined as grade 4 neutropenia (ANC < 500/mcL) without fever of >7 days, grade 3 or 4 neutropenia (ANC <1,000/mcL) of any duration associated with fever (≥38.5° C) requiring antibiotics, grade 4 thrombocytopenia (platelets ≤10,000/mcL), grade 3 or 4 thrombocytopenia (platelets ≤50,000/mcL) associated with bleeding requiring platelet transfusion, grade 3 or higher non-hematological toxicity (excluding nausea and vomiting reduced to grade 1 <48 hours or diarrhea reduced to grade 1 <6 days), or any treatment-related toxicity causing a delay of >14 days.

Dose modifications for docetaxel included dose delays and reductions. Docetaxel and radiation were delayed if any of the following toxicities were present on the day of treatment: ANC <500/mcL without fever of >7 days duration, ANC <1,000/mcL with fever requiring antibiotics, platelet count <50,000/mcL with bleeding requiring platelet transfusion or <10,000/mcL, increase of >1 grade from baseline bilirubin, alanine transaminase, and/or aspartate transaminase, and any grade 3 non-hematologic toxicities excluding nausea and vomiting. Treatment was resumed when toxicities recovered to the following values: ANC ≥1,500/mcL, platelet count ≥100,000/mcL, LFT(s) within one grade of the baseline value(s), and resolution of grade 3 non-hematologic toxicities to ≤ grade 1. Docetaxel was reduced one dose level for any delay in treatment due to hematologic toxicity. Treatment delays of up to two weeks were allowed for recovery of toxicities, and patients were removed from study for delays greater than two weeks.

Antitumor response was evaluated by physical examination and/or imaging pre-study, one-month post-treatment, and every three months of post-treatment follow-up. Responses were defined by Response Evaluation Criteria in Solid Tumors (RECIST) [19].

Statistical considerations

The primary objective of this dose finding study was to identify the maximum tolerated dose (MTD) and its associated acute toxicities of weekly docetaxel with concurrent radiation therapy. Acute toxicity was defined by events having onset during or within 30 days of completing therapy. A dose-escalation trial of weekly docetaxel dose with whole abdomen radiation dose was designed. A cohort of three patients were treated at each dose level of docetaxel and if they successfully completed radiation therapy and 6 weekly treatments of docetaxel followed by four weeks of follow-up without a DLT, dose escalation continued. If a dose-limiting toxicity occurred in one of the three patients treated at a given dose level, up to three additional patients were treated at that dose level. If two patients at any dose level experienced a DLT, enrollment at this dose level would be terminated; in this case, an additional three patients would be entered at the previous dose if only three patients had previously been entered at that dose level to be sure that no more than one patient in six experiences a DLT. If two or more patients experience a DLT, de-escalation would continue. The maximum tolerated dose (MTD) of weekly docetaxel and low dose whole abdomen radiation was defined as the highest dose level where less than or equal to one out of six patients experienced a dose-limiting toxicity. Secondary endpoints included objective tumor response by RECIST and PFS. Time at risk for disease progression or death was measured from the date of study entry. Since patients were followed for no more than one year, overall survival for patients was not characterized in this study. It was anticipated that the primary dose-limiting toxicities would be hematologic, with modifications in docetaxel dose considered when dose-limiting events became apparent as described above.

RESULTS

Patient characteristics

Thirteen eligible patients were enrolled from June 2004 to June 2008. Characteristics of those enrolled are summarized in Table 1. All patients had received at least one prior chemotherapy regimen, and all 13 patients had received a taxane.

Treatment and toxicities

Thirteen patients received 70 cycles (median, 6 cycles) of treatment, and all were evaluable for toxicity. Eleven patients were evaluable for dose-limiting toxicities over the full course of treatment (3 patients on dose level 1, 2 patients on dose level 2, and 6 patients on dose level -1). Two patients had disease-related symptomatic deterioration, which, in the opinion

of the investigator, indicated that further radiation and docetaxel therapy was not in the best interest of the patient. One experienced disease-related small bowel obstruction and subsequent septicemia after the third cycle of study therapy, and was subsequently taken off study. The other patient withdrew consent for study therapy because of quality-of-life impairing dyspnea from progressive chest disease and her desire for palliative chest radiation.

At dose level 1 (docetaxel 25 mg/m^2), four patients were treated, and three completed therapy. One patient did not complete treatment due to progressive disease. Two patients each experienced grade 3 fatigue. In addition, one of these patients experienced grade 3 thrombocytopenia without bleeding following completion of therapy. Though all grade 3 non-hematologic toxicities (excluding nausea and vomiting reduced to grade 1 <48 hours or diarrhea reduced to grade 1 <6 days) were written in this protocol to be dose-limiting, it was felt that grade 3 fatigue should not be dose-limiting given the nature of this treatment. Therefore, dose escalation occurred. At dose level 2 (docetaxel 30 mg/m^2), two patients were treated, both of whom completed therapy. One patient experienced grade 4 thrombocytopenia, grade 3 hemorrhage (epistaxis), and grade 3 febrile neutropenia. One patient experienced grade 3 diarrhea. Given the toxicities at both dose levels, the protocol was amended adding dose level −1 (docetaxel 20 mg/m^2), and 7 patients were treated at this level with one out of 7 patients experiencing a DLT. The first two patients completed therapy without any dose-limiting toxicities. The first patient did have a week delay in the fourth week and again in the seventh week of treatment due to grade 1 thrombocytopenia. The third patient did not complete treatment due to progressive disease, did not have a DLT, and was thus replaced; the fourth patient experienced dose-limiting toxicity as she was not able to receive her sixth and final week of docetaxel and radiation due to grade 3 thrombocytopenia lasting greater than 14 days. Given this DLT, 3 more patients were accrued at this dose level as per protocol. The first of the three additional patients had grade 2 thrombocytopenia on week 3 of treatment and had a 14 day delay before proceeding with week 4. The second and third of the three additional patients each had a week delay, one due to grade 4 neutropenia (week 6) and the other due to grade 1 thrombocytopenia (week 4). None of these toxicities were dose-limiting, and therefore, dose level -1 was deemed the maximum tolerated dose.

Table 2 represents the highest toxicity grade for the treatment-related toxicities of the thirteen patients treated on this study. All patients experienced hematological toxicities, and the majority were grade 1 or 2. Thrombocytopenia, the most frequent hematological toxicity observed, was dose-limiting in patients at each of the dose levels as noted above. Six patients (four at docetaxel 20 mg/m^2 and two at docetaxel 30 mg/m^2) had 8 treatment cycles held due to hematological toxicity, resulting in a dose reduction of docetaxel in four patients. This toxicity first occurred after cycle 3 in five of these patients, and only one had a treatment delay greater than one week. The most common non-hematologic toxicities were grades 1 or 2 fatigue, diarrhea, nausea/vomiting and arthralgia/myalgia (Table 2). Grade 3 fatigue and diarrhea were observed and were dose-limiting as noted above.

Secondary Endpoints

The median duration of PFS for all patients enrolled was 3.3 months (90% C.I. 1.4 − 6.2 months). Ten of thirteen patients had measurable disease at the time of study entry. No clinical or radiographic complete or partial responses were recorded. Six and four of the measurable patients had stable disease and progressive disease, respectfully. Three of the 10 patients with measurable disease survived progression-free for at least 6 months. Two of these 3 patients had no further treatment until progression by RECIST criteria or death. One of these patients was noted to have an elevation in the CA 125 with no measurable disease and began chemotherapy 2.3 months after study entry because of this elevation. Of the three

patients with non-measurable disease, one patient experienced recurrence-free survival of 21.2 months. This patient received 8 cycles of carboplatin and paclitaxel chemotherapy following surgical debulking and had persistent disease by PET scan with an elevation of the CA 125 (56.9 U/ml). Following study treatment, this patient's CA 125 normalized and there was no evidence of disease for almost 2 years at which time patient received further chemotherapy.

DISCUSSION

Epithelial ovarian cancer is known to be a chemosensitive disease with initial response rates to systemic therapy exceeding 80% following cytoreductive surgery. However, intraperitoneal persistence or recurrence of disease after chemotherapy remains a significant impediment to the cure of this disease. In women with recurrent ovarian and peritoneal cancer, the taxane derivative, docetaxel, has shown clinical activity and a favorable toxicity profile [8–11]. This Phase I study determined the MTD to be intravenous docetaxel 20 mg/m^2 administered once a week concurrently with twice daily low-dose whole abdomen radiation administered twice a week for 6 weeks. Although our selection of initial docetaxel dose levels appeared conservative, the incidence of hematological toxicity, especially thrombocytopenia, did not allow for dose escalation. Toxicity emerged by the third treatment week. Even at the MTD, docetaxel administered weekly at 20 mg/m^2 concurrently with LDWART was safely administered with acceptable hematological toxicity, but was still associated commonly with one-week treatment delays. The longest duration of stable disease (21.2 months) was achieved after abdominal radiation and docetaxel administered weekly at 30 mg/m^2.

The concept of low-dose radiation as a chemosensitizer has precedent. A previous phase II study conducted in patients with squamous cell carcinomas of the head and neck was undertaken with low-dose fractionated radiation (four 80 cGy fractions, two each on days 1 and 2, 22 and 23) given during two cycles of carboplatin (area under the curve of 6) plus paclitaxel (225 mg/m^2 over 24 hrs) chemotherapy [20]. Among the 40 patients treated, radiation and chemotherapy were well-tolerated with manageable hematological, skin, and pulmonary toxicity. Complete or partial responses were recorded in 35 of 39 (90%) evaluable patients. In our current study, we have tested further the concept of low-dose radiation promoting docetaxel-related cytotoxicity. While it is difficult to ascertain whether the expected radiobiological effect of radiation-mediated G_2/M arrest enhancing docetaxel cytotoxicity actually occurred, treatment did result in stable disease for 6 patients (out of 10 measurable) who were previously treated with a taxane. These results suggest low-dose radiation and docetaxel treatment may be a reasonable treatment option for women with recurrent ovarian or peritoneal cancer and intraperitoneal disease progression.

There are exciting opportunities for implementing abdominopelvic radiation in patients with paclitaxel-resistant ovarian or peritoneal cancer. Observational studies have suggested that human oocytes and supporting epithelial ovarian cells are exquisitely sensitive to radiation, with an estimated radiation dose of 2 to 6 Gy needed to sterilize cells [21,22]. And yet, abdominopelvic radiation use has dwindled due to a perceived lack of efficacy and high toxicity [23–25]. Our study indicated that weekly docetaxel chemotherapy administered at 20 mg/m^2 with concurrent twice daily low-dose whole abdominopelvic radiation given twice weekly was well-tolerated and indicated a possible chemosensitization effect. With improvements in radiation delivery such as intensity-modulated and helical tomotherapy radiation that lower the incidence of radiation-related adverse events, low-dose radiation may serve as a meaningful therapeutic tool for restoring cancer cell sensitivity to anticancer cytotoxic or targeted agents. Due to our observed stable disease in these women,

translational clinical trials incorporating optimally-timed and sequenced low-dose radiation with novel, targeted cancer therapeutics would be of considerable interest.

Research Highlights

- Radiotherapy as a chemosensitizer to docetaxel in the treatment of ovarian cancer.
- Chemoradiation resulted in stable disease in women with recurrent ovarian cancer.
- Radiotherapy with docetaxel is tolerable in women with recurrent ovarian cancer.

Acknowledgments

This study was supported in part by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469) and the Gynecologic Oncology Group Statistical and Data Center (CA 37517).

The following Gynecologic Oncology Group member institutions participated in this study: Case Western Reserve University, Indiana University School of Medicine, University of Chicago, University of Iowa Hospitals and Clinics, University of Kentucky, and University of Oklahoma. The authors would like to thank Kia Neff, Patricia Brehm, and Anne Reardon of the Gynecologic Oncology Group Administrative Office and Statistical and Data Center, for their expertise assistance in protocol development and data management and coordination. In addition, we wish to thank all the women who participated in this study.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics, 2009. CA Cancer J Clin 2009;59:225–49. [PubMed: 19474385]
2. Cannistra SA. Cancer of the ovary. New Engl J Med 2004;351:2510–529.
3. Mauer A, Masters G, Haraf D, et al. A phase I study of docetaxel with concomitant thoracic radiation therapy. J Clin Oncol 1998;16:1. [PubMed: 9440714]
4. Hainsworth J, Burris HI, Greco F. Weekly administration of docetaxel (Taxotere): summary of clinical data. Semin Oncol 1999;26:19–24. [PubMed: 10437747]
5. Kavanagh J, Kudelka A, de Leon C, et al. Phase II study of docetaxel in patients with epithelial ovarian carcinoma refractory to platinum. Clin Cancer Res 1996;2:837–42. [PubMed: 9816238]
6. Kaye S, Piccart M, Aapro M, et al. Phase II trials of docetaxel (Taxotere) in advanced ovarian cancer--an updated overview. Eur J Cancer 1997;33:2167–70. [PubMed: 9470802]
7. Verschraegen C, Sittisomwong T, Kudelka A, et al. Docetaxel for patients with paclitaxel-resistant Mullerian carcinoma. J Clin Oncol 2000;18:2733–39. [PubMed: 10894873]
8. Rose P, Blessing J, Ball H, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2003;88:130–35. [PubMed: 12586591]
9. Hall, E.; Garcia, A. Radiobiology for the Radiologist. 6. Philadelphia: Lippincott Williams & Wilkins; 2006. Clinical response of normal tissues; p. 341
10. Randall M, Barrett R, Spirtos N, et al. Chemotherapy, early surgical reassessment, and hyperfractionated abdominal radiotherapy in stage III ovarian cancer. Int J Radiat Oncol Biol Phys 1996;34:139–47. [PubMed: 12118543]
11. Reddy S, Lee M, Yordan E, et al. Salvage whole abdomen radiation therapy: its role in ovarian cancer. Int J Radiat Oncol Biol Phys 1993;27:879–84. [PubMed: 8244818]
12. Eifel P, Gershenson D, Delclos L, et al. Twice-daily, split-course abdominopelvic radiation therapy after chemotherapy and positive second-look laparotomy for epithelial ovarian carcinoma. Int J Radiat Oncol Biol Phys 1991;21:1013–18. [PubMed: 1917596]

13. Corn B, Lanciano R, Boente M, et al. Recurrent ovarian cancer. Effective radiotherapeutic palliation after chemotherapy failure. Cancer 1994;74:2979–83. [PubMed: 7525039]
14. Dembo A, Bush R, Beale F, et al. Ovarian carcinoma: Improved survival following abdominopelvic irradiation in patients with a completed pelvic operation. Am J Obstet Gynecol 1979;134:793–800. [PubMed: 463982]
15. Firat S, Murray K, Erickson B. High-dose whole abdominal and pelvic irradiation for treatment of ovarian carcinoma: Long-term toxicity and outcomes. Int J Radiat Oncol Biol Phys 2003;57:201–207. [PubMed: 12909234]
16. Chendil D, Oakes R, Alcock R, et al. Low dose fractionated radiation enhances the radiosensitization effect of paclitaxel in colorectal tumor cells with mutant p53. Cancer 2000;89:1893–900. [PubMed: 11064345]
17. Hall, E.; Garcia, A. Radiobiology for the Radiologist. 6. Philadelphia: Lippincott Williams & Wilkins; 2006. Time, dose, and fractionation in radiotherapy; p. 378-97.
18. Briasoulis E, Karavasillis V, Anastasopoloulos D, et al. Weekly docetaxel in minimally pretreated cancer patients: A dose-escalation study focused on feasibility and cumulative toxicity of long-term administration. Ann Oncol 1999;10:701–06. [PubMed: 10442193]
19. Therasse P, Arbuck S, Eisenhauer E, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16. [PubMed: 10655437]
20. Arnold S, Regine W, Ahmed M, et al. Low-dose fractionated radiation as a chemopotentiator of neoadjuvant paclitaxel and carboplatin for locally advanced squamous cell carcinoma of the head and neck: results of a new treatment paradigm. Int J Radiat Oncol Biol Phys 2004;58:1411–17. [PubMed: 15050317]
21. Wallace W, Thomson A, Kelsey T. The radiosensitivity of the human oocyte. Hum Reprod 2003;18:117–121. [PubMed: 12525451]
22. Adriaens I, Smitz J, Jacquet P. The current knowledge on radiosensitivity of ovarian follicle development stages. Hum Reprod Update 2009;15:359–377. [PubMed: 19151106]
23. Thomas G. Radiotherapy in early ovarian cancer. Gynecol Oncol 1994;55:S73–S79. [PubMed: 7835813]
24. Dembo A. Epithelial ovarian cancer: The role of radiotherapy. Int J Radiat Oncol Biol Phys 1992;22:835–845. [PubMed: 1555974]
25. Engelen M, Snel B, Schaapveld M, Pras E, de Vries E, Gietema J, van der Zee A, Willemse P. Long-term morbidity of adjuvant whole-abdominal radiotherapy (WART) or chemotherapy for early stage ovarian cancer. Eur J Cancer 2009;45:1193–1200. [PubMed: 19201598]

Table 1

Patient characteristics

Characteristic	No. patients (*n* = 13)
Age (y)	
Median (range)	61 (38–74)
GOG performance status	
0	10
1	3
Diagnosis	
Ovarian	10
Peritoneal	3
Prior therapy	
Chemotherapy	13
Mean no. regimens (range)	2 (1–5)

Abbreviation: GOG, Gynecologic Oncology Group.

Table 2

Incidence of hematological and non-hematologic toxicity

	Docetaxel dose level											
Adverse event	**1 (*n* = 4)**				**2 (*n* = 2)**				**−1 (*n* = 7)**			
Grade of adverse event	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Blood/Bone Marrow												
Hemoglobin	2	1	1	0		2			2	3		
Neutrophils	1						2		3	2		1
Platelets	2	1	1					1	3	1	1	
Cardiovascular (General)												
Hypotension		1										
Constitutional Symptoms												
Fatigue	1		2			1			2	5		
Fever			1									
Gastrointestinal												
Anorexia						1			1	1		
Constipation	1								3			
Diarrhea	2	2			1		1		4			
Nausea/vomiting	2	2				1			2			
Stomatitis/pharyngitis	2				1							
Hemorrhage												
Epistaxis							1					
Infection/Febrile Neutropenia												
Febrile Neutropenia							1					
Neurology												
Neuropathy - sensory									1	1		
Pain												
Arthralgia/myalgia	1								3			