Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 108 (2008) 201–206
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Pilot phase II trial of radiation "sandwiched" between combination paclitaxel/platinum chemotherapy in patients with uterine papillary serous carcinoma (UPSC)

Abbie L. Fields [a,*], Mark H. Einstein [b,c,d], Akiva P. Novetsky [b,c], Juliana Gebb [b,c], Gary L. Goldberg [b,c,d]

[a] *Virginia Gynecologic Oncology, 7603 Forest Avenue, Suite 207, Richmond, VA 23229, USA*
[b] *Department of Obstetrics and Gynecology and Women's Health, Division of Gynecologic Oncology-Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA*
[c] *Albert Einstein College of Medicine, Bronx, NY, USA*
[d] *Albert Einstein Cancer Center, Bronx, NY, USA*

Received 13 June 2007
Available online 8 November 2007

Abstract

Objectives. To evaluate disease-free survival (DFS) and overall survival (OS) in patients treated with pelvic radiation "sandwiched" between six cycles of paclitaxel(T)/platinum(P) chemotherapy with optimally reduced uterine papillary serous carcinoma (UPSC).

Methods. Surgically staged patients with UPSC and no visible residual disease were enrolled. Treatment involved T (175 mg/m^2) and either cisplatin (75 mg/m^2) or carboplatin (AUC = 6.0, 6.5, 7.5) every 21 days × 3 doses, followed by pelvic RT (45 Gy). Fields were extended for >2 positive pelvic or confirmed para-aortic node disease. Three additional cycles of T/P were administered after RT. Toxicity was graded by NCI CTC Version 3.0. Kaplan–Meier survival statistics were used for DFS/OS.

Results. 30 women were enrolled between 1999 and 2004. Median age was 69 years (45–82 years). 60% (18/30) of patients had disease confined to the uterus (Stage I/II) and 40% (12/30) had extra-uterine disease (Stage III/IV). 29 patients completed protocol treatment. One patient was discontinued due to non-compliance and recurred at 7 months. All 30 patients are included in survival analysis. Three-year DFS and OS with Stage I/II disease was 69% and 75% and Stage III/IV disease was 54% and 52%, respectively. Of 177 chemotherapy cycles administered, grade 3 or 4 neutropenia, thrombocytopenia or anemia occurred in 42%, 1% and 3% of cycles, respectively. Six cycles were delayed 1 week for neutropenia. 43% of all neutropenic episodes occurred after RT.

Conclusion. Radiation "sandwiched" between T/P chemotherapy is a well-tolerated and efficacious regimen for patients with completely resected UPSC. A larger multi-institutional clinical trial should be considered to confirm these pilot data.

Keywords: Uterine papillary serous carcinoma (UPSC); Paclitaxel; Carboplatin; Radiation therapy; Uterine cancer

Introduction

Endometrial adenocarcinomas occur with an estimated annual incidence of 41,200, making it the 4th most common cancer to affect women and, the most common gynecologic malignancy in the United States [1]. Deaths from endometrial cancers account for 7310 (3%) of cancer deaths in women. The majority of these tumors (75%), present at an early stage and are confined to the uterus with an uncorrected survival rate, exceeding 75% [2].

Uterine papillary serous carcinoma (UPSC) stands in stark contrast to the favorable outcome of most women with endometrioid adenocarcinoma. UPSC was first identified as a distinct disease entity in 1982 [3]. Although representing only 10% of endometrial carcinomas, UPSC is responsible for more than 50% of disease recurrences and deaths due to endometrial cancer. Histologically, this aggressive variant of endometrial carcinoma closely resembles papillary serous carcinomas of the

* Corresponding author. Fax: +1 804 200 7026.
E-mail address: abbiefields@comcast.net (A.L. Fields).

0090-8258/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2007.09.025

ovary and fallopian tube, frequently presenting with marked nuclear atypia, psammoma bodies, Her-2neu overexpression and absence of ER/PR expression [4].

Staging of endometrial carcinomas changed from clinical to surgical staging in 1988. With this change, it became clear that whereas only 25–30% of endometrioid adenocarcinomas have metastatic disease at diagnosis, more than 70% of women with UPSC have metastatic disease at diagnosis [5]. Metastatic disease and recurrence have been reported in situations where only superficial myometrial invasion or invasion limited to a polyp was documented. A recent study of 86 women with Stage I UPSC demonstrated good survival in women with Stage IA UPSC but almost a 30% recurrence rate in women with Stage IB/IC UPSC [6]. Lymph-node and intraperitoneal metastases have been identified in 36% and 43% of women, respectively, in absence of myometrial invasion [7]. Five-year overall survival for patients with UPSC has been reported at 46% [8].

Due to the aggressive nature of UPSC, its propensity for early metastases, and frequent upper abdominal and pelvic recurrence, treatment with surgery alone is not sufficient [9,10]. Numerous small retrospective studies have suggested different methods of treatment including radiation therapy (whole abdominal, pelvic, vaginal brachytherapy, IP-32), chemotherapy (single agent verses combination), multimodality therapy. None of these studies have provided a consensus as to the optimum management of women with UPSC, especially in the adjuvant setting [9,10]. Havrilesky et al. demonstrated 3-year overall survival and progression-free survival in women with Stage I UPSC treated with adjuvant radiotherapy alone of 63% and 44%, respectively {Havrilesky, 2007 #24}. Clearly radiotherapy alone for the treatment of UPSC is inadequate and there is a clear need for clinical trials using additional combination of new or standard therapies.

These studies, as well as recently reported prospective studies, have been useful in providing data regarding patterns of failure following various types of therapy [8–15]. It is becoming clear, that patients who receive radiotherapy alone recur intra-abdominally, and those treated with chemotherapy alone develop pelvic/vaginal recurrences. This suggests that a combination of chemotherapy and radiation would theoretically be beneficial for patients with UPSC.

The objective of this prospective pilot trial is to evaluate the disease-free (DFS) and overall-survival (OS) in patients treated with pelvic radiation "sandwiched" between six cycles of paclitaxel/platinum chemotherapy in women who have undergone complete surgical staging, and have no visible residual disease.

Patients and methods

Institutional review board (IRB) approval was granted prior to initiation of this study. Written, voluntary informed consent was obtained from each patient according to institutional and federal guidelines before enrollment. Eligible patients were those with histologically documented UPSC and no visible residual disease following surgery. Patients underwent surgical staging, which included total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling and peritoneal washings. Infracolic omentectomy was preferred, but not required. Patients were required to have an ECOG performance status of 0 to 1, adequate hematologic function (WBC $\geq 3000/mm^3$, hematocrit $\geq 30\%$, platelets $\geq 100{,}000/mm^3$), normal renal function (BUN ≤ 25 mg %, creatinine ≤ 2 mg %), and normal hepatic function (total serum bilirubin ≤ 1.5 mg/dl, aminotransferase ≤ 2.5 times the institutional upper limit of normal). Patients with a severe or uncontrolled concurrent medical condition limiting life expectancy to ≤ 3 months, or those previously treated with chemotherapy or radiotherapy for pelvic malignancy, were excluded.

Pre-treatment evaluation and follow up

At study entry, patients underwent complete medical history, physical examination, complete blood count, serum electrolytes/chemistry profile, CA-125, CA 19-9 chest X-ray, EKG, and CT scan of the chest, abdomen, and pelvis.

A complete physical examination, CBC, serum electrolyte/chemistry profile, CA-125 and CA 19-9 were performed prior to each cycle of chemotherapy, upon completion of the study, every 3 months for 24 months, and then every 6 months thereafter. Adverse events (clinical and laboratory) were monitored weekly during radiation therapy and every 3 weeks during chemotherapy treatment and graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. CT scans of the chest, abdomen and pelvis were performed upon completion of the study and repeated every 6 months, or as clinically indicated.

Treatment plan

Chemotherapy

Initiation of treatment was required to be ≤ 30 days after surgery. Paclitaxel was administered at a dose of 175 mg/m^2/3 h. Choice of platinum was per treating physician preference and could be selected from the following three options: cisplatin (CDDP) at a dose of 75 mg/m^2, carboplatin at an AUC of 7.5 before RT and 6.5 after RT or carboplatin at an AUC of 6, both before and after RT. Chemotherapy was administered every 21 days for 3 cycles followed by a five-week chemotherapy break, while external beam radiotherapy was administered. The fourth cycle of chemotherapy was initiated the same week as the high dose rate brachytherapy, to avoid a prolonged delay in chemotherapy. The remainder of the planned six cycles of paclitaxel/platinum continued to be administered every 21 days. Standard premedications for prevention of hypersensitivity reactions to paclitaxel were given.

Prior to each subsequent cycle of therapy, patients were required to have an ANC $\geq 1500/mm^3$ or WBC $\geq 3000/mm^3$, platelets $\geq$ $100{,}000/mm^3$ and renal and hepatic parameters as described earlier. Treatment modifications for hematologic toxicity included cycle delay until recovery, dose reduction or addition of G-CSF and/or erythropoietin. A treatment delay of more than 2 weeks was considered a major deviation from the protocol, and the patient was removed from the study.

Radiation

The total dose of external-beam pelvic radiation was 45 Gy over 5 weeks. Patients were treated, 5 days a week with a daily fraction size of 1.8 Gy. Four-field technique was used with a megavoltage beam of greater than 6 MV, and a minimum source axis distance of 100 cm. The fields were extended in the case of greater than two positive pelvic nodes, or documented para-aortic nodal disease. Sites of known positive lymph nodes had been marked at the time of surgery with identifiable hemoclips.

HDR brachytherapy covered the upper 2/3 of the vagina and the dose was prescribed to 5 mm depth (5 mm from the surface of the applicator). Segmented cylinders of the largest size the vagina would accommodate were used. One fraction of 5 Gy was given once a week for 3 weeks using the nucleotron microselection remote afterloading technique. The vaginal surface dose was calculated at the vaginal surface, lateral to the midpoint of the surface of the cylinder.

Survival

Disease-free survival (DFS) was calculated from the date of study entry to date of recurrence. Overall survival (OS) was calculated from the date of study entrance until the date last seen. Site and date of relapse were recorded. Recurrent disease was defined as pelvic or distant. Pelvic sites were specified as