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Adjuvant pelvic radiation “sandwiched” between paclitaxel/ carboplatin chemotherapy in women with completely resected uterine serous carcinoma (USC): long term follow-up of a prospective phase II trial

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Abstract

Objective: We prospectively evaluated patients with completely resected USC treated with radiation “sandwiched” between carboplatin/paclitaxel (C/T). The primary objective was the safety profile and the secondary outcome was to evaluate progression free and overall survival.

Methods: Surgically staged patients with completely resected USC were enrolled to receive 3 cycles paclitaxel 175mg/m² and carboplatin (AUC 6–7.5) every 21 days, followed by radiotherapy (RT) and an additional 3 cycles of T/C at AUC 5–6 (6 cycles + RT). Toxicity was graded according to NCI.CTC, v4.03. Kaplan-Meier and log-rank tests were used to compare survival probabilities.

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Results: 140 patients were enrolled, of which 132 were evaluable, completed at least 3 cycles of chemotherapy and radiation. 107 (81%) completed 6 cycles of chemotherapy and radiation. Early stage (I/II) patients have survival probabilities of 0.96 and 0.81 at 2 and 5 years. Patients with stage I USC and lympho-vascular invasion (LVSI) have considerably worse OS, with 2.7 times higher risk of death than those without LVSI. Late stage (III/IV) patients had an overall survival probability of 0.64 and 0.18 at 2 and 5 years which is far higher survival than what has been reported in single modality trials. Interestingly, and different than what is reported in other studies, there is no difference in survival in African Americans vs. Whites/other races who were evaluable. Of the 779 cycles administered, 22% and 14% of cycles were associated with grade 3 and 4 hematologic toxicities, respectively. Grade 3 and 4 non-hematologic toxicities occurred in 6.9% of cycles.

Conclusions: The long-term follow up in this study demonstrates that “sandwich” therapy is an efficacious, well tolerated treatment approach with acceptable toxicities. LVSI is a significantly poor prognostic factor in stage I USC. Multimodal “sandwich” therapy should be considered in all USC patients who have undergone complete surgical resection and staging.

Introduction

Uterine serous carcinoma (USC) is the most common non-endometrioid subtype of endometrial cancer, accounting for approximately 10% of all endometrial cancer cases. Usually diagnosed at an advanced stage, USC is an aggressive histologic subtype associated with a disproportionate number (39%) of endometrial cancer deaths [1]. The Cancer Genome Atlas molecular characterization data indicates that tumors in the “serous-like” cluster had significantly worse progression free survival than endometrioid histology. Recurrence of USC is common, occurring in up to 50% of patients with early disease, and higher in patients with advanced disease [2]. The optimal adjuvant treatment following surgery for USC remains controversial. Studies have evaluated the role multimodal therapy, combining pelvic radiation therapy (RT) for local control with chemotherapy (CT) for systemic control. Studies have shown that sequential use of chemotherapy followed by pelvic RT in patients with stage III/IV endometrial cancer was associated with few pelvic recurrences, improved survival, and an acceptable toxicity profile [3–6].

In a multi-institutional retrospective analysis of 356 patients with stages III/IV endometrial cancer (90% without measurable disease), including 86 patients with USC, Secord et al. compared outcomes in patients who received RT alone, chemotherapy alone, or various regimens of combined chemotherapy + RT[7]. CT+RT was associated with the best survival outcomes when compared with either chemotherapy or RT alone with acceptable toxicity[7]. A second multi-institutional retrospective analysis of 265 patients with optimally resected stage IIIC endometrial cancer demonstrated that adjuvant treatment with either RT alone or CT+RT was associated with improved survival outcomes compared with those that received chemotherapy only[8]. The same group subsequently evaluated the sequence of multimodal adjuvant therapy in 109 patients with advanced endometrial cancer and found a progression free survival (PFS) and overall survival (OS) advantage for patients that received chemoradiation in “sandwich” fashion compared with patients that received chemotherapy followed by radiation or radiation followed by chemotherapy[9]. Importantly, there was no

difference in toxicity, dose modifications, and dose reductions between the three groups. These studies are limited by the inclusion of multiple histologic subtypes[9].

Our group previously reported the safety, tolerability, and 3-year survival data of a “non-randomized” phase II trial of adjuvant pelvic radiation “sandwiched” between paclitaxel and carboplatin in 81 women with completely resected USC[10]. The “sandwich” strategy hypothetically allows for control of systemic disease with chemotherapy while treating pelvic micro-metastasis with RT. The sequential delivery of chemotherapy and RT limits the overall toxicity and allows for maximum therapeutic dosing for chemotherapy and RT. Treatment was well tolerated with grade 3 and 4 non-hematologic toxicity, dose reduction, and dose delay in 2.5%, 6%, and 8.5% of patients, respectively[10]. Based on promising survival data, this treatment became an institutional standard and we continued to treat patients with this regimen. Here we present the combined tolerability and efficacy data for patients treated with “sandwich” therapy during and following the study protocol, allowing for extended 5-year follow-up after completion of adjuvant “sandwich” therapy.

Methods

After IRB approval and clinical trials registration, eligible patients were initially recruited from 1999–2009 at Montefiore Medical Center/Albert Einstein College of Medicine to our previously reported phase II trial (clinicaltrials.gov identifier: NCT00231868)[10]. Eligible patients underwent surgical staging for histologically confirmed stage I-IV USC, which included hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling and peritoneal washings. Infracolic omentectomy was preferred but not required in patients without visible omental disease. Inclusion criteria included women who had at least 6 months of follow-up. Patients who died within the first 6 months of surgery were included in the analysis. Patients with grossly visible residual disease following surgery were excluded. In addition to following survival endpoints in subjects enrolled on the original “non-randomized” phase 2 protocol, patients who received the same therapy but treated “off protocol” were included in this analysis. The treatment and toxicity data for patients who received treatment on and off protocol were followed until 2015. Surgical criteria remained the same for patients recruited off protocol, including lymph node sampling without application of sentinel lymph node biopsy. The IRB approval was expanded to include the retrospective review of all patients who received this treatment off protocol until 2015.

Chemotherapy

Postoperatively, all patients received adjuvant platinum/taxane chemotherapy and radiation in “sandwich” fashion. Paclitaxel was administered at a dose of 175 mg/m² over 3 hours. Carboplatin was administered at AUC 6–7.5 for cycles 1–3 and AUC 5–6 for cycles 4–6. In the original pilot phase of this study, we optimized the carboplatin dosing, specifically due to hematologic toxicity often seen after RT with the higher carboplatin doses[11]. Optimization led to our standard carboplatin dose of AUC 6 before RT and AUC 5 after RT, for the subsequent phase II trial. Chemotherapy was administered every 21 days for 3 cycles prior to proceeding with pelvic RT. Following completion of RT, patients received an additional 3 cycles of platinum/taxane chemotherapy at 21 day intervals, for a total of 6 chemotherapy

cycles. Cycle 4 of chemotherapy was initiated within 1–2 weeks of completion of the external beam radiotherapy (overlapping with brachytherapy). Standard paclitaxel and carboplatin pre-medications were administered to minimize hypersensitivity and nausea. Treatment modifications for hematologic toxicities included cycle delay until recovery with subsequent dose reduction. Cycle delays were defined as delay in chemotherapy ≥ 1 week. Granulocyte-colony stimulating factor (G-CSF) was administered based on provider preference.

Radiation Therapy

RT began one week after the 3rd cycle of chemotherapy. Patients received a total of 45 Gy of external beam pelvic radiation therapy (EBRT). Patients received a daily fraction of 1.8 Gy, 5 days per week for a total of 5 weeks. A four-field conformal RT (AP-PA opposed and lateral opposed fields) or intensity modulated radiation therapy (IMRT) technique was used with a megavoltage beam of 6MV. Once IMRT was introduced at our institution in 2005, all patients prescribed EBRT received IMRT. The fields were extended to include the para-aortic nodal region in the case of ≥ 2 positive pelvic nodes or documented positive para-aortic lymph nodes. In addition to EBRT, most patients received high dose rate (HDR) brachytherapy via vaginal cylinder to boost the dose to the proximal $\frac{1}{2}$ - $\frac{2}{3}$ of the vagina. Segmented cylinders of the largest size accommodated by the vagina were used. Three fractions of 5 Gy each prescribed to 0.5 cm depth from the vaginal surface were given once weekly using the Nucletron microSelectron HDR Ir-192 remote afterloading technique.

Adverse events were monitored for each cycle during therapy and graded with attributions using the National Cancer Institute Common Toxicity Criteria, version 4.03.

Statistical methods

The distribution of continuous variable was numerically summarized using mean and standard deviation while non-normal data were presented with median and range. The categorical variables were presented as frequency and percentage. The probability of survival was examined using Kaplan-Meier survival procedure and log-rank test to assess the association between exploratory variables and outcomes: PFS and OS. Cox regression was used to analyze the risk factors for PFS and OS. Proportional hazards assumption was checked and variables that were significant at 20% at univariate level along with a priori confounding variables such as age, race and BMI were considered for multivariable models. All analyses were performed using SAS version 9.4

Results

A total of 140 patients were prescribed “sandwich” therapy on (n=48) and off (n=92) protocol, 132 women were evaluable defined as completing at least 3 cycles of chemotherapy and RT (Figure 1). The distribution of the patient characteristics is presented in Table 1. This is an ethnically and racially diverse population.

At diagnosis, 74.3 % had stage I or II disease and 25.7% had completely resected stage III or IV disease. The patients were followed for a median of 46.7 months (range: 2.1, 179.4 months). Over the 15-year evaluation period, 33% (n=46) of the cohort died, 34 patients died

of disease and 12 patients died of other causes. Of the patients who had treatment, 107 (76%) had completed the protocol-specified treatment, 25 (17.8%) had received at least 3 cycles of chemotherapy followed by RT and 8 (5.7%) completed less than 3 cycles of chemotherapy or had incomplete RT. Thus, a total of 132 patients who completed at least 3 cycles of chemotherapy followed by RT were considered evaluable for all time to event analysis. Of those (n=8) who were excluded from the analysis and did not complete at least 3 cycles of chemotherapy followed by RT, 38% (n=3) died of disease. Of the 132 patients who completed at least 3 cycles of chemotherapy followed by RT, 116 patients were prescribed EBRT and brachytherapy, 9 patients were prescribed EBRT alone, and 7 patients brachytherapy alone. 107/140 (76.4%) of patients completed the full prescribed treatment – 6 cycles of chemotherapy and RT – 94 patients received 6 cycles of chemotherapy, EBRT and brachytherapy, and 13 patients had 6 cycles of chemotherapy followed by EBRT or brachytherapy.

Time to event outcomes

Survival analyses was considered only in those patients that completed at least 3 cycles of chemotherapy and RT (n=132). PFS results were similar to OS, therefore only OS is reported here.

Progression free survival:

The probability of PFS in early stage (I/II) at 1, 2 and 5 years were 0.97, 0.89 and 0.80, respectively. Late stage (III/IV) patients have PFS probabilities of 0.85, 0.41 and 0.22 at 1, 2, and 5 years, respectively. The median PFS time in stage III/IV patients were 22.3 months (95% CI: 16.7, 34.5). Focusing on the Stage III patients alone, yields PFS probabilities of 0.96, 0.48, 0.34, and 0.34 at 1, 2, 3, and 5 years.

Overall survival:

The probability of OS among study participants at year 1, 2 and 5 is 0.97, 0.89 and 0.68 respectively. (Figure 2) Early stage (I/II) patients have survival probabilities of 0.97, 0.96 and 0.81 at 1, 2 and 5 years, respectively. Late stage (III/IV) patients have an OS probability of 0.93, 0.64 and 0.18 at 1, 2 and 5 years. The median survival among late stage patients is 28 months (95% CI: 23.4, 48.8). The difference in survival distribution between early and late stage is statistically significant. (Figure 2) Stage III patients alone, mostly due to node metastasis, have OS probabilities of 1.0, 0.74, 0.44, and 0.26 at 1, 2, 3, and 5 years. A multivariable cox model showed that the estimate hazard of death is 8 times greater in late stage patients compared to early stage patients, adjusting for other covariates. A non-significant 43% reduction in risk of death was observed among those who received complete versus partial treatment. While statistically not significant, there were lower recurrence rates observed in women who completed the prescribed treatment compared to those who did not complete all treatment.

In the multivariable model, no difference in PFS and OS was observed between African Americans vs. Whites and other races. Interestingly, there is a trend toward higher risk of disease progression in Hispanics compared with White patients (hazard ratio 2.7), approaching statistical significance, $p=0.07$. (Table 3)

We further performed a subgroup analysis of patients with stage I disease (n=92) evaluating the effect of the presence of lympho-vascular invasion (LVSI) on OS. (Figure 3) Of the stage I patients, 27.2% (25/92) had LVSI and 6.6% (6/92) were indeterminate and were excluded in the analysis. The probability of OS at 1,2, and 5 years among those patients with LVSI and no LVSI were 0.96, 0.94, and 0.78 and 0.98, 0.96, and 0.89, respectively, which was statistically significant (p=0.03)(Figure 3). Patients with Stage I disease and LVSI had a 2.7 times higher risk of death (HR: 2.7; 95%CI: 1.02, 6.91, p=0.04) compared to patients without LVSI.

Toxicity

Table 2 describes observed hematologic and non-hematologic toxicities. A total of 779 cycles of chemotherapy were administered and grade 3 and 4 toxicities were tabulated. Of the 779 cycles administered, 22% and 14% of cycles were associated with grade 3 and grade 4 hematologic toxicities, respectively. More neutropenia occurred in cycles 1–3 and more thrombocytopenia occurred in cycles 4–6.(S1) There was one chemotherapy-related death after cycle 2 of chemotherapy in an 82 year old patient with stage IIIC2 disease who suffered grade 4 neutropenia, grade 3 anemia, and grade 4 thrombocytopenia. This patient developed Klebsiella urosepsis and died of sepsis after receiving cycle 2 of CT. Furthermore, grade 3 and grade 4 non-hematologic toxicities occurred in 6.9% of cycles, including infectious (n=14), neurologic (n=7), deep vein thrombosis/pulmonary embolus (n=7), metabolic disturbances (n=13), and gastrointestinal (n=5). Overall, 33/54 (61.1%) of dose reductions and 51/81 (62.9%) of all chemotherapy delays occurred after RT.

Of note, 57 patients (40.7%) required no granulocyte colony-stimulating factor (G-CSF) support, while 81 patients (57.9%) received G-CSF support. Of the 81 patients who received G-CSF support, 3 (2.1%) patients received it with all 6 chemotherapy cycles, 40 (28.6%) initiated it prior to RT with cycles 2 or 3, 13 (9.3%) received it immediately after RT starting with cycle 4, and 11 (7.9%) with cycles 5 or 6. Fourteen additional patients received G-CSF support with 1–2 random but non-consecutive cycles. Of note, 56 patients (40%) received G-CSF support by cycle 4 of chemotherapy.

Discussion

We report the largest prospective phase II single-institution clinical trial investigating the role of radiation “sandwiched” between chemotherapy in the management of patients with optimally resected USC. The long-term follow up demonstrates that “sandwich” therapy is a feasible, well tolerated treatment approach with acceptable toxicities and high efficacy compared to the literature data of single modalities of RT or chemotherapy alone. The survival probability in stage I/II patients was 96% at 2 years and 81% at 5 years supporting the treatment of patients with early stage disease, especially the higher risk patients with LVSI. We demonstrate high survival rates even in stage III patients, with an OS probability of 74% at 2 years and 44% at 5 years. As expected, the majority of the chemotherapy delays and dose reductions occurred after the RT. However, these numbers were slightly improved when compared to our prior reports likely secondary to increased G-CSF use.

In our follow-up period, we noticed a significant relationship of early stage USC with LVSI. While PFS was unaffected, patients with stage I USC and LVSI had considerably worse OS, with a 2.7 times higher risk of death. This is consistent with recent literature suggesting that LVSI is an important predictor of advanced disease and LVSI an independent prognostic factor associated with worse OS[12–14]. The presence of LVSI in early stage disease may further change the management recommendations for adjuvant RT in patients who would previously have been recommended vaginal brachytherapy alone. Recent pooled analysis of PORTEC 1 and 2 trials aimed to quantify LVSI and correlate this to risk and type of recurrence in patients with endometrioid endometrial cancer of all grades[15]. This trial concluded that “substantial” LVSI, in contrast to focal or no LVSI, was the strongest independent risk factor for pelvic recurrence and the authors recommended treatment with EBRT in patients with stage I, high grade, endometrioid cancer with “substantial” LVSI[15]. To our knowledge, this is the first prospective report evaluating the prognostic effect of LVSI on OS in patients with USC.

Recently, two phase III trials were initiated to investigate the role of multimodal therapy using chemotherapy and RT compared to single modality alone. PORTEC 3 investigated the benefit of adjuvant chemotherapy during and after RT compared to RT alone in women with high risk endometrial cancer, 16% of which had serous histology[16]. Serous histology was defined as at having at least a 25% serous component[16]. Data indicated that adjuvant chemotherapy given during and after RT did not significantly improve the 5 year OS compared to radiotherapy alone. Failure free survival in all stage USC was 58% with chemoradiotherapy versus 48% with radiotherapy ($p=0.11$). Interestingly, among all women with stage III endometrial cancer, failure-free survival was significantly improved by 11% in women treated with both chemoradiotherapy; however OS was not affected[16]. Furthermore, the preliminary data from GOG 258 reported on PFS after treatment with cisplatin with volume directed radiation followed by 4 cycles of carboplatin and paclitaxel compared to 6 cycles of carboplatin and paclitaxel alone in patients with either advanced endometrioid endometrial cancer or early stage USC or clear cell cancer[17]. USC comprised 17% of cancers in each arm. While cisplatin-RT reduced the incidence of local recurrences, distant recurrences were more common compared to the chemotherapy only arm. The combined modality regimen did not increase PFS in optimally debulked advanced uterine cancer[17]. Although our trial encompasses a large number of women with USC, the lack of a comparison arm in our trial makes it difficult to directly compared to the subset of USC subjects in prior phase 3 trials powered to assess survival. Also, those prior trials included all histologies, while this study assesses arguably one of the highest risk histologies, USC. Since USC represents the minority of patients in these studies, it remains challenging to extrapolate management recommendations for women with USC, specifically since the definition of USC is less stringent than ours. Therefore, multimodal treatment remains the standard of care for patients with early and advanced stage USC.

Despite the prospective nature of our study, we recognize that there are limitations: this is a single institution experience with minor differences in the carboplatin dosing during the initial pilot phase of the trial. However, with optimization during the pilot phase, the final prescribed dose regimen remained consistent. While our report represents the largest prospective study among women with USC, the relatively low number of advanced stage

patients enrolled continues to be a limitation of the data. Additionally, further phase 3 trials would be necessary to elucidate the role of the “sandwich” approach in patients with USC. However, USC is rare and such a trial would likely require a significant number of subjects. Furthermore, our study was conducted prior to the publication of the 2014 American Society for Radiation Oncology guidelines on the role of postoperative RT for endometrial cancer, which highlights use of concomitant brachytherapy with EBRT only in patients with significant risk of vaginal recurrence[18]. Given these new guidelines, patients would only receive either EBRT or brachytherapy based on risk factors. Grouping all patients stages I-IV to receive the same treatment further limits the study given current guidelines stratify patients to generally receive brachytherapy or EBRT alone.

The strengths of our study is the large number of participants and the prospective nature of this report in women with pure USC. Also, the high number of patients with advanced stage, completely resected and no gross visible disease. The patients represented in this single institution study is ethnically and racially diverse in the Bronx, NY. Furthermore, this study represents a large number of patients who have had complete surgical staging for USC and 74% (103/140) of patients underwent omentectomy or an omental biopsy as part of the surgical staging procedure.

In summary, our long-term study demonstrates that “sandwich” therapy is a well-tolerated treatment approach with acceptable toxicities and reasonable efficacy in patients with completely resected stage I-IV USC. The increased risk of death in stage I patients with LVSI suggests that LVSI is an independent predictor of outcome and further highlighted the importance of multimodal treatment in this group of patients. Finally, contrary to other reports, our study does not demonstrate racial disparity in OS. This data emphasizes the need to increase recruitment of racially diverse patients into clinical trials[19, 20]. Further studies are needed to establish the optimal sequencing of adjuvant treatment in patients with USC, which would require a multi-institutional approach given the rarity of the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Consort diagram of patients receiving “sandwich” therapy. Of the 140 subjects receiving “sandwich” therapy, 48 were treated on protocol and 92 were treated with the same regimen but not on protocol. Survival analysis was performed in all patients who received at least 3 cycles of CT followed by RT (n=132). Toxicity analysis performed on all cycles administered (n=779). Of the 107 patients receiving the fully prescribed therapy, 13 patients received 6 cycles and EBRT or brachytherapy and 94 patients received 6 cycles, EBRT and brachytherapy.

Figure 2.

Kaplan-Meier overall survival curve by early stage (stage I/II) and late stage (stage III/IV) USC patients who were prescribed radiation “sandwiched” between 3 cycles of paclitaxel/ carboplatin chemotherapy before and after RT.

Figure 3. Kaplan-Meier overall survival curve for Stage I patients with and without LVSI in USC patients who were prescribed radiation “sandwiched” between 3 cycles of paclitaxel/ carboplatin chemotherapy before and after RT.

Table 1.

Characteristics of patients treated with “sandwich” therapy.

Characteristic		
Age (yr) (mean)	67.6(SD+/-8.1)	n=140
BMI (mean)	32.1(SD+/-7.2)	n=140
Race	Number	Percent
Black	77	55
White	41	29.3
Asian	2	1.4
Other	20	14.3
Ethnicity		
Hispanic	30	21.5
Non-hispanic	58	41.4
Unknown	52	37.1
FIGO Stage		
Stage I	93	66.4
IA	80	57.1
IB	13	9.3
Stage II	11	7.9
Stage III	28	20
IIIA	2	1.4
IIIB	1	0.7
IIIC1	12	8.6
IIIC2	13	9.3
Stage IV	8	5.7
IVA	0	0
IVB	8	5.7

Table 2.

Summary of Grade 3 and 4 Hematologic and Non-Hematologic Toxicities (n=779 total cycles administered) in patients being treated with “sandwich” therapy.

	Grade 3	Grade 4	Grade 5
Hematologic Toxicities			
Neutropenia	103	93	1
Anemia	29	2	0
Thrombocytopenia	37	12	0
Total	169(21.7)	107(13.7%)	1(0.13%)
Non-hematologic Toxicities			
Infection	13	1	0
Deep vein thrombosis/ Pulmonary Embolus	3	4	0
Neurologic	7	0	0
Metabolic disturbances	12	1	0
Hypertension	1	0	0
musculoskeletal pain	4	0	0
Gastrointestinal	4	1	0
Respiratory	2	0	0
Taxol reaction	0	1	0
Total	46 (5.9%)	8(1%)	54(6.9%)

Table 3.

Multivariate cox model of patients treated with “sandwich” therapy.

		Progression Free survival		
		HR	95%CI	p-value
Age	unit=1	1.011	(0.973,1.051)	0.5675
Body Mass Index	unit=1	0.991	(0.944,1.039)	0.6953
Race and Ethnicity				0.1977 *
	African American vs White/others	1.327	(0.572,3.081)	0.5104
	Hispanic vs White/others	2.765	(0.898,8.512)	0.0763
Early v late Stage				
	Stage III/IV vs Stage I/II	9.302	(4.291,20.164)	<0.0001
At least 3C v complete tx				
	6C+RT vs at least 3C+RT	0.546	(0.265,1.126)	0.1015

		Overall survival		
		HR	95%CI	p-value
Age	unit=1	1.029	(0.989,1.071)	0.1588
Body Mass Index	unit=1	0.98	(0.935,1.028)	0.4085
Race and Ethnicity				0.3818 *
	African American vs White/others	1.371	(0.624,3.011)	0.4315
	Hispanic vs White/others	2.086	(0.738,5.895)	0.1655
Early v late Stage				<0.0001
	Stage III/IV vs Stage I/II	8.185	(3.9955,16.939)	
At least 3C v complete tx				0.1386
	6C+RT vs at least 3C+RT	0.571	(0.272,1.199)	

* Type 3 test