

Concurrent Cisplatin/Radiation Followed by Adjuvant Cisplatin/Paclitaxel in Treatment of Patients with Stage IB Grade 3, IC and IIA Endometrial Carcinoma

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ABSTRACT

Background: Postoperative radiotherapy (RT) is the most commonly used adjuvant treatment in high risk endometrial carcinoma (HREC), it reduces the incidence of pelvic relapses but doesn't improve survival.

Objective: This study was conducted to evaluate the efficacy and safety of concomitant weekly cisplatin and postoperative RT in HREC (stages IB grade 3, IC and IIA) followed by adjuvant cisplatin and weekly paclitaxel.

Patients and Methods: Eighteen patients with pathologically confirmed endometrial carcinoma were enrolled in this study. All patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH-BSO) and surgical staging. Five patients (28%), 4 patients (22%) and 9 patients (50%) presented with stages IB grade 3, IC and IIA respectively. All patients received cisplatin once weekly during the 6 weeks of RT. After the chemoradiation course, 4 additional adjuvant courses of cisplatin and paclitaxel were administered.

Results: Between May 2000 and March 2002, a total of 18 patients with pathologically confirmed endometrial carcinoma, presented to Radiation Oncology & Nuclear Medicine Department, Ain Shams University Hospitals, were enrolled in this study. Their median age was 59 years. No severe toxicity was encountered during concomitant chemoradiation. Grade 3 hematological toxicities, leucopenia, neutropenia and anemia were recorded in one patient (5.6%) each during adjuvant chemotherapy. Two patients (11%) relapsed with distant metastases and one patient (5.6%) developed pelvic recurrence. Median time to progression was 67 months. Five year disease free survival and the 5 year overall survival were 89% (95% CI: 74-100).

Conclusion: Concomitant cisplatin and postoperative RT followed by adjuvant cisplatin and weekly paclitaxel is safe and acceptable treatment in patients with HREC.

This study verifies the feasibility of this treatment to potentially reduce the incidence of local and distant relapses in order to improve survival. Randomized phase III studies with large number of patients are necessary to evaluate the benefits of this approach.

Key Words: Endometrium – Surgery – Cisplatinum – Paclitaxel – Radiation.

INTRODUCTION

Surgery is the mainstay of both tumor staging and treatment of endometrial carcinoma, usually total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) [1].

For patients with G1 and G2, stages IA and IB tumors, prognosis will be excellent and no further treatment is needed beyond surgery [2]. For patients with high risk endometrial carcinoma (HREC) [grade 3 tumors, stage IC or higher], who have been rendered macroscopically free of disease by surgery, there is an advantage to adjuvant radiotherapy (RT) both for the control of occult nodal disease [3] and for vaginal vault recurrence in three randomized controlled trials [4-6]. However, none of these trials revealed a significant beneficial effect of radiotherapy on survival.

The adjuvant medical therapy of endometrial carcinoma remains poorly investigated. A systematic review and meta-analysis of the Cochrane Collaboration revealed that the adjuvant use of progestational agents may indeed be dangerous. They do not significantly reduce the risk of recurrence and endometrial cancer-related death, but significantly increase the risk of non-cancer-related death [7].

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Though large-scale randomized trials are still few, post-operative chemotherapy alone seem to be more effective in the control of distant recurrence than in pelvic relapses. Several trials evaluated adjuvant chemotherapy without locoregional radiation. Tsunoda et al. [8] noted recurrences in 25% of patients, all within the pelvis. Fujimura et al. [9] reported 15 recurrences in 25 high-risk patients treated with adjuvant chemotherapy alone; 53% were in the pelvis. Mundt et al. [10], in a retrospective study, evaluated the efficacy of adjuvant chemotherapy on 43 HREC patients and reported a 32% and 34% pelvic recurrence and distant relapse rates respectively. This may highlight the importance of postoperative irradiation in controlling the local disease and subsequently improving the distant metastas rate.

For better control of both pelvic and distant failures, combination of chemotherapy and RT after surgery has been tested. The Gynecologic Oncology Group (GOG) evaluated adjuvant doxorubicin after surgery and RT for HREC in a randomized trial. There was no significant difference in survival and progression-free interval between patients receiving adjuvant doxorubicin or placebo after surgery and RT [11]. Other investigators utilized postoperative chemotherapy followed by RT or postoperative concomitant chemoradiation but the results were disappointing [2].

Aim of study:

This study was conducted to evaluate the efficacy and safety of concomitant weekly cisplatin and postoperative RT in HREC (stages IB grade 3, IC and IIA) followed by adjuvant cisplatin and weekly paclitaxel.

PATIENTS AND METHODS

Subjects

Eighteen patients with Stage IB grade 3, IC and IIA endometrial carcinoma underwent primary surgery and were referred for adjuvant therapy. All were surgically treated with TAH-BSO, para-aortic lymph node dissection and peritoneal cytology. All patients should have pathologically confirmed endometrial carcinoma.

Inclusion criteria

All the following criteria were satisfied: age >18 years and <70 years, ECOG performance

status 0-1; adequate bone marrow reserve (neutrophil count >1.5/ μ L, platelet count >100000/ μ L and Hb >10 g/dL), adequate liver function (serum bilirubin <1.5, serum transaminases < twice the upper limit of normal), adequate renal function (serum creatinine <1.5 mg/dL and creatinine clearance (Cr Cl) \geq 60 ml/min), no chronic cardiac or bowel diseases. The interval between surgery and RT was less than eight weeks.

Exclusion criteria

Patients who had prior RT to pelvis, prior chemotherapy, history of other malignancy (with the exception of non-melanomatous skin cancer unless disease free for >5 years), gross residual disease, suspected extrapelvic disease, distant metastasis, uterine sarcoma or cardiac dysrhythmias were excluded.

Pretreatment evaluation

Pretreatment evaluation included complete history and physical examination, Eastern Cooperative Oncology Group (ECOG) Performance Status [12] and body surface area (BSA). All patients had complete blood count (CBC), serum chemistries, chest radiograph (PA and lateral), computerized tomographic scan (CT) of abdomen and pelvis and an audiogram within 6-8 weeks prior to treatment.

Radiation therapy

Patients were treated with external beam irradiation by a Cobalt 60 machine, with a source-axis distance of 80 cm or 6-15 MV linear accelerator with a source-axis distance of 100 cm. The pelvis was treated to a total dose of 50.4 Gy in 5.5 weeks. Patients were treated once-a-day, 5 days per week with a daily fraction size of 1.8 Gy. Anteroposterior/posteroanterior parallel opposed fields with or without lateral fields were used. All fields were treated daily throughout the treatment course.

Radiation treatment interruption

If interruption of two weeks or less occurred, radiation was completed to the prescribed total dose. When therapy interruptions of more than two weeks occurred, this was considered a major deviation from the study protocol.

Treatment plan

Patients received cisplatin (35mg/m²) IV over 1-2 hours, once weekly, 30-60 minutes

before the radiation session, during 6 weeks radiation course starting from day 1. At least 3 weeks post-chemoradiotherapy, after complete hematological and biochemical recovery, patients received adjuvant chemotherapy comprising weekly paclitaxel (80 mg/m²) IV days 1, 8, and 15 every 4 weeks and cisplatin (75mg/m²) IV on day 1. Adjuvant chemotherapy was repeated every 4 weeks for 4 cycles in the absence of disease progression or unacceptable toxicity. Thirty minutes before the paclitaxel infusion began, the patient was premedicated with dexamethasone IV, diphenhydramine 50 mg intravenously and cimetidine 300 mg intravenously, in addition an antiemetic regimen was administered (granisetron 2-3 mg or ondansetron 8-16 mg, Other antiemetics (e.g., dexamethasone, diphenhydramine) were used during paclitaxel administration, if necessary. Paclitaxel at a dose of 80 mg/m² was infused intravenously in normal saline over 1 hour. Polyvinylchloride (PVC) infusion sets were not used. Following the completion of the paclitaxel infusion, intravenous hydration consisting of 1 liter normal saline with 20 mEq KCl and 2 gm MgSO₄ was given over 2-4 hours. Immediately following completion of the intravenous hydration, cisplatin 75 mg/m² was mixed in 1 liter normal saline with 50 gm mannitol and administered intravenously over 2-4 hours.

Evaluation criteria

All patients underwent weekly examinations during RT course then before each cycle of adjuvant chemotherapy. Examination included general physical assessment, ECOG performance status, bowel/bladder complaints and assessment of skin in the irradiated area. CBC with differential and platelet counts, kidney function test and electrolytes were performed during radiation before the weekly cisplatin and prior to each cycle of adjuvant chemotherapy.

Dose modifications

No subsequent treatment course began until all toxicities (except anemia) \geq grade 2 have been abolished, the granulocyte count was \geq 1500/ μ L and the platelet count \geq 100,000/ μ L. If the Cr Cl <60 ml/min or the patient developed \geq grade 3 otologic toxicity or \geq grade 2 neurologic toxicity, cisplatin was stopped totally and the patient was withdrawn from the protocol.

Evaluation of toxicity:

Toxicities were graded using the WHO Toxicity Criteria [13].

Follow-up

Patients were followed by history & physical examination that included a pelvic examination. Pap Smears and chest x-rays were obtained every four months for the first two years post therapy, every six months in the third to fifth year post therapy and annually thereafter. CT abdomen and pelvis were obtained annually. Other metastatic work-up scan was obtained whenever there were symptoms suggesting metastases.

Statistical methods

Overall survival and Progression-free survival rates were estimated using the Kaplan-Meier method [14]. Overall Survival was defined as observed length of life from entry into this study to death or, for living patients, date of last contact. Disease free survival was estimated from the onset of treatment until documentation of recurrence.

RESULTS

Patient characteristics

A total of 18 patients with histologically proven endometrial carcinoma presented to Radiation Oncology & Nuclear Medicine Department, Ain Shams University Hospitals were enrolled in the study. They had a median age of 59 years (range 50-64 years). Mean follow-up was 62 \pm 14.3 months (range 19-76 months). Table (1) summarizes patient characteristics. Four patients (22%) had non endometrioid pathology, 11 patients had grade III tumors (61%) and 7 patients (39%) had lymphovascular invasion. Nine patients (50%) had stage IIA according to FIGO.

Patient compliance and toxicity

All patients completed their course of concomitant cisplatin with irradiation. RT was delayed in 2 patients for only 3 and 5 days because of cystitis and proctitis respectively. Table (2) shows acute toxicity encountered during concomitant cisplatin and radiation. There were no grade 3 or 4 toxicities during concomitant chemoradiation. All patients had variable mild degree (grade 1 and 2) of skin reaction. After radiation, seventeen patients

(94%) completed their planned adjuvant chemotherapy and one patient received 3 courses of the planned 4 courses because of persistent grade 3 neutropenia. No dose reduction was required. Table (3) shows the WHO toxicity during adjuvant chemotherapy. Grade 3 leukopenia, neutropenia and anemia were encountered in 1 patient each. No patients developed hypersensitivity reaction or ototoxicity.

Pattern of failure and survival

Recurrence occurred in 3 patients, median time to progression was 67 months (range 12-76 months). Two patients (11%) relapsed with distant metastases and the remaining patient (5.6%) had pelvic recurrence. The five year disease free survival and overall survival were 89% (CI 95% 74-100%) as shown in Figs. (1,2).

Table (1): Patient characteristics (18 patients).

	No	%
Age (years)	median: 59 (range: 50-64)	
<i>Performance status (ECOG):</i>		
0	5	28
1	13	72
<i>Endometrioid carcinoma</i>		
Papillary serous carcinoma	14	77
Clear cell carcinoma	3	17
	1	5.6
<i>Grade:</i>		
I	2	11
II	5	28
III	11	61
<i>Lymphovascular invasion:</i>		
Present	7	39
Absent	11	61
<i>Stage:</i>		
IB	5	28
IC	4	22
IIA	9	50
<i>Grade and stage:</i>		
IB G3	5	28
IC G1	1	5.6
IC G2	2	11
IC G3	1	5.6
IIA G1	1	5.6
IIA G2	3	16.7
IIA G3	5	28

Table (2): WHO toxicity scale during concomitant cisplatin and radiation (18 patients).

	Grade I	Grade II
Leukopenia	2 (11%)	2 (11%)
Neutropenia	1 (5.6%)	1 (5.6%)
Anemia	2 (11%)	1 (5.6%)
Diarrhea	1 (5.6%)	1 (5.6%)
Cystitis	4 (22%)	1 (5.6%)
Proctatitis	4 (22%)	1 (5.6%)

Table (3): WHO Toxicity scale during adjuvant chemotherapy (18 patients).

	Grade I	Grade II	Grade III
Leukopenia	3 (17%)	6 (33%)	1 (5.6%)
Neutropenia	2 (11%)	3 (17%)	1 (5.6%)
Anemia	3 (17%)	1 (5.6%)	1 (5.6%)
Diarrhea	1 (5.6%)	1 (5.6%)	0
Cystitis	2 (11%)	2 (11%)	0
Alopecia	2 (11%)	2 (11%)	0
Neuropathy	1 (5.6%)	1 (5.6%)	0

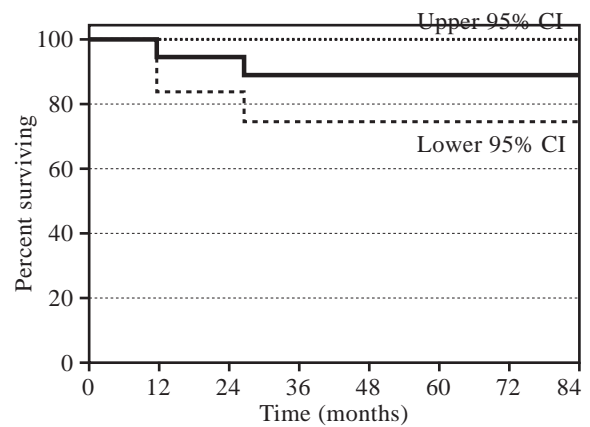


Fig. (1): Overall survival.

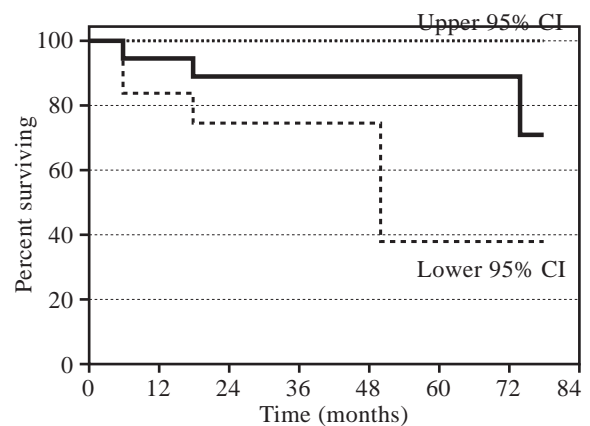


Fig. (2): Disease-free survival.

DISCUSSION

Patients with endometrial carcinoma and high-risk features (high grade histology, deep myometrial invasion, or extrauterine disease) who have not received adjuvant irradiation have been reported to have a recurrence rate ranging from 15-20% [4-16]. Adjuvant pelvic radiation for patients with disease confined to the uterus results in local recurrences in 0-6.5% [6]. In Viani et al. trial [17], 5 year overall survival, disease free survival and locoregional control for high risk patients were 78%, 72% and 92% respectively. However, postoperative pelvic irradiation as a sole adjuvant treatment for those high risk patients was associated with significantly increased distant relapse rate and endometrial carcinoma-related death independently of salvage treatment modality. Moreover, salvage treatment with chemotherapy was associated with poor survival. This raised the question whether adjuvant chemotherapy would lower the risk of distant metastases and thus improve survival.

Recently, a randomized phase III study on adjuvant treatment with radiation and/or chemotherapy in HREC (surgical Stage I, II, IIIA; positive peritoneal fluid cytology only and IIIC; positive pelvic lymph nodes only) showed a statistically significant improvement of progression free survival for radiochemotherapy versus radiotherapy alone (82% versus 75%, respectively) [18].

Paclitaxel was introduced for the treatment of endometrial carcinoma after its success in ovarian and breast cancers. Three trials achieved response rates of 36-43% when paclitaxel was used as single agent in advanced or recurrent endometrial adenocarcinoma [19-21]. Paclitaxel has also shown activity in platinum-resistant patients [19]. Hoskins [22] tested paclitaxel and carboplatin, alone or followed by RT, in a phase II study in advanced and recurrent endometrial carcinoma patients, obtaining response rates of 78% and 56% respectively in the two groups; toxicity was manageable, reversible and mainly hematological.

The present sequential approach; concomitant chemoradiation followed by adjuvant chemotherapy, addresses the dual risks of local and distant failure in the high-risk group of patients selected. The 35 mg/m² dose for cisplatin was selected

because of known activity at this dose level and concern for inducing significant neutropenia and neurotoxicity if larger doses were employed. The weekly dose for paclitaxel (80 mg/m²) was selected on the basis of experience in women with breast cancer who tolerated paclitaxel with less morbidity and better efficacy than paclitaxel 175 mg/m² every 3 or 4 weeks [23].

In the present study, the treatment was well tolerated with no grade 4 toxicity recorded during the whole course of treatment. The 5-year disease free survival and overall survival were 89%. Considering that 22% of patients in the present study had non endometrioid carcinoma and 61% had grade 3 disease, these results might be encouraging. The regimen was associated with a very low rates of pelvic relapse (5.6%) and distant metastases (11%). RTOG 97-08 [24] has accrued patients with high-risk stage I-III endometrial carcinoma to a phase II protocol combining cisplatin with radiation to the pelvis followed by four cycles of cisplatin and paclitaxel given every 4 weeks. In RTOG trial, about 30% of patients experienced grade 4 hematologic toxicity with a 4-year overall and disease-free survival rates of 85% and 81% respectively. The better tolerability and toxicity profile in the present study might be attributed to the weekly regimen of paclitaxel rather than every 4 weeks as used by RTOG. Additionally, the reported pelvic relapse rate, in RTOG trial, was only 4% but the distant metastasis was recorded in 19%. This discrepancy between distant metastases rates in the present study and RTOG trial might be explained by the fact that, RTOG trial included 66% of patients with stage III disease that were excluded from the present study.

Comparing the recurrence rates between different trials of postoperative chemoradiation treatment in endometrial carcinoma and the present study is shown in Table (4). In the present study, the 11% distant metastases rate is compared favorably to the distant metastases rates in Smith et al. [25] trial who utilized neo-adjuvant chemotherapy followed by radiation and Magnili et al. [26] trial who used concomitant paclitaxel and radiation without adjuvant chemotherapy. They reported distant metastases rates of 31% and 21% subsequently. This may raise the importance and the complementary effect of adjuvant chemotherapy after concomitant chemoradiation in enhancing both the locoregional and distant metastases control.

Table (4): Post-operative treatment and recurrence rates in endometrial cancer: comparison between current study and other trials.

Author (Ref)	Stage	No.	Treatment	Total recurrence (%)	Distant relapse (%)	Pelvic recurrence (%)
Smith (25)	IC-IV	39	CAP/RT*	38	31	7
Magnili (26)	ICG3-III	23	Chemo/RT+	21	21	None
RTOG 9708 (24)	IC-III	46	Chemo/RT**	23	19	4
Present study	IBG3, IC, IIA	18	Chemo/RT	16	11	5.6

* CAP/RT : Cisplatin, doxorubicin and cyclophosphamide followed by radiotherapy.

**Chemo/RT concomitant chemoradiation, cisplatin days 1/28 followed after radiotherapy by cisplatin and paclitaxel.

+ Concomitant radiotherapy with paclitaxel.

Conclusion: Concomitant cisplatin and post-operative RT followed by adjuvant cisplatin and weekly paclitaxel is safe and acceptable treatment in patients with HREC. This study verifies the feasibility of this treatment to potentially reduce the incidence of local and distant relapses in order to improve survival. Randomized phase III studies with large number of patients are necessary to evaluate the benefits of this approach.

REFERENCES

- Homesley HD, Boike G, GW. Spiegel: Feasibility of laparoscopic management of presumed stage I endometrial carcinoma and assessment of accuracy of myoinvasion estimates by frozen section: a gynecologic oncology group study. *Int J Gynecol Cancer*. 2004, 14 (2): 341-7.
- Curtin JP, Shapiro F. Adjuvant therapy in gynecologic malignancies. Ovarian, cervical and endometrial cancer. *Surg Oncol Clin N Am*. 1997, 6 (4): 813-30.
- Creasman WT, Morxow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer*. 1987, 60 (8 Suppl): 2035-41.
- Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet Gynecol*. 1980, 56: 419-27.
- Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004, 92: 744-51.
- Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, De Winter KA, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage I endometrial carcinoma: multicentre randomized trial. PORTEC Study Group. *Post operative Radiation Therapy in Endometrial carcinoma*. *Lancet*. 2000, Apr 22; 355 (9213): 1404-11.
- Martin-Hirsch PL, Jarvis G, Kitchener H, Lilford R. Progestagens for Endometrial Cancer (Cochrane Review). The Cochrane Library, Issue 1. Oxford: Update Software. 2003.
- Tsunoda H, Nishida M, Arisawa Y, Sato T, Oki A, Nishide K, Ichikawa Y, Kubo T. Adjuvant chemotherapy with cyclophosphamide, adriamycin and CDDP (CAP) for high-risk endometrial cancer after complete surgery. *Nippon Sanka Fujinka Gakkai Zasshi*. 1996, 48: 45-51.
- Fujimura H, Kikkawa F, Oguchi H, Nakashima N, Mizutani S. Adjuvant chemotherapy including cisplatin in endometrial carcinoma. *Gynecol Oncol Invest*. 2000, 50: 127-32.
- Mundt AJ, McBride R, Rotmensch J, Waggoner SE, Yamada SD, Connel PP. Significant pelvic recurrence in high-risk pathologic stage I-IV endometrial carcinoma patients after adjuvant chemotherapy alone: implications for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys*. 2001, 50: 1145-53.
- Morrow CP, Bundy BN, Homesley HD, Creasman WT, Hornback NB, Kurman R, Yhigpen JT. Doxorubicin as an Adjuvant following Surgery and Radiation Therapy in Patients with High-Risk Endometrial Carcinoma, Stage I and Occult Stage II: A Gynecologic Oncology Group Study. *Gynecol Oncol*. 1990, 36: 166-71.
- Zubrod CG, Schneiderman M, Frei E III, Brindley C, Gold GL, Shnider B, et al. Appraisal of methods for the study of chemotherapy of Cancer in man: Comparative therapeutic trial of nitrogen Mustard and Triethylene, Thiophosphamide. *J Chronic Dis*. 1960, 11 (1): 7-33.
- Miller AB. Recommendation for grading of acute and subacute toxicity (WHO) criteria. *Cancer*. 1981, 47: 207.
- Kaplan El, Meier P. Non parametric estimation from incomplete observations. *Journal of the American Statistical Association*. 1958, 53: 457-481.
- Carey MS, O'Connell GJ, Johanson CR, Goodyear MD, Murphy KJ, Daya DM, et al. Good outcome associated with a standardized treatment protocol

- using selective postoperative radiation in patients with clinical stage I adenocarcinoma of the endometrium. *Gynecol Oncol.* 1995, 57: 138-144.
- 16- Elliott P, Green D, Coates A, Krieger M, Russell P, Coppleson M, Solomon J, Tattersall M. The efficacy of postoperative vaginal irradiation in preventing vaginal recurrence and endometrial cancer. *Int J Gynecol Cancer.* 1994, 4: 84-90.
- 17- Viani GA, Patia BF, Pellizzon AC, De Melo MD, Novas PE, Fogarolli RC, et al. High-risk surgical stage I endometrial cancer: analysis of treatment outcome. *Radiation Oncology.* 2006, 1: 24.
- 18- Hogberg T, Rosenberg P, Kristensen G, de Oliveira CF, de Pont Christensen R, Sorbe B, et al. A randomized phase-III study on adjuvant treatment with radiation (RT) {+/-} chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991). *J Clin Oncol (Meeting Abstracts).* 2007, 25 (18_suppl): p. 5503.
- 19- Woo HI, Swenerton KD, Hoskins PJ. Taxol is active in platinum-resistant endometrial adenocarcinoma. *Am J Clin Onc.* 1996, 19: 290-1.
- 20- Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: A Gynecologic Oncology Group study. *Gynecol Oncol.* 1996, 62: 278-81.
- 21- Lissoni A, Zanetta G, Losa G, Gabriele A, Parma G, Mangioni C. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. *Ann Oncol.* 1996, 7: 861-3.
- 22- Hoskins PJ, Swenerton KD, Pike JA, Wong F, Lim P, Acquino-Parsons C, Lee N. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: A phase II study. *J Clin Oncol.* 2001, 19 (20): 4048-53.
- 23- Hans-Joachim Luck, Henri Roche: Weekly paclitaxel: an effective and well tolerated treatment in patients with advanced breast cancer. *Critical Reviews in Oncology/Hematology.* 2002, 44, 15-30.
- 24- Greven K, Winter K, Underhill K, Fontenesi J, Cooper J, Burke T. Final analysis of RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol.* 2006, 103, 155-9.
- 25- Smith MR, Peters WA, Drescher CW. Cisplatin, doxorubicin hydrochloride, and cyclophosphamide followed by radiotherapy in high-risk endometrial carcinoma. *Am J Obstet Gynecol.* 1994, 170 (6): 1677-82.
- 26- Mangili G, Marzi PD, Beatrice S. Paclitaxel and concomitant radiotherapy in high-risk endometrial cancer patients: preliminary findings, *BMC Cancer.* 2006, 6: 198.