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Cisplatin and Concomitant Radiotherapy Followed by Chemotherapy. Towards an Optimal Adjuvant Therapy Protocol for High-risk Endometrial Cancer Patients

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Abstract

Background: As there are no current definite guidelines, there is still much debate about the best adjuvant therapy after surgery for endometrial cancer (EC). Radiotherapy (RT) alone does not seem to improve overall survival. We investigated whether concomitant Cisplatin (C) and RT gave better clinical results.

Patients and methods: Ninety four patients with high-risk EC (stage II, IIIA or IB G3 without lymphadenectomy) underwent primary surgery and were then referred for adjuvant therapy. Cisplatin was given at a dose of 40 mg/m^2 once weekly for five weeks during RT, which consisted of a total radiation dose of 50.4 Gy. Two cycles of cisplatin 75 mg/m^2 and paclitaxel 175 mg/m^2 were given after finishing the radiotherapy. Overall survival and disease-free survival were calculated from the time of surgery. Patterns of failure were recorded by the sites of failure.

Results: Median overall Survival was 36 months. Median time to recurrence was 26 months (range 3-37). Relapses occurred in twenty nine patients (30.8%). Adverse events were mild with three cases having grade 3 neutropenia. Local recurrence was encountered in 14% and distant metastases in 8%.

Conclusion: This phase II study demonstrates pelvic radiotherapy in combination with weekly cisplatin followed by two cycles of consolidation chemotherapy as a tolerable and efficient combined approach in high risk endometrial carcinoma patients.

Keywords: Endometrial cancer; Radiochemotherapy; Adjuvant-Endometrial cancer; Cis-platin

Introduction

Cancer of the endometrium is the most common gynecologic malignancy and accounts for 6% of all cancers in women. It is a highly curable tumor [1]. Patients with endometrial cancer (EC) are traditionally divided into risk categories, conventionally based on anatomical-surgical prognostic factors. The most significant prognostic factors are stage, histologic type, depth of myometrial invasion, grade of differentiation and lymph-node metastases [2]. Stage IB poorly differentiated and stages II and III-IV show five-year survival rates ranging from approximately 20 to 60%, thus all requiring additional treatment [3]. Traditional prognostic factors, however, cannot define the prognosis for all patients. DNA content analysis can be useful to assess the risk of recurrence more precisely and ploidy appears to be one of the most important prognostic factors in EC [4]. For patients without extrauterine spread, the greatest determinants of recurrence were grade III histology, deep myometrial invasion. The frequency of recurrence is also greatly increased with positive pelvic nodes, adnexal metastasis, positive peritoneal cytology, capillary space involvement, involvement of the isthmus or cervix and, particularly, positive para-aortic nodes (includes all grades and depth of invasion) [5].

Patients with localized and well-differentiated disease are usually cured by hysterectomy and bilateral salpingo-ophorectomy alone. However, other patients may benefit from adjuvant therapy. It is important to keep in mind that adjuvant radiotherapy in patients with early-stage endometrial cancer has not been proven to increase overall survival. Its main role is that of preventing local recurrences which indirectly can have an important impact in the quality of life of these patients. Therapeutic modalities include the use of vault brachytherapy (vaginal cylinders), standard external pelvic and/or extended field irradiation and intensity modulated radiotherapy. The incidence of major complications after radiotherapy approaches 4-5% and can be even higher following transperitoneal lymphadenectomies [6].

There is much debate about the best adjuvant therapy after surgery and there are no accepted guidelines for this treatment. EC patients often receive adjuvant radiation therapy to reduce the risk of pelvic relapse [7] but this does not seem to improve overall survival because it cannot reduce the risk of distant recurrences. On the other hand, the efficacy of adjuvant chemotherapy alone has not been proved yet. A new combined adjuvant treatment is therefore needed to improve results in high-risk EC patients [8]. Within 15 years, cisplatin's effectiveness in ovarian cancer, lung cancer, head and neck cancer, bladder cancer and other malignancies led to its becoming the most widely used anticancer drug worldwide [9,10] and its use as a radiosensitizer is well known in many solid tumors in a dose of 40 mg/m^2 weekly as in cervical cancer [11].

The current phase II study is aiming at studying the side effects of giving radiation therapy together with cisplatin followed by paclitaxel

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and cisplatin and to see how well it works in treating patients who have undergone surgery for high-risk endometrial cancer primarily. Secondarily to assess disease free survival, overall survival and patterns of failure by the sites of failure: locoregional within the irradiated area, distant outside the irradiated area, or both.

Patients and Methods

Ninety four patients with high-risk EC underwent primary surgery in Ain Shams University Hospitals or were referred just for adjuvant therapy along the period between May 2008 to September 2011. All were surgically treated with abdominal hysterectomy, bilateral salpingo-oophorectomy and peritoneal cytology; pelvic lymphadenectomy was done in 25 patients. In the other cases lymph node status was unknown because these patients were either referred to our hospital after primary surgery or nodes sampling only was done.

Inclusion criteria

- Histopathologically proven endometrioid adenocarcinoma with stages included II, IIIA (patients with positive washings without other unfavorable prognostic factors were omitted), or IB G3 without lymphadenectomy.

- WHO performance status 0-1.

- No positive common iliac or positive para-aortic nodal disease (defined as lymph nodes ≥ 2 cm in any dimension on CT scan or biopsy).

- No evidence of metastatic extrauterine disease, gross or residual disease as revealed by CT scan (not including pelvic nodal disease), or distant metastases.

- Adequate bone marrow reserve (neutrophil count >1.5×10^9/L, platelet count >100000 and Hb >10 g/dl).

- Adequate liver function (serum bilirubin <1.5 mg/dl, serum transaminases < 2 × the upper limit of normal), adequate renal function (serum creatinine <1.5 mg/dl).

- No chronic cardiac or bowel diseases.

- Age >18 years and <75 years.

- The interval between surgery and RT had to be less than six weeks.

Exclusion criteria

- Patients with history of other invasive cancer (except basal cell carcinoma of the skin) and previous chemotherapy or radiotherapy.

- Histologic types other than endometroid adenocarcinoma.

- Neuropathy ≥ CTCAE grade 1.

- Ototoxicity > CTCAE grade 2.

- Serious, active comorbidity, including any of the following: Unstable angina and/or NYHA class II-IV congestive heart failure requiring hospitalization within the past 12 months, Transmural myocardial infarction within the past 12 months, Acute bacterial or fungal infection requiring IV antibiotics, Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy, Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects, Active gastrointestinal (GI) ulcers, GI bleeding, inflammatory bowel disease, or GI obstruction , Inadequately controlled hypertension, defined as systolic BP > 150 mm Hg and/or diastolic BP > 90 mm Hg on antihypertensive medications, Serious cardiac arrhythmia on medication (well-controlled atrial fibrillation on medication allowed) and history of hypertensive crisis or hypertensive encephalopathy.

Cisplatin at a dose of 40 mg/m^2 was infused intravenously in 250 ml of normal saline or glucose 5% for 1 hour once weekly during RT for five weeks. Standard anaphylaxis and antiemetic premedication were given. The radiation plan consisted of 2D treatment planning for a total dose of 50.4 Gy/6 weeks, delivered using linear accelerator with energies 9-18 MV while patient was prone if convenient through 2 parallel opposing portals. The irradiation field encompassed the entire pelvis as follows: the high limit was tangential to the upper surface of L5, the lower limit comprised the upper third of the vagina and the lateral limits were 1.5 cm outside the ileopectineal ligament. Additional two cycles of cisplatin 75 mg/m^2 plus paclitaxel 175 mg/m^2 every 21 days were given after finishing radiotherapy. Both chemotherapy and radiotherapy were delayed if, at the time of recovery, the neutrophil count was less than 1.0 × 10^9/L or platelets were less than 100 × 10^9/L. For all other toxicity we used the CTCAE version 4. Chemotherapy was discontinued after two consecutive weeks of delay; when this happened, patients continued RT alone. Patients were assessed every three months for the first two years, every six months for the third year, then yearly.

Statistical Analysis

Data was revised, coded, tabulated and introduced to a PC. Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Analytical statistics- Kaplan-Meier Survival Analysis was performed using Graph Pad Prism version 5. Overall and disease-free survivals were evaluated from the time of surgery. Survival rates were calculated according to intent to treat. Secondary we studied survival rates in the patients who completed all the radiochemotherapy in assessing the efficacy of this treatment. Patterns of failure were recorded by the sites of failure: locoregional within the irradiated area, distant outside the irradiated area, or both.

Results

All patients followed up for 16-40 months (median 27 months). Table 1 shows the main characteristics of the whole group. Five had metastatic lymph nodes. Twenty were having stage IB, forty nine patients had stage II and twenty five patients had stage IIIA. Twenty one patients had more than 50% myometrial infiltration; 61 patients were having well to moderately differentiated tumors, while 33 patients showed grade 3 tumors.

Adverse effects were individually evaluated and recorded. There was no life-threatening toxicity. No patients required hospitalization or ER visits for acute toxicity. Five patients who stopped chemotherapy before the end of RT did not complete at least five cycles of chemotherapy. Three had a tumor stage IIIA and presented a marked renal impairment with reduction in GFR after the first 2 cycles and continued RT alone. The other two, with a tumor stage II, refused to continue chemotherapy at the second cycle of cisplatin, without any toxicity.

Adverse effects are summarized in Table 2.

No dose reduction was required. Seven cycles were delayed more than 4 days, in 3 cases for grade 3 neutropenia, in 2 for severe diarrhea

and only 1 case for grade 2-3 renal toxicity. Eighteen patients presented emesis. Hematological toxicity was mild in other cases without reduction of doses or delay of treatment. No blood transfusions or hematologic support were administered in these patients. One patient developed alopecia. Delayed toxicity included 2 cases of incomplete small intestinal obstruction 11 weeks after the end of the treatment with medical resolution. Five patients reported mild recurrent intestinal dysfunctions (diarrhea). Three patients presented grade 2 related to the treatment. Relapses occurred in 29 patients (30.8%). Median time to recurrence was 26 months (range 3-37). (Tables 3, 4 and Figure 1).

Median overall survival was 36 months. The probabilities of survival at 3 years for overall survival and DFS were 67% and 45% respectively. Thirteen patients showed local recurrences. Eight patients presented a periaortic relapse and 8 relapsed to lung and bone. The patients with cancer relapse were treated in 16 cases with chemotherapy (Cisplatin and Doxorubicin).

	Number of patients	%
Age :		
< 50 years	30	32
≥ 50 years	64	68
Grade :		
1-2	61	65
3	33	35
Stage :		
IB	20	21.2
II	49	52.2
IIIA	25	26.6

Table 1: Patients' characteristics.

	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	17	8	3	-
Thrombocytopenia	8	2	-	-
Anaemia	21	11	2	-
GIT **Esophageal pain** **Diarrhea** **Anal pain** **Abdominal pain** **Intestinal Obstruction**	15 5 5 3 1 1	12 4 5 2 1	2 - 2	-
Neuropathy	8	2	-	-
Renal **Urgency** **↓ GFR**	6 5 1	2 2	-	-
Bladder	8	3	-	-
Alopecia	1	-	-	-
Emesis	19	9	-	-

Table 2: Toxicities encountered in the study.

Site of relapse	Number	%
Local recurrence	13	14
Para-aortic LN	8	8.5
Lung	6	6.3
Bone	2	2.1

Table 3: Patterns of failure after treatment.

Site of relapse	Stage IB	Stage II	Stage IIIC
Local recurrence	2(2.1%)	9(9.6%)	2(2.1%)
Para-aortic LN	1(1.06%)	3(3.15%)	4(4.25%)
Lung	1(1.06%)	2(2.1%)	3(3.15%)
Bone	0	0	2(2.1%)

Table 4: Patterns of failure by stage.

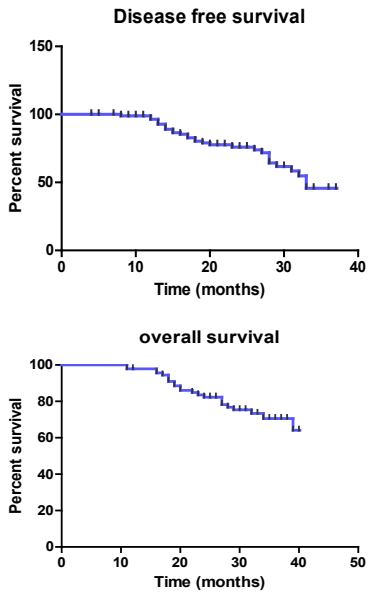

Figure 1: Relapse free survival and overall survival.

Discussion and Conclusion

There is still much debate about the best adjuvant therapy after surgery for endometrial cancer (EC). Röper et al. [12] reported the major prognostic factors for early-stage EC to include older age, histologic type (i.e., serous or clear cell type), high histologic grade, deep myometrial invasion, lymphovascular space invasion (LVSI), large tumor size (>2 cm) and involvement of the lower uterine segment or cervix. The indication of adjuvant chemotherapy or radiotherapy is based on the presence or absence of these risk factors of recurrence. Nowadays, controversies still exist about postoperative adjuvant chemotherapy or radiotherapy for early EC with adverse prognostic factors and for advanced EC. Although there have been improvements in RT and chemotherapy, during the last few years, survival for high-risk EC has not increased. Reported five-year survival rates are 70% for stage II, 50% for stage III and 27% for stage IV [13]. The National Comprehensive Cancer Network (NCCN) guidelines [14], recommend observation for stage IA, grade 1 (G1) or grade 2 (G2) and stage IB, G1 patients with no adverse prognostic factors, while for stages IB, II and IIIA radiotherapy could be recommended in adjuvant sessions. Radiotherapy (RT) alone does not seem to improve overall survival. This has prompted the search for new therapeutic strategies in recent decades specially for those with high risk of locoregional recurrence (patients with G1and G2 endometrioid cell type and superficial (<50%) myometrial invasion is about 5% or less) [15]. There is no evidence of benefit to support the use of adjuvant therapy for low and low-intermediate risk groups; therefore, these patients can be safely treated by surgery only, despite vaginal brachytherapy (VBT) use for adjuvant treatment for low-intermediate risk patients. Besides, it was concluded

that postoperative radiotherapy is not indicated in stage I patients <60 years of age and patients with G2 tumors with superficial invasion from the result of the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial (external beam radiotherapy 46 Gy versus observation) [16].

The adjuvant treatment of choice for high-intermediate and high risk EC patients remains undetermined. Adjuvant therapy should be considered according to individual risk factors. Systemic chemotherapy has been investigated in an effort to improve the outcome of advanced or recurring EC. Doxorubicin and Cisplatin have been the most frequently used cytotoxic drugs [17]. In the GOG 122 trial, patients with stage III or IV and <2cm of postoperative residual tumor were randomized to receive doxorubicin-cisplatin or whole-abdominal irradiation (30 Gy, with an additional 15 Gy pelvic ± para-aortic boost). PFS and OS were better in the CT group compared that of the RT group [18]. Thus, adjuvant CT seemed not to be inferior to RT in the treatment of high risk patients. In a series of patients submitted to adjuvant chemotherapy without locoregional RT, Tsunoda et al. [19] noted recurrences in 25%, all within the pelvis. Fujimura et al. [20] reported 15 recurrences in 25 high-risk patients treated with adjuvant chemotherapy alone; 53% were in the pelvis.

Another question is whether the combined chemoradiotherapy is a better treatment choice for high risk EC patients. In the EORTC 55991 trial, patients with stages I, II, IIIA (positive cytology only) and IIIC (excluding para-aortic metastases) and clear, serous and anaplastic cell types were enrolled. Most patients had two or more risk factors including G3, deep myometrial invasion, or DNA nondiploidy. Enrolled patients were randomized to RT (EBRT ± VBT) or combined chemoradiotherapy [21]. The chemotherapy regimen before August 2004 was cisplatin-doxorubicin or epirubicin; thereafter, it was changed to cisplatin-doxorubicin or epirubicin, paclitaxel-epirubicin-carboplatin, or paclitaxel-carboplatin. The hazard ratio for PFS was 0.58 in favor of the combined chemoradiotherapy group and a 7% difference in estimated 5-year PFS was found [22]. There is an ongoing PORTEC-3 trial in which high-intermediate and high risk patients (stage IB with LVSI and G3, stage II and G3, stage IIIA or IIIC and stage IB-III and serous or clear cell type) were randomized to pelvic EBRT (48.6 Gy) alone or concurrent chemoradiotherapy (EBRT and two courses of cisplatin) followed by adjuvant CT (carboplatin and paclitaxel for four courses). The results could tell us if the addition of concurrent and adjuvant CT to postoperative RT will increase 5-year OS and failure-free survival or not [23]. Gabriele [24], in a series of high-risk EC patients (19 stage III, 2 stage IV) treated with 3-5 cycles of PAC followed by RT, reported an overall incidence of recurrence of 57.1%, similar to other studies. These data show that platinum and doxorubicin chemotherapy followed by RT is feasible and well tolerated, but the impact of chemotherapy before adjuvant external RT on survival has not been demonstrated in high-risk EC.

Cisplatin was introduced for the treatment of EC after its success in ovarian and cervical cancers. The combination of cisplatin and pelvic RT was analyzed as adjuvant treatment in high-risk EC patients in the current study. The primary mechanism of cell killing for this drug is covalent binding to purine bases of cellular DNA. This covalent binding leads to bending of the DNA helix at a fixed angle, with local denaturing of the DNA strand. This DNA damage is detected by components of the repair complex and is converted into a strand break. Adducts are removed and breaks are repaired by the nucleotide-excision repair process. When not effectively repaired, cell killing may occur through apoptotic or nonapoptotic pathways. The possible contribution of drug-induced, immune-mediated cell killing, which may occur in the intact host [25]. Its radiosensitizing action is well known. Several studies have defined the toxicity of concomitant cisplatin and RT. The possibility of using cisplatin at dosages of 40 mg/m^2, together with RT has already been demonstrated in other tumors, without serious adverse effects [26]. In our study we employed a 40 mg/m^2 dosage of cisplatin without severe side effects, except in 3 cases for grade 3 neutropenia, two for severe diarrhea and one for grade 2-3 renal toxicity. Weekly cisplatin in association with pelvic RT is a well tolerated regimen. We observed local recurrence in 14% of cases, whereas two other Italian studies [26] reported high rates of pelvic relapse after sequential chemoradiation therapy. These data support the radiosensitizing effect of cisplatin. Greven [27], in a preliminary analysis of adjuvant combined chemoradiotherapy (radiotherapy of 45 Gy with brachytherapy followed by 4 cycles of cisplatin and paclitaxel), also reported a low relapse rate with overall survival and disease-free survival (DFS) rates at 4 years are 85% and 81%, respectively. Four-year rates for survival and DFS for Stage III patients are 77% and 72%, respectively. There have been no recurrences for patients with stage IC, IIA, or IIB. Compared to our current study which revealed improvement in time to relapse (median of 26 months) and overall survival (median of 36 months). This difference in local recurrence may be attributed to the usage of brachytherapy, better patient's characteristics and more number of chemotherapy cycles in the RTOG trial. In conclusion, the encouraging result of this phase II study is confirming the enhancing effect of this approach in high-risk EC. Obviously the number of patients is small to prove that concomitant radiotherapy and cisplatin do actually reduce relapse rates and improve overall survival. Longer follow-up is now needed to assess the outcome and randomized trials are required.

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