

ADJUVANT CHEMOTHERAPY IN THE TREATMENT OF ENDOMETRIAL CANCER

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Summary. Endometrial carcinoma is the most common and curable gynecologic neoplasm. The five-year survival for women with surgical stage I disease ranges from 85% to 90%, stage II 74% to 83%, stage III 57% to 66%, and stage IV 20% to 25%. The staging of endometrial cancer, according to the International Federation of Gynecology and Obstetrics (FIGO), is surgical. Recent studies suggest a therapeutic benefit associated with extensive retroperitoneal lymph node evaluation to determine the disease extent and thereby more effectively direct potentially life-saving adjuvant therapy. Due to the increasing number of endometrial cancer patients who undergo surgical staging, some independent prognostic factors have been identified in early stages (stage I-II), including lymph-vascular space involvement, histologic grade 3, aggressive histologic subtypes (uterine papillary serous carcinoma, clear cell carcinoma), depth of myometrial invasion, cervical invasion and the age of patients. Adjuvant radiation therapy, known to have survival benefit in advanced-stage disease, may also have survival benefit in intermediate-risk surgical stage I on the basis of results from a Gynecologic Oncology Group study, but it is followed by a significant risk of serious complications. Based on randomized clinical trials, this review has identified that there is a limited body of evidence that is available to help clinicians make decisions about the adjuvant chemotherapy treatment of patients with high-risk stage I and II, as well as stage IIIA endometrial cancer. Further investigations should be required to define the subgroup of patients who benefit from postoperative adjuvant chemotherapy. Furthermore, the optimal regimen is still in question as all of them (AP, CAP, TC, TAP) cause significant toxicity. Thereby, combination of carboplatin plus paclitaxel represents an efficacious, low-toxicity regimen for managing intermediate-risk surgical stage I, as well as advanced or recurrent endometrial cancer.

Key words: Endometrial cancer, adjuvant chemotherapy, cisplatin, paclitaxel, doxorubicin

Introduction

In developed countries, endometrial cancer is the most common malignancy of the female reproductive tract, the fourth most common malignancy in women, and it accounts for 6% of all cancers at this population. There were approximately 200 000 cases of endometrial adenocarcinoma worldwide in 2005 with about 50 000 deaths (1). There is, however, wide geographical variation in disease incidence with the highest in North America (22.0 per 100000 per year) and Europe (11.8–12.5 per 100000 per year) (1). Women usually present with peri- or postmenopausal bleeding as their only presenting complaint and this fortunately leads to the early diagnosis of the majority of the cases. To date there is no consensus on the utility of screening procedures for early detection. Following the revision of the International Federation of Gynecology and Obstetrics (FIGO) staging system in 1988 (2), surgery became the recommended treatment for patients with early endometrial cancer allowing the possibility of surgical staging (omentectomy, peritoneal washings and pelvic and para-aortic lymph

node assessment). FIGO surgical stage is considered the most important independent prognostic indicator of progression-free or overall survival, and has a significant impact on treatment decisions. Fortunately, a majority of patients (75%) are diagnosed as being at an early stage, without clinical evidence of extrauterine spread (FIGO stage I and II), so the prognosis is generally favorable. A five-year survival for women with surgical stage I disease ranges from 85 to 90%, stage II 74 to 83%, stage III 57 to 66%, and stage IV 20 to 25% (3).

Once endometrial adenocarcinoma is identified by uterine biopsy, the treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Women with certain histological subtypes, high-grade lesions, deep myometrial invasion, tumor extending to the cervix or ovaries, positive peritoneal cytology, spread to lymphatic or blood vessels or outside the uterus are at high risk of recurrence (4) and may be offered adjuvant radiotherapy. However, the use of radiation therapy for FIGO stages IB, IC and II still remains controversial. Three previous randomized studies have shown that postoperative radiation therapy decreases the risk of

locoregional recurrence, but does not improve the overall survival rate (5-7). Furthermore, radiation therapy is followed by a significant increase in risk of serious complications when compared to surgery alone and is not indicated in women under 60 years and those with grade 2 superficially invasive tumors. Nevertheless, Naumann *et al.* (8) have reported that most gynecologic oncologists continue to recommend radiation therapy for stage IC or grade 3 endometrial cancers. Jolly *et al.* (9) reported that vaginal brachytherapy alone has similar overall survival and cumulative recurrence rates to standard external pelvic radiotherapy with the benefit of much lower toxicity rates and shorter duration of treatment in stage I-II endometrial cancer. Analyses of those studies are limited because complete surgical staging was not an entry requirement and the actual number of women with FIGO stage I endometrial adenocarcinoma remains unclear. There are relatively few reports dealing with postoperative adjuvant chemotherapy for the treatment of patients with early stage endometrial cancer with risk factors (10-12).

In order to examine the current evidence regarding the use of chemotherapy in early stages of endometrial cancer, we conducted a search of the literature to identify all relevant articles. The aim of our debate is to discuss the evidence available at the present time from the literature regarding the risk factors for relapse and chemotherapy in adjuvant setting.

Adjuvant chemotherapy as treatment of high-risk stage I and II endometrial cancer

Due to the increasing number of endometrial cancer patients who undergo surgical staging, some independent prognostic factors have been identified in early stages (stage I-II), including lymph-vascular space involvement, histologic grade 3, aggressive histologic subtypes (uterine papillary serous carcinoma, clear cell carcinoma), depth of myometrial invasion, cervical invasion and the age of patients. The depth of myometrial invasion has been demonstrated to be a strong predictor of prognosis and distant recurrences in patients with stage I endometrial cancer (13,14)

Histologic grade 3 is the most relevant independent prognostic factor in patients with endometrial cancer confined to the uterus (12). Tumors extended to the cervix tend to be high grade and deeply invasive into the myometrium. Hirai *et al.* (10) assessed the efficacy of adjuvant chemotherapy in stage I uterine endometrial carcinoma with lymph-vascular space invasion. In 54 patients, they reported statistically significant differences between the survival rates of patients who had surgery followed by adjuvant chemotherapy and patients who had surgery alone. Aoki *et al.* (11) defined subgroups of patients with stage I and II endometrial carcinomas that benefited from postoperative chemotherapy (CAP regimen). These patients were divided into low-risk and high-risk groups based on a score system of the prognostic factors (histologic grade 3, invasion of outer half of the myometrium,

lymph-vascular space invasion and cervical invasion). Among high-risk group patients, 5-year disease-free and 5-year overall survival rates were significantly better in patients treated with adjuvant chemotherapy (12).

Uterine papillary serous carcinoma and clear cell cancers comprise the vast majority of type II endometrial cancers (15). These cancers, unlike type I cancers, are characterized by a high recurrence rate and a poor prognosis.

Uterine papillary serous carcinoma is an aggressive histologic type of endometrial cancer which was first reported in 1981 by Lauchlan (16). The subsequent year Hendrickson and co-workers (17) reported that although papillary serous carcinoma account for only 3 to 5% of endometrial cancers, it represents more than 50% of the recurrences in women with disease thought to be confined to the uterus. The other authors (15,18) announced that papillary serous carcinoma represents 3 to 10% of all endometrial cancers, but account for 25% of the disease mortality. Microscopically, it is characterized by complex papillary architecture, high nuclear/cytoplasmic ratio, and irregular epithelial tufting. Biologically, papillary serous carcinoma is extremely aggressive, with a propensity for lymph-vascular space invasion, myometrial invasion, and extrauterine spread (19). Even patients with disease confined to the endometrium may have microscopic evidence of extrapelvic metastases. At the time of presentation, 70 to 87% of women with papillary serous carcinomas will have disease outside the uterus, in contrast to only 15 to 20% of women with endometrioid adenocarcinomas having metastatic disease at presentation (19,20). Therefore, thorough surgical staging including omentectomy, pelvic and paraaortic lymphadenectomy, multiple biopsies of the upper abdomen, and saline washings of the pelvic and para-colic spaces should be performed in patients with this disease (18,21). Surgical staging by gynecologic oncologists reduces the risk of including occult stage III and IV patients in analysis of stage I disease, which has been a significant problem with many earlier studies.

Survival rates for papillary serous carcinoma vary from 30 to 80% in patients with stage I-II disease and from 0 to 25% in patients with stage III-IV disease, both significantly lower than those reported in endometrioid carcinoma (7,18,22,23). There are other significant differences between endometrioid carcinomas and papillary serous carcinomas. Women with papillary serous carcinoma tend to be older (median age 65-70), nonobese and parous. Atypical hyperplasia is not a precursor lesion for this disease, these tumors are not associated with estrogen excess, usually do not express ER or PR, but they frequently have p53 mutations and high degrees of aneuploidy. In contrast to endometrioid adenocarcinoma, microsatellite instability, k-RAS and PTEN mutations are uncommon in papillary serous carcinoma (24)

While much has been learned from retrospective studies regarding pathology and surgical management for papillary serous carcinoma, the optimal adjuvant treatment, particularly in stage I and II disease, is unclear and a consensus on how to treat these patients is lacking. Treatment recommendations have included observation, whole ab-

dominal radiation, pelvic radiation, vaginal cuff radiation, intraperitoneal chemotherapy, intravenous chemotherapy and combinations of these modalities. Most of these studies have been retrospective chart reviews with small numbers of patients treated in such a heterogeneous manner that it has been difficult to draw meaningful conclusions.

Patients with stage IA uterine papillary serous carcinoma in the hysterectomy specimens may benefit from concomitant platinum-based chemotherapy and brachytherapy (referred to as chemoirradiation) (18,25)

Because papillary serous carcinoma spreads over the peritoneal surfaces like ovarian carcinoma, and therefore often presents at a more advanced stage at diagnosis than other uterine carcinomas (17), there have been many attempts to treat this disease with chemotherapy. Initial studies in the setting of measurable disease with single chemotherapy agents (cytoxan, adriamycin, cisplatin) resulted in response rates of only 15 to 20%. In more recent GOG (Gynecology Oncology Group) studies, papillary serous carcinoma response rates to doxorubicin/cisplatin were 42%, doxorubicin/paclitaxel were 37% and doxorubicin/paclitaxel/cisplatin were 50% (26). None of the three recent studies addressing the role of adjuvant therapy in surgical stage I uterine papillary serous carcinoma patients found that chemotherapy was effective (27-29), in contrast to the study of Kelly and co-workers (18) whose results highlights the effectiveness of adjuvant platinum-based chemotherapy (paclitaxel 175 mg/m² and carboplatin AUC 5) and vaginal brachytherapy in treating stage I uterine papillary serous carcinoma. Those results are consistent with other recent studies which indicate that platinum- and taxane-based regimens may be an appropriate approach for the adjuvant treatment of high risk endometrial cancers (30-32).

In summary, the data on adjuvant chemotherapy for stage I uterine papillary serous carcinoma are limited, and the available studies are generally under-powered to assess if chemotherapy improves survival and which chemotherapeutic regimen is the most beneficial.

Adjuvant chemotherapy as treatment of stage IIIA endometrial cancer

FIGO stage IIIA endometrial cancer includes heterogeneous population of patients whose disease has metastasized to the uterine serosa, fallopian tubes and ovaries or with positive peritoneal cytology. This stage comprises two intuitively separate groups: those with histologic proof of disease in tissue outside the uterus (IIIA2) and those with positive peritoneal cytology alone (IIIA1). While extrauterine spread is a well recognized poor prognostic factor in endometrial cancer, the clinical significance of malignant cells identified by cytology of peritoneal washings is unclear. Some studies have suggested that positive cytology has no association with survival (33-35), while others have observed worse outcomes for patients with positive cytology, even when controlling for other prognostic factors (36-39).

Patients with stage III disease are usually considered candidates for aggressive adjuvant therapies, including

combination chemotherapy and radiotherapy. Analysis of patterns of recurrence shed light on the appropriateness of systemic versus local adjuvant treatment. Havrilesky *et al.* (39) noted that 61% of the recurrences were outside the pelvis, compared to 29% local recurrences. This is similar to the findings of Mariani *et al.* (14) (88% of all recurrences were distant). Now, there is increasing evidence that patients with stage IIIA disease are at risk for recurrence at sites not amenable to standard pelvic external beam radiotherapy. A recently published randomized controlled trial suggests that adjuvant combination chemotherapy is superior to whole abdominal radiotherapy in the treatment of all patients with stage III endometrial cancer (32).

Chemotherapy regimens

There is no standard adjuvant chemotherapy regimen for patients with endometrial cancer. From a historical perspective, several agents have been demonstrated as having antitumor activity (Table 1). Doxorubicin with or without cisplatin has been used by most clinicians as the preferred cytotoxic chemotherapy for the treatment of this disease, although substituting carboplatin for cisplatin may improve tolerability without sacrificing efficacy (Table 2) (40). Myelosuppression may be more frequent but nephrotoxicity, neurotoxicity and emesis were all less frequent reported and were milder with carboplatin than those in cisplatin-based regimens.

Table 1. Single agent chemotherapy regimens

Day of cycle	Drug	Dose/way of administration	Number of cycles	Frequency of cycles
1	Doxorubicin	60 mg/m ² iv	4-6	3 weeks
1	Cisplatin	50-60 mg/m ² iv	4-6	3 weeks
1	Carboplatin	300-400 mg/m ² iv inf 30-60 min	4-6	3 weeks

Table 2. Combined chemotherapy regimens

Day of cycle	Drug	Dose/way of administration	Number of cycles	Frequency of cycles
1	Cisplatin	50 mg/m ² iv	4-6	3 weeks
	+ Doxorubicin	50 mg/m ² iv		
1	Carboplatin	AUC 5 iv	4-6	3 weeks
	+ Epirubicin	75 mg/m ² iv		

Cyclophosphamide/adriamycin/cisplatin (CAP) regimen was commonly used too as adjuvant chemotherapy, as well as in advanced disease (41).

Recently, newer agents such as paclitaxel have shown promising survival and response rates in endometrial cancer patients (42). Paclitaxel has been associated with favorable response rates either as a single agent or in combination with platinum-based chemotherapy (Table 3). Zanotti *et al.* (30) performed a retrospective study of 24 uterine papillary serous carcinoma patients treated with platinum-based chemotherapy and paclitaxel in an

adjuvant setting or for recurrence. Eight patients had surgical stage I disease. The reported response rate was 89% (8/9) in patients treated for residual disease after initial surgery, and 64% (7/11) for those with recurrent disease, although more specific outcomes for the stage I subgroup were not presented. Rosenberg *et al.* (43) investigated the use of combination chemotherapy in eight clinical stage I patients after radical surgery. Pelvic radiotherapy was followed by cisplatin/epirubicin chemotherapy regimen. No recurrences were seen at 32 months of follow-up. Low *et al.* (44) treated nine stage I patients with chemotherapy (cisplatin/epirubicin, carboplatin/paclitaxel or gemcitabine/carboplatin) followed by pelvic and/or vaginal brachytherapy. Only 1 recurrence (lung) was reported after a median follow-up of 28 months.

Table 3. Chemotherapy regimens during controlled clinical studies

Day of cycle	Drug	Dose/way of administration	Number of cycles	Frequency of cycles
1	Paclitaxel	175 mg/m ² iv	4-6	4 weeks
	+ Carboplatin	AUC 5-7 iv		
1	Paclitaxel	160 mg/m ² iv	4-6	3 weeks
	+ Doxorubicin	45 mg/m ² iv		
	+ Cisplatin	60 mg/m ² iv		
	with G-CSF			

The combination of paclitaxel, carboplatin and adriamycin (TAC) combines the three most effective single agent drugs in endometrial cancer with potentially less toxicity than TAP (paclitaxel/doxorubicin/cisplatin). In addition, the regimen was further simplified by delivering all drugs on day 1 of each cycle (45).

Conclusion

Most patients with endometrial cancer present their symptoms early in their course, leading to an overall favorable outcome. However, some patients who are in early-stage diseases may carry some risk features that would hamper their prognoses. For these early-stage diseases with high risk of recurrences, radiation therapy certainly plays a major role as an adjuvant treatment. Despite an excellent local disease control by radiation, systemic failures are still encountered. To improve the prognosis, other types of adjuvant therapy have been attempted. In this review, adjuvant chemotherapy for early-stage endometrial cancer is discussed.

FIGO surgical stage is considered the most important independent prognostic indicator of progression-free or overall survival, and has a significant impact on treatment decisions. However, some histological subtypes, like papillary serous carcinoma and clear cell carcinoma, are associated with a high rate of recurrence compared to non-papillary serous carcinoma after surgical treatment alone. Therefore, the need for effective adjuvant therapy is apparent. However, currently, no randomized data have determined if adjuvant chemotherapy improves the outcome and what is the optimal treatment. Unfortunately, in most published works there is imprecision in the proportion of patients who underwent complete surgical staging, and confusion about what should be considered as complete surgical staging. Some authors believe that complete staging includes standard endometrial staging, but for others, complete staging should also comprise omentectomy and randomized peritoneal biopsies. Therefore, it is possible that in some reports, occult stage IV may have been included as presumed stage I and, hence, under-evaluated the efficacy of adjuvant therapy. This paper illustrates that we need appropriate powered, randomized, controlled trials with completely staged patients to determine the optimal adjuvant treatment for uterine papillary serous carcinoma.

Based on the available scientific evidence, we believe that, firstly, patients with uterine papillary serous carcinoma should receive complete surgical staging, including omentectomy and peritoneal biopsies. Secondly, until the results of large series or randomized controlled trials will be available, we feel that combined radiotherapy (pelvic or vaginal cuff) and chemotherapy (platinum-based and paclitaxel) is justified for all stage I uterine papillary serous carcinoma.

A number of drugs have some activity in endometrial cancer. The most commonly investigated drugs include platinum, anthracyclines and taxanes, either alone or in combinations. The patients, however, were selected according to different criteria. Therefore, in the absence of a randomized control group, it is not possible to tell whether any of the combinations are superior in terms of progression free survival, overall survival or effects on quality of life.

A significant percentage of poorly differentiated tumors, often with serous papillary or clear cell histology, have been found to overexpress the epidermal growth factor type II receptor. Anti-HER-2/neu-targeted therapy might be a novel and attractive therapeutic strategy in patients harboring this biologically aggressive variant of endometrial cancer.

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ADJUVANTNA HEMIOTERAPIJA U LEČENJU KARCINOMA ENDOMETRIJUMA

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Kratak sadržaj: Karcinom endometrijuma je najčešća i uglavnom izlečiva neoplazma genitalnih organa žene. Petogodišnje preživljavanje u stadijumu I bolesti je 85-90%, stadijumu II 74-83%, stadijumu III 57-66% i stadijumu IV 20-25%. Stadiranje karcinoma endometrijuma je hirurško u skladu sa preporukama Internacionalnog udruženja ginekologa i akušera (FIGO). Rezultati nedavno sprovedenih studija ukazuju na značaj evaluacije retroperitonealnih limfnih nodusa sa ciljem da se odredi proširenost bolesti i primeni adjuvantna terapija. S obzirom na činjenicu da se sve češće sprovodi hirurški steidžing karcinoma endometrijuma, definisani su nezavisni prognostički faktori u ranom stadijumu bolesti (st.I i II) koji podrazumevaju limfo-vaskularnu invaziju, histološki gradus 3, agresivne histološke tipove (serozni papilarni karcinom, svetločelijski karcinom), dubinu invazije miometrijuma, zahvatanje grlića materice i godine života bolesnice. Na osnovu rezultata Ginekološko-onkološke grupe (GOG), adjuvantna radioterapija u hirurškom stadijumu I i II poboljšava preživljavanje, mada je praćena sa ozbiljnim komplikacijama. Do sada sprovedeni randomizovani klinički trajai u vezi sa primenom adjuvantne hemioterapije nisu brojni i ne sadrže dovoljno podataka koji mogu da pomognu kliničarima u donošenju odluke o primeni ovog vida terapije kod bolesnica sa visokim rizikom u ranom stadijumu karcinoma endometrijuma. Potrebna su dalja istraživanja koja će omogućiti da se definišu visoko rizične grupe bolesnica sa karcinomom endometrijuma koje će imati koristi od primene adjuvantne hemioterapije, kao i da se ustanovi koji je od hemioterapijski protokola (AC, CAP, TC, TAP) najefikasniji.

Ključne reči: karcinom endometrijuma, adjuvantna hemioterapija, cisplatin, paclitaxel, doxorubicin