Chemotherapy for Early-stage High-risk Endometrial Cancer

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Abstract

Endometrial cancer generally has a good prognosis because most cases are diagnosed in stage I. It is possible to identify subgroups of patients with early-stage endometrial cancer with a poor prognosis. Despite a traditional generous use of adjuvant radiotherapy, these patients have five-year overall survival of approximately 80%. In this group there is a need for an effective systemic adjuvant therapy. Mainly based on superior response rates, doxorubicin + cisplatin was for many years the standard chemotherapy in endometrial cancer. Gynecologic Oncology Group (GOG)-177 was the first phase III study on chemotherapy in endometrial cancer that showed a survival advantage. Paclitaxel + doxorubicine + cisplatin was better than doxorubicine + cisplatin, but the toxicity of the three-drug regimen has precluded general acceptance. Paclitaxel + carboplatin has produced high response rates and is widely used, despite the lack of evidence based on randomised studies. GOG-122 compared doxorubicine + cisplatin with whole abdominal radiotherapy in advanced optimally operated endometrial cancer and showed that chemotherapy with doxorubicine + cisplatin resulted in superior survival. Two recent studies have compared adjuvant chemotherapy (cyclophosphamide + doxorubicine + cisplatin) with adjuvant radiotherapy in early-stage endometrial cancer. Both studies failed to show a difference between the treatments. Another study (NSGO-EC-9501/EORTC-55991) compared adjuvant radiotherapy plus chemotherapy with adjuvant radiotherapy, and showed better survival with the sequential combination.

Keywords

Adjuvant, chemotherapy, endometrial neoplasms, micrometastases, review

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Endometrial cancer (EC) is the most common gynaecological cancer in the developed world, and in 2002 it was estimated that worldwide around 200,000 women were diagnosed with the disease.[1] In Sweden, between 1970 and 2006 the age-standardised incidence increased by 37%, but because of an ageing population the number of cases increased by 80% during the same period.[2] EC has a good prognosis, but per stage it is about the same as for ovarian cancer.[3] In International Organization for Gynaecology and Obstetrics (FIGO) stage I there are subgroups with a high risk of micrometastatic disease. For example, patients with stage IC grade 3 disease have 79% five-year overall survival (OS) despite liberal use of adjuvant radiotherapy (RT).[3] Four large trials have randomised patients to adjuvant pelvic RT or observation after surgery.[4–7] All four failed to show an improvement in OS, despite the fact that RT prevented up to 80% of progressions in the irradiated field. Thus, most patients harbouring micrometastatic disease also have dissemination outside the irradiated field and there is a need for systemic adjuvant therapy, either added to or instead of RT.

Chemotherapy in Advanced or Recurrent Endometrial Cancer

Phase II studies on chemotherapy (CT) in advanced or recurrent EC have shown response rates exceeding 20%, mainly with anthracyclines, platinum compounds and taxanes.[8] Two randomised studies (European Organisation for Research and Treatment of Cancer [EORTC 55872] and Gynecologic Oncology Group [GOG-107]) have compared doxorubicin and cisplatin (AP) with doxorubicin.[9,10] Both studies found that the combination gave better response rates but no significant differences in survival. AP has for many years been regarded as the standard in EC. In GOG-122 a taxane combination (paclitaxel, doxorubicin, cisplatin [TAP]) was compared with AP in 273 (263 eligible) women with advanced or recurrent EC of any cell type.[11] Response rate (RR), OS and progression-free survival (PFS) were significantly better with TAP. However, the toxicity of this regimen may have precluded its use in many centres. Paclitaxel–carboplatin (TcP) is a commonly used drug combination in gynaecological cancer. Apart from its neurotoxicity, it is a well tolerated and manageable regimen. Phase II studies in EC have demonstrated high RR (60–70%).[8,12] Currently, two large randomised studies with TcP in the experimental arm are running: GOG-209 and Japanese Gynecologic Oncology Group (JGOG)-2043.[13,14] It will be some years before we know the results. Despite the lack of evidence based on randomised studies, TcP is considered by many as the *de facto* standard.

Gynecologic Oncology Group-122

GOG-122 was a pivotal study[15] that changed the way many considered EC and CT. After surgical staging and optimal tumour resection (no single site of residual tumour greater than 2cm), patients with FIGO stage III or IV EC of any histology were randomised to CT (doxorubicin 60mg/m^2 and cisplatin 50mg/m^2 every three weeks for seven cycles,

followed by one cycle of cisplatin) or whole abdominal radiotherapy (WART) (30Gy in 20 fractions, with an additional 15Gy pelvic boost). Both OS and PFS were significantly better for patients in the CT arm. The treatment effect was comparable in subgroup analyses according to stage, substage, age, cell type and residual disease status. Grade 3 and four adverse effects (particularly haematological, gastrointestinal [GI], cardiac and neurological) were significantly more common in the AP arm. Treatment may have contributed to the death of five patients in the WAR arm and eight patients in the AP arm.

Randomised Studies on Adjuvant Chemotherapy in Early Endometrial Cancer

Gynecologic Oncology Group-34

The first randomised study (GOG-34) on the addition of adjuvant CT (doxorubicin) after RT in EC was initiated in the late 1970s.[16] The study has merely historical interest. It was terminated prematurely because of slow recruitment, and the authors concluded that the study was unable to determine what effect CT had on recurrence because of protocol violations, small sample size and the number of patients lost to follow-up.

Italian Study

Between 1990 and 1997, an Italian study[17] randomised 345 (340 evaluable) patients with endometrioid or adenosquamous carcinoma and FIGO stage IC grade 3 or stage IIA–B grade 3 with ≥50% mechanical index myometrial invasion (MI) or FIGO stage III disease to either adjuvant CT with cyclophosphamide 600mg/m^2, doxorubicin 45mg/m^2 and cisplatin 50mgm^2 (CAP) administered every four weeks for five cycles or pelvic RT at 45–50Gy. All patients underwent primary surgery. Pelvic and para-aortic node sampling was optional. The death rate was 36% in the RT arm and 34% in the CT arm. The hazard ratios (HRs) for PFS and OS were 0.95 (confidence interval [CI] 0.66–1.36; p=0.78) and 0.88 (CI 0.63–1.23; p=0.45), respectively. Major late toxic effects in patients who received RT were mainly gastrointestinal (GI), including 3% with bowel obstruction, with three of five requiring surgical intervention. The toxicity of CAP was mainly myelotoxicity. There were no treatment-related deaths. The distribution of local and distant relapses in the respective randomisation arms suggests that RT may achieve better loco-regional control while systemic CT may better control distant metastases. The authors speculated if the combination of concurrent or sequential adjuvant RT and CT could further improve the results.

Japanese Gynecologic Oncology Group-2033

Between 1994 and 2000, 475 (385 eligible) patients with FIGO stage IC–IIIC EC with ≥50% MI were randomised in JGOG-2033.[18] Patients were required to be under 75 years of age and to have undergone an initial surgery with no residual tumour. Pelvic lymphadenectomy was performed in 96% of the patients and para-aortic lymphadenectomy in 29%. Patients in the experimental arm received CAP – cyclophosphamide 333mg/m^2, doxorubicin 40mg/m^2 and cisplatin 50mg/m^2 – every four weeks for three or more courses. Patients in the control arm received pelvic RT at 45–50Gy. The five-year PFS was 84% in the RT group and 82% in the CT group (HR 1.07, CI 0.65–1.76; p=0.726), and five-year OS was 85% in the RT group and 87% in the CT group (HR 0.72, CI 0.40–1.29; p=0.268). The pattern of progression did not differ between the groups. Grade 3–4 toxicities were experienced in 2% of the RT and 5% of the CT group. Bowel obstructions were the main complications in the RT group, and myelosuppression in the CT group. No treatment-related deaths occurred in either group. CT significantly improved PFS and OS in a subgroup of high- to intermediate-risk patients (stage IC patients over 70 years of age or having G3 endometrioid adenocarcinoma or stage II or IIIA [positive cytology]). However, the authors rightly pointed out that the validity of such a subgroup analysis is limited.

Nordic Society of Gynaecologic Oncology–Endometrial Cancer-9501/European Organisation for Research and Treatment of Cancer-55991

Early results of Nordic Society of Gynaecologoic Oncology–Endometrial Cancer (NSGO-EC-9501/EORTC-55991) were presented at the American Society of Clinical Oncology (ASCO) in 2007.[19] Between 1996 and 2007, 382 patients were randomised to adjuvant RT + CT or RT only. Patients with surgical stage I, II, IIIA (positive peritoneal fluid cytology only) or IIIC (positive pelvic lymph nodes only) were eligible if they, according to departmental guidelines, had a sufficiently high risk of micrometastatic disease to qualify for adjuvant therapy. Patients with serous, clear-cell or anaplastic carcinomas were eligible regardless of other risk factors. Lymph-node exploration at staging surgery was optional. All patients underwent at least total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO).

CT was given before or after pelvic RT (≥44Gy ± vaginal brachytherapy [VBT]). Before August 2004, CT consisted of four courses of cisplatin 50mg/m^2 and doxorubicin 50mg/m^2 or epirubicin 75mg/m^2 (AP) every four weeks. Thereafter, several CT regimens were allowed, of which AP (usually with cisplatin 75mg/m^2), paclitaxel 175mg/m^2, epirubicin 60mg/m^2 and carboplatin area under curve (AUC) 5 (TEcP) and paclitaxel 175mg/m^2 + carboplatin AUC 5–6 (TcP) were used (all alternatives usually every three weeks). The compliance to RT was very good – over 90% of the patients in each arm completed RT, while compliance to CT was worse: 27% did not complete or did not receive CT. The median follow-up time was 4.3 years. The HR for the primary end-point, PFS, was 0.62 (CI 0.40–0.97; p=0.03), estimated five-year PFS was 72 and 79% and for OS 0.65 (CI 0.40–1.06; p=0.08) and estimated five-year OS was 74 and 82%, both in favour of RT + CT. The progression rate in the irradiated area in the RT group was 4% compared with 1% in the RT + CT group, suggesting a favourable interaction between RT and CT.

Finnish Study

A randomised Finnish study also tried to combine CT and RT in an unconventional way.[20] They gave split-course RT (2x28Gy separated by a pause of three weeks) (n=72). In the CT + RT arm (n=84), one course of cyclophosphamide 500mg/m^2, epirubicin 60mg/m^2 and cisplatin 50mg/m^2 (CEP) was given before RT, one in between the RT courses and one after RT. Eligible patients had stage IA–B grade 3 or stage IC–IIIA grade 1–3. All patients underwent TAH-BSO and at least a pelvic lymphadenectomy was performed in 80% of the patients. The study was designed to detect a difference in OS of 20% with 60% survival in the RT group. However, no significant survival difference could be registered. The authors concluded that: "Age-adjusted sequential radio- and CT compared to radiotherapy alone did not alter the risk of death: HR 1.21 (95% CI 0.56–2.65)". The study was not powered to detect equality, and it is not appropriate to state that there is no difference – the result is consistent with the possibility that RT + CT was 44% better or 165% worse than RT alone.[21]

Radiation Therapy Oncology Group-9708

The Radiation Therapy Oncology Group (RTOG) performed a pilot study (RTOG-9708)[22] combining adjuvant pelvic RT (45Gy + VBT) with

concomitant cisplatin (50mg/m^2) on days one and 28 (RT–CT) followed by four courses of paclitaxel (175mg/m^2) and cisplatin (50mg/m^2) at four-week intervals. Patients with grade two or three endometrial adenocarcinoma with either >50% MI, cervical stromal invasion or pelvic-confined extrauterine disease were eligible. This treatment was feasible with excellent loco-regional control, suggesting additional effects of CT and radiation. Distant metastases continued to occur in more advanced staged patients.

Post-operative Radiation Therapy for Endometrial Carcinoma-3

The Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC) group has started an international randomised study (PORTEC-3) with the RTOG concept.[23] They plan to randomise 800 patients meeting one of the following criteria: FIGO stage IB grade 3 disease with documented lymph-vascular space invasion, stage IC–IIA grade 3 disease, stage IIB, IIIA or IIIC any grade disease (stage IIIA disease based on peritoneal cytology alone allowed if disease is grade 3) or stage IB–III disease with serous or clear-cell histology after TAH-BSO with no residual macroscopic tumour. They used TcP instead of the TP used in the RTOG pilot. The primary end-points are OS and failure-free survival at five years. Secondary end-points are quality of life, severe treatment-related morbidity, rate of vaginal or pelvic relapse and rate of distant metastases.

Discussion

There is one study showing superiority of CT over WART.[15] However, this study is not a pure study of adjuvant therapy because it was performed on a mixture of patients with no residual post-operative tumour and patients with remaining residuals. The RT was WART, which is not normally used in the adjuvant situation in early-stage EC.

Two fairly big randomised studies have failed to show differences in OS or PFS between CT and RT.[17,18] Neither of these trials was designed or dimensioned to show non-inferiority, which actually means that they are inconclusive.[21] Early results from an NSGO/EORTC-trial comparing RT + CT with RT showed a significantly improved PFS and a trend to better OS with the addition of CT.[19] Why, then, could neither the Italian[17] nor the JGOG[18] study show any difference between CT and RT? One reason might be that both used CAP with fairly low dose intensities and low total doses. At the time these studies were planned, CAP was a common regimen in ovarian cancer.[24] However, there is not much evidence that CAP is an active regimen in EC.[8] However, both doxorubicin and cisplatin are included in CAP and the majority of the patients in the NSGO/EORTC trial were treated with AP with a fairly low dose intensity and a low total dose. A notable difference between the NSGO/EORTC study and the Italian and JGOG trials is the sequential combination of RT and CT in the NSGO/EORTC trial.

It has almost taken half a century to show that adjuvant RT adds little to surgery as far as OS is concerned.[7] It now seems that CT + RT might be more effective than RT alone.[19,22] However, we do not know whether adequate CT alone is as effective as CT + RT. We must not repeat the mistake of adding together two toxic therapies without testing what RT adds to CT by carrying out the comparison of CT versus RT + CT. ■

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