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Systemic Therapy for Advanced or Recurrent Endometrial Cancer, and Advanced or Recurrent Uterine Papillary Serous Carcinoma Practice Guideline Report #4-8

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SUMMARY

Guideline Questions

1. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
2. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma?

Target Population

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Recommendations

For women with advanced or recurrent endometrial cancer:

- Combination chemotherapy is favoured over single agent chemotherapy because of higher response rates.
- Paclitaxel in combination with cisplatin/doxorubicin chemotherapy improves both response rate and median survival; however, the use of this three-drug combination is associated with increased toxicity.
- Hormonal therapy may be a therapeutic option for those patients with minimal symptoms or non-life threatening advanced or recurrent endometrial cancer.

For women with uterine papillary serous carcinoma:

- Evidence supporting or refuting various chemotherapy regimens for uterine papillary serous carcinoma is limited.
- Patients should be encouraged to participate in randomized trials.

Qualifying Statements:

- The decision to use the three-drug combination, consisting of cisplatin/doxorubicin/paclitaxel, should be made in consultation with the patient. Consideration needs to be given to both the greater toxicity and the three-month increase in median survival time achieved with the three-drug combination in comparison with the two-drug doxorubicin/cisplatin regimen.

- For uterine papillary serous carcinoma treatment, the most studied regimen is a paclitaxel/platinum combination. The addition of paclitaxel in small, non-comparative studies is associated with improved response rates and survival compared to non-platinum containing regimens.

Methods

Entries to MEDLINE (1966 to April 2004), CANCELIT (1975 to October 2002), and Cochrane Library (2004, Issue 1) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2003) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by four members of the Practice Guidelines Initiative's Gynecology Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gynecology Cancer Disease Site Group, which comprises gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, and patient representatives.

External review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Seventeen randomized trials (including six abstracts and four phase II randomized trials) provided the evidence for systemic therapy of advanced or recurrent endometrial cancer. There were no randomized trials identified that compared systemic therapy to a control group of patients who received no treatment.
- Limitations of the evidence include: heterogeneous patient populations with respect to histology; type of previous treatment (surgery, radiation, chemotherapy, or hormonal therapy); results that are still maturing; and non-comparable outcome measurements.
- Chemotherapeutic options studied for the treatment of advanced or recurrent carcinoma of the endometrium have included single-, double-, and triple-agent therapies. There is limited information available on quality of life and meaningful survival data.
- Single-agent chemotherapy has reported response rates as follows: doxorubicin 17-27% and platinum agents 21%.
- For double-agent chemotherapy, randomized trials of doxorubicin/cisplatin reported response rates ranging from 28-45%, other agents in combination with doxorubicin reported response rates of 30% (cyclophosphamide) and 43% (paclitaxel).
- A randomized trial reported a 57% response rate in the doxorubicin/paclitaxel/cisplatin arm compared to 34% in the doxorubicin/cisplatin arm ($p < 0.01$).
- One randomized trial has compared doxorubicin/cisplatin to whole abdominal radiotherapy and preliminary reports indicate that doxorubicin/cisplatin is more beneficial than radiotherapy in patients with advanced endometrial cancer in terms of overall survival and progression-free survival ($p < 0.01$). However, recurrence rates are still high (55%) in both treatment arms.
- Neuropathy, hematological, and gastrointestinal toxicities were the most common adverse effects reported; toxicity increased in incidence with the increase in the number of agents used.

- One randomized trial comparing two dosages of medroxyprogesterone acetate (hormonal therapy) for advanced or recurrent endometrial cancer detected that patients receiving a lower dosage of medroxyprogesterone acetate had significantly increased overall survival ($p=0.026$) and response rate ($p<0.05$) than patients receiving a higher dosage. Hormonal agents were well tolerated: adverse effects were reported at less than 5%.
- Four non-comparative trials (two retrospective and one abstract) provided the evidence for systemic therapy of advanced or recurrent uterine papillary serous carcinoma. Response rates in the four small non-comparative studies ranged from 50-89%

Future Research

In terms of future studies, it is important to be able to control for prognostic factors that affect outcome in these patient populations. Patients should be properly stratified with respect to their disease status (advanced versus recurrent), the amount of previous treatment, type of previous treatment (radiation or chemotherapy), and disease recurrence either in or out of the radiated field. Patients with uterine papillary serous carcinoma should be analyzed separately. Results relating to systemic therapy should be first assessed and proven in those patients with measurable disease so that an accurate assessment of any prolongation in disease-free survival can be made with reasonable assurance that these improvements are due to treatment. Treatment-related toxicity must be studied very carefully in the future in this patient population in order to ensure that the treatment itself has acceptable morbidity in relation to the patient's quality of life, as median survival is generally limited and rarely more than a year in this patient population. Survival, response and toxicity should be studied with regard to impact on quality of life. Comparing tumour responses for both chemotherapy and hormonal agents, stratified by grade, would provide valuable data for making treatment decisions.

Related Guidelines

Practice Guidelines Initiative's Evidence Summary Report #4-14: *Adjuvant Chemotherapy for Early Stage Endometrial Cancer and Uterine Papillary Serous Carcinoma (in progress)*.

For further information about this practice guideline report, please contact Dr. Michael Fung Kee Fung, Chair, Gynecology Cancer Disease Site Group, Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario; Telephone: 613-737-8560, FAX: 613-737-8828.

*The Practice Guidelines Initiative is sponsored by:
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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit the CCO Internet site at:

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FULL REPORT

I. QUESTION

1. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
2. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma (UPSC)?

II. CHOICE OF TOPIC AND RATIONALE

Endometrial carcinoma is the most common gynecologic malignancy in Ontario, with an estimated 1,450 new cases in 2003 (1). At least 75% of cases present with early-stage (I/II) disease, and the majority of these patients are cured with surgery (2,3). Since most patients with the disease have a good prognosis, patients presenting with advanced or recurrent disease are relatively uncommon (4). Isolated pelvic recurrences are treated with radiation, whereas most other patients with advanced or recurrent disease receive systemic therapy (either chemotherapy or hormonal therapy). Response rates to systemic therapy reported in the literature vary considerably, ranging from 10-78%, due to marked differences in the studied patient populations (4). Reported median duration of survival in such patients is rarely more than one year.

Recently, newer agents such as paclitaxel have shown promising survival and response rates in phase II studies (5,6). This new evidence has generated renewed interest in systemic chemotherapy for cases of advanced or recurrent carcinoma of the endometrium.

From an historical perspective, doxorubicin with or without cisplatin is considered by most as standard chemotherapy for this disease, although some practitioners substitute carboplatin because of its more favourable side-effect profile (7). Previous studies have shown that hormonal systemic therapy, with either megestrol or progesterone, represents a good treatment option in selected patients, based on reported response rates that approach or exceed those for more toxic chemotherapy (8).

Impressive response rates with new agents like paclitaxel have also been reported in patients with adverse histological subtypes such as UPSC. Systemic chemotherapy is a subject of interest in this malignancy, with the recognition that biologic spread patterns are similar to those in patients with ovarian carcinoma (9). Unfortunately, our experience with either chemotherapy or hormonal therapy in this setting has been disappointing. UPSC patients are infrequently cured and rarely live more than a year or two from the diagnosis of advanced or recurrent disease, which has prompted investigators to look to newer agents with different mechanisms of action as promising new treatments for this disease (9).

In view of the volume of literature that has been published, the Gynecology Cancer Disease Site Group (Gynecology Cancer DSG) decided to conduct a systematic review of the available evidence. We examined the efficacy of systemic therapy, either chemotherapy or hormonal therapy, in the management of patients with advanced or recurrent carcinoma of the endometrium. We elected to review the evidence on UPSC separately as this adverse histological variant has a predilection for metastatic spread, presenting frequently in an advanced stage.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (10). Evidence was selected and reviewed by four members of the PGI's Gynecology Cancer Disease Site Group (Gynecology Cancer DSG) and

methodologists. Members of the Gynecology Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on systemic therapy for endometrial cancer, developed through systematic reviews and evidence synthesis. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

The MEDLINE (1966 to April 2004), CANCELIT (1975 to October 2002), and Cochrane Library (2004, Issue 1) databases were searched using the medical subject headings (MeSH) endometrial neoplasms, uterine neoplasms, and antineoplastic agents, and the following text words: endometrium, endometrial, serous, uterus, uterine, cancer, carcinoma, chemotherapy, hormone(s), hormonal. Search terms related to study design or publication type included systematic review, clinical trial, meta-analysis, controlled clinical trials, clinical trials/phase II, clinical trials/phase III, multicentre studies, and randomized controlled trials (MeSH). Proceedings of the 1997 to 2003 meetings of the American Society of Clinical Oncology (ASCO) and reference lists of papers and review articles were scanned for additional citations. The Canadian Medical Association Infobase (<http://www.cma.ca/cma/common/start.do?lang=2>), the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>) Web sites were searched for existing evidence-based practice guidelines.

Inclusion Criteria

Evidence-based clinical practice guidelines or systematic reviews regarding systemic therapy for advanced disease from other guideline-development groups were eligible for inclusion.

To address the question regarding the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer, full articles or abstracts were selected for inclusion if they met the following criteria:

1. Randomized controlled trials (RCT) or meta-analyses comparing regimens of systemic chemotherapy or hormonal therapy to the standard treatment for advanced or recurrent endometrial cancer reporting at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
2. RCTs that reported on heterogeneous populations (e.g., included women with a range of disease stages) were eligible if results were given separately for the group with advanced or recurrent endometrial cancer.
3. When RCTs were not available, phase II trials of chemotherapy and hormonal therapy agents were included.

To address the question regarding the chemotherapeutic options for women with advanced or recurrent UPSC, full articles or abstracts were selected for inclusion if they met the following criteria:

1. RCTs comparing systemic therapy regimens that included women with stage IIIc or IV UPSC with measurable or evaluable disease at the start of systemic therapy, and reported at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
2. When RCTs were not available, phase II trials of chemotherapy agents were included.

Exclusion Criteria

1. Non-English language publications were excluded.
2. Studies evaluating the role of radiotherapy, administered with chemotherapy or hormonal therapy, were excluded.

Synthesizing the Evidence

The Gynecology Cancer DSG identified 17 RCTs that compared various chemotherapy regimens for the treatment of advanced or recurrent endometrial cancer, including abstracts and randomized phase II trials. The results of RCTs could not be pooled because of the differences among the studies in terms of:

1. The number of advanced versus recurrent cases. Advanced cases actually have a poorer prognosis with a shorter expected survival than most patients presenting with recurrence.
2. The greater proportion of patients previously treated with radiation therapy and documentation with respect to the site of recurrence (either in or out of the radiated field). Patients with disease in the radiated field are known to have lower response rates to systemic chemotherapy than patients with disease outside the field.
3. The inclusion or exclusion of adverse histologic subtypes. Trials differed with respect to the inclusion or exclusion of patients with adverse histologic subtypes. It was only within the last three to five years that the Gynecologic Oncology Group (GOG) decided to separate patients with serous carcinomas as a distinct entity in subsequent GOG studies.
4. The inclusion criteria concerning previous systemic therapy. There were marked differences among studies with respect to the number of prior chemo-hormonal regimens administered to patients.

IV. RESULTS

Literature Search Results

Practice Guidelines

No evidence-based clinical practice guidelines on systemic therapy for advanced or recurrent endometrial cancer or UPSC were identified.

Systematic reviews

No relevant systematic reviews were found. However, a recently published narrative review by two Gynecology Cancer DSG members was used to complement the literature search (4). The authors of the narrative review searched the CANCELIT, EMBASE, MEDLINE, Investigational Drug and R&D Focus databases. Search terms included: endometrial cancer, chemotherapy, endocrine/hormonal therapies, molecular biologics, and specific drug names (personal communication). This review by Elit and Hirte (4) includes an extensive list of phase II and III studies of chemotherapy and hormonal therapy for endometrial cancer.

Clinical trials

There are 13 RCTs (7,11-22) that compare chemotherapy regimens in women with advanced or recurrent endometrial cancer (Table 1a). Two of the 13 RCTs compared different chemotherapy regimens given with hormonal therapy (20,21), while the other eleven studies compared chemotherapy regimens, without hormonal therapy. Two RCTs used an intention-to-treat approach to survival analysis (7,12), and only one described the number of patients lost to follow-up (12). Eight RCTs have been published in full reports that included detailed descriptions of eligibility criteria (7,11,16,19-22). The randomized trial by Long et al (17), reported in an abstract for ASCO 1995, was closed prematurely because of low accrual. There was one RCT (abstract) identified that compared chemotherapy to radiotherapy in women with advanced endometrial cancer (13).

There were three RCTs (8,23,24) identified that measured hormonal therapy in women with advanced or recurrent endometrial cancer (Table 1a). None of the randomized trials of hormonal therapy assessed quality of life. The RCTs appear to have used an intention-to-treat approach to survival analysis; however, only Thigpen et al (8) describe the number of patients lost to follow-up. The RCTs have been published in full reports that included detailed descriptions of eligibility criteria. There is one RCT (25) that compares chemotherapy-to-chemotherapy plus hormonal therapy in women with advanced or recurrent endometrial cancer.

In addition to the RCTs, 19 prospective phase II studies (5,6,26-42) of agents that have not been used in randomised trials were also identified: carboplatin, paclitaxel, oral etoposide, dactinomycin, topotecan, liposomal doxorubicin, vinorelbine, gonadotrophin-releasing hormone agonist, luteinizing hormone-releasing hormone agonist, aromatase inhibitors, and LY353381. This is not an exhaustive list of all prospective single-cohort studies of systemic therapy for advanced or recurrent endometrial cancer but includes the results of a systematic search for all relevant studies of specific agents that are of current interest to Gynecology Cancer DSG members (mostly agents that are currently used in Ontario). Seven phase II studies examining hormonal therapies for women with advanced endometrial cancer were also identified (43-49). The details of the chemotherapy and hormonal therapy phase II studies are described in Appendix 1, for information.

Four non-comparative studies (two retrospective) have been identified that measure systemic therapy in women with UPSC; no RCTs were found. Table 1b lists studies of chemotherapy for UPSC. Doses and schedules of administrations used in the clinical trials are listed in Appendix 2.

Table 1a. Studies on systemic therapy for advanced or recurrent endometrial cancer.

Drug or combination	Evidence	Reference number
Chemotherapy		
doxorubicin/cyclophosphamide vs doxorubicin alone	1 RCT	(7)
doxorubicin/cisplatin vs doxorubicin/cisplatin/paclitaxel	1 RCT	(11)
doxorubicin/cisplatin vs doxorubicin alone	2 RCTs: - 1 phase II/III - 1 phase III	(12) (18) [abstract]
doxorubicin/cisplatin vs radiotherapy	1 RCT	(13) [abstract]
doxorubicin/cisplatin vs carboplatin/paclitaxel	1 RCT (phase II)	(14) [abstract]
doxorubicin/cisplatin vs doxorubicin/paclitaxel	1 RCT	(15) [abstract]
ifosfamide vs cyclophosphamide	1 RCT (phase II)	(16)
methotrexate/vinblastine/doxorubicin/cisplatin vs doxorubicin/cisplatin	1 RCT	(17) [abstract]
doxorubicin/cyclophosphamide/cisplatin vs cisplatin alone	1 RCT (phase II)	(19)
cyclophosphamide/doxorubicin/5-FU vs melphalan/5-FU (+ megestrol in both groups)	1 RCT	(20)
doxorubicin/cyclophosphamide vs cyclophosphamide/doxorubicin/5-FU (+ megestrol in both groups)	1 RCT	(21)
doxorubicin vs cyclophosphamide	1 RCT	(22)
Hormonal Therapy		
oral medroxyprogesterone acetate 200mg/day vs oral medroxyprogesterone acetate 1,000mg/day	1 RCT	(8)
megestrol acetate vs megestrol acetate + tamoxifen	1 RCT (phase II)	(23)
medroxyprogesterone acetate vs tamoxifen	1 RCT	(24)
Combined chemotherapy and hormonal therapy		
cyclophosphamide/doxorubicin/5-FU vs cyclophosphamide/doxorubicin/5-FU + medroxyprogesterone + tamoxifen	1 RCT	(25)

Note: RCT, randomized controlled trial; vs, versus.

Table 1b. Studies on systemic therapy for uterine serous papillary carcinoma.

Drug or combination	Evidence	Reference number
platinum + paclitaxel	1 phase II study 1 retrospective review	(6) [abstract] (9)
paclitaxel	1 prospective cohort	(50)
cisplatin/doxorubicin/cyclophosphamide	1 retrospective review	(51)

Characteristics of Study Participants

Characteristics of the patients who participated in studies of chemotherapy or hormonal therapy for advanced or recurrent endometrial cancer are summarized in Tables 2a and 2b.

Six GOG RCTs included patients with high-risk histology (7,11,13,15,18,20). Three to five percent of participants in these studies had clear cell carcinoma and 4% to 19% had UPSC. Chemotherapy was given intravenously in all of the RCTs.

Table 2a. Description of participants in randomized trials of chemotherapy.

Study	Chemotherapy	# entered (eligible)	Recurrent disease (%)	Advanced disease (%)	Performance status	% with prior HT	% with prior CT	% with prior RT
Fleming, 2004 (11) (GOG)	dox/cisplatin vs dox/cisplatin/paclitaxel	273 (263)	170 (65%)	93 (35%)	GOG 0-2: 100%	NR	none	51% vs 46%
Aapro, 2003 (12) (EORTC)	dox/cisplatin vs dox	177 (177)	105 (59%)	72 (41%)	WHO 0-1: 78% 2: 18%	23%	0.5%	50%
Randall, 2003 (13) (GOG)	dox/cisplatin vs radiotherapy	422 (388)	NR	NR	NR	NR	NR	NR
Weber, 2003 (14)	dox/cisplatin vs carboplatin/paclitaxel	70	NR	NR	NR	NR	NR	NR
Fleming, 2000 (15) (GOG)	dox/cisplatin vs dox/paclitaxel	314	NR	NR	GOG 0-2: 100%	NR	none	52%
Pawinski, 1999 (16) (EORTC)	ifosfamide vs cyclo	74 (61)	47 (77%)	14 (23%)	WHO 0-1: 79% 2: 21%	28%	51%	67%
Long, 1995 (17) (NCCTG)	methotrexate/vinblastine/dox/cisplatin vs dox/cisplatin	28 (28)	none	28 (100%)	NR	NR	NR	NR
Thigpen, 1994 (7) (GOG)	dox/cyclo vs dox	387 (356)	NR	NR	GOG 0-1: 69% 2-3: 31%	NR	none	70%
Thigpen, 1993 (18) (GOG)	dox/cisplatin vs dox	297 (223)	NR	NR	NR	NR	none	NR
Edmonson, 1987 (19) (NCCTG)	dox/cyclo/cisplatin vs cisplatin	30 (30)	none	30 (100%)	ECOG 0-1: 53% 2-3: 47%	100%	NR	63%
Cohen, 1984 (20) (GOG)	cyclo/dox/5-FU/megestrol vs melphalan/5-FU/megestrol	295 (257)	115 (74%)	40 (26%)	0-1: 74% 2-3: 26%	NR	none	NR
Horton, 1982 (21)	dox/cyclo/megestrol vs cyclo/dox/5-FU/megestrol	149 (126)	none	126 (100%)	ECOG 0-1: 70% 2-3: 30%	38%	none	74%
Horton, 1978 (22) (ECOG)	dox vs cyclo	47 (40)	none	40 (100%)	ECOG 0-1: 53% 2-3: 47%	100%	none	NR

Note: 5-FU, 5-fluorouracil; CT, chemotherapy; cyclo, cyclophosphamide; dox, doxorubicin; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GOG, Gynecologic Oncology Group; HT, hormonal therapy; NCCTG, North Central Cancer Treatment Group; NR, not reported; RT, radiotherapy; vs, versus; WHO, World Health Organization

Table 2b. Description of participants in trials of hormonal therapy.

Study	Hormonal therapy	# entered (eligible)	Performance status	Recurrent disease (%)	Advanced disease (%)	% with prior HT	% with prior CT	% with prior RT
Pandya, 2001 (23)	megestrol vs megestrol/tamoxifen	66 (62)	ECOG 0-1: 82% 2: 18%	NR	NR	none	6%	82%
Thigpen 1999 (8)	MPA 200mg/day vs MPA 1,000mg/day	324 (299)	GOG 0-1: 77% 2: 23%	214 (72%)	85 (28%)	none	none	65%
Rendina, 1984 (24)	MPA vs tamoxifen	93 (93)	NR	0	93 (100%)	NR	NR	NR

Note: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; GOG, Gynecologic Oncology Group; HT, hormonal therapy; MPA, medroxyprogesterone acetate; NR, not reported; RT, radiotherapy; vs, versus.

Chemotherapy for Advanced or Recurrent Endometrial Cancer Survival

Survival data have been reported in nine randomized trials (Table 3) (7,11-15,17,19,20). Median survival ranged between 4.2 to 15 months in the nine studies. Two RCTs detected a significant difference in survival between treatment groups ($p < 0.05$) (11,13). Fleming et al's RCT (11) detected a significant improvement in median survival for women receiving doxorubicin/cisplatin/paclitaxel/G-CSF compared to women receiving doxorubicin/cisplatin. The death hazard relative to the doxorubicin/cisplatin arm (stratified by performance status) was 0.75 (95% CI 0.57-0.988, $p = 0.037$).

The other RCT that detected a survival difference between treatment arms compared doxorubicin/cisplatin to radiotherapy (13). Randall et al (13) reported the results of their GOG study (abstract) which included 388 evaluable women. They detected a progression-free survival (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.52-0.89; $p < 0.01$) and overall survival (HR, 0.67; 95% CI, 0.51-0.89; $p < 0.01$) advantage for the women receiving chemotherapy. Despite the advantages in survival, they reported that recurrences in both treatment arms were frequent (55% overall). They also noted that the adverse events were more common among the patients receiving chemotherapy than the patients receiving radiotherapy, but did not provide any details of the events.

The remaining seven RCTs did not detect a significant difference in median survival. Two of those trials were small, including about 30 patients each (17,19). The two oldest RCTs (19,20) compared combination chemotherapy with doxorubicin to a chemotherapy regimen that did not include doxorubicin. Two other RCTs that did not detect a significant difference in survival compared combination chemotherapy including doxorubicin with doxorubicin by itself (7) or doxorubicin in combination (15). The phase II/III RCT by Aapro et al (12) that compared doxorubicin and cisplatin with doxorubicin alone did not detect a survival difference; however, they did detect a significant difference in tumour response in favour of the combination therapy. One abstract of a phase II RCT comparing doxorubicin/cisplatin to carboplatin/paclitaxel has only presented preliminary results at this point (14). Weber et al (14) need to follow the patients in their study for a longer period before they can establish the role of carboplatin/paclitaxel in the treatment of advanced endometrial cancer. However, Weber et al report that thus far carboplatin/paclitaxel seems promising in terms of response rate and overall survival when compared to doxorubicin/cisplatin.

Table 3. Survival data of chemotherapy for advanced or recurrent endometrial cancer.

Study	Chemotherapy	# patients	Median Survival (months)	log-rank p value
Fleming, 2004 (11)	doxorubicin + cisplatin	129	12.3	0.037
	doxorubicin + cisplatin + paclitaxel	134	15.3	
Aapro, 2003 (12) (Phase II/III)	doxorubicin	87	7	NS p=0.064
	doxorubicin + cisplatin	90	9	
Randall, 2003 (13) [abstract]	doxorubicin + cisplatin	190	NR	PFS hazard ratio 0.68 (95% CI 0.52-.089) favouring chemotherapy p<0.01
	radiotherapy	198	NR	
Weber, 2003 (14) [abstract] (Phase II)	doxorubicin + cisplatin	34	6.7 (time to progression)	NR
	carboplatin + paclitaxel	36	7.7 (time to progression)	
Fleming, 2000 (15)	doxorubicin + cisplatin + GCSF	157	12.4	NS
	doxorubicin + paclitaxel + GCSF	160	13.6	
Long, 1995 (17) [abstract]	MVAC	13	15	NS
	doxorubicin + cisplatin	15	15	
Thigpen, 1994 (7)	doxorubicin	132	6.7	NS
	doxorubicin + cyclophosphamide	144	7.3	
Edmonson, 1987 (19) (Phase II)	cisplatin	14	4.2	NS
	cyclophosphamide/doxorubicin/cisplatin	16	6.7	
Cohen, 1984 (20)	melphalan + 5-fluorouracil + megestrol	122	10.6	NS
	doxorubicin/cyclophosphamide/5-fluorouracil + megestrol	131	10.1	

Note: CI, confidence interval; MVAC, methotrexate/vinblastine/doxorubicin (Adriamycin)/cisplatin; NS, not significant; PFS, progression-free survival

Tumour Response

Tumour response data from 12 randomized trials are listed in Table 4. Three RCTs detected a statistically significant difference in response rate between treatment groups (11,12,18). Two of those RCTs detected that patients treated with doxorubicin/cisplatin had significantly improved tumour response rates compared to patients who had received doxorubicin alone (12,18). No other RCT compared doxorubicin with cisplatin to doxorubicin alone. The report by Aapro et al (12) reported a significant difference in favour of combination therapy with doxorubicin plus cisplatin over doxorubicin alone in a randomized phase II/III trial ($p=0.001$). The difference in the response rates reported by Thigpen et al (18) for their phase III trial of doxorubicin versus doxorubicin plus cisplatin were also significant ($p<0.001$, Gynecology Cancer DSG calculation), in favour of combined therapy.

The other RCT that detected a significant difference in tumour response compared doxorubicin, cisplatin and paclitaxel to doxorubicin and cisplatin (11). They found that patients receiving doxorubicin, cisplatin and paclitaxel had greater tumour response than patients receiving doxorubicin, and cisplatin ($p<0.001$). Another randomized phase III trial prepared for

the 2000 ASCO meeting (GOG #163) by Fleming et al (15) comparing doxorubicin with cisplatin to doxorubicin with paclitaxel did not detect a significant difference in response rates between treatment groups (no p-value reported).

The other nine RCTs failed to detect a significant difference between the treatments being compared. Four of these RCTs included less than 65 patients which suggests that these studies were not powered to detect significant differences between treatment groups (16,17,19,22). Weber et al (14) reported preliminary results and thus could not make conclusions regarding tumour response. Four of the RCTs that failed to detect a significant difference between the treatments did not compare a platinum-based agent to a non-platinum-based regimen (7,20-22). However, two of the three RCTs that did detect a significant difference between treatment groups compared a platinum-based agent (in combination) to treatment not including platinum (12,18).

Table 4. Tumour response data from clinical trials of chemotherapy for advanced or recurrent endometrial cancer.

Study	Regimen	# evaluated	# complete responses (CR)	# partial responses (PR)	Response rate (CR + PR) (%)
Fleming, 2004 (11)	- doxorubicin/cisplatin - doxorubicin/cisplatin/ paclitaxel	263	7% 22%	26% 35%	(34%)* (57%)*
Aapro, 2003, (12)	- doxorubicin - doxorubicin/cisplatin	87 90	8 13	7 26	15 (17%) * 39 (43%) *
Weber, 2003 (14) [abstract] (Phase II)	- doxorubicin/cisplatin - carboplatin/paclitaxel	63	NR	NR	(27.6%) (35.3%)
Fleming, 2000 (15) [abstract]	- doxorubicin/cisplatin - doxorubicin/paclitaxel	157 160	23 27	40 42	63 (40%) 69 (43%)
Pawinski, 1999 (16)	- cyclophosphamide - ifosfamide	29 32	0 2	2 2	2 (7%) 4 (12%)
Long, 1995 (17) [abstract]	- MVAC - doxorubicin/cisplatin	13 15	4 2	5 2	9 (69%) 4 (26%)
Thigpen, 1994 (7)	- doxorubicin - doxorubicin/cyclophosphamide	132 144	7 18	22 25	29 (22%) 43 (30%)
Thigpen, 1993 (18) [abstract]	- doxorubicin - doxorubicin/cisplatin	122 101	10 22	23 23	33 (27%) * 45 (45%) *
Edmonson, 1987 (19)	- cisplatin - CAP	14 16	1 0	2 5	3 (21%) 5 (31%)
Cohen, 1984 (20)	- megestrol/melphalan/5-FU - MCAF	77 78	12 13	17 15	29 (38%) 28 (36%)
Horton, 1982 (21)	- MCA - MCAF	55 56	4 3	11 6	15 (27%) 9 (16%)
Horton, 1978 (22)	- doxorubicin - cyclophosphamide	21 19	1 0	3 0	4 (19%) 0 (0%)

Note: 5-FU, 5-fluorouracil; CAP, cyclophosphamide/Adriamycin) cisplatin; MCA, megestrol/cyclophosphamide/doxorubicin (Adriamycin); MCAF, MCA+5-fluorouracil; MVAC, methotrexate/vinblastine/Adriamycin/cisplatin

* p value statistically significant

Quality of Life

One RCT assessed quality of life during chemotherapy (14), and one RCT was identified that assessed quality of life before, during, and after chemotherapy (52). At this point, both trials are only published in abstract form, and Weber et al (14) have only published preliminary results. Weber et al conducted a randomized phase II study comparing six cycles of doxorubicin/cisplatin to six cycles of carboplatin/paclitaxel. Every cycle tolerance was evaluated, and every two cycles of efficacy and quality of life were evaluated.

Watkins-Bruner et al (52) reported the quality-of-life data for the GOG 122 RCT, which compared whole abdominal radiation therapy to doxorubicin and cisplatin in women with advanced endometrial cancer. They used several quality-of-life measurement scales including: the Fatigue Scale (FS), Assessment of Peripheral Neuropathy (APN), Functional Alterations due to Changes in Elimination (FACE), and Functional Assessment of Cancer Therapy (FACT). FACT is a measure of overall quality of life. Watkins et al reported that after six months women treated with radiation therapy have similar FS and FACE scores as their pre-treatment scores; however, they had significantly worse FS and FACE scores than the women receiving chemotherapy ($p<0.01$). Women receiving chemotherapy had higher APN scores than the women receiving radiation therapy ($p<0.01$), and those high scores for women receiving chemotherapy were maintained beyond the six months of treatment. The results of that trial will require more investigation once the full report has been published.

One small phase II study measured performance status and pain, before and after treatment with paclitaxel plus cisplatin (29). Dimopoulos et al (29) reported that the performance status (defined by the Eastern Cooperative Oncology Group [ECOG]) improved in eight of 14 women with a pre-treatment performance status of 1 or 2. Improvement was defined as an increase of at least one point on the ECOG scale. Before starting chemotherapy, ten of 24 patients enrolled in the study were taking opioid analgesics regularly to manage pain. After chemotherapy, six of those ten women were no longer using pain medication or had substituted nonsteroidal anti-inflammatory drugs for the opioid analgesics. The remaining four women reported no change in pain after chemotherapy or a worsening of symptoms. It is important to note that the study included patients with all stages of endometrial cancer in their study, not just advanced stage as in the other studies mentioned.

Adverse Events

Data on severe adverse events (grade 3 or 4) were reported for seven randomized trials (Table 5). Thirteen deaths possibly related to treatment were reported across the seven studies: seven with doxorubicin alone or with cyclophosphamide (7), one with carboplatin (17), and five with paclitaxel/doxorubicin/cisplatin (11). In the Fleming et al RCT (11), there were five treatment-related deaths in the paclitaxel/doxorubicin/cisplatin arm ($n=134$) and no treatment-related deaths in the doxorubicin/cisplatin arm ($n=129$). The authors of the RCT report, however, that only two of the deaths were clearly treatment-related (one case of acute myeloid leukemia and one case of neutropenic sepsis). The other three patients died due to possible hemolytic uremic syndrome and disease, infection and disease, or superior mesenteric artery thrombus. Fleming et al also reported that more deaths among patients being treated cisplatin/doxorubicin have been reported in the GOG trials with identical cisplatin/doxorubicin treatment arms (53).

Table 5. Serious adverse event data (Grade 3/4) from clinical trials of chemotherapy for advanced or recurrent endometrial cancer.

Study	# of patients	Treatment	Leukopenia	Thrombocytopenia	Gastrointestinal	Neurological
Fleming, 2004 (11)	263	doxorubicin/cisplatin	50%	3%	25%	1%
		doxorubicin/cisplatin/paclitaxel	36%	22%	34%	12%
Aapro 2003 (12)	165	doxorubicin	30%	5%	12%	0
		doxorubicin/cisplatin	55%	13%	36%	0
Fleming, 2000 (15) GOG 163	314	doxorubicin/cisplatin	54%	6%	13%	8%
		doxorubicin/paclitaxel/GCSF	48%	9%	11%	9%
Pawinski, 1999 (16)	61	cyclophosphamide	52%	0	not reported	not reported
		ifosfamide	46%	4%		
Thigpen, 1993 (18) GOG 107	223	doxorubicin	39%	2%	2%	not reported
		doxorubicin/cisplatin	61%	14%		
Cohen, 1984 (20)	155	megestrol/melphalan/5-fluorouracil	52%	18%	not reported	not reported
		MCAF	31%	0		
Horton, 1982 (21)	111	MCA	32%	5%	not reported	not reported
		MCAF	18%	5%		

Note: GOG, Gynecologic Oncology Group; MCA, megestrol/cyclophosphamide/doxorubicin (Adriamycin); MCAF, MCA + /5-fluorouracil

Hormonal Therapy for Advanced or Recurrent Endometrial Cancer

Survival

Survival data have been reported from two randomized studies that considered hormonal therapy (Table 6). Median survival ranged from seven to 12 months in these studies. However, the median survival data could not be pooled across studies because of the variability among the studies due to chemotherapy regimens and outcome measures.

Table 6. Survival data of hormonal therapy for advanced or recurrent endometrial cancer.

Study	Hormonal therapy	Median Survival (months)	Log-rank p-value
Pandya, 2001 (23) (phase II randomized)	megestrol	12	(no p-value)
	megestrol/tamoxifen	8.6	
Thigpen, 1999 (8)	MPA 200 mg	11.1	p=0.026
	MPA 1,000 mg	7.0	

Note: MPA, medroxyprogesterone acetate

Tumour Response

Tumour response data from three randomized studies (8,23,24) appear in Table 7. Only the RCT by Thigpen et al (8) detected a difference between the treatment groups. They reported that low-dose medroxyprogesterone acetate (MPA) showed marginally better response rates than high-dose MPA (p=0.051). When Thigpen et al (8) calculated response rates for subgroups of participants, they reported that grade I, progesterone-receptor-positive or estrogen-positive tumours had response rates of 37%, 37%, and 26%, respectively, and median

survival of 18.8, 12.1, and 8.3 months, respectively. However, participants with grade III, progesterone-receptor-negative or estrogen-receptor-negative tumours had response rates of 9%, 8%, and 7%, respectively and survival of 6.9, 6.8, and 6.7 months, respectively, based on univariant analysis (8).

Table 7. Tumour response data from clinical trials of hormonal therapy for advanced or recurrent endometrial cancer.

Study	Regimen	# evaluated	# complete responses (CR)	# partial Responses (PR)	Response rate (CR + PR) (%)
Pandya, 2001 (23)	- megestrol	20	1	3	4 (20%)
	- megestrol/tamoxifen	41	1	7	8 (20%)
Thigpen, 1999 (8)	- MPA 200 mg	145	25	11	36 (25%)
	- MPA 1,000 mg	154	14	10	24 (15%) p=0.051
Rendina, 1984 (24)	- MPA	48	8	14	22 (46%)
	- tamoxifen	45	6	10	16 (36%)

Note: MPA = medroxyprogesterone acetate

Adverse Events

Three randomized trials examining the use of hormonal therapy in the treatment of endometrial cancer provided details of adverse effects (8,23,24). Pandya et al reported that 5% of patients on megestrol plus tamoxifen experienced life-threatening adverse events, including one case of pulmonary embolism (23). Rendina et al reported that none of the participants in their trial experienced adverse effects severe enough to require withdrawal of therapy (24). Thigpen et al (8) reported that thrombophlebitis (5%) was the most frequently reported adverse effect, followed by gastrointestinal upset, somnolence, fatigue, edema (all less than 3%), and pulmonary embolus (1%) (8).

Combination Therapy for Advanced or Recurrent Endometrial Cancer

Ayoub et al (25) reported the results of the only randomized trial identified that compared chemotherapy to combined chemotherapy and hormonal therapy for advanced or recurrent endometrial cancer. The trial was not blinded and did not describe an appropriate method for concealing allocation up to the time of randomization. An intention-to-treat approach was not used for survival analysis, and the number of patients lost to follow-up was not described.

Forty-six women with metastatic endometrial cancer (37% newly diagnosed and 62% recurrent) and an ECOG performance status between 0 and 2 entered the trial. None had received previous chemotherapy or hormonal therapy, but all had been treated with radiation. Details of dose and schedule for the chemotherapy and hormonal therapy regimens evaluated are listed in Appendix 1.

Median survival was 11 months with chemotherapy alone (cyclophosphamide/doxorubicin/5-fluorouracil) and 14 months with chemotherapy plus cyclical hormonal therapy (Provera followed by tamoxifen) ($p>0.05$). Response rates were 15% with chemotherapy alone (1 complete and 2 partial, $n=20$) and 43% with chemotherapy plus hormonal therapy group (6 complete and 4 partial, $n=23$). The difference in response rates between groups was of borderline statistical significance ($p=0.05$). Quality of life was not assessed.

Ayoub et al reported that five of 23 women (22%) treated with combined chemo-hormonal therapy experienced phlebitis (25). Toxicity data were not presented separately for the two treatment groups, but 14% overall experienced grade 3 or 4 hematologic adverse events, and 12% grade 3 or 4 nausea or vomiting.

Chemotherapy for Advanced or Recurrent Uterine Papillary Serous Carcinoma (UPSC)

There were two prospective and two retrospective single-cohort studies of chemotherapy for advanced or recurrent UPSC (6,9,50,51) (Table 8). These studies included women with UPSC who received chemotherapy for early-stage, advanced or recurrent disease, but only data for patients with measurable disease in the latter two groups were extracted for this practice guideline.

There is limited survival and response data available from those studies. The Canadian prospective phase II study by Hoskins et al (6) reported response rates for both patients with UPSC and patients with non-papillary serous cancers. They reported that, out of the 46 women assessable for response, there was an overall response rate of 78%. Among the women with advanced non-papillary serous cancer there was a 78% response rate, compared to a 60% response rate among women with UPSC. The response rate for women with recurrent non-papillary serous cancer was 56% compared to 50% among women with recurrent UPSC. These findings need to be interpreted with caution because of the small sample size of the study.

Toxicity data are also sparse. Ninety percent of the participants in the study by Ramondetta et al experienced grade 3 or 4 neutropenia after treatment with paclitaxel; 45% were hospitalized for neutropenic fever (50). Ramondetta also reported that one patient developed congestive heart failure (50). Price et al reported that 64% of patients with recurrent disease treated with cisplatin/doxorubicin/ cyclophosphamide experienced grade 3 or 4 neutropenia, 9% experienced grade 3 or 4 thrombocytopenia, and 9% experienced grade 3 or 4 nausea or vomiting (51). In that study, Price et al also reported one death that was associated with cardiotoxicity from doxorubicin (51).

Table 8. Studies of chemotherapy for UPSC.

Study	Hoskins, 2001 (6)	Ramondetta, 2001 (50)	Zanotti, 1999 (9)	Price, 1993 (51)
Type of study	Prospective	Prospective	Retrospective	Retrospective
Dose	175 mg/m ² paclitaxel over 3 hours + AUC 5-7 carboplatin, every 4 weeks	200 mg/m ² paclitaxel over 24 hours, every 3 weeks	175 mg/m ² paclitaxel over 3 hours + 75mg/m ² cisplatin or AUC 5 carboplatin, every 3 weeks	50 mg/m ² cisplatin + 50 mg/m ² doxorubicin + 500 mg cyclophosphamide
Total UPSC patients	24	13	24	11
# with recurrent disease	4	9	Second line: 5 (platinum) 6 (no platinum)	11
# with advanced disease	20 (only 15 evaluable)	4	Second line: 8 (platinum) Initial chemotherapy: 9 (platinum)	0
% with prior chemotherapy	0%	0%	Second line: 0% (platinum) 83% (no platinum) Initial chemotherapy: 0% (platinum)	Not reported
Median survival for advanced patients (months)	26	11	56	Not applicable
Median survival for patients with recurrence (months)	15	19	Not reported	7
# complete responses (CR)	3 advanced 1 recurrent	4	11 second line	1
# partial responses (PR)	6 advanced 1 recurrent	6	4 second line	2
Response rate (CR + PR) (%)	9 (60%) advanced 2 (50%) recurrent	10 (77%)	15 (75%) second line 8 ^a (89%) initial chemotherapy	3 (30%)

Note: AUC, area under curve

^a based on normalization of elevated pre-chemotherapy CA 125 level

V. INTERPRETIVE SUMMARY

Chemotherapeutic options studied for the treatment of advanced or recurrent carcinoma of the endometrium have included single-, double-, and triple-agent therapies. Single-agent chemotherapy has reported response rates as follows: doxorubicin 17-27% (7,12,18,22) and platinum agents 21% (19). For combination chemotherapy, randomized trials of doxorubicin/cisplatin reported response rates of 34%, 40%, 45%, and 43% (11,12,15,18); however, other agents in combination with doxorubicin revealed response rates of 30% (cyclophosphamide) (7) and 43% (paclitaxel) (15). When three agents are combined, the response rates seem to be higher. One RCT compared doxorubicin/cisplatin to doxorubicin/paclitaxel/cisplatin and reported a 57% response rate for the doxorubicin/paclitaxel/cisplatin arm compared to a 34% response for the doxorubicin/cisplatin arm (11).

Paclitaxel-containing regimens seem to be promising. A non-comparative study of paclitaxel/carboplatin reported a response rate of 78% and 50% in advanced and recurrent disease, respectively (6). Median survival was 15 months for recurrent disease and has not yet been reached in advanced disease (6). Although newer studies, particularly those using a combination of carboplatin and paclitaxel, report promising results, caution should be exercised in interpreting reported favourable response rates in the absence of a well-designed clinical trial.

One randomized trial compared whole abdominal radiotherapy to cisplatin/doxorubicin and detected an advantage in both progression-free survival and overall survival in the chemotherapy arm but also an increase in adverse events. Recurrences were frequent in both arms (13).

The only randomized phase III trial comparing the effects of hormonal therapy in patients with advanced or recurrent endometrial cancer concluded that patients receiving low-dose medroxyprogesterone acetate (MPA) survived longer and responded to treatment better than patients treated with high-dose MPA. The best response seems to be in patients with well-differentiated tumours and positive progesterone receptor status (8,24). However, response rates varied considerably from 15% to 46% (8,23,24). This variation suggests a considerable selection bias in the patient populations studied and again speaks to the need for a properly designed trial in the future. Hormonal agents are well tolerated with adverse events occurring at a rate of less than 5% (8), although thromboembolic events have been reported as a complication in a number of studies (23,44,46,48).

There have been no randomized controlled trials regarding a treatment for patients with UPSC; however, response rates in four small non-comparative (two prospective, two retrospective) studies have ranged from 30-89% (6,9,50,51). In a Canadian prospective trial, the response rates for UPSC were lower than in advanced or recurrent non-serous endometrial cancers (60% advanced UPSC and 50% recurrent UPSC versus 78% advanced non-UPSC and 56% recurrent non-UPSC) (6), which is unexpected since previous trials have reported better responses.

VI. ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials) was searched in April 2004 for reports of ongoing randomized trials.

Protocol ID(s)	Title and details of trial
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<i>GOG-189:</i>	Phase III randomized study of doxorubicin, cisplatin, paclitaxel, and filgrastim (G-CSF) versus tamoxifen and megestrol in patients with stage III or IV or recurrent endometrial cancer. This trial will recruit approximately 630 patients and will assess quality of life. This trial is closed.
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<i>GOG-0184:</i>	Phase III randomized adjuvant study of tumour volume-directed pelvic radiotherapy with or without paraaortic radiotherapy followed by cisplatin and doxorubicin with or without paclitaxel in patients with stage III or IV endometrial carcinoma. This trial will recruit approximately 434 patients and will assess survival, progression-free survival and short and long term toxicity. (Summary last modified June 2003)
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<i>EORTC-55984:</i>	Phase III randomized study of doxorubicin and cisplatin with or without paclitaxel in patients with locally advanced, metastatic, and/or relapsed endometrial cancer. This trial will recruit 312 patients and will assess survival, progression-free survival, toxicity and quality of life. (Summary last modified July 2003).
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VII. IMPLICATIONS FOR POLICY

This guideline was submitted to the Policy Advisory Committee (PAC) for their meeting on September 23, 2003. At that time, PAC chose not to recommend funding because they felt that the guideline did not have a specific enough recommendation regarding the use of paclitaxel. The Gynecology Cancer DSG re-examined the evidence and decided that there was insufficient evidence to make a stronger recommendation regarding the use of paclitaxel at this time. Sub-optimal toxicity comparisons between patients with ovarian and endometrial cancer

appear to demonstrate that paclitaxel/carboplatin is associated with less leukopenia, nausea, and vomiting than is doxorubicin/cisplatin, although neurotoxicity is comparable.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the Gynecology Cancer DSG drafted the following recommendations:

Target Population

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Draft Recommendations

- Non-taxane combination chemotherapy is favoured over single-agent chemotherapy, in terms of response rate but not survival. The optimum regimen is yet to be defined.
- Platinum/paclitaxel is associated with substantially less high-grade (3 and 4) leukopenia and nausea and vomiting than doxorubicin/platinum, although neurological adverse effects are comparable.
- The addition of paclitaxel to the combination of cisplatin/doxorubicin has shown a significant response and survival advantage over doxorubicin/cisplatin; however, the use of three agents increases toxicity.
- Hormonal therapy may present a therapeutic option for the treatment of patients with minimal symptoms or non-life threatening advanced or recurrent endometrial carcinoma.
- Evidence supporting or refuting various chemotherapy regimens for UPSC is limited.
- Patients should be encouraged to participate in randomized trials.

Qualifying Statements

- The recommendation that the combination of doxorubicin/cisplatin/paclitaxel is better than doxorubicin/cisplatin in terms of survival is based on one randomized trial whose results are only published in abstract form at this time.
- When considering chemotherapy regimens for advanced or recurrent endometrial cancer, it is important to consider the toxicity of treatments—the small improved survival benefit of combination (2 or 3 agents) may not outweigh the harms associated with toxicity.
- For UPSC treatment, the most studied regimen is a paclitaxel/platinum combination. The addition of paclitaxel in small, non-comparative studies is associated with improved response rates and survival compared to non-paclitaxel containing regimens.

Future Research

In terms of future studies, it is important to be able to control for prognostic factors that affect outcome in these patient populations. Patients should be properly stratified with respect to their disease status (advanced versus recurrent), the amount of previous treatment whether it is radiation or chemotherapy, and disease recurrence either in or out of the radiated field. Patients with UPSC should be analyzed separately. Results relating to systemic therapy should be first assessed and proven in those patients with measurable disease so that an accurate assessment of any prolongation in disease-free survival can be made with reasonable assurance that these improvements are due to treatment. Treatment-related toxicity must be studied very carefully in the future in this patient population in order to ensure that the treatment

itself has acceptable morbidity in relation to the patient's quality of life, as median survival is generally limited and rarely more than a year in this patient population. Survival, response, and toxicity should be studied with regard to impact on quality of life. Comparing tumour responses for both chemotherapy and hormonal agents, stratified by grade, would provide valuable data for making treatment decisions.

Related Guidelines

Practice Guidelines Initiative's Evidence Summary Report # 4-14: *Adjuvant Chemotherapy for Early Stage Endometrial Cancer and Uterine Papillary Serous Carcinoma (in progress)*.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 81 practitioners in Ontario (11 gynecologists, 39 medical oncologists, 18 radiation oncologists, and 13 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 27, 2003]. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology Cancer DSG reviewed the results of the survey.

Results

Thirty-five responses were received out of the 81 surveys sent (43% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 18 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 9.

Table 9. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	17 (94%)	1 (6%)	--
There is a need for a clinical practice guideline on this topic.	15 (83%)	3 (17%)	--
The literature search is relevant and complete.	15 (88%)	2 (12%)	--
The results of the trials described in the report are interpreted according to my understanding of the data.	13 (72%)	3 (17%)	2 (11%)
The draft recommendations in this report are clear.	10 (56%)	6 (33%)	2 (11%)
I agree with the draft recommendations as stated.	11 (61%)	6 (33%)	1 (6%)
This report should be approved as a practice guideline.	10 (59%)	4 (24%)	3 (17%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	9 (50%)	5 (28%)	4 (22%)

Summary of Written Comments

Seven respondents (39%) provided written comments. The main points contained in the written comments were:

1. It appears as if no recommendations can actually really be made, so why try to make them for endometrial cancer? The recommendations are vague.
2. The recommendations are a bit too soft on the benefits of taxanes, it is surprising that non-taxane is favoured over taxane.

Modifications/Action

1. The Gynecology Cancer DSG acknowledges that there is limited evidence to make recommendations and thus the recommendations are vague. Nonetheless, the Gynecology Cancer DSG felt it was important to present the available evidence and to make recommendations based on the evidence. This guideline will be updated as new evidence becomes available, and as the data emerges, the Gynecology Cancer DSG will revise their recommendations as necessary.
2. The Gynecology Cancer DSG reviewed their original recommendations regarding taxanes and non-taxanes. The DSG agreed that the recommendation regarding non-taxanes was misleading and thus have modified the recommendation.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the PGCC for review and approval. Seven of 14 members of the PGCC returned ballots. Four PGCC members approved the practice guideline report as written, and one member approved the report with a minor editorial change to the recommendations required. One member approved the report conditional on the Gynecology DSG clarifying the recommendations. One PGCC member did not approve the report because the member was concerned that the guideline placed too much emphasis on the abstract by Fleming et al comparing doxorubicin/cisplatin to doxorubicin/paclitaxel/cisplatin. The PGCC member thought that the Gynecology DSG should wait until the RCT was reported in a full publication before making recommendations based on the trial.

Modifications/Actions

The wording of the recommendations was clarified as per the suggestions of two PGCC members. This practice guideline was submitted to the PGCC members for review on May 15, 2004. On June 1, 2004 the Fleming et al RCT comparing doxorubicin/cisplatin to doxorubicin/paclitaxel/cisplatin was published in a full report in the *Journal of Clinical Oncology* (11). The Gynecology Cancer DSG has updated the guideline to include the full publication. The results of the full publication are consistent with the abstract data presented previously and thus the Gynecology Cancer DSG did not revise their recommendations based on the full publication.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Gynecology Cancer DSG and by the Practice Guidelines Coordinating Committee.

Target Population

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Recommendations

For women with advanced or recurrent endometrial cancer:

- Combination chemotherapy is favoured over single-agent chemotherapy because of higher response rates.
- Paclitaxel in combination with cisplatin/doxorubicin chemotherapy improves both response rate and median survival; however, the use of this three-drug combination is associated with increased toxicity.
- Hormonal therapy may be a therapeutic option for those patients with minimal symptoms or non-life threatening advanced or recurrent endometrial cancer.

For women with UPSC:

- Evidence supporting or refuting various chemotherapy regimens for UPSC is limited.
- Patients should be encouraged to participate in randomized trials.

Qualifying Statements:

- The decision to use the three-drug combination, consisting of cisplatin/doxorubicin/paclitaxel, should be made in consultation with the patient. Consideration needs to be given to both the greater toxicity and the three-month increase in median survival time achieved with the three-drug combination in comparison with the two drug doxorubicin/cisplatin regimen.
- For UPSC treatment, the most studied regimen is a paclitaxel/platinum combination. The addition of paclitaxel in small, non-comparative studies is associated with improved response rates and survival compared to non-platinum containing regimens.

Future Research

In terms of future studies, it is important to be able to control for prognostic factors that affect outcome in these patient populations. Patients should be properly stratified with respect to their disease status (advanced versus recurrent), the amount of previous treatment, type of previous treatment (radiation or chemotherapy), and disease recurrence either in or out of the radiated field. Patients with UPSC should be analyzed separately. Results relating to systemic therapy should be first assessed and proven in those patients with measurable disease so that an accurate assessment of any prolongation in disease-free survival can be made with reasonable assurance that these improvements are due to treatment. Treatment-related toxicity must be studied very carefully in the future in this patient population in order to ensure that the treatment itself has acceptable morbidity in relation to the patient's quality of life, as median survival is generally limited and rarely more than a year in this patient population. Survival, response and toxicity should be studied with regard to impact on quality of life. Comparing tumour responses for both chemotherapy and hormonal agents, stratified by grade, would provide valuable data for making treatment decisions.

Related Guidelines

Practice Guidelines Initiative's Evidence Summary Report # 4-14: *Adjuvant Chemotherapy for Early Stage Endometrial Cancer and Uterine Papillary Serous Carcinoma (in progress)*.

X. JOURNAL REFERENCE

A systematic review based on this guideline has been published in the peer-reviewed journal *Gynecologic Oncology*, available from:

(http://www.elsevier.com/wps/find/journaldescription.cws_home/622840/description#description)

- Carey MS, Gawlik C, Fung-Kee-Fung M, Chambers A, Oliver T; Cancer Care Ontario Practice Guidelines Initiative Gynecology Cancer Disease Site Group. Systematic review

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XI. ACKNOWLEDGEMENTS

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*For a complete list of the Gynecology Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at:
http://www.cancercare.on.ca/access_PEBC.htm.*

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Appendix 1.

Table A. Studies on systemic therapy for advanced or recurrent endometrial cancer.

Drug or combination	Evidence	Reference number
Chemotherapy		
carboplatin	2 phase II trials 1 prospective cohort	(40-42)
paclitaxel - alone	3 phase II trials	(5,37,39)
paclitaxel - with carboplatin	2 phase II trials	(6,28) [1 abstract]
- with cisplatin	1 prospective cohort	(36)
- with epirubicin and cisplatin	1 phase II trial	(29)
	1 prospective cohort	(33) [abstract]
	1 prospective cohort	(35)
oral etoposide	2 phase II trials	(32,38)
dactinomycin	1 phase II trial	(31)
topotecan - alone	1 phase II trial	(26)
- with cisplatin	1 phase II trial	(30) [abstract]
liposomal doxorubicin	1 phase II trial	(27)
vinorelbine – with carboplatin	1 prospective cohort	(34) [abstract]
Hormonal Therapy		
gonadotrophin-releasing hormone and luteinizing hormone-releasing hormone analogs	1 prospective cohort 2 phase II trials	(49) (47,48)
aromatase inhibitors	2 phase II trials	(44,46) [1 abstract]
LY353381 (selective estrogen receptor modulator)	2 phase II trials	(45) (43)[abstracts]

Table B. Description of participants in prospective single-cohort studies of chemotherapy.

Study	Chemotherapy	# entered (eligible)	Recurrent disease (%)	Advanced disease (%)	Performance status	% with prior HT	% with prior CT	% with prior RT
Muggia, 2002 (27)	liposomal doxorubicin	46 (42)	42 (100%)	0	GOG 0-1: 86% 2: 14%	26%	95%	69%
Hoskins, 2001 (6)	paclitaxel/ carboplatin	39 (39)	18 (46%)	21 (54%)	ECOG <=3	NR	none	NR
Miller, 2002 (26)	topotecan	29 (22)	NR	NR	0-1: 91% 2: 9%	14%	100%	41%
Scudder, 2001 (28)	paclitaxel/ carboplatin	57 (49)	NR	NR	NR	NR	none	NR
Dimopoulos, 2000 (29)	paclitaxel/ cisplatin	24 (24)	14 (59%)	10 (42%)	ECOG 0-1: 84% 2: 17%	NR	none	4%
Hall, 2000 (30)	topotecan/ cisplatin	8 (8)	NR	NR	0-2: 100%	NR	none	75%
Moore, 1999 (31)	dactinomycin	27 (27)	NR	NR	GOG 0-3: 100%	NR	100%	48%
Poplin, 1999 (32)	oral etoposide	47 (44)	23 (52%)	21 (48%)	0-1: 84% 2: 16%	47%	none	77%
Trudeau, 1999 (33)	paclitaxel/ cisplatin	8 (8)	NR	NR	NR	NR	none	NR
Santoro, 1998 (34)	vinorelbine/ carboplatin	13 (13)	0	13 (100%)	ECOG 0-3: 100%	NR	NR	NR
Lissoni, 1997 (35)	paclitaxel /cisplatin/ epirubicin	27 (27)	10 (37%)	17 (63%)	WHO 0-1: 100%	NR	none	20%
Price, 1997 (36)	paclitaxel/ carboplatin	14 (8)	5 (63%)	3 (37%)	NR	NR	NR	NR

Study	Chemotherapy	# entered (eligible)	Recurrent disease (%)	Advanced disease (%)	Performance status	% with prior HT	% with prior CT	% with prior RT
Ball, 1996 (5)	paclitaxel	30 (28)	NR	NR	GOG 0-1: 86% 2: 14%	18%	none	50%
Lissoni, 1996 (37)	paclitaxel	19 (19)	7 (37%)	12 (63%)	NR	NR	100% (PAC)	32%
Rose, 1996 (38)	oral etoposide	26 (25)	NR	NR	GOG 0-2: 100%	NR	96%	56%
Woo, 1996 (39)	paclitaxel	7 (7)	6 (86%)	1 (14%)	NR	NR	all platinum resistant	NR
Burke, 1993 (40)	carboplatin	33 (33)	16 (48%)	17 (52%)	Zubrod \leq 2	21%	none	67%
Green, 1990 (41)	carboplatin	32 (23)	NR	NR	0-1: 70% 2: 30%	43%	none	78%
Long, 1988 (42)	carboplatin	26 (25)	NR	NR	ECOG 0-1: 72% 2-3: 28%	76%	none	80%

Note: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; GOG, Gynecologic Oncology Group; HT, hormonal therapy; NR, not reported; PAC, paclitaxel; RT, radiotherapy; WHO, World Health Organization

Table C. Description of participants in trials of hormonal therapy.

Study	Hormonal therapy	# entered (eligible)	Performance status	Recurrent disease (%)	Advanced disease (%)	% with prior HT	% with prior CT	% with prior RT
McMeekin, 2001 (43)	LY353381	37 (29)	NR	NR	NR	allowed	none	NR
Sidhu, 2001 (44)	letrozole	17 (17)	NR	NR	NR	29%	none	82%
Klijn, 2000 (45)	LY353381	37 (35)	Karnofsky 50-100	NR	NR	NR	8%	53%
Rose, 2000 (46)	anastrozole	23 (23)	GOG 0-1: 74% 2-3: 26%	15 (65%)	8 (35%)	17%	none	35%
Lhomme, 1999 (47)	triptorelin	25 (24)	WHO 0-2	21 (84%)	4 (16%)	8%	12%	84%
Covens, 1997 (48)	leuprolide acetate	25 (25)	GOG 0-1: 68% 2-3: 32%	17 (68%)	8 (32%)	72%	8%	36%
Jeyarajah, 1996 (49)	leuprolide acetate	32 (32)	NR	32 (100%)	0	72%	NR	88%

Note: CT, chemotherapy; GOG, Gynecologic Oncology Group; HT, hormonal therapy; NR, not reported; RT, radiotherapy; WHO, World Health Organization

Table D. Survival data of chemotherapy for advanced or recurrent endometrial cancer.

Study	Chemotherapy	# patients	Median Survival (months)
Muggia, 2002 (27)	liposomal doxorubicin	41 ^a	8.2
Hoskins, 2001 (6)	paclitaxel/carboplatin	49	Advanced 23 ^b Recurrent 15
Scudder, 2001 (28) [abstract]	paclitaxel/carboplatin	49	10
Dimopoulos, 2000 (29)	paclitaxel/cisplatin	10	17.6 ^d
Poplin, 1999 (32)	oral etoposide	44 ^c	11
Ball, 1996 (5)	paclitaxel	28	9.5
Green, 1990 (41)	carboplatin	23	9.4
Long, 1988 (42)	carboplatin	25	7.2

^a Includes five patients with UPSC

^b Median failure-free survival (overall survival not yet reached)

^c Patients with metastases

^d Includes patients with stage I-IV disease

Table E. Tumour response data from clinical trials of chemotherapy for advanced or recurrent endometrial cancer.

Study	Regimen	# evaluated	# complete responses (CR)	# partial responses (PR)	Response rate (CR + PR) (%)
Miller, 2002 (26)	topotecan	22	1	1	2 (9%)
Muggia, 2002 (27)	liposomal doxorubicin	42	0	4	4 (10%)
Hoskins, 2001 (6)	paclitaxel/carboplatin	advanced 9 recurrent 18	2 1	5 9	7 (78%) 10 (50%)
Dimopoulos, 2000 (29)	paclitaxel/cisplatin	24	7	9	16 (67%)
Hall, 2000 (30) [abstract]	topotecan/cisplatin	6	3	0	3 (38%)
Moore, 1999 (31)	dactinomycin	24	1	2	3 (12%)
Poplin, 1999 (32)	oral etoposide	44	1	5	6 (14%)
Trudeau, 1999 (33) [abstract]	paclitaxel/cisplatin	8	1	5	6 (75%)
Santoro, 1998 (34) [abstract]	carboplatin/vinorelbine	13	3	6	9 (69%)
Lissoni, 1997 (35)	paclitaxel/cisplatin/epirubicin	27	6	15	21 (78%)
Price, 1997 (36)	paclitaxel/carboplatin	8	0	5	5 (63%)
Ball, 1996 (5)	paclitaxel	28	4	6	10 (36%)
Lissoni, 1996 (37)	paclitaxel	19	2	5	7 (37%)
Rose, 1996 (38)	oral etoposide	22	0	0	0
Woo, 1996 (39)	paclitaxel	7	0	3	3 (43%)
Burke, 1993 (40)	carboplatin	27	3	6	9 (33%)
Green, 1990 (41)	carboplatin	23	2	5	7 (30%)
Long, 1988 (42)	carboplatin	25	0	7	7 (28%)

Table F. Serious adverse event data (Grade 3/4) from clinical trials of chemotherapy for advanced or recurrent endometrial cancer.

Study	# patients	Treatment	Leukopenia	Thrombocytopenia	Gastro-intestinal
Miller, 2002 (26)	28	topotecan	75%	39%	14%
Scudder, 2001 (28) [abstract]	49	paclitaxel/carboplatin	33%	not reported	4%
Dimipoulos, 2000 (29)	24	paclitaxel/cisplatin/GCSF	22%	0%	9%
Hall, 2000 (30) [abstract]	6	topotecan/cisplatin	63%	25%	not reported
Moore, 1999 (31)	24	dactinomycin	44%	11%	15%
Poplin, 1999 (32)	44	oral etoposide	11%	2%	9%
Lissoni, 1997 (35)	27	paclitaxel/cisplatin/epirubicin	61%	8%	not reported
Price, 1997 (36)	8	paclitaxel/carboplatin	79%	5%	0
Ball, 1996 (5)	28	paclitaxel	62%	7%	17%
Lissoni, 1996 (37)	19	paclitaxel	11%	0	0
Rose, 1996 (38)	22	oral etoposide	52%	16%	4%
Long, 1988 (42)	25	carboplatin	not reported	not reported	28%

Note: GCSF, granulocyte-colony-stimulating factor

Table G. Survival data of hormonal therapy for advanced or recurrent endometrial cancer.

Study	Hormonal therapy	Median Survival (months)	Log-rank p-value
Rose, 2000 (46)	anastrozole	6	-
Lhomme, 1999 (47)	triptorelin	7.2	-
Covens, 1997 (48)	leuprolide acetate	9	-

Table H. Tumour response data from clinical trials of hormonal therapy for advanced or recurrent endometrial cancer.

Study	Regimen	# evaluated	# complete responses (CR)	# partial Responses (PR)	Response rate (CR + PR) (%)
Sidhu, 2001 (44) [abstract]	letrozole	10	0	2	2 (20%)
Klijn, 2000 (45) [abstract]	LY353381	32	0	7	7 (22%)
Rose, 2000 (46)	anastrozole	23	0	2	2 (9%)
Lhomme, 1999 (47)	triptorelin	23	1	1	2 (9%)
McMeekin, 1999 (43) [abstract]	LY353381	29	1	8	9 (31%)
Covens, 1997 (48)	leuprolide acetate	25	0	0	0
Jeyarajah, 1996 (49)	leuprolide acetate	32	2	7	9 (28%)

Appendix 2. Regimens studied in clinical trials of systemic therapy for advanced or recurrent endometrial cancer.

Table A. Chemotherapy.

Study	Drugs*	Doses	Schedule
Comparative studies (Randomized trials)			
Fleming, 2004 (11)	Doxorubicin + cisplatin	60 mg/m ² 50 mg/m ²	every 3 weeks
	Doxorubicin + cisplatin + paclitaxel	45 mg/m ² 50 mg/m ² 160 mg/m ²	
Aapro, 2003 (12)	doxorubicin	60 mg/m ²	every 4 weeks
	doxorubicin + cisplatin	60 mg/m ² 50 mg/m ²	
Fleming, 2000 [abstract] (15)	doxorubicin + cisplatin	60 mg/m ² 50 mg/m ²	every 3 weeks
	doxorubicin + paclitaxel	50 mg/m ² 150 mg/m ² over 24 hours	
Pawinski, 1999 (16)	cyclophosphamide	1200 mg/m ²	every 3 weeks
	ifosfamide	5g/m ²	
Thigpen, 1994 (7)	doxorubicin	60 mg/m ²	every 3 weeks
	doxorubicin + cyclophosphamide	60 mg/m ² 500 mg/m ²	
Thigpen, 1993 [abstract] (18)	doxorubicin	60 mg/m ²	every 3 weeks
	doxorubicin + cisplatin	60 mg/m ² 50 mg/m ²	
Edmonson, 1987 (19)	cisplatin	60 mg/m ²	every 3 weeks
	cyclophosphamide + doxorubicin + cisplatin	400 mg/m ² 40 mg/m ² 40 mg/m ²	every 4 weeks
Cohen, 1984 (20)	megestrol (oral) + melphalan (oral) + 5-fluorouracil	180 mg 7 mg/m ² 525 mg/m ²	daily for 8 weeks day 1-4 of 28 day 1-4 of 28
	megestrol (oral) + cyclophosphamide + doxorubicin + 5-fluorouracil	180 mg 400 mg/m ² 40 mg/m ² 400 mg/m ²	daily for 8 weeks day 1 of 21 day 1 of 21 day 1 of 21
Horton, 1982 (21)	megestrol (oral) + cyclophosphamide + doxorubicin	80 mg 400 mg/m ² 40 mg/m ²	three times daily day 1 of 28 day 1 of 28
	megestrol (oral) + cyclophosphamide + doxorubicin + 5-fluorouracil	80 mg 250 mg/m ² 30 mg/m ² 300 mg/m ²	three times daily day 1 of 28 day 1 of 28 days 1-3 of 28
Horton, 1978 (22)	doxorubicin	50 mg/m ²	every 3 weeks
	cyclophosphamide	666 mg/m ²	

* intravenous unless noted otherwise

Table A. Chemotherapy (cont.).

Study	Drugs*	Doses	Schedule
Non-comparative studies (single-cohort)			
Muggia, 2002 (27)	liposomal doxorubicin	50 mg/m ²	every 4 weeks
Miller, 2002 (26)	topotecan	1.5 mg ² /day X 5 days	every 3 weeks
Scudder, 2001 [abstract] (28)	paclitaxel + carboplatin	175 mg/m ² over 3 hours area under the curve = 5	not reported
Dimopoulos, 2000 (29)	paclitaxel + cisplatin	175 mg/m ² over 3 hours 75 mg/m ²	every 3 weeks
Hall, 2000 [abstract] (30)	topotecan + cisplatin	0.75 mg ² /day X 5 days 50 mg/m ²	not reported
Moore, 1999 (31)	dactinomycin	2 mg/m ²	every 4 weeks
Poplin, 1999 (32)	etoposide (oral)	50 mg on days 1-21	every 4 weeks
Trudeau, 1999 [abstract] (33)	paclitaxel + cisplatin	135 mg/m ² over 24 hours 75 mg/m ²	every 3 weeks
Santoro, 1998 [abstract] (34)	carboplatin + vinorelbine	300 mg/m 25 mg/m ² on days 1 & 8	every 3 weeks
Lissoni, 1997 (35)	paclitaxel + cisplatin + epirubicin	175 mg/m ² over 3 hours 50 mg/m ² 70 mg/m ²	every 3 weeks
Price, 1997 (36)	paclitaxel + carboplatin	175 mg/m ² over 3 hours area under the curve = 5	every 4 weeks
Ball, 1996 (5)	paclitaxel	250 mg/m ² over 24 hours	every 3 weeks
Lissoni, 1996 (37)	paclitaxel	175 mg/m ² over 3 hours	every 3 weeks
Rose, 1996 (38)	etoposide (oral)	50 mg/m ² on days 1-21	every 4 weeks
Woo, 1996 (39)	paclitaxel	170 mg/m ² over 3 hours	every 3 weeks

* intravenous unless noted otherwise

Table B. Hormonal therapy.

Study	Drugs	Doses	Route	Schedule
Comparative studies (Randomized trials)				
Pandya, 2001 (23)	megestrol acetate	80 mg	oral	twice daily
	megestrol acetate + tamoxifen	80 mg 10 mg	oral	
Thigpen, 1999 (8)	medroxyprogesterone acetate	200 mg	Oral	Daily
	vs medroxyprogesterone acetate	1,000 mg	oral	Daily
Rendina, 1984 (24)	medroxyprogesterone acetate	1 g	intramuscular	weekly
	tamoxifen	20mg	oral	twice daily
Non-comparative studies (single-cohort)				
McMeekin, 2001 [abstract] (43)	LY353381	20 mg	oral	Daily
Sidhu, 2001 [abstract] (44)	letrozole	2.5 mg	oral	daily
Klijn, 2000 [abstract] (45)	LY353381	20 mg	oral	daily
Rose, 2000 (46)	anastrozole	1 mg	oral	daily
Lhomme, 1999 (47)	triptorelin	3.75 mg	intramuscular	every 4 weeks
Covens, 1997 (48)	leuprolide acetate	7.5 mg	intramuscular	every 4 weeks
Jeyarajah, 1996 (49)	leuprolide acetate	3.5 - 7.5 mg	intramuscular	monthly

Table C. Combined chemotherapy and hormonal therapy.

Study	Drugs	Doses	Route	Schedule
Ayoub, 1988 (25) (randomized trial)	cyclophosphamide	400 mg/m ²	intravenous	days 1 and 8 of 28
	+ doxorubicin	30 mg/m ²	intravenous	day 1 of 28
	+ 5-fluorouracil	400 mg/m ²	intravenous	days 1 and 8 of 28
	cyclophosphamide	400 mg/m ²	intravenous	days 1 and 8 of 28
	+ doxorubicin	30 mg/m ²	intravenous	day 1 of 28
	+ 5-fluorouracil	400 mg/m ²	intravenous	days 1 and 8 of 28
	+ medroxyprogesterone*	200 mg	oral	daily for 3 weeks*
	followed by tamoxifen*	20 mg	oral	daily for 3 weeks*

* medroxyprogesterone and tamoxifen were given sequentially for one year