Original Article

Chemotherapy for Endometrial Cancer: Survey of Practice among Thai Gynecologic Oncologists

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Objective: To assess practice of the Thai gynecologic oncologists on the use of chemotherapy for endometrial cancer (EMC).

Materials and Methods: The present study was a part of the Thai Gynecologic Cancer Society survey which collected data of practice on gynecologic cancer of the Thai gynecologic oncologists who were currently working in the country for at least one year. The web-based questionnaire was open for a response from August to October, 2019. This study retrieved data of chemotherapy for EMC regarding the type or regimen of chemotherapy, settings when chemotherapy was used of either first-, second-, third- or further-line, and also the setting when non-chemotherapy palliative treatment was used.

Results: Out of 258 gynecologic oncologists who met inclusion criteria, 169 responded to the questionnaire regarding chemotherapy use for EMC (65.5%). The duration of practice ranged from 1 to 42 years (median 5 years). More than 80% worked in government hospitals and tertiary-level hospitals. Paclitaxel/carboplatin (97.6%) was the most common first-line regimen whereas doxorubicin/cisplatin (75.2%) was most commonly used as a second-line chemotherapy regimen. Single-agent was more commonly used as third- or further-line drugs than combination regimens. Among the single agent, liposomal doxorubicin was the most common agent. Hormonal treatment was selected by 12.9% of the respondents as the third- or further-line treatment. Of note, 51.4% of respondents selected palliative treatment after failure from second-line chemotherapy especially when doxorubicin/cisplatin was used as the first-line drug.

Conclusion: Thai gynecologic oncologists used paclitaxel/carboplatin and doxorubicin/cisplatin regimens as the most common first- and second-line chemotherapy for EMC patients, respectively. Single-agent was commonly selected as third- or further-line of chemotherapy, with liposomal doxorubicin as the most common drug.

Keywords: Gynecologic oncologists, Endometrial cancer, Chemotherapy

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Chemotherapy (CMT) has had an increasing role in management for endometrial cancer (EMC). The drug which was originally used as a salvage treatment for advanced or recurrent diseases has been expanded as an adjuvant and neoadjuvant treatment.

Among several chemotherapeutic agents which had been extensively tested in EMC, the most common drugs which showed clinical activity included doxorubicin[(1)], cisplatin[(2,3)], carboplatin[(4,5)], and paclitaxel[(6-8)]. The response rates (RR) yielded from these drugs ranged from 3% to 43%. This wide range of efficacy may depend on many factors aside from the activity of the drug themselves, such as, histologic subtype and grade of tumor cell, setting when CMT is given (primary advanced disease or recurrence), previous exposure to other chemotherapeutic drugs, or other treatment before CMT.

These single chemotherapeutic agents which showed satisfactory efficacy were often used as a base in combination therapy. Combination drugs often yielded higher RR than a single drug[(9-11)]. Doublets regimens which showed significant higher RR than a single agent were doxorubicin plus cyclophosphamide or cisplatin, compared to doxorubicin alone[(9-11)]. The progression-free survival (PFS) could be demonstrated by some[(11)] and not the others[(9,10)]. Another doublet regimen of doxorubicin/ paclitaxel was also studied and found to have comparable efficacy in terms of RR, PFS, and overall survival (OS) with doxorubicin/cisplatin[(12)]. However, patients receiving doxorubicin/paclitaxel experienced higher toxicity requiring granulocyte-colony stimulating factor (G-CSF) support. Hence, doxorubicin/

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cisplatin was used as the most common CMT regimen in the past.

To date, the only chemotherapeutic regimen which had superior activity over other regimens was the triplet combination of doxorubicin/cisplatin/paclitaxel. Aside from higher RR and longer PFS, this 3-drug regimen also yielded longer OS[13]. Despite a definite superior activity of doxorubicin/cisplatin/paclitaxel regimen, it was uncommonly used in clinical practice due to its pronounced side effects of neuropathy and gastrointestinal toxicity. Paclitaxel/carboplatin, which showed excellent activity (high RRs of 40% to 87%) in many retrospectives or phase II studies[14-18], was later studied in comparison with doxorubicin/cisplatin/paclitaxel in a large trial[19]. The comparable efficacy of both regimens with lesser toxicity had probably led paclitaxel/carboplatin to become a common CMT use nowadays.

In the recurrent setting, the status of platinum sensitivity in EMC had not been well settled as it is in ovarian cancer. Nevertheless, few studies found platinum-free interval was an important prognostic indicator of response to second-line drug and survival in recurrent EMC[20-22]. Hence, platinum re-induction may have a certain role in EMC patients who had recurrence long after primary platinum treatment. Non-platinum drugs including targeted therapy have been tested and may be selectively used in those who had failed from prior platinum treatment.

With the evolution of CMT treatment in EMC, this survey study evaluated the type of CMT used in EMC as the first- or further-line treatment. The setting when palliative treatment was selected was also studied.

Materials and Methods

The present study on the practice of the Thai gynecologic oncologists regarding the type of CMT regimen for EMC patients was a part of the national cross-sectional survey project of the Thai Gynecologic Cancer Society (TGCS). An approval from the Ethics Committees for Human Research of each collaborating institution was obtained (COAs: Rajavithi Hospital, 104/2562; Faculty of Medicine Chiang Mai University, OBG-2562-06506; Faculty of Medicine Vajira Hospital, 097/2562). Details of inclusion/exclusion criteria and materials/methods were presented in the main report[23]. In brief, Thai gynecologic oncologists who had been practicing in this field for at least 1 year and currently practiced in the country at the time of this survey were invited to participate in the study. A self-administered questionnaire was opened for an on-line response via https://forms.gle/e1WsBLcX5jVsXVg G8 from August to October, 2019.

The questionnaire comprised of demographic data, problems related to work, and current clinical practice for cancers of the cervix, endometrium, and epithelial ovarian cancer in various aspects. The detail description of questions of each cancer was detailed and presented elsewhere. This study abstracted data of CMT used for endometrial cancer. Options of CMT and open-end questions about the type of CMT drugs/regimens used as first-, second-, third-, and further-line of treatment for endometrial cancer were queried. The option of palliative treatment was also queried in all settings.

Data were analyzed using SPSS statistical software, version 22 (IBM Corporation, Armonk, NY, USA). Descriptive data were summarized as numbers with the percentage. The sequence of CMT used in different settings was also presented.

Results

Out of 258 gynecologic oncologists who met inclusion criteria, 169 responded to the questions of CMT use. The mean age of the respondents was 41.1±8.25 years. The median duration of practice was 5 years (range 1 to 42 years). The majority (more than 80%) worked government hospitals and tertiary-level hospitals. Slightly more than half or 50.6% were involved in gynecologic oncology fellowship training.

Among several CMT regimens listed as options in the questionnaire, all reported paclitaxel with carboplatin (97.6%) or with cisplatin (2.4%) as the first-line drugs whereas doxorubicin/cisplatin was selected as the most common regimen in both second-and third-line settings (74.6% as second-line and 8.9% as third-line drugs). Paclitaxel/cisplatin was still used as high as 20% as second-line drugs and dropped to only 2.4% as third-line agents.

Palliative treatment was selected as an option after failing from first-line CMT in only a few and sharply increased to slightly more than half (51.2%) after the failure of second-line CMT. Other drugs were reported in over one-third (36.7%) either in third-or further-line of treatment.

Table 1. The chemotherapy regimens commonly used for endometrial cancer in different settings (n = 169)

Chemotherapy regimens/treatment in different settings	n (%)
First-line treatment	
Paclitaxel/carboplatin	165 (97.6)
Paclitaxel/cisplatin	4 (2.4)
Doxorubicin/cisplatin	-
Second-line treatment	
Paclitaxel/carboplatin	4 (2.4)
Paclitaxel/cisplatin	34 (20.1)
Doxorubicin/cisplatin	126 (74.6)
Palliative treatment	5 (2.9)
Third-line treatment	
Paclitaxel/carboplatin	1 (0.6)
Paclitaxel/cisplatin	4 (2.4)
Doxorubicin/cisplatin	15 (8.9)
Palliative treatment	87 (51.4)
Others*	62 (36.7)

One respondent may report one or more than 1 regimen
* Others included various drugs (see Table 2)

From 62 respondents who reported the use of various chemotherapeutic agents as third- or further line drugs (Table 2), majority selected single agent. The most common single drug reported was liposomal doxorubicin. Among a few who reported combined regimens, liposomal doxorubicin and paclitaxel were the 2 most common agents used in the combination regimens.

The authors assessed the shift or sequence of CMT use from first- to second- and third-line settings (Table 3). Among 165 respondents who selected paclitaxel/carboplatin as the first-line drugs, the majority used doxorubicin/cisplatin (75.2%) as second-line drugs or switched to paclitaxel/cisplatin (20.6%). On the contrary, among the 4 respondents who used paclitaxel/cisplatin as first-line drugs, 3 switched to doxorubicin/cisplatin or paclitaxel/carboplatin whereas another one provided palliative treatment.

Among the respondents who selected doxorubicin/cisplatin as a second-line drug, most (42.7% or 50.0%) switched to non-platinum CMT whereas approximately one-third (33% or 38%) of those who had received paclitaxel with carboplatin or cisplatin selected doxorubicin/cisplatin as the third-line drugs.

Table 2. Other chemotherapeutic agents used in third- or further-line of treatment for endometrial cancer patients

Chemotherapeutic agents	n (%*)
Single agent	
Liposomal doxorubicin	21 (33.9)
Doxorubicin	11 (17.7)
Hormone	8 (12.9)
Ifosfamide	7 (11.3)
Carboplatin	6 (9.7)
Paclitaxel	5 (8.1)
Gemcitabine	5 (8.1)
Topotecan	1 (1.6)
Etoposide	1 (1.6)
Combined agents	
Liposomal doxorubicin/carboplatin or paclitaxel	4 (6.5)
Paclitaxel/gemcitabine or ifosfamide	3 (4.8)
Docetaxel/gemcitabine	1 (1.6)

* Percentage obtained from 62 respondents who reported using other chemotherapeutic agents

Discussion

There had been no direct comparison between paclitaxel/carboplatin to other doublets especially doxorubicin/cisplatin which showed significant benefit over doxorubicin alone and had been commonly used as the backbone of CMT for EMC in the past[11]. However, this survey found almost all Thai gynecologic oncologists who responded reported paclitaxel/carboplatin as the first-line CMT for EMC. This might have been influenced by the indirect evidence from the large randomized controlled trial which found the comparable activity of paclitaxel/carboplatin and doxorubicin/cisplatin/paclitaxel which was the only regimen showing OS benefit over doxorubicin/cisplatin[19]. The PFS yielded from both regimens was 14 months with OS of 38 months and 32 months from paclitaxel/carboplatin and doxorubicin/cisplatin/paclitaxel, respectively[19]. With this comparable efficacy of the 2 drug regimens but with manageable toxicity and the familiarity of its use in ovarian cancer, paclitaxel/carboplatin had become the most common drug used in EMC among most gynecologic oncologists as evidenced in this survey.

Although few previous studies reported poor

Table 3. The sequence of chemotherapy regimens commonly used for endometrial cancer in different settings

First-line chemotherapy	n (%)	Third-line chemotherapy or treatment, n (%*)				
		Paclitaxel/ carboplatin n = 1	Paclitaxel/ cisplatin n = 4	Doxorubicin/ cisplatin n = 15	Others** n = 62	Palliative n = 87
Paclitaxel/carboplatin, n = 165						
Second-line						
Doxorubicin/cisplatin	124 (75.2)	-	4 (3.2)	-	53 (42.7)	67 (54.0)
Paclitaxel/cisplatin	34 (20.6)	-	-	13 (38.2)	7 (20.6)	14 (41.2)
Paclitaxel/carboplatin	3 (1.8)	1 (33.3)	-	1 (33.3)	1 (33.3)	-
Palliative treatment	4 (2.4)	-	-	-	-	4 (100.0)
Paclitaxel/cisplatin, n = 4						
Second-line						
Doxorubicin/cisplatin	2 (50.0)	-	-	-	1 (50.0)	1 (50.0)
Paclitaxel/carboplatin	1 (25.0)	-	-	1 (100.0)	-	-
Palliative treatment	1 (25.0)	-	-	-	-	1 (100.0)

* Percentage obtained among the type of third-line regimen/treatment according to second-line regimen/treatment
** Others included various regimens of drugs

activity of doxorubicin as a second-line CMT after paclitaxel/carboplatin with either no response[24] or a stable disease as the best response[25], doxorubicin/cisplatin was still selected as the most common second-line drugs in this survey (75%). This was probably based on its proven efficacy in previous studies and familiarity with its use in the past[11]. Moreover, not many effective CMT regimens for EMC are available in clinical practice. Although other doublets of docetaxel/cisplatin or docetaxel/carboplatin were reported to have similar activity with paclitaxel/ carboplatin[26], no respondents in this survey selected them as second-line drugs at all. Few possible reasons for this finding were the respondents might be cautious about the cross-resistance of taxane and platinum drugs after paclitaxel/carboplatin. Furthermore, the hematologic toxicity of docetaxel may not be well tolerated among EMC patients who were generally old and who had been treated with prior CMT and/or radiation therapy.

The present study still found paclitaxel/cisplatin being selected as high as 20% as the second-line drugs in place of paclitaxel/carboplatin. This might partly be due to the question in this survey that did not specify a certain scenario especially the treatment- or platinum-free interval when second-line drugs were required. Similar to ovarian cancer patients, the EMC patients with long platinum- or treatment-free intervals were associated with better treatment outcomes and survival[20-22]. This may also influence the regimen of second-line CMT. The gynecologic oncologist would rather consider re-induction with a platinum drug in the second setting among the patients who had long platinum treatment-free intervals similar to that used in ovarian cancer despite data from the previous study did not find any impact of second-line therapy (platinum vs. non-platinum) on survival regardless of the primary CMT regimen (platinum-based or other CMT)[20].

Few and slightly more than half of the respondents selected palliative treatment as an option after failing first- and second-line CMT, respectively. Few possible reasons were explored. First, only a few drugs had a definite activity to justify its use in clinical practice especially when the diseases were primarily resistant to treatment or had a short treatment-free interval. Data from the previous study showed none of the second-line CMT regimens (platinum or non-platinum) was effective when the diseases recurred within 6 months after first-line treatment[21]. Second, the EMC patients were generally old, accompanyed with several co-morbidities resulting in suboptimal performance. They might or were anticipated to be unable to tolerate further treatment. Nevertheless, slightly more than one-third still pursued the use of other drugs (Table 2). This decision rather depended on many factors aside from the diseases' features e.g. performance status of the patients, preference of the patient and her caretaker, experience or preference of the gynecologic oncologist, financial status and reimbursement problem especially when most of these other third-line drugs are not generally covered in the national essential drug lists.

Of note, no respondents selected hormonal therapy as the first- or second-line drug for EMC treatment at all. Hormonal treatment has activity in EMC because of its nature as hormone-related cancer. Data showed better activity of hormones in tumors of endometrioid type, low grade, and hormonal receptor expression[27,28]. These may limit its clinical use because most advanced or recurrent cancers frequently were aggressive with non-endometrioid type or high grade with low hormone receptor expression. Furthermore, the respondents might be more appeallng to use CMT which has cytotoxic (with higher efficacy) and have been more commonly used in later years. Nevertheless, the hormone which is a cytostatic agent was selected as an option as the third-line drug in approximately 13%. This may be considered as palliative treatment because the respondents may still want to provide some treatment with minimal side effects to the patients who had failed from chemotherapy.

In summary, this survey found paclitaxel/carboplatin as the most common first-line CMT used for EMC patients. Doxorubicin/cisplatin, which was the most common drug used in the past, was instead selected as the most common second-line agents. The triplet regimen of doxorubicin/cisplatin/paclitaxel, which had definite activity in EMC from research data, was not used in the clinical practice of the Thai gynecologic oncologists at all. Hormonal therapy which theoretically had an activity for EMC was also selected as third- or further line treatment by only a few of the gynecologic oncologists. Several other drugs were also reported as third- or further-line drugs in various percentages, with liposomal doxorubicin as the most frequently selected CMT.

What is already known on this topic?

There were evidence-based data of chemotherapy for advanced or recurrent endometrial cancer showing combination chemotherapy of more drugs were more effective than single or fewer drugs. Cisplatin and doxorubicin which showed superior survival benefit over cisplatin alone had been used for quite a while. Although the combination of cisplatin, doxorubicin, and cyclophosphamide also showed survival benefit over cisplatin and doxorubicin, the triplet regimen was uncommonly used in clinical practice due to its toxicity. Paclitaxel and carboplatin were later found to have comparable efficacy with this triplet regimen, so it was commonly used in current practice worldwide including in Thailand. However, the sequence of chemotherapy use in different settings after failure from the first-line drugs was not clear.

What this study adds?

The practice of chemotherapy use among the Thai gynecologic oncologists was in harmony that paclitaxel with carboplatin and doxorubicin with cisplatin were the most common first- and second-line chemotherapy regimens for endometrial cancer. However, various agents were reported as the third- or further-line chemotherapy. Slightly more than half selected palliative treatment as an option in the third- or further-line of treatment instead of additional chemotherapy.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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การให้ยาเคมีบำบัดสำหรับมะเร็งเยื่อบุโพรงมดลูก: การสำรวจแนวปฏิบัติของแพทย์มะเร็งนรีเวชไทย

ศรัญญา ชาญพานิชกิจโชติ, ปิยะวรรณ ปริยวาทีกุล, ฉลอง ชีวเกรียงไกร, ศิริวรรณ ตั้งจิตกมล, สมาคมมะเร็งนรีเวชไทย

วัตถุประสงค์: เพื่อศึกษาแนวปฏิบัติของแพทย์มะเร็งวิทยานรีเวชไทยเกี่ยวกับการให้ยาเคมีบำบัดสำหรับมะเร็งเยื่อบุโพรงมดลูก

วัสดุและวิธีการ: รายงานนี้เป็นส่วนหนึ่งของการศึกษาโดยสมาคมมะเร็งนรีเวชไทยที่รวบรวมข้อมูลของแนวทางปฏิบัติในการรักษามะเร็งนรีเวชจากแบบสอบถามทางเว็บที่เปิดให้แพทย์มะเร็งนรีเวชไทยที่ปฏิบัติงานในประเทศมาแล้วอย่างน้อย 1 ปี ตอบคำถาม ตั้งแต่เดือนสิงหาคมถึงเดือนตุลาคม พ.ศ. 2562 รายงานนี้ทำการวิเคราะห์ข้อมูลของการให้ยาเคมีบำบัด ได้แก่ ชนิดหรือสูตรของยา ลำดับที่ใช้ยา ได้แก่ ลำดับแรก ลำดับที่ 2 ลำดับที่ 3 และลำดับถัดไป รวมทั้งการให้การรักษาแบบประคับประคองโดยไม่ใช้ยาเคมีบำบัด

ผลการศึกษา: จากผู้ตอบแบบสอบถามทั้งหมดที่ตรงตามเกณฑ์การคัดเข้า 258 ราย มีผู้ตอบข้อที่เกี่ยวกับยาเคมีบำบัด 169 ราย คิดเป็น ร้อยละ 65.5 มีอายุเฉลี่ย 41.1±8.25 ปี ค่ามัธยฐานของระยะเวลาการทำงานเท่ากับ 5 ปี (พิสัย 1 ถึง 42 ปี) ส่วนใหญ่ (มากกว่าร้อยละ 80) ทำงานในโรงพยาบาลรัฐและโรงพยาบาล ระดับตติยภูมิประมาณครึ่งหนึ่ง (ร้อยละ 50.6) ทำงานในโรงพยาบาลที่มีการฝึกอบรมแพทย์ประจำบ้านอนุสาขามะเร็งวิทยานรีเวช ยาเคมีบำบัดสูตรที่ใช้เป็นลำดับแรกและลำดับที่ 2 ที่ใช้บ่อยที่สุด ได้แก่ paclitaxel/carboplatin (ร้อยละ 97.6) และ doxorubicin/cisplatin (ร้อยละ 75.2) ตามลำดับ ยาเคมีบำบัดสูตรที่ใช้เป็นลำดับที่ 3 และลำดับถัดไปมักเป็นยาชนิดเดี่ยว โดย liposomal doxorubicin เป็นชนิดที่ใช้บ่อยที่สุด มีการใช้ยาฮอร์โมนเพียงร้อยละ 12.9 ของการรักษาในลำดับที่ 3 และลำดับถัดไป ข้อสังเกตที่พบคือ ร้อยละ 51.4 ของผู้ตอบแบบสอบถามเลือกการรักษาแบบประคับประคองหลังจากที่ล้มเหลวจากยาเคมีบำบัดลำดับที่ 2 โดยเฉพาะอย่างยิ่งเมื่อมีการใช้ doxorubicin/cisplatin เป็นยาลำดับแรก

สรุป: ยาเคมีบำบัดสูตรที่ใช้บ่อยที่สุดเป็นลำดับแรกและลำดับที่ 2 ได้แก่ paclitaxel/carboplatin และ doxorubicin/cisplatin ตามลำดับ ยาเคมีบำบัดในลำดับที่ 3 และลำดับถัดไปมักเป็นยาเดี่ยวโดยมีการใช้ liposomal doxorubicin บ่อยที่สุด