Modulated electro-hyperthermia with weekly paclitaxel or cisplatin in patients with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma: The KGOG 3030 trial

KIDONG KIM[1], JAE-HOON KIM[2], SEUNG CHEOL KIM[3], YONG BEOM KIM[1,4], BYUNG-HO NAM[5], JAE HONG NO[1], HANBYOUL CHO[2], WOONG JU[6], DONG HOON SUH[1] and YUN HWAN KIM[3]

[1]Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnami, Gyeonggi 13620; [2]Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul 06273; [3]Department of Obstetrics and Gynecology, Ewha Womans University Mokdong Hospital, Seoul 07985; [4]Department of Obstetrics and Gynecology, College of Medicine, Seoul National University, Seoul 03080; [5]Herings Co., Ltd., Seoul 06144; [6]Department of Obstetrics and Gynecology, College of Medicine, Ewha Womans University, Seoul 03760, Republic of Korea

Received January 29, 2021; Accepted April 28, 2021

DOI: 10.3892/etm.2021.10219

Abstract. The present study (KGOG 3030) aimed to evaluate the safety of modulated electro-hyperthermia (mEHT) therapy with weekly administration of paclitaxel or cisplatin in female patients with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. A total of 12 patients were randomized into the paclitaxel or cisplatin arm at a 1:1 ratio. Patients received weekly administration of paclitaxel (70 mg/m^2) or cisplatin (40 mg/m^2) intravenously on days 1, 8 and 15, and underwent mEHT therapy for 1 h on days 1, 4, 8, 11, 15, 18, 21 and 24 for each 4-week cycle. The primary endpoint was the occurrence of dose-limiting toxicity (DLT). The secondary endpoints were treatment-emergent adverse events (TEAEs), objective response rate, carbohydrate antigen 125 (CA125) response rate, progression-free survival (PFS) and overall survival (OS). In total, 16 patients were recruited, but four patients dropped out. None of the 12 remaining patients (6 each in the two arms) experienced DLT. Overall, 0 and 4 grade 3 TEAEs (anemia, nausea, neutrophil count decreased and platelet count decreased) occurred in the paclitaxel and cisplatin arm, respectively. Furthermore, one confirmed partial response and two CA125 responses were observed in the cisplatin arm. The median PFS time in the paclitaxel and cisplatin arms was 3.0 months (range, 1.7-4.6 months) and 6.8 months (range, 3.9-11.8 months), respectively, while the median OS time was 11.5 months (range, 8.4-28.8+ months) and not reached (range, 3.9-38.5+ months), respectively. In conclusion, mEHT therapy with weekly paclitaxel or cisplatin appeared safe and warrants further investigation. The present trial was registered with www.clinicaltrials.gov on January 22, 2015 (trial registration no. NCT02344095).

Correspondence to: Dr Yong Beom Kim, Department of Obstetrics and Gynecology, College of Medicine, Seoul National University, 103 Daehak-ro, Jongno, Seoul 03080, Republic of Korea
E-mail: ybkimlh@snubh.org

Key words: cisplatin, induced hyperthermia, ovarian epithelial carcinoma, paclitaxel, toxicity

Introduction

Recurrent ovarian cancer is incurable and, accordingly, has poor prognosis. In a study analyzing survival data from clinical trials of ovarian cancer, the median overall survival (OS) after the first, second, third, fourth and fifth recurrence was 17.6, 11.3, 8.9, 6.2 and 5.0 months, respectively (1). Therefore, novel treatment options are urgently required for such patients. Radiofrequency hyperthermia (RFH) therapy involves heating of the body using radiofrequency energy. While it has been applied for the treatment of different cancer types, its efficacy remains conflicting. For instance, in a randomized trial of 73 patients with advanced ovarian cancer, those who received chemotherapy with RFH achieved better tumor remission rates than those who received chemotherapy alone (2). However, in a randomized trial of patients with cervical cancer, there was no significant difference in survival between those who received RFH with radiotherapy and those who received radiotherapy alone. In addition, acute toxicity was significantly worse in the RFH plus radiotherapy arm (3).

Modulated electro-hyperthermia (mEHT) is a type of RFH that uses impedance coupling with amplitude-modulated 13.56 MHz carrier radiofrequency (4). Similar to conventional RFH, mEHT is usually administered for 60 min, 1-3 times per week (3,5-7). However, unlike conventional RFH, the energy of radiofrequency is selectively absorbed by the tumor cells in mEHT (8). In addition, an *in vitro* study reported

that the cellular response to mEHT is different from that to conventional RFH. Specifically, in contrast to conventional RFH, mEHT activates caspase-dependent pathways and induces apoptosis (9). Therefore, it was hypothesized that the oncologic effect of mEHT may be different from that of conventional RFH.

To the best of our knowledge, only 3 trials investigating the effects of mEHT therapy on cancer have been published to date. Although the trials were on different cancers, the results all suggested that the addition of mEHT was beneficial for achieving a higher response rate (5) and better local control (6) than conventional treatments and was highly feasible (7). However, evidence on the usefulness and safety of mEHT combined with chemotherapy in the treatment of ovarian cancer is currently lacking (10). Thus, the present study aimed to evaluate the safety of mEHT therapy with weekly paclitaxel or cisplatin administration in females with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma.

Materials and methods

Trial design and randomization. The present trial (KGOG 3030) was a phase 1 trial with 1 dose level performed at three tertiary hospitals (Seoul National University Bundang Hospital, Seongnam, Gyeonggi; Gangnam Severance Hospital, Seoul; Ewha Womans University Mokdong Hospital, Seoul) in the Republic of Korea between February 2015 and November 2017. The study was conducted according to the tenets of the Declaration of Helsinki and its later amendments, and the protocol was approved by the Institutional Review Board (IRB) of each hospital (Seoul National University Bundang Hospital IRB, approval no. E-1407/258-001, approval date 17th Sep 2014; Yonsei University Gangnam Severance Hospital IRB, approval no. 3-2014-0272, approval date 14th January 2015; Ewha Womans University Medical Center IRB, approval no. EUMC 2014-09-009, approval date 1st December 2014) and registered at www.clinicaltrials.gov (on January 22, 2015; registration no. NCT02344095). Written informed consent was obtained from all subjects. The present study was reported in line with the Consolidated Standards of Reporting Trials guidelines (11).

There is already a widely used protocol for mEHT therapy and numerous cases in which mEHT therapy was combined with various chemotherapy modalities were encountered in our clinical practice. Therefore, the widely used protocol for mEHT therapy (1 h; 2 sessions per week; maximum energy, 140 W) (10) was adopted. In addition, it was decided not to test several dose levels of chemotherapy and adopt a 3+3 design with only 1 dose level (70 mg/m^2 for paclitaxel, 40 mg/m^2 for cisplatin). Specifically, 3 patients were enrolled and underwent therapy with a dose level of chemotherapy plus mEHT. If dose-limiting toxicity (DLT) was observed in <2 of 3 patients, 3 more patients were enrolled. If DLT occurred in <2 of 6 patients, it was concluded that the dose was safe enough for use in a further investigation. There was no dose escalation or de-escalation. Therefore, the anticipated number of patients was 12 (6 in each arm).

The optimal chemotherapy drug to be combined with mEHT therapy in recurrent ovarian cancer has remained undetermined. *In vitro* studies suggested that hyperthermia potentiates the cytotoxic effects of cisplatin (12,13). Furthermore, weekly paclitaxel administration is an effective regimen in recurrent ovarian cancer (14). After a thorough review of the literature and discussion, paclitaxel and cisplatin were selected (12-14). To determine which drug should be selected for further investigation at the completion of the present trial, both the paclitaxel and cisplatin arms were launched and compared using randomization. Patients were randomized into the paclitaxel arm or the cisplatin arm at a 1:1 ratio using block randomization with 'hospital' as a stratification factor. Randomization and notification of results were performed by the independent data center and the randomization result was not concealed.

Eligibility and intervention. The inclusion criteria were as follows: i) Recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma; ii) tumor evaluable with radiologic study or serum carbohydrate antigen (CA)125; and iii) Eastern Cooperative Oncology Group performance status score (15) of 0-2. The exclusion criteria were as follows: i) Tumor located in previously irradiated area; ii) brain metastasis; iii) residual neurotoxicity or history of severe neurotoxicity; iv) hypersensitivity to paclitaxel or cisplatin; and v) pacemaker or metal implants. The number of previous chemotherapy regimens was limited to <3 at initiation. However, due to slow accrual, the limit was changed to <4 in August 2015 and was removed in July 2016.

Patients in the paclitaxel arm received 4 cycles of mEHT therapy with weekly paclitaxel chemotherapy, with each cycle lasting 4 weeks. After steroids and anti-histamines were administered to prevent infusion reactions, 70 mg/m^2 of paclitaxel was intravenously infused for 1 h on days 1, 8 and 15 every 4 weeks. Within 3 h of completion of paclitaxel infusion, mEHT therapy was initiated. The mEHT therapy was performed 2 times weekly (days 1, 4, 8, 11, 15, 18, 21 and 24 per cycle) using an EHY 2000 plus device (Oncotherm GmbH) and each mEHT therapy session lasted 60 min. During the mEHT therapy, patients were placed in a supine position and a 30-cm diameter circular mEHT electrode was attached to the abdominal wall over the tumor. No precise targeting of the tumor was performed. Starting from 60 W, energy was gradually increased to 140 W. If the patient felt hot or had any discomfort, the energy was decreased to the previous level and then maintained at that level throughout the duration of the session. When tumors were present in the abdomen and chest area, mEHT therapy was performed sequentially (starting at the abdomen and then the chest).

Patients in the cisplatin arm received 4 cycles of mEHT therapy plus weekly cisplatin chemotherapy, with each cycle lasting 4 weeks; 40 mg/m^2 of cisplatin was intravenously infused for 1 h on days 1, 8 and 15 every 4 weeks. The mEHT therapy protocol was the same as that for the paclitaxel arm.

Endpoints. The primary endpoint was the occurrence of DLT from enrollment to fourth cycle completion in evaluable patients of each arm. DLT was defined as the occurrence of any of the following: i) Neutropenic fever requiring inotropics or intensive care unit admission; ii) hematologic toxicity not recovered to grade 1 or 2 within 3 weeks (except anemia); iii) non-hematologic toxicity not recovered to grade 1 or 2 within 3 weeks (except

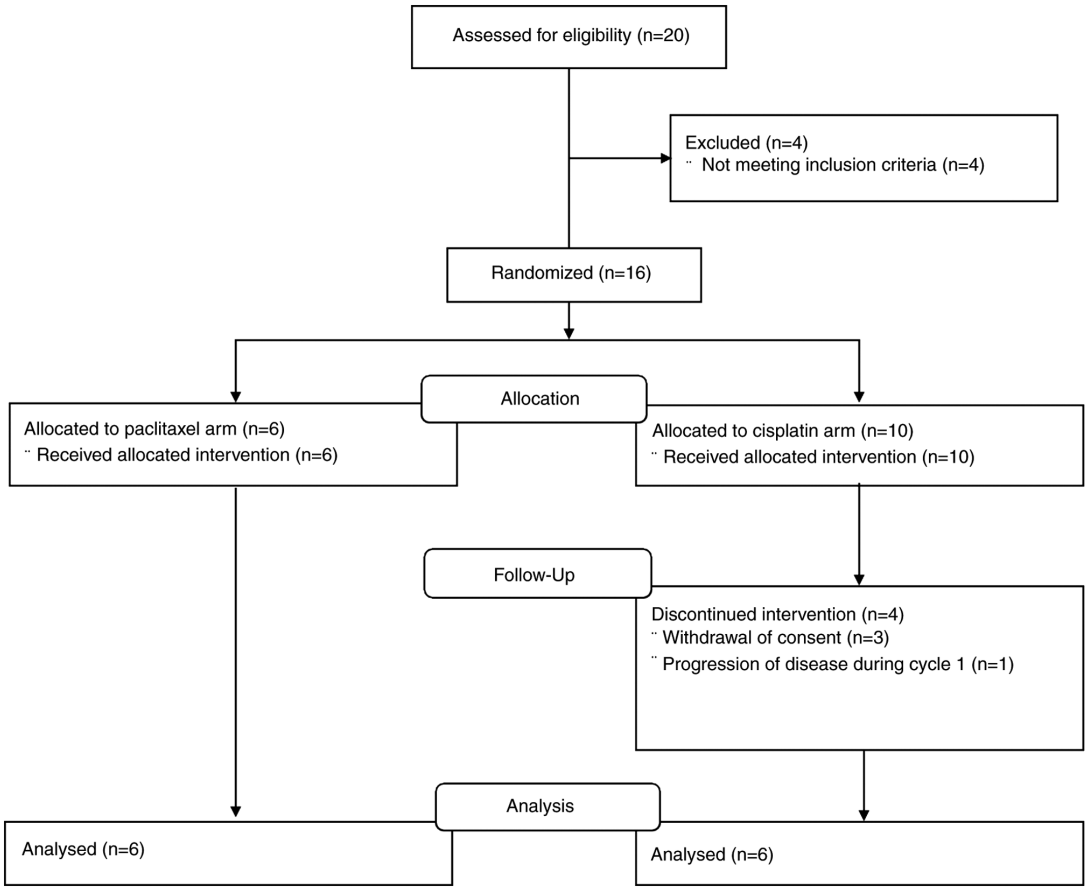

Figure 1. Flowchart depicting the movement of patients throughout the present trial.

alopecia); and iv) death. Evaluable patients were defined as patients who completed the second cycle.

The secondary endpoints were safety and preliminary efficacy. Safety was measured according to the type, grade and incidence of treatment-emergent adverse events (TEAEs) evaluated using the Common Terminology Criteria for Adverse Events version 4.0 (16). The efficacy endpoints were objective response rate in patients with measurable disease as evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (17), CA125 response rate in patients with elevated baseline CA125, progression-free survival (PFS) and OS. The CA125 response was defined as a decrease of >50% from the baseline with confirming repeat test results. During treatment, physical examination and CA125 test were performed every cycle. After treatment was completed, patients were followed up every 3 months until death. CA125 and imaging tests were performed at the discretion of the physician

Statistical analysis. All statistical analyses were performed using SPSS version 25 (IBM Corp.). Continuous variables were presented as the median and range. Categorical variables were presented as counts and percentages. PFS and OS were estimated using the Kaplan-Meier method.

Results

Baseline characteristics. In total, 16 patients were recruited for the present study. A flowchart depicting the movement of the patients throughout the study is provided in Fig. 1. Of 16 patients, four patients in the cisplatin arm did not complete the first cycle and were not evaluable. The time-point and reasons for treatment discontinuation of the 4 patients were as follows: Patient 1 (prior to cycle 1, withdrawal of consent), patient 2 (cycle 1 day 1, withdrawal of consent), patient 3 (cycle 1 day 15, clinical deterioration due to presumed cancer progression) and patient 4 (cycle 1 day 8, withdrawal of consent). No TEAEs of grade 3 or above were observed in the 4 patients. The 4 patients were excluded from the efficacy and safety analysis according to the protocol.

The baseline characteristics of the 12 evaluable patients are summarized in Table I. The median age was 64 years and the high-grade serous type was the most common histological type. The number of previous chemotherapy regimens ranged from 1 to 5 and most of patients were platinum-resistant or refractory.

Safety. None of the 12 evaluable patients experienced DLT. No severe TEAE occurred in the paclitaxel arm. The common TEAEs were constipation, dyspepsia, headache and neutropenia. A total of, four grade-3 TEAEs occurred in the cisplatin arm. These were grade-3 anemia (n=1), nausea (n=1), neutropenia (n=1) and thrombocytopenia (n=1). The common TEAEs were neutropenia and nausea. TEAEs according to type and grade in the paclitaxel and cisplatin arms are summarized in Tables II and III, respectively.

Table I. Baseline characteristics of the patients.

Variable	Paclitaxel + mEHT (n=6)	Cisplatin + mEHT (n=6)
Age, years	67 (53-71)	61 (56-72)
Body height, cm	155 (143-163)	153 (149-156)
Body weight, kg	60 (50-64)	55 (47-86)
Origin of cancer		
Ovary	5 (83)	4 (67)
Peritoneal	1 (17)	2 (33)
FIGO stage		
3	4 (67)	5 (83)
4	2 (33)	1 (17)
Histologic type		
High-grade serous	4 (67)	5 (83)
Clear cell	1 (17)	0 (0)
Low-grade serous	0 (0)	1 (17)
Carcinosarcoma	1 (17)	0 (0)
Number of previous regimens	2 (1-4)	2 (1-5)
Treatment-free interval from previous treatment, months	5 (1-16)	6 (0-27)
Sensitivity to platinum		
Sensitive	2 (33)	1 (17)
Resistant	2 (33)	4 (67)
Refractory	2 (33)	1 (17)

Values are expressed as the median (range) or n (%). mEHT, modulated electro-hyperthermia; FIGO, International Federation of Gynecology and Obstetrics.

Table II. Treatment-emergent adverse events in the paclitaxel arm.

Type	Grade 1	Grade 2	Sum
Abdominal distension	1	0	1
Abdominal pain	0	1	1
Alopecia	1	0	1
Anorexia	0	1	1
Constipation	1	1	2
Creatinine increased	0	1	1
Dysarthria	0	1	1
Dyspepsia	2	0	2
Dyspnea	0	1	1
Fatigue	1	0	1
Flank pain	0	1	1
Headache	2	1	3
Hyperkalemia	1	0	1
Hypocalcemia	1	0	1
Neutrophil count decreased	0	2	2
Pain	1	0	1
Peripheral sensory neuropathy	0	1	1
Productive cough	1	0	1
Toothache	0	1	1
Tremor	0	1	1
Wound complication	1	0	1
Sum	13	13	26

Patients who experienced multiple treatment-emergent adverse events were counted more than one time.

Efficacy. Of the 12 patients, 9 patients (5 in the paclitaxel arm, 4 in the cisplatin arm) had measurable disease at baseline. Of the 9 patients, 1 confirmed partial response was observed in the cisplatin arm (platinum-resistant, high-grade serous). The duration of response was 4 months. Furthermore, 9 of the 12 patients (4 in the paclitaxel arm, 5 in the cisplatin arm) had elevated baseline CA125 levels. Among them, 2 CA125 responses (2 in the cisplatin arm, both were platinum-resistant, high-grade serous) were observed. The duration of response was 4 and 10 months. Progression was observed in all patients. The median PFS in the paclitaxel and cisplatin arms was 3.0 months (range, 1.7-4.6 months) and 6.8 months (range, 3.9-11.8 months), respectively. At the cut-off of September 12, 2018, 5 of the 12 patients had died (4 in the paclitaxel arm, 1 in the cisplatin arm). The median OS in the paclitaxel and cisplatin arms was 11.5 months (range, 8.4-28.8+ months) and not reached (range, 3.9-38.5+ months), respectively (data not shown).

Discussion

In a previous study, chemotherapy combined with conventional RFH was reported to be more effective than chemotherapy alone for the treatment of advanced ovarian cancer (2). However, to the best of our knowledge, no previous study has examined the efficacy and safety of chemotherapy combined with mEHT for ovarian cancer. Therefore, the present study is novel and it is the first to examine the safety and efficacy of chemotherapy combined with mEHT for the treatment of ovarian cancer.

Table III. Treatment-emergent adverse events in the cisplatin arm.

Type	Grade 1	Grade 2	Grade 3	Sum
Abdominal pain	1	1	0	2
Anemia	0	0	1	1
Anorexia	0	1	0	1
Back pain	1	1	0	2
Dizziness	0	1	0	1
Dry mouth	0	1	0	1
Dyspepsia	1	0	0	1
Edema face	1	0	0	1
Fatigue	1	0	0	1
Gastrointestinal pain	1	0	0	1
Headache	2	0	0	2
Mucositis oral	1	0	0	1
Nausea	2	1	1	4
Neutrophil count decreased	2	2	1	5
Periodontal disease	1	0	0	1
Peripheral sensory neuropathy	1	1	0	2
Platelet count decreased	0	1	1	2
Productive cough	1	0	0	1
Skin and subcutaneous tissue disorders-others	1	0	0	1
Skin hyperpigmentation	0	1	0	1
Superficial thrombophlebitis	0	1	0	1
Telangiectasia	1	0	0	1
Vomiting	1	0	0	1
Sum	19	12	4	35

Patients who experienced multiple treatment-emergent adverse events were counted more than one time.

The results of the present phase 1 trial indicated that mEHT therapy combined with weekly chemotherapy is safe enough to proceed to be investigated in further clinical trials. Specifically, no DLT occurred in both the paclitaxel and cisplatin arms, and only 4 grade 3 TEAEs were observed. Therefore, both modalities appeared tolerable. The safety of RFH therapy combined with chemotherapy has been reported in previous studies. In a trial on RFH therapy combined with weekly docetaxel in patients with locally advanced non-small cell lung cancer, grade 3 or 4 neutropenia occurred in only 24% of the patients (18). In a randomized trial comparing RFH plus chemotherapy with chemotherapy alone in advanced ovarian cancer, toxicity was similar between arms (2). Collectively, these findings and the results of the current trial indicated that mEHT therapy may be safely combined with chemotherapy.

To the best of our knowledge, no study has reported superiority of RFH with chemotherapy over chemotherapy alone in the treatment of platinum-resistant ovarian cancer. In the present study, mEHT therapy combined with weekly chemotherapy showed intermediate efficacy. Of the 9 patients, only 1 partial response was confirmed (response rate, 11%). Response based on CA125 was observed in 2 of 9 patients (22%). All responses were observed in the cisplatin arm. Specifically, in the cisplatin arm, 1 of 4 patients with measurable disease responded (response rate, 25%), and 2 of 5 patients with elevated baseline CA125 levels exhibited CA125 response (40%). This suggests that when combined with mEHT, while cisplatin appeared to be slightly more toxic, it was also more efficacious than paclitaxel. Supporting the present results, previous cell line studies suggested that hyperthermia enhanced the cytotoxicity of cisplatin but inhibited that of paclitaxel (12,13,19,20). Thus, mEHT therapy combined with weekly cisplatin administration should be considered a regimen for further investigation.

Of note, one radiologically confirmed partial response and two CA125 responses were observed in the present study in platinum-resistant patients in the cisplatin arm. A single-arm trial testing the efficacy of oral etoposide plus weekly cisplatin reported a 46% response rate in platinum-resistant patients and high-dose intensity achieved by weekly dosing was suggested as a mechanism for overcoming platinum resistance (21). Both weekly dosing and synergy between cisplatin and mEHT may be the mechanisms accountable for the responses observed in the present study.

The present study has certain limitations. First, the safety of therapy was determined using data from only 6 patients per group. Therefore, the safety of therapy should be considered preliminary and only be used to make decisions for further investigations. As another limitation, the present trial did not test multiple dose levels and did not investigate the

maximum tolerated dose of mEHT. This may have resulted in undertreatment. However, a recent study indicated that the optimal dose of mEHT in the treatment of recurrent ovarian cancer is 150 W for 1 h (7), and that dose is similar to the energy used in the present study (140 W). Nevertheless, a strength of the present study was that it was a multi-center study.

Our group is planning a subsequent phase 2 trial, testing the efficacy and safety of weekly cisplatin plus mEHT for recurrent ovarian cancer, and efficacy will be evaluated in platinum-sensitive and -resistant subgroups separately.

In conclusion, mEHT therapy with weekly paclitaxel or cisplatin appeared safe in female patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, thus warranting further investigation in clinical trials.

Acknowledgements

The abstract of this study was previously e-published for presentation at the 2019 Annual Meeting of the American Society of Clinical Oncology (Chicago, USA). The authors would like to thank Ms. EunSun Park (Clinical Research Nurse, Gangnam Severance Hospital) and Ms. Moon Kyoung Bae (Clinical Research Nurse, Ewha Womans University Medical Center) (both Seoul, South Korea) for conducting this trial. Professor Soyeon Ahn (Division of Statistics, Medical Research Collaborating Center, Seoul National University Bundang Hospital, Seongnam, South Korea), Professor Jae Yong Chung (Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, South Korea) and Professor Seok Ju Seong (Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, Seoul, South Korea) contributed to this study as Data Safety Monitoring Board members.

Funding

This work was supported by a grant (grant no. E-1407/258-001) from Hospicare Co. Ltd. (Seoul, Republic of Korea). The funder was not involved in the study design, writing of the manuscript and the decision to submit the manuscript for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KK contributed to protocol/project development, follow-up/examination/treatment of the patients, data collection or management, data analysis and manuscript writing/editing. YBK and BHN contributed to protocol/project development, data collection or management and manuscript writing/editing. JHK, SCK, JHN, HC, WJ, DHS and YHK contributed to follow-up/examination/treatment of the patients, data collection or management and manuscript writing/editing. KK and DHS checked and approved the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was performed according to the tenets of the Declaration of Helsinki and its later amendments, and the protocol was approved by the IRB of each hospital [Seoul National University Bundang Hospital IRB (Seongnam, South Korea), approval no. E-1407/258-001, approval date 17th Sep 2014; Yonsei University Gangnam Severance Hospital IRB (Seoul, South Korea), approval no. 3-2014-0272, approval date 14th January 2015; Ewha Womans University Medical Center IRB (Seoul, South Korea), approval no. EUMC 2014-09-009, approval date 1st December 2014]. Written informed consent was obtained from all individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, Ray-Coquard I, Sehouli J, Harter P, du Bois A; AGO and GINECO study group: The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol 23: 2605-2612, 2012.
2. Li Z, Sun Q, Huang X, Zhang J, Hao J, Li Y and Zhang S: The efficacy of radiofrequency hyperthermia combined with chemotherapy in the treatment of advanced ovarian cancer. Open Med (Wars) 13: 83-89, 2018.
3. Vasanthan A, Mitsumori M, Park JH, Zhi-Fan Z, Yu-Bin Z, Oliynychenko P, Tatsuzaki H, Tanaka Y and Hiraoka M: Regional hyperthermia combined with radiotherapy for uterine cervical cancers: A multi-institutional prospective randomized trial of the international atomic energy agency. Int J Radiat Oncol Biol Phys 61: 145-153, 2005.
4. Yang W, Han GH, Shin HY, Lee EJ, Cho H, Chay DB and Kim JH: Combined treatment with modulated electro-hyperthermia and an autophagy inhibitor effectively inhibit ovarian and cervical cancer growth. Int J Hyperthermia 36: 9-20, 2019.
5. Lee SY, Lee NR, Cho DH and Kim JS: Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation. Oncol Lett 14: 73-78, 2017.
6. Minnaar CA, Kotzen JA, Ayeni OA, Naidoo T, Tunmer M, Sharma V, Vangu MDT and Baeyens A: The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: Early results from a phase III randomised controlled trial. PLoS One 14: e0217894, 2019.
7. Yoo HJ, Lim MC, Seo SS, Kang S, Joo J and Park SY: Phase I/II clinical trial of modulated electro-hyperthermia treatment in patients with relapsed, refractory or progressive heavily treated ovarian cancer. Jpn J Clin Oncol 49: 832-838, 2019.
8. Hegyi G, Szigeti GP and Szász A: Hyperthermia versus oncothermia: Cellular effects in complementary cancer therapy. Evid Based Complement Alternat Med 2013: 672873, 2013.
9. Yang KL, Huang CC, Chi MS, Chiang HC, Wang YS, Hsia CC, Andocs G, Wang HE and Chi KH: In vitro comparison of conventional hyperthermia and modulated electro-hyperthermia. Oncotarget 7: 84082-84092, 2016.

10. Szasz AM, Minnaar CA, Szentmártoni G, Szigeti GP and Dank M: Review of the clinical evidences of modulated electro-hyperthermia (mEHT) method: An update for the practicing oncologist. Front Oncol 9: 1012, 2019.
11. Schulz KF, Altman DG, Moher D; CONSORT Group: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. Ann Intern Med 152: 726-732, 2010.
12. Haveman J, Bergs JWJ, Franken NAP, van Bree C and Stalpers LJA: Effect of hyperthermia on uptake and cytotoxicity of cisplatin in cultured murine mammary carcinoma cells. Oncol Rep 14: 561-567, 2005.
13. Raaphorst GP and Yang DP: The evaluation of thermal cisplatin sensitization in normal and XP human cells using mild hyperthermia at 40 and 41 degrees C. Anticancer Res 25: 2649-2653, 2005.
14. Gynecologic Oncology Group; Markman M, Blessing J, Rubin SC, Connor J, Hanjani P and Waggoner S: Phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: A gynecologic oncology group study. Gynecol Oncol 101: 436-440, 2006.
15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP: Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 5: 649-655, 1982.
16. U.S.Department of Health and Human Services: Common Terminology Criteriafor Adverse Events (CTCAE). Version 4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed June 14, 2010.
17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
18. Jiang Z, Yan W, Ming J and Yu Y: Docetaxel weekly regimen in conjunction with RF hyperthermia for pretreated locally advanced non-small cell lung cancer: A preliminary study. BMC Cancer 7: 189, 2007.
19. Leal BZ, Meltz ML, Mohan N, Kuhn J, Prihoda TJ and Herman TS: Interaction of hyperthermia with taxol in human MCF-7 breast adenocarcinoma cells. Int J Hyperthermia 15: 225-236, 1999.
20. Rietbroek RC, Katschinski DM, Reijers MH, Robins HI, Geerdink A, Tutsch K, d'Oleire F and Haveman J: Lack of thermal enhancement for taxanes in vitro. Int J Hyperthermia 13: 525-533, 1997.
21. van der Burg MEL, de Wit R, Van Putten WL, Logmans A, Kruit WH, Stoter G and Verweij J: Weekly cisplatin and daily oral etoposide is highly effective in platinum pretreated ovarian cancer. Br J Cancer 86: 19-25, 2002.