Abandon ifosfamide-based regimen and use paclitaxel-carboplatin regimen for the treatment of uterine carcinosarcoma

Szu-Ting Yang[a,b], Peng-Hui Wang[a,b,c,d,*]

[a]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Female Cancer Foundation, Taipei, Taiwan, ROC; [d]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC

DEAR EDITOR,

Uterine carcinosarcoma (UCS) is a rare but highly lethal disease due to its highly aggressive clinical behavior.[1] Additionally, due to its biphasic histological characteristics composing both epithelial and sarcomatous components, traditionally UCS has been classified as a subtype of uterine sarcomas, contributing to the belief that therapy should follow the guideline in the management of patients with uterine sarcoma. Furthermore, the clinical trial targeting the uterine cancer often excludes the UCS patient population, resulting in the delayed knowledge about the new strategy or protocol in the management of patients with UCS.[1] Moreover, based on the observation of active and effective response of ifosfamide for the treatment of UCS (35%) compared to other single agents tests, such as cisplatin (18%), paclitaxel (18%), doxorubicin (10%), and etoposide (6.5%), many experts often prescribed the ifosfamide-based regimen as the standard therapy in the management of patients with UCS.[1] Finally, according to the findings that UCS patients treated with an ifosfamide-cisplatin regimen had a better progression-free survival (PFS) rate with the hazard ratio (HR) of 0.73 (p = 0.02) and a trend of a better overall survival (OS) rate with the HR of 0.80 (p = 0.07) than those treated with five-day ifosfamide single-agent therapy did (Gynecologic Oncology Group-108 [GOG-108]) as well as that addition of paclitaxel to ifosfamide induced significant benefits in prolonging both PFS and OS (HR of 0.71, 95% CI of 0.51-0.97; HR of 0.69, 95% CI of 0.49-0.97) (GOG-161),[2,3] ifosfamide-based regimen (ifosfamide-paclitaxel) has been considered the preferred regimen for UCS.[1] However, ifosfamide-based regimen is associated not only with high hematologic and neurologic toxicity but also with higher costs, which requires growth factor support or cumbersome multiple day dosing of ifosfamide (a longer hospitalization), hinting at the development of new strategy or protocol is urgently needed if treatment can provide the following benefits, such as convenience, less bone marrow suppression, a better cost profile, and less toxicity.[4] In our previous report,[4] we attempted to evaluate the outcome of advanced UCS patients who were treated either with ifosfamide-based regimen or with nonifosfamide-based regimen and found that a certain trend of favoring non-ifosfamide-based regimen (paclitaxel-carboplatin regimen) in the management of advanced UCS patients.[4] The results showed a longer median PFS in the paclitaxel-platinum regimen group than that in the ifosfamide-platinum regimen group (23.1 months versus 4.9 months, p = 0.04).[4] Although the statistical analysis about measuring OS failed to reach the significance, patients treated with paclitaxel-platinum regimen still showed a trend of the longer median OS than ifosfamide-platinum regimen did (28.7 months versus 9.5 months, p = 0.06).[4] Because only 16 patients were enrolled in our study, we cannot make a strong conclusion to recommend that using paclitaxel-platinum regimen for the treatment of advanced UCS patients may be a better choice.[4] It is so lucky for us that our suggestion favoring the regimen containing paclitaxel and carboplatin in place of the regimen containing ifosfamide has been confirmed by the randomized phase III trial of paclitaxel and carboplatin versus paclitaxel and ifosfamide in UCS patients, which has been published in the *Journal of Clinical Oncology*, Volume 40, number 9, March 20, 2022 issue.[5] The following has a summary of this report.

The GOG-0261 study enrolled 536 UCS patients (228 patients treated with paclitaxel-carboplatin regimen and the other 221 patients treated with ifosfamide-paclitaxel regimen), and the results showed that UCS patients treated with paclitaxel-carboplatin had a median PFS of 16 months and OS of 37 months compared to 12 months and 29 months in the ifosfamide-paclitaxel regimen, respectively (HR, 0.73, p < 0.01; HR, 0.87, 90% CI, 0.70-1.075, respectively), concluding that paclitaxel-carboplatin regimen should be standard treatment for UCS.[5] The study confirmed the new direction of using paclitaxel-carboplatin regimen for the treatment of UCS, including a backbone of this regimen that can add any new targeted agents and a one-size-fits-all strategy to enroll UCS patients into the uterine carcinoma patient population accelerates the path to approval of new agents for this aggressive UCS and fulfills a high unmet need, and both of which are important, since the therapy for UCS has not been progressed until now, and the change in treatment paradigms has lagged when compared with the far advances made for other endometrial cancer subtypes.[1]

*Address Correspondence. Dr. Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail addresses: phwang@vghtpe.gov.tw; pongpongwang@gmail.com (P.-H. Wang).

Conflicts of interest: Dr. Peng-Hui Wang, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 649-650.

Received March 18, 2022; accepted March 31, 2022.

doi: 10.1097/JCMA.0000000000000729.

ACKNOWLEDGMENTS

This article was supported by grants from the Taiwan Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 109-2314-B-075B-014-MY2 and MOST 110-2314-B-075-016-MY3), and Taipei Veterans General Hospital (V110C-082, and V111C-103). The authors appreciate the support from Female Cancer Foundation, Taipei, Taiwan.

REFERENCES

1. Roque DR, Matei D. Paclitaxel and carboplatin for uterine carcinosarcoma: a path to inclusion. *J Clin Oncol* 2022;**40**:924–6.
2. Sutton G, Brunetto VL, Kilgore L, Soper JT, McGehee R, Olt G, et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study. *Gynecol Oncol* 2000;**79**:147–53.
3. Homesley HD, Filiaci V, Markman M, Bitterman P, Eaton L, Kilgore LC, et al; Gynecologic Oncology Group. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 2007;**25**:526–31.
4. Su MH, Wu HH, Huang HY, Lee NR, Chang WH, Lin SC, et al. Comparing paclitaxel-platinum with ifosfamide-platinum as the frontline chemotherapy for patients with advanced-stage uterine carcinosarcoma. *J Chin Med Assoc* 2022;**85**:204–11.
5. Powell MA, Filiaci VL, Hensley ML, Huang HQ, Moore KN, Tewari KS, et al. Randomized Phase III trial of paclitaxel and carboplatin versus paclitaxel and ifosfamide in patients with carcinosarcoma of the uterus or ovary: an NRG oncology trial. *J Clin Oncol* 2022;**40**:968–77.