J Gynecol Oncol. 2024 May;35(3):e87
https://doi.org/10.3802/jgo.2024.35.e87
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Review Article

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Current treatment strategies for ovarian cancer in the East Asian Gynecologic Oncology Trial Group (EAGOT)

Yusuke Kobayashi,[1] **Muneaki Shimada**,[2] **Masato Tamate**,[3] **Hyun Woong Cho**,[4] **Jun Zhu**,[5] **Hung-Hsueh Chou**,[6,7] **Hiroaki Kajiyama**,[8] **Aikou Okamoto**,[9] **Daisuke Aoki**,[10] **Sokbom Kang**,[11] **Jeong-Won Lee**,[12] **Jae-Weon Kim**,[13] **Jae-Hoon Kim**,[14] **Zhongqiu Lin**,[15] **Jihong Liu**,[16] **Xiaohua Wu**,[17] **Hung-Cheng Lai**,[18] **Ting-Chang Chang**,[6,19] **Chyong-Huey Lai**,[19] **Yong Man Kim**,[20] **Takayuki Enomoto**[21]

[1]Department of Obstetrics and Gynecology, Institute of Medicine, University of Tsukuba, Ibaraki, Japan
[2]Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Miyagi, Japan
[3]Department of Obstetrics and Gynecology, Sapporo Medical University, Hokkaido, Japan
[4]Department of Obstetrics and Gynecology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea
[5]Department of Gynecologic Oncology, Cancer Hospital of Fudan University, Shanghai, China
[6]Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Branch, Taoyuan, Taiwan
[7]National Tsing Hua University, School of Medicine, Hsinchu, Taiwan
[8]Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[9]Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan
[10]International University of Health and Welfare Graduate School, Tokyo, Japan
[11]Center for Gynecologic Oncology, National Cancer Center, Goyang, Korea
[12]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[13]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea
[14]Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[15]Department of Gynecologic Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China
[16]Department of Gynecologic Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China
[17]Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, Shanghai, China
[18]Department of Obstetrics and Gynecology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan
[19]Chang Gung University College of Medicine, Taoyuan, Taiwan
[20]Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[21]Department of Obstetrics and Gynecology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

OPEN ACCESS

Received: Mar 24, 2024
Accepted: Mar 24, 2024
Published online: Apr 3, 2024

Correspondence to
Muneaki Shimada
Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan.
Email: muneaki.shimada.b7@tohoku.ac.jp

ORCID iDs
Yusuke Kobayashi
https://orcid.org/0000-0002-4503-2845
Muneaki Shimada
https://orcid.org/0000-0003-1826-6723
Masato Tamate
https://orcid.org/0000-0003-1447-9297
Hyun Woong Cho
https://orcid.org/0000-0002-0724-9971
Jun Zhu
https://orcid.org/0000-0003-1224-2771
Hung-Hsueh Chou
https://orcid.org/0000-0002-7049-3280

ABSTRACT

Ovarian cancer, notable for its severe prognosis among gynecologic cancers, has seen substantial progress in treatment approaches recently. Enhanced protocols in chemotherapy and the introduction of poly (ADP-ribose) polymerase (PARP) inhibitors for maintenance therapy have markedly improved outcomes for patients with specific genetic profiles, such as those positive for BRCA mutations or exhibiting homologous recombination deficiency (HRD). Additionally, the method of intraperitoneal chemotherapy administration has

Hiroaki Kajiyama
https://orcid.org/0000-0003-0493-1825
Aikou Okamoto
https://orcid.org/0000-0002-5079-0464
Daisuke Aoki
https://orcid.org/0000-0002-9596-8326
Sokbom Kang
https://orcid.org/0000-0002-8428-9555
Jeong-Won Lee
https://orcid.org/0000-0002-6110-4909
Jae-Weon Kim
https://orcid.org/0000-0003-1835-9436
Jae-Hoon Kim
https://orcid.org/0000-0001-6599-7065
Zhongqiu Lin
https://orcid.org/0000-0002-3202-5072
Jihong Liu
https://orcid.org/0000-0003-3464-2901
Xiaohua Wu
https://orcid.org/0000-0002-6889-3541
Hung-Cheng Lai
https://orcid.org/0000-0001-8048-3943
Ting-Chang Chang
https://orcid.org/0000-0003-1870-7453
Chyong-Huey Lai
https://orcid.org/0000-0002-9977-9645
Yong Man Kim
https://orcid.org/0000-0003-3225-5748
Takayuki Enomoto
https://orcid.org/0000-0003-4538-5541

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: K.Y., S.M., K.H.; Investigation: K.Y., T.M., C.H.W., Z.J., C.H.H.; Project administration: K.Y., S.M., K.S., L.J.W., L.Z., L.H.C.; Supervision: O.A., A.D., K.J.W., K.J.H., L.J., W.X., C.T.C., L.C.H., K.Y.M., E.T.; Writing - original draft: K.Y., T.M., C.H.W., Z.J., C.H.H.; Writing - review & editing: S.M., K.H., K.S., L.Z., L.H.C., L.C.H.

emerged as a valuable alternative to traditional transvenous routes, showing promise for wider clinical adoption. The field of surgery has also evolved, with increasing exploration into the benefits and feasibility of laparoscopic methods over more invasive traditional surgeries, aiming for complete tumor removal but with reduced patient impact. The hereditary nature of ovarian cancer underscores the importance of genetic testing, which has become integral in tailoring treatment strategies, particularly in determining suitability for PARP inhibitors. The formation of the East Asian Gynecologic Oncology Trial Group (EAGOT) aims to optimize treatment across Japan, Korea, China, and Taiwan. The ovarian cancer committee of EAGOT shared the current policies, focusing on 5 topics: 1) strategies for maintenance therapy after initial surgery and chemotherapy, 2) drug regimens for platinum-sensitive and platinum-resistant recurrence, 3) intraperitoneal chemotherapy, 4) laparoscopic surgery as an alternative to laparotomy, and 5) current status of genetic testing (BRCA, HRD, and panel tests) for ovarian cancer and its prospects. EAGOT's multi-national trials aim to harmonize these evolving treatment strategies, ensuring that the latest and most effective protocols are accessible across the region, thereby significantly impacting patient outcomes in East Asia.

Keywords: East Asian Gynecologic Oncology Trial Group; Ovarian Cancer; PARP Inhibitors; Laparoscopic Surgery; Intraperitoneal Chemotherapy; Genetic Testing

INTRODUCTION

Although ovarian cancer has the poorest prognosis for gynecologic malignancies, treatment strategies for it have drastically changed in recent years. With regards to chemotherapy, regimens for initial treatment and relapse therapy have been verified, and a firm protocol has been established. With the clinical introduction of poly (ADP-ribose) polymerase (PARP) inhibitors, maintenance therapy for BRCA-positive ovarian cancer, homologous recombination deficiency (HRD)-positive ovarian cancer, and platinum-sensitive ovarian cancer has been established; consequently, the prognosis for ovarian cancer is improving. In addition to the conventional transvenous drug administration route, intraperitoneal administration has also been deemed useful, and can be widely used in clinical practice in the future. In terms of surgery, while aiming for complete tumor removal, the question of whether laparoscopic surgery is appropriate, considering the invasiveness of the procedure, has been raised. Furthermore, ovarian cancer is a hereditary tumor, and has been widely recognized as a companion diagnosis for PARP inhibitors; moreover, genetic testing has become a familiar part of ovarian cancer treatment.

The East Asian Gynecologic Oncology Trial Group (EAGOT) was formed in 2021 by national clinical trial groups in East Asia—Japanese Gynecologic Oncology Group (JGOG), Korean Gynecologic Oncology Group (KGOG), Chinese Gynecological Cancer Society, and Taiwanese Gynecologic Oncology Group (TGOG). The EAGOT aimed to coordinate and conduct international clinical trials to provide the best treatment for East Asian women suffering from gynecological cancer. As EAGOT conducts future joint clinical trials in the Asian region, specifically in the four EAGOT participating countries, it is necessary to share and be aware of the rapidly changing treatment strategies for ovarian cancer. Therefore, this study is divided into 5 topics: 1) strategies for maintenance therapy after initial surgery and chemotherapy, 2) drug regimens for platinum-sensitive and platinum-resistant recurrence, 3) intraperitoneal chemotherapy, 4) laparoscopic surgery as an alternative to laparotomy, and 5) current status of genetic testing (BRCA, HRD, and panel tests) for ovarian cancer and its prospects.

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STRATEGIES FOR MAINTENANCE THERAPY FOLLOWING INITIAL SURGERY AND CHEMOTHERAPY

1. Japan

Fig. 1 depicts the strategies for maintenance therapy after initial treatment. Adjuvant chemotherapy can be omitted for patients with low-grade and stage IA or IB non-clear cell carcinoma defined by staging laparotomy. For accurately staged stage IC1–IC3 and stage II cases, postoperative chemotherapy is performed, and patients are followed up if they are in remission [1]. Adjuvant chemotherapy for early-stage ovarian cancer in Japan is based on two clinical trials, ICON1 and EORTC-ACTION, showing that adjuvant chemotherapy was effective (hazard ratio=0.67) [2]. However, in a subset analysis of accurately staged cases (34%), the prognosis was not different between the follow-up and adjuvant chemotherapy groups [3]. In cases of stage III/IV disease where complete remission was achieved by first-line chemotherapy with bevacizumab, following options are available: 1) bevacizumab + olaparib maintenance therapy for those with HRD, and 2) bevacizumab maintenance therapy for those with negative or unknown HRD status. In cases of stage III/IV disease where complete remission is achieved by first-line chemotherapy without bevacizumab, the following options are available: 3) olaparib or niraparib maintenance therapy for those with BRCA1/2 variants, 4) niraparib maintenance therapy for those without BRCA1/2 variants but HRD-positive, and 5) niraparib maintenance therapy for HRD-negative patients. Although the National Comprehensive Cancer Network (NCCN) guidelines often search for BRCA status first, HRD status is often examined at the time of surgery in Japan. Patients with persistent disease after bevacizumab treatment following primary surgery have 2 options:

Omission of adjuvant chemotherapy is suggested for non-CCC patients with low grade and stage IA or IB, as defined by staging laparotomy.

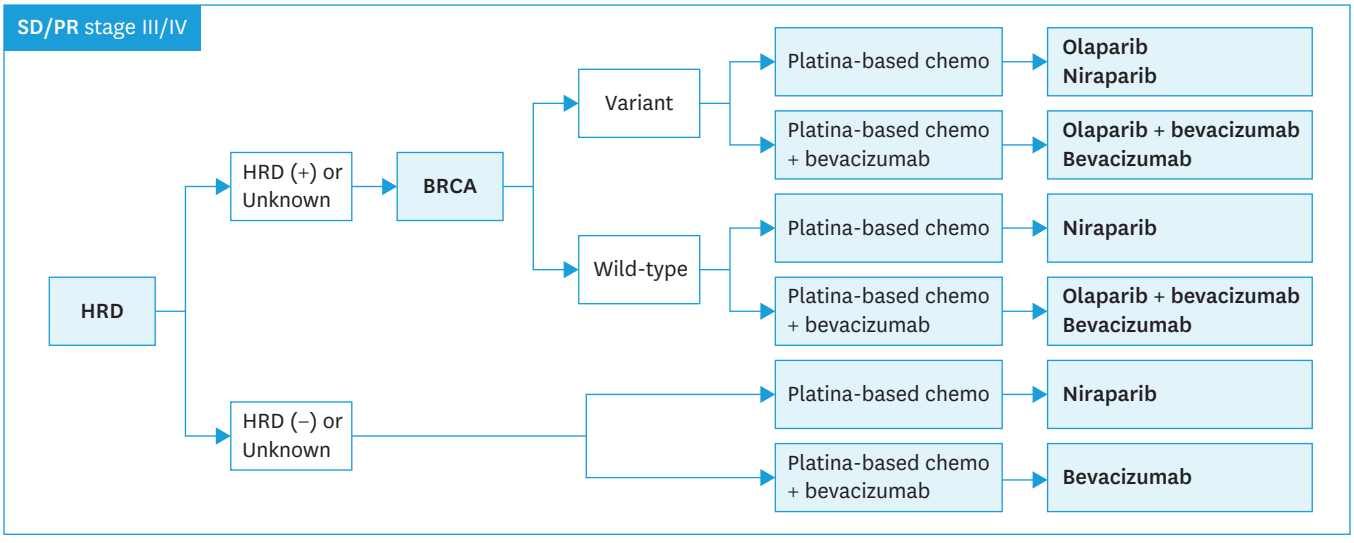

Fig. 1. Strategies for maintenance therapy following initial surgery and chemotherapy in Japan.
HRD, homologous recombination defect.

https://doi.org/10.3802/jgo.2024.35.e87

1) bevacizumab maintenance therapy for patients with stage III/IV disease if bevacizumab results in stable disease or partial response in cases with negative or unknown HRD status; and 2) bevacizumab + olaparib maintenance therapy for HRD-positive patients with stage III/IV disease if a partial response is achieved by bevacizumab. Patients with persistent disease after first-line chemotherapy without bevacizumab following primary surgery have the following options: 1) olaparib or niraparib maintenance therapy for patients with BRCA1/2 variants; 2) niraparib maintenance therapy for patients without BRCA1/2 variants but who are HRD-positive; 3) niraparib maintenance therapy for HRD-negative patients. Another treatment (i.e., second-line chemotherapy or radiation therapy), participation in clinical trials, or best supportive care is recommended for patients who fail to respond to first-line chemotherapy and those exhibiting tumor progression. Moreover, the AURELIA trial recommends the addition of bevacizumab maintenance. PARP inhibitor indications in ovarian cancer have recently evolved as new overall survival (OS) data have emerged [4]. Furthermore, rucaparib, a PARP inhibitor not yet approved in Japan, is effective as first-line treatment of advanced ovarian cancer [5]. Clinical trials are currently underway that combine immune checkpoint inhibitors and viral vectors with conventional chemotherapy.

2. Korea

Bevacizumab is the first drug approved for maintenance therapy in ovarian cancer [6]. Additionally, the United States Food and Drug Association (FDA) has approved PARP inhibitors for the maintenance of primary ovarian cancer based on SOLO1, PRIMA, and VELIA trials [7-9]. First-line maintenance with olaparib improved OS in advanced ovarian cancer, which was recently reported in SOLO1 and PAOLA-1 trials [10]. Thus, based on previous trials, the national health insurance covers olaparib and niraparib as first-line maintenance in Korea since 2021. Based on the practice guidelines of the Korean Society of Gynecologic Oncology (**Fig. 2**), PARP inhibitors, such as olaparib or niraparib, are recommended for maintenance after primary chemotherapy (level 1A) [8-10]. Additionally, bevacizumab can be used for 12–22 cycles after primary chemotherapy to delay progression (level 2A) [11-13]. However, new challenges have emerged since the introduction of PARP inhibitors, which have led to a paradigm change in ovarian cancer treatment. The benefit of PARP inhibitors was less prominent in patients with homologous recombinant proficient tumors [14]. Additionally, the development of resistance is inevitable in approximately 40%–70% of patients [15]. Thus, several trials are ongoing for PARP inhibitor combinations for first-line treatment and maintenance to enhance PARP inhibitor efficacy and prevent recurrence or resistance [16].

3. China

First-line maintenance therapy for ovarian cancer refers to the follow-up of patients who have completed initial chemotherapy to achieve a clinical complete response (CR) or partial response (PR) to delay recurrence and improve survival outcomes. Evidence-based regimens for first-line maintenance treatment include antiangiogenetic drugs and PARP inhibitors. **Fig. 3** illustrates the specific selection for patients with advanced epithelial ovarian cancer who are considering first-line maintenance therapy. For patients with stage III/IV disease who have achieved CR/PR status after initial surgery and chemotherapy, BRCA and/or HRD test is recommended. 1) Patients only received tissue BRCA genes test, those with mutated tumor BRCA are recommended to receive the maintenance treatment with olaparib or niraparib. 2) Patients with wild-type tumor BRCA (tBRCAwt) status are recommended to receive an HRD test, and those with tBRCAwt/HRD (+) are recommended to receive the maintenance treatment with niraparib. 3) Patients with tBRCAwt/HRD (−) are recommended

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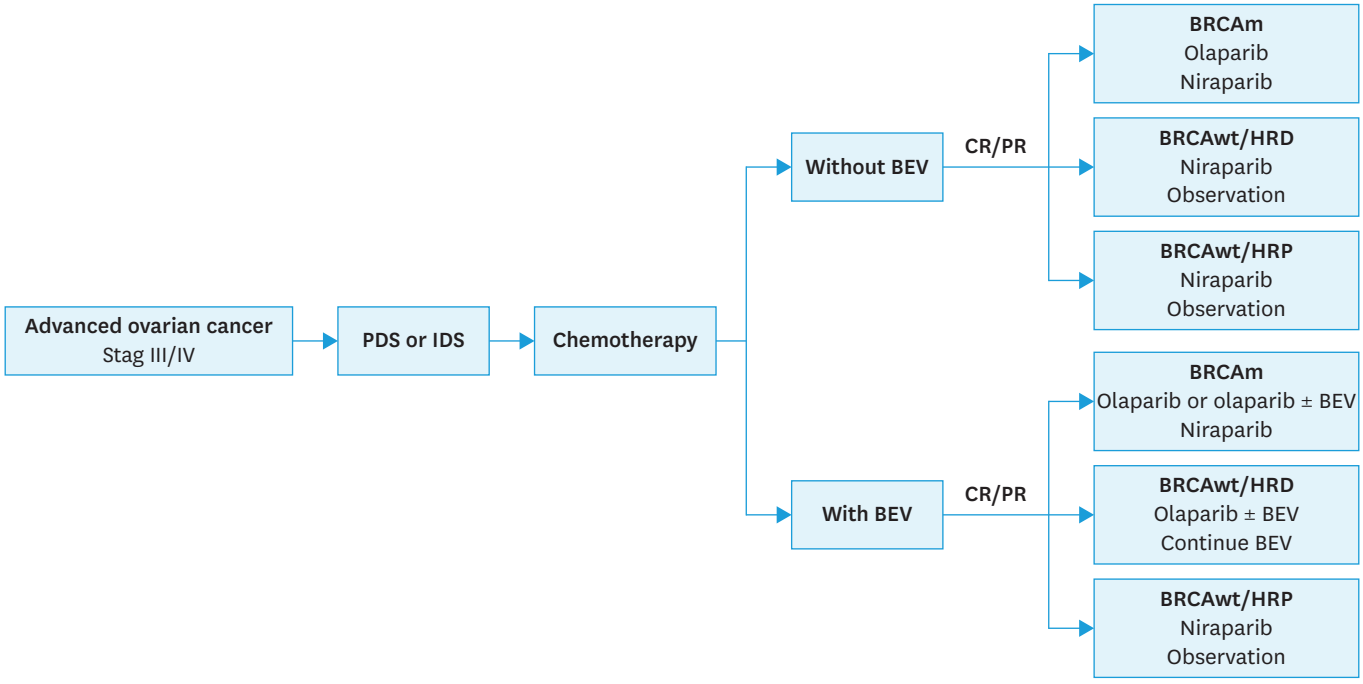

Fig. 2. Strategies for maintenance therapy following initial surgery and chemotherapy in Korea.
BEV, bevacizumab; BRCAm, mutated BRCA; BRCAwt, wild-type BRCA; CR, complete response; HRD, homologous recombination defect; HRP, homologous recombination proficient; IDS, interval debulking surgery; PDS, primary debulking surgery; PR, partial response.

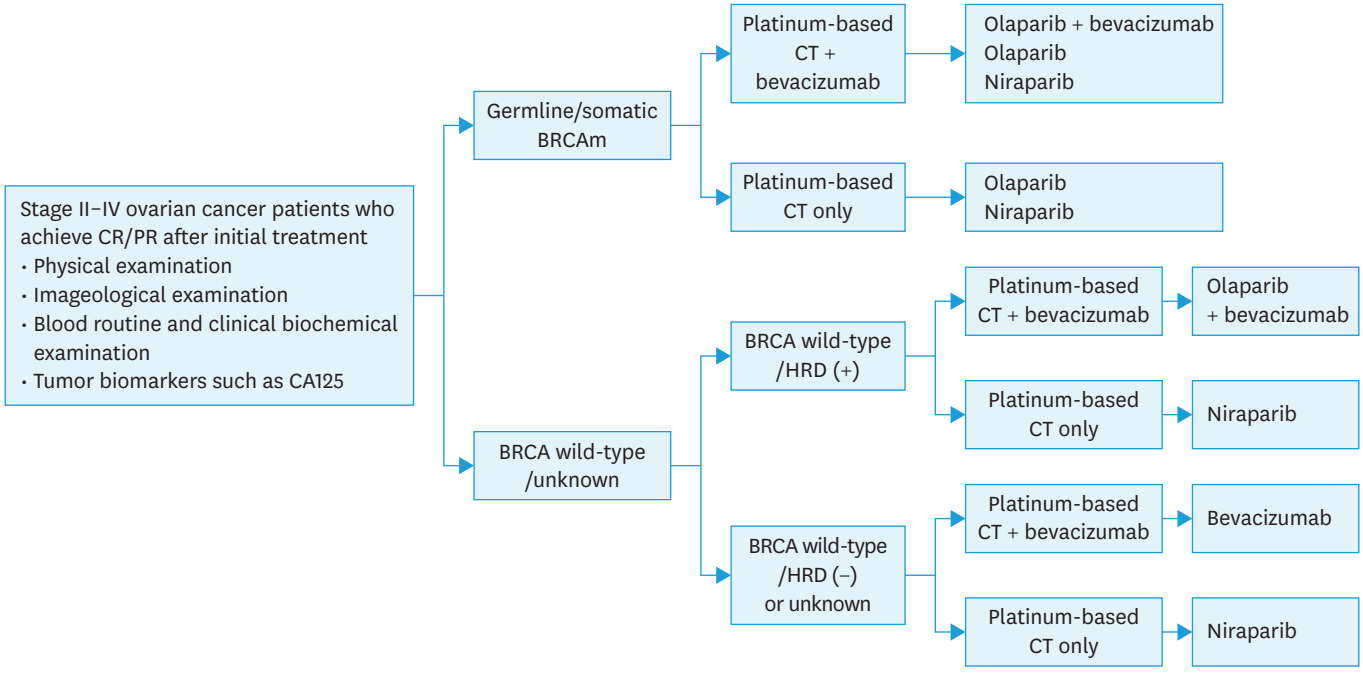

Fig. 3. Strategies for maintenance therapy following initial surgery and chemotherapy in China.
BRCAm, mutated BRCA; CR, complete response; CT, chemotherapy; HRD, homologous recombination defect; PR, partial response.

to receive the maintenance treatment with niraparib. 4) The use of antiangiogenic agents such as bevacizumab as maintenance therapy usually requires its combination with initial chemotherapy. However, the duration of progression-free survival (PFS) with antiangiogenic

https://doi.org/10.3802/jgo.2024.35.e87

agents as maintenance therapy is not promising in the general population except in patients at high risk of recurrence.

4. Taiwan

Gynecological oncologists usually provide counseling regarding the evidence and reimbursement policy of maintenance therapy with either bevacizumab and/or PARP inhibitors to patients with advanced ovarian cancer (**Fig. 4**). Furthermore, bevacizumab is recommended as maintenance for those without genetic information or those with wild-type BRCA1/2 and proficient HRD. Moreover, olaparib or niraparib is recommended as maintenance for those with BRCA1/2 mutations, and either niraparib or bevacizumab is recommended for those with wild-type BRCA1/2 and HRD. The National Health Insurance (NHI) has reimbursed olaparib since November 1, 2020, and niraparib since December 1, 2022, for 1L maintenance therapy for 2 years for patients with advanced ovarian cancer with BRCA1/2 mutations. However, the reimbursement does not include HRD status yet. NHI will reimburse 1st-line bevacizumab (with paclitaxel and carboplatin) and maintenance in stage IV diseases with unknown genetic status or BRCA1/2 wild-type from March 1, 2024, because the final analysis of GOG218 showed a significant OS benefit of adding bevacizumab (42.8 vs. 32.6 months, HR=0.75; 95% confidence interval=0.59–0.95) [17].

DRUG REGIMENS FOR PLATINUM-SENSITIVE AND PLATINUM-RESISTANT RECURRENCES

1. Japan

Combination chemotherapy with a platinum agent is recommended for patients with platinum-sensitive recurrence ovarian cancer (PSROC) **(Fig. 5)**. Based on phase III trial results,

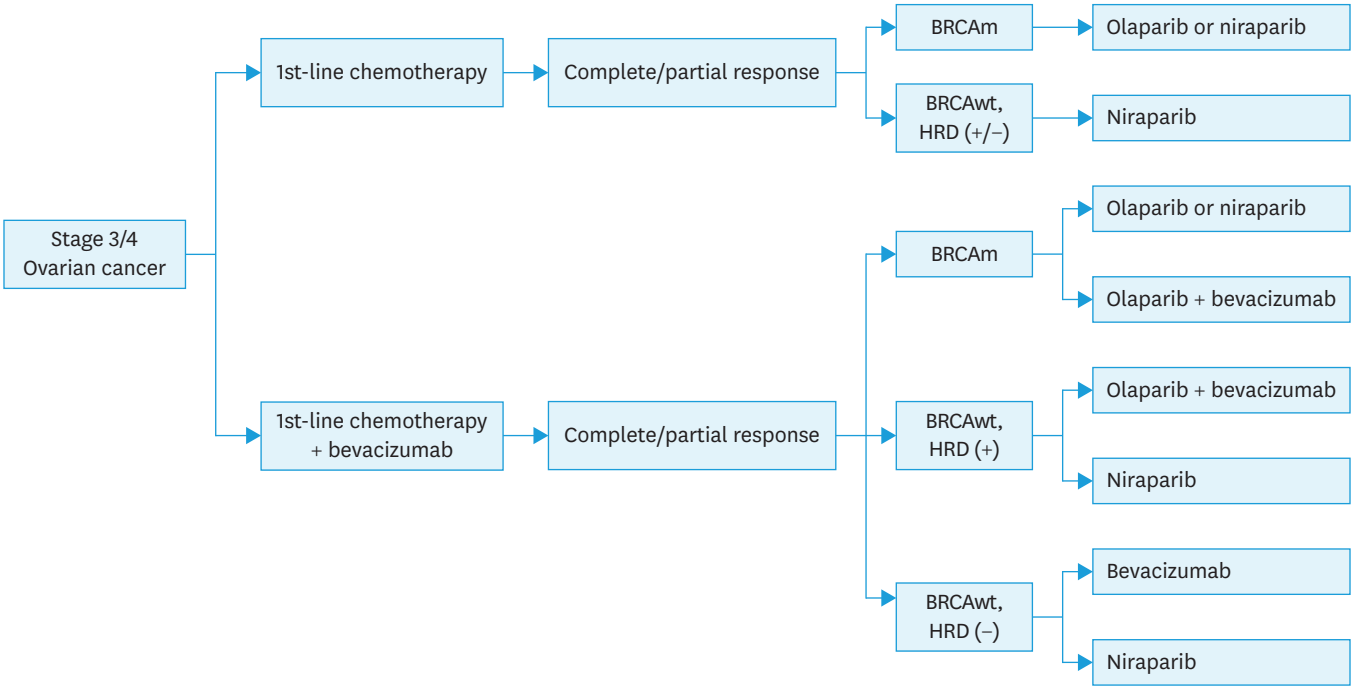

Fig. 4. Strategies for maintenance therapy following initial surgery and chemotherapy in Taiwan.
BRCAm, mutated BRCA; BRCAwt, wild-type BRCA; HRD, homologous recombination defect.

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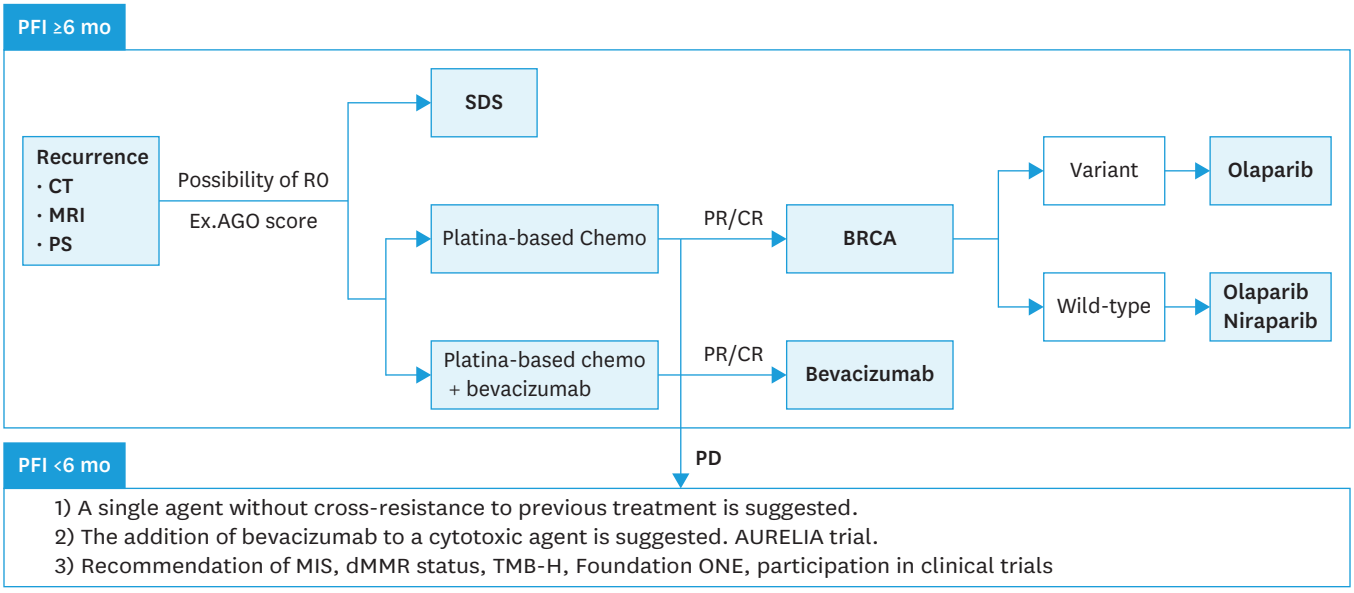

Fig. 5. Treatment algorithm for recurrent ovarian cancer in Japan.
CR, complete response; CT, computed tomography; dMMR, deficient mismatch repair; MIS, minimally invasive surgery; MRI, magnetic resonance imaging; PR, partial response; PS, performance status; SDS, secondary debulking surgery; TMB-H, tumor mutational burden-high.

multiple-drug combination therapy, including a platinum-based agent, is recommended over platinum-based monotherapy [18-20]. Furthermore, in Japan, paclitaxel + carboplatin, gemcitabine + carboplatin, and pegylated liposomal doxorubicin + carboplatin are commonly used. The addition of bevacizumab, followed by bevacizumab maintenance therapy, is recommended [21-23]. Maintenance therapy with olaparib and niraparib is recommended for patients with PSROC with a history of platinum-based chemotherapy, achieving CR with at least four cycles of chemotherapy immediately prior [24-27]. Olaparib and niraparib are recommended for patients with any BRCA or HRD status because some clinical trials have reported prolonged PFS regardless of BRCA or HRD status [25-27]. A clinical trial showed that rucaparib was effective in patients with a similar course [28], but rucaparib is not covered by insurance in Japan. Otherwise, the use of niraparib as a single agent is recommended for HRD-positive patients with PSROC who received third- or higher-line chemotherapy [29]. Although niraparib is currently covered by Japanese insurance, the FDA withdrew its use as maintenance and single agent for patients without germline BRCA variants. Therefore, these recommendations may be withdrawn in the future in Japan. A single agent without cross-resistance to previous treatment is recommended for patients with platinum-resistant recurrence ovarian cancer (PRROC) **(Fig. 5)**. Multiple-drug combination therapy being superior to monotherapy has not been reported [30,31]. The insurance in Japan covers the following drugs: irinotecan, etoposide, gemcitabine, nogitecan hydrochloride, docetaxel, paclitaxel, and pegylated liposomal doxorubicin. The AURELIA trial showed prolonged PFS with the addition of bevacizumab to a cytotoxic agent (pegylated liposomal doxorubicin, paclitaxel, and nogitecan hydrochloride) [32]. Combination therapy with bevacizumab is recommended for patients with PRROC; however, physicians must be cautious in recommending different chemotherapy regimens for patients with PRROC who have failed to respond to a single agent with or without bevacizumab and those exhibiting tumor progression. After adequate discussion with the patients and careful assessment of their condition, chemotherapy with different regimens is recommended if they are considered to be less disadvantageous owing to their adverse effects. Additionally, microsatellite instability (MSI) testing is recommended for

https://doi.org/10.3802/jgo.2024.35.e87

pembrolizumab [33]. As pembrolizumab is used for patients with ovarian cancer, they must be MSI-high in Japanese insurance.

2. Korea

The management of relapsed ovarian cancer is frequently stratified based on the platinum-free interval (PFI) (date of the last platinum dose and relapse detection) [34,35]. As PARP inhibitors and bevacizumab have now become first-line maintenance therapies for ovarian cancer, the choice of second-line maintenance therapy depends on the first-line therapy based on whether the patient has a BRCA mutation or HRD. According to the practice guidelines of the Korean Society of Gynecologic Oncology (**Fig. 6**), platinum doublets, such as carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, carboplatin/gemcitabine, carboplatin/weekly paclitaxel, and carboplatin/docetaxel, can be recommended for platinum-sensitive disease assessed by a PFI of >6 months. Bevacizumab can be incorporated (level 1A), and PARP inhibitors can be considered (level 1A). Immuno-oncologic agents and hormone agents are allowed without the recommendation level. For platinum-resistant disease, a nonplatinum singlet is recommended (topotecan, gemcitabine, liposomal doxorubicin, oral etoposide, belotecan, docetaxel, irinotecan, or weekly paclitaxel). Moreover, bevacizumab can be used in combination with nonplatinum agents. The abovementioned treatments have no assigned recommendation level. PFI is a key concept for selecting subsequent therapy but has some limitations. After the introduction of PARP inhibitors in ovarian cancer treatment, the effect of maintenance therapy on the subsequent PFI is critical. Based on a retrospective study of a Korean group and post-hoc analysis of SOLO2, the response to subsequent chemotherapy is significantly decreased in patients with relapsed ovarian cancer before PARP inhibitor maintenance [36,37]. A recent MITO study showed that 11%–22% of patients treated with PARP inhibitors responded to subsequent therapy despite PFI of >6 months [38]. At present, maintenance PARP inhibitors are widely used, and overcoming the resistance of PARP inhibitors is a major challenge in ovarian cancer treatment.

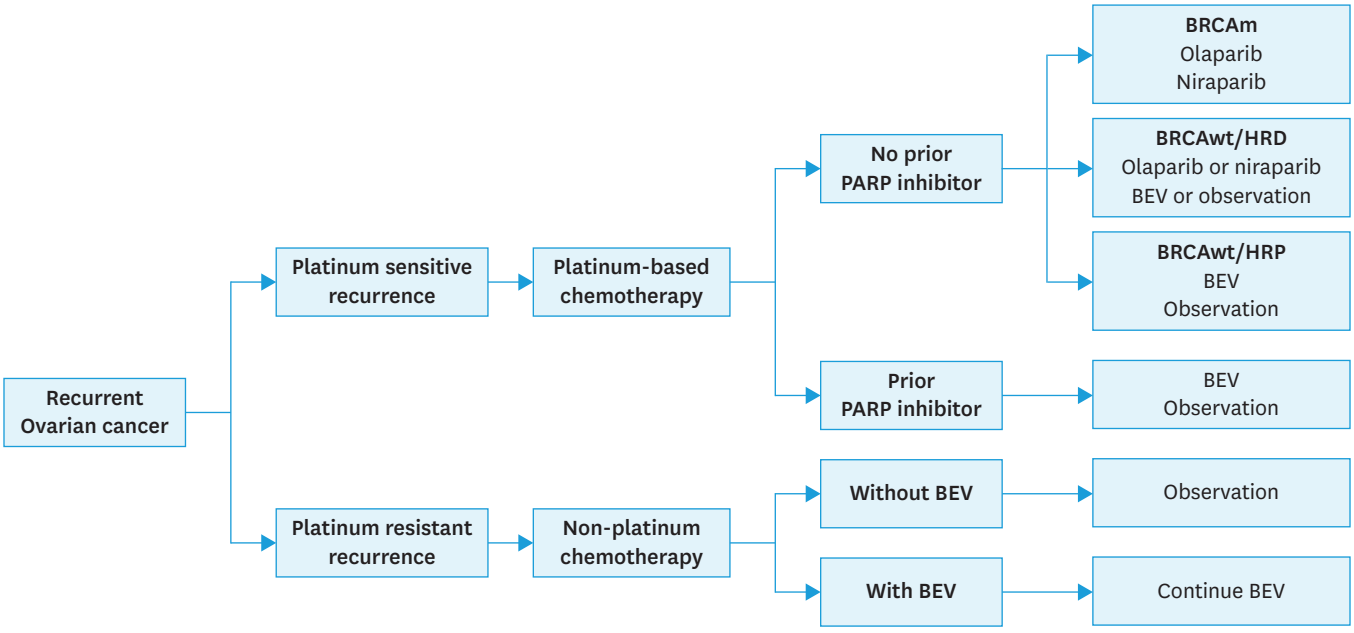

Fig. 6. Treatment algorithm for recurrent ovarian cancer in Korea.
BEV, bevacizumab; BRCAm, mutated BRCA; BRCAwt, wild-type BRCA; HRD, homologous recombination defect; HRP, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase.

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3. China

For patients with PSROC, secondary cytoreduction is recommended for those who can be satisfactorily resected again after evaluation (R0 resection) [39]. Unified standards are lacking for selecting patients undergoing secondary cell reduction surgery. Generally, isolated or oligometastases have recurred in patients undergoing secondary cytoreduction, and ascites or extensive peritoneal metastasis should be absent [40]. For patients with platinum-sensitive relapsed disease who cannot be treated with secondary cytoreduction, platinum-based combination chemotherapy or combination of bevacizumab with PARP inhibitors or bevacizumab maintenance therapy is preferred, such as paclitaxel + carboplatin ± bevacizumab, gemcitabine + carboplatin ± bevacizumab, and doxorubicin liposomes + carboplatin ± bevacizumab. Moreover, maintenance therapy with PARP inhibitors is recommended for patients with PSROC achieving CR/PR [41]. Patients with PSROC with systemic treatment are recommended platinum-based chemotherapy or combination with bevacizumab, followed by maintenance treatment of PARP inhibitors or bevacizumab (**Fig. 7**). Thus, reuse of PARP inhibitors is not recommended for those who have previously be treated using PARP inhibitors. Platinum-based chemotherapy or combination with bevacizumab followed by bevacizumab maintenance therapy is recommended for patients with PSROC who have previously used PARP inhibitors. In the absence of combination bevacizumab, maintenance therapy is not recommended, and participation in clinical trials is encouraged. **Fig. 7** depicts the recommendation for maintenance treatment options for patients without a history of PARP inhibitor use [27]. Because secondary cytoreduction is usually not helpful for patients with PRROC, platinum single-agent chemotherapy or targeted antiangiogenetic

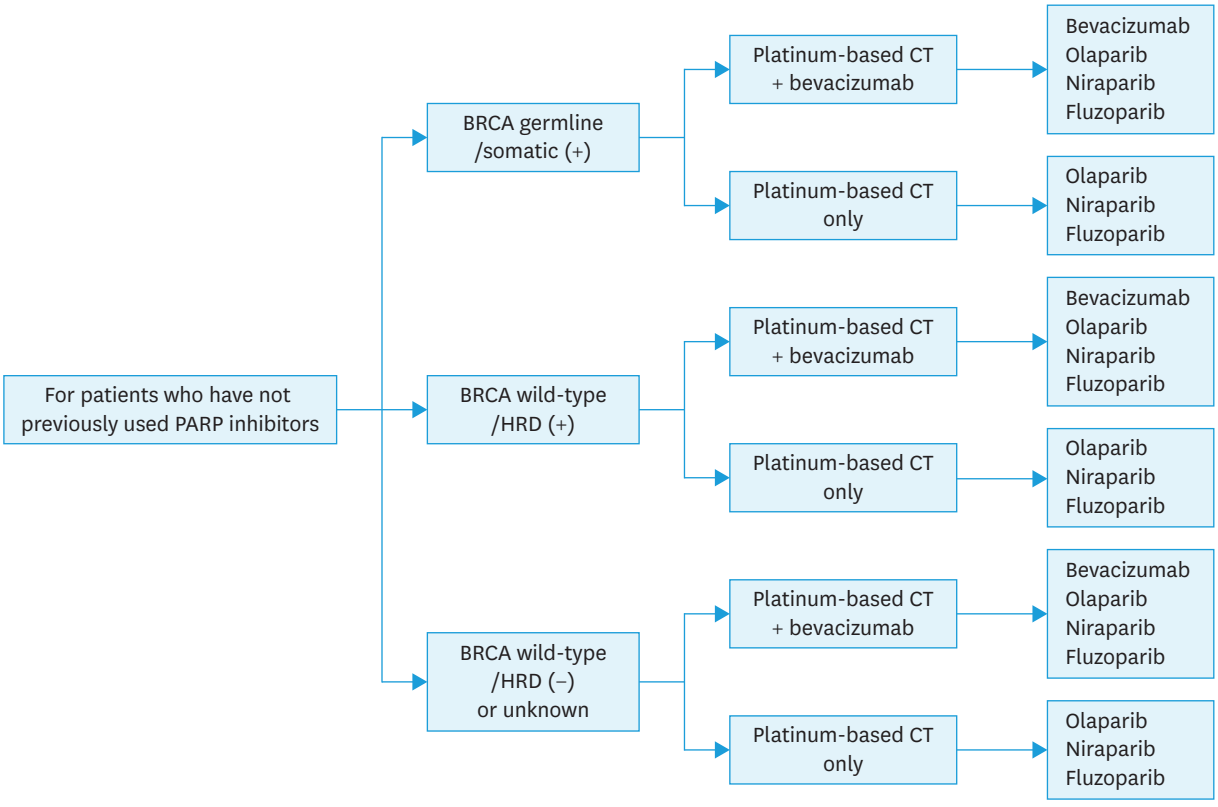

Fig. 7. Treatment algorithm for recurrent ovarian cancer in China.
CT, chemotherapy; HRD, homologous recombination defect; PARP, poly (ADP-ribose) polymerase.

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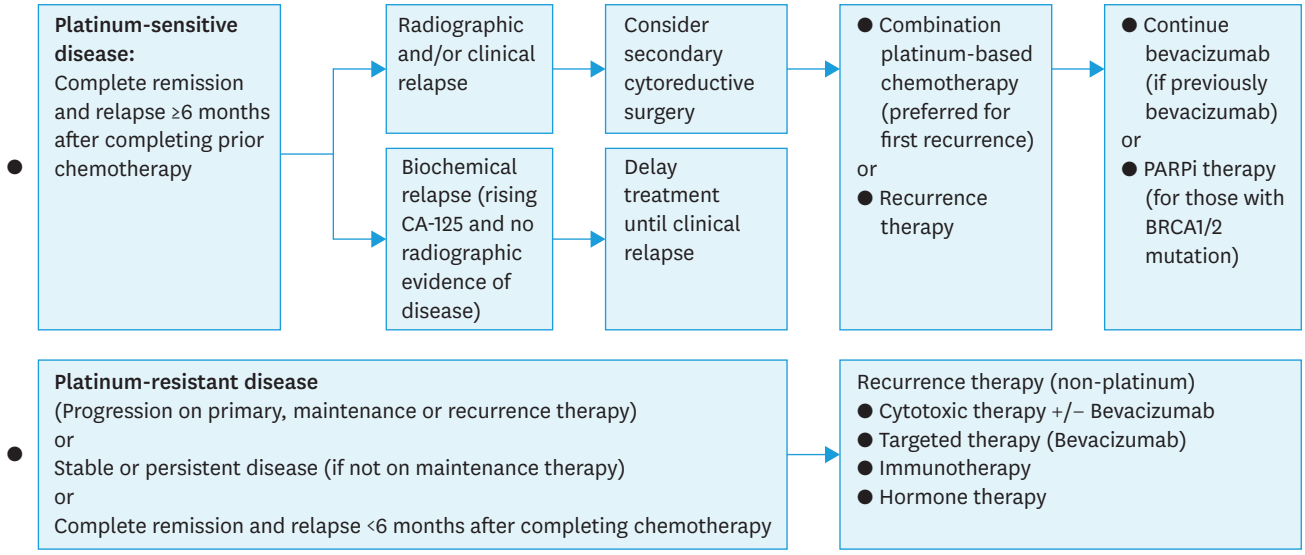

Fig. 8. Treatment algorithm for recurrent ovarian cancer in Taiwan.
PARPi, poly (ADP-ribose) polymerase inhibitors.

combination chemotherapies, such as cyclophosphamide ± bevacizumab, docetaxel, etoposide, gemcitabine, and doxorubicin liposomes ± bevacizumab, are considered. For some patients with recurrent ovarian cancer with specific biomarkers, treatment including neurotrophic tyrosine receptor kinase inhibitors and immune checkpoint inhibitors may also be considered. In China, pembrolizumab for patients with ovarian cancer must meet the following requirements: 1) high MSI or deficient mismatch repair status; or 2) tumor mutational burden-high (≥10 muts/MB) and lack of other satisfactory alternative treatment options for solid tumors.

4. Taiwan

The use of carboplatin/cisplatin plus either paclitaxel, pegylated liposomal doxorubicin, or gemcitabine is allowed in platinum-sensitive recurrence (**Fig. 8**). For later lines, these regimens could be used based on the physician's discretion. Cyclophosphamide and etoposide can be used without limitation. Topotecan is limited to platinum-resistant ovarian cancer. Topotecan could be used with a 5-day regimen, 1.2 mg/kg/day every 3 weeks, or a weekly regimen, 4.0 mg/kg weeks on, 1 week off every 4 weeks. Dose-dense chemotherapy, as used in JGOG 3016 [42], is allowed in first- and late-line chemotherapy. The NHI system reimburses bevacizumab in combination with carboplatin and paclitaxel only in partial in partially sensitive (6–12 months) recurrent ovarian cancer since June 1, 2020.

INTRAPERITONEAL CHEMOTHERAPY

1. Japan

Intraperitoneal (IP) chemotherapy should be administered in an appropriate facility with the provision of adequate informed consent concerning risks and benefits. However, it is not covered by insurance in Japan. Only IP carboplatin can be administered as a combined therapy with intravenous paclitaxel through advanced medical treatment. The GOTIC-001/JGOG3019 trial is a phase III open-label randomized controlled trial (RCT) investigating whether IP carboplatin in combination with dose-dense paclitaxel prolongs prognosis in

https://doi.org/10.3802/jgo.2024.35.e87

stage II–IV primary epithelial ovarian/fallopian/peritoneal cancer. JGOG3019 did not involve bevacizumab or maintenance therapy. Moreover, the IP carboplatin group significantly prolonged PFS compared with the intravenous group, but OS was comparable [43]. The study included Japanese subjects and was based on previous clinical trials, such as GOG104 and GOG114 [44,45]. These trials showed a survival benefit in the IP cisplatin (CDDP) group, but more toxic events occurred in the CDDP group. In Japan, bevacizumab is not covered by insurance for IP therapy, considering that the GOG252 results show that IP therapy is not beneficial in the presence of bevacizumab. Hyperthermic intraperitoneal chemotherapy (HIPEC) is not recommended in the Japanese guidelines and is currently proposed to be conducted as a well-designed clinical trial. The OVHIPEC trial reported that HIPEC significantly improved PFS and OS [46]. However, another study identified many problems: 1) the relatively small size of the trial, 2) bias in the tissue types of the two groups, and 3) the inappropriateness of the randomization [47]. Although some studies showed the efficacy of IP treatment as the first-line therapy for primary epithelial ovarian/fallopian/peritoneal cancer, the association with maintenance therapy is unclear. Thus, its association with PARP inhibitors should be clarified because maintenance therapy is the standard of care in primary ovarian/fallopian/peritoneal cancer. Further studies are needed before it can be established as the standard of care.

2. Korea

Although 3 large, randomized trials have reported the survival benefits of IP chemotherapy, front-line IP chemotherapy has not been widely used because of toxicities and complexities in administration [44,45,48]; recently, GOG252 failed to show superiority over IV chemotherapy [49]. Based on the practice guidelines of the Korean Society of Gynecologic Oncology, IP chemotherapy can be offered when the residual tumor size is <1 cm, and the disease stage is II or III (no evidence level). Therefore, further studies are required to elucidate the role of IP chemotherapy in the PARP inhibitor era.

3. China

RCTs have confirmed that the survival benefits of IP chemotherapy are superior over intravenous chemotherapy [44,45,48]. In China, cisplatin is most commonly used for IP chemotherapy, and the treatment cost is covered by the China National Medical Insurance (CNMI). However, acceptance of IP chemotherapy remains limited because of complications associated with catheter use and significant toxicity [50]. Additionally, catheters have limited availability in China, and they are not covered by CNMI. Four prospective trials showed that adding HIPEC to interval cytoreductive surgery (ICS) yields superior PFS and OS outcomes compared with ICS alone, without increasing the risk of complications [46,51-53]. A post-hoc subgroup analysis of the KGOG 3042 trial found that HIPEC added to ICS was associated with better PFS in patients receiving PARP inhibitor maintenance therapy [51]. The ongoing GOG-3068 trial (NCT05659381) further discerns the benefits of cisplatin-based HIPEC in patients on niraparib as maintenance. Currently, the Chinese Anti-Cancer Association (CACA) has developed clinical guidelines for the use of HIPEC and recommends its administration to patients with International Federation of Gynecology and Obstetrics (FIGO) stage III–IV disease following ICS. Additionally, Chinese researchers have explored HIPEC treatment regimens for Asian women with ovarian cancer, including single-agent cisplatin [54], cisplatin + paclitaxel [55], and cisplatin + docetaxel [56]. CACA is leading further clinical research to determine the therapeutic role of HIPEC in patients undergoing primary cytoreductive surgery for FIGO stage III–IV disease (NCT03373058). Currently, HIPEC is covered by CNMI.

https://doi.org/10.3802/jgo.2024.35.e87

4. Taiwan

IP chemotherapy as a first- or late-line treatment is rarely used in Taiwan. However, HIPEC is recommended to patients accepting interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) and secondary debulking surgery (SDS) for recurrent ovarian cancer in approximately 10 hospitals with established HIPEC teams. A study showed that 28 of 51 (56%) patients with recurrent ovarian cancer had no subsequent intraperitoneal recurrence after HIPEC, with a follow-up time of 20.2 months and PFS of 16.3 months [57].

LAPAROSCOPIC SURGERY AS AN ALTERNATIVE TO LAPAROTOMY

1. Japan

Laparoscopic surgery is not currently recommended in Japan. Diagnostic laparoscopy is recommended for predicting complete surgery, staging, or collecting tissues. Laparoscopy may also be performed to determine the possibility of primary debulking surgery (PDS).

With reference to the NCCN guidelines [58], some studies showed no difference in surgical outcomes, recurrence rates, or survival for those who received minimally invasive versus open surgical staging. Patients whose disease cannot be optimally determined using minimally invasive techniques should be converted to an open procedure. Minimally invasive surgery (MIS) is recommended for patients with ovarian cancer in some cases. However, MIS is not covered by insurance in Japan. Therefore, MIS for ovarian cancer in Japan is currently performed as a Fagotti score to explore the possibility of PDS, the feasibility of SDS, and histological examination for genetic testing. The MISSION trial reported the efficacy of MIS in NAC in ovarian cancer. A residual tumor of 0 and 0.5 cm was achieved in 29 (96.6%) patients and 1 (3.4%) patient, respectively [59]. The CILOVE study reported that all except one patient had optimal cytoreduction (97% complete cytoreduction, 3% incomplete cytoreduction) [60]. Both trials indicated that the role of laparoscopy has become more crucial in the management of ovarian cancer. IDS in patients with clinically CR to NAC seems to be feasible and safe in terms of perioperative outcomes, psycho-oncological impact, and survival rate. The equivalence between MIS and laparotomy should be confirmed with longer follow-ups and a larger number of patients. Furthermore, more randomized controlled trials are needed to compare laparoscopy and laparotomy in this selective group of patients. It would be relevant to enroll patients in the LANCE trial that compares open and laparoscopic procedures in advanced ovarian cancer after NAC [61]. MIRRORS is an ongoing prospective controlled trial of robotic IDS versus open laparotomy for ovarian cancer after NAC [62]. In summary, Japan should cooperate with international trials and encourage the inclusion of these products in the insurance system.

2. Korea

Because MIS was introduced to surgical staging for early-stage ovarian cancer in the mid-1990s [63], several retrospective studies showed that minimally invasive surgical staging for ovarian cancer may be feasible and effective for treating ovarian cancers [64-70]. However, these studies are retrospective studies with limited numbers of patients. Additionally, RCTs for MIS for ovarian cancer have not been conducted; therefore, the evidence for its use in ovarian cancer remains insufficient. Based on the practice guidelines of the Korean Society of Gynecologic Oncology, gynecologic oncologists should perform MIS for comprehensive staging surgery in ovarian cancer. Although the procedure has limited evidence, MIS can be performed at the

https://doi.org/10.3802/jgo.2024.35.e87

surgeon's discretion (evidence level IV, recommendation level C). High-quality studies are necessary to confirm the benefits of MIS and develop adequate selection criteria for MIS.

3. China

Laparoscopic surgery is not recommended in ovarian cancer surgery. Based on a 2022 survey, open surgery is the most used primary treatment for advanced ovarian cancer, with MIS accounting for approximately 23% of all surgical procedures. The low rate of clinical application of MIS may be due to the following reasons: 1) MIS is less effective than open surgery; 2) risk of tumor metastasis; 3) few suitable patients and narrow available range; and 4) difficult procedure. Complete tumor reduction is an important prognostic factor for advanced ovarian cancer. However, for those whose tumors cannot be completely reduced, intermittent tumor cell reduction followed by NAC is a better treatment option. Moreover, laparoscopy can accurately evaluate the feasibility of ideal tumor cell reduction. Laparoscopic treatment is only considered safe and feasible for stage I epithelial ovarian cancer patients [71]. For advanced ovarian cancer, NAC followed by laparoscopic intermittent cytoreduction is also beneficial [72]. The scope and content of the procedure are the same as those of staging surgery for early ovarian cancer, with reduced surgical difficulty and risk. Despite the growing acceptance of minimally invasive and intermittent cytoreduction for ovarian cancer, no strong studies have demonstrated that survival outcomes are not affected.

4. Taiwan

Although concerns remain regarding the potential risk of laparoscopy in ovarian cancer surgery [73], laparoscopic staging surgery for early-stage ovarian cancer does not compromise the survival outcome in trained gynecological oncologists [74,75]. Patients with suspected ovarian cancer are not an absolute contraindication for laparoscopy in Taiwan if optimal debulking surgery without spillage can be achieved at the initial assessment. For advanced diseases, diagnostic laparoscopy may be used for tissue proofing and to assess the extent of disease for optimal debulking.

CURRENT STATUS OF GENETIC TESTING (BRCA, HRD, AND PANEL TESTS) FOR OVARIAN CANCER AND ITS PROSPECTS

1. Japan

Genetic testing for PARP inhibitor use is increasingly important. This study demonstrated how the indication for PARP inhibitors has changed based on the BRCA variant. Japan has a universal health insurance system and few uninsured patients. Thus, the PARP inhibitors available are olaparib and niraparib. Based on the SGO2022 report, second-line or more line maintenance following response to platinum-based chemotherapy for patients with PSROC has been updated according to FDA-approved indications. Niraparib can be used as maintenance therapy for germline or suspected germline BRCA variants. However, niraparib for the nongermline BRCA variant is no longer FDA approved. Rucaparib can be used as maintenance therapy for germline or somatic BRCA variants. Similarly, rucaparib therapy for non-BRCA will no longer be FDA approved. The NOVA study results led to the withdrawal of the FDA approval of niraparib as maintenance therapy for patients with PSROC not associated with germline BRCA, and the Japanese government is now considering how to proceed. Rucaparib is not approved in Japan, and its indications for use have not yet been determined

https://doi.org/10.3802/jgo.2024.35.e87

based on the ARIEL3 study. Many genes other than BRCA1/2 are involved in ovarian cancer. Because of the difficulty of classifying the boundaries between hereditary and nonhereditary tumors, all patients with ovarian cancer can be "hereditary." For example, when breast cancer-related single-nucleotide variations (SNVs) are considered, each morbidity variant holder had a clear risk distribution [76], indicating that polygenic risk should be added to risk assessment. This would individualize the risk of morbidity and determine surveillance and preventive interventions. However, few studies have examined the extent to which polygenic SNV (formerly single-nucleotide polymorphism) scores modify the risk for pathogenic variant carriers in ovarian cancer susceptibility genes. Future work might extend risk modification to the estimation of a second breast cancer for women with a personal and/or family history of breast cancer. Refinement of risk models may enable a better definition of personalized risks for women and enhance the quality of clinical care. The strength of "relative involvement" should be recognized rather than "absolute involvement" of genetic status, such as BRCA/HRD.

2. Korea

Strong evidence indicates that women with BRCA mutations have improved PFS with PARP inhibitor maintenance therapy [7-9]. Therefore, offering BRCA test is important to all women with newly diagnosed epithelial ovarian cancer for PARP inhibitor treatment decisions. In 2020, the American Society of Clinical Oncology recommended early germline and somatic BRCA testing in epithelial ovarian cancer. In Korea, germline and somatic BRCA tests are covered by NHI for patients with advanced ovarian cancer, and the following tests for 5 HRDs are available: Foundation One CDx, Myriad Mychoice, GC Genome, AmoyDx HRD Focus panel, and SOPHiA® DDM HRD solution. Although assays evaluating HRD have been used to guide treatment, evidence supporting routine tumor testing using HRD assays is insufficient [7,8,77]. Based on the practice guidelines of the Korean Society of Gynecologic Oncology, the germline BRCA test should be offered to any patient with ovarian cancer. Somatic BRCA tests can be used to detect additional BRCA variants (Evidence level II, recommendation level A). HRD or multigene testing is not recommended. The development of optimized HRD biomarkers to provide effective treatment stratification is urgently needed, and translational research on these biomarkers should be prioritized.

3. China

Based on the 2022 White Paper on the Diagnosis and Treatment of Ovarian Cancer in China, 93% of doctors recommend BRCA1/2 testing, indicating that doctors have reached a consensus on the understanding and importance of BRCA gene testing and routinely recommend patients to undergo BRCA gene testing. When asked for specific recommendations, 97% of physicians considered options and medications they could use to guide maintenance. Only 70% of patients received BRCA1/2, 23% less than the 93% recommended by doctors. Of the patients studied, 16% had mutations of unknown type, 19% carried germline mutations, and 11% carried somatic mutations, indicating information asymmetry between doctors and patients regarding their understanding of BRCA testing. The survey results showed that 72.3% of doctors would recommend patients to undergo HRD testing, mainly for maintaining treatment plans and drug selection as well as guiding patients' prognosis and survival. BRCA1/2 gene mutation is the most specific homologous recombination repair (HRR) gene causing HRD and the most ideal predictor of the efficacy of PARP inhibitors to date. BRCA germline and somatic mutations are equally effective in predicting the efficacy of PARP inhibitors in ovarian cancer. Additionally, embryonic and/or somatic mutations of HRR-related genes, such as *RAD51B/C/D*, *BRIP1*, *PALB2*, *NBN*, *ATM*, *CHK1/2*, and *CDK12*, can also lead to tumor HRD. A retrospective analysis based on Study19

https://doi.org/10.3802/jgo.2024.35.e87

found that patients with CDK12, RAD51B, and BRIP1 gene mutations and those with BRCA1/2 gene mutations received similar PFS benefits from olaparib maintenance therapy [78]. Because individuals carrying these mutations are rare, more prospective studies are needed to confirm the results. The NCCN guidelines recommend testing for 15 HRR-related genes, including *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, and *PPP2R2A*. Furthermore, the types of variation detected should include point mutation, insertion/deletion, and amplification. BRCA1 and RAD51C promoter methylation also cause HRD, which is usually mutually exclusive with BRCA gene mutations in tumor tissues. However, there is insufficient evidence that HRR gene promoter methylation is related to the clinical efficacy of PARP inhibitors, and results are conflicting. Genome-based mutation lineage analysis can fully reflect the endogenous and exogenous mutation processes of tumor cells, and each mutation includes DNA damage, repair, replication, and other components. The corresponding mutation lineage characteristics can be obtained through bioinformatics technology. Because of its low diagnostic specificity and lack of an exact threshold value, it cannot be used as a marker to predict the efficacy of PARP inhibitors. HRD detection and clinical application should be standardized, but its application prospects are worth looking forward to.

4. Taiwan

All patients with newly diagnosed ovarian cancer will be counseled regarding genetic testing. There is no consensus regarding the methodology of BRCA/HRD/panel tests. However, all laboratories should be certified and approved by the new regulations regarding laboratory-developed tests, which will become mandatory from February 2024. NHI does not reimburse these panel genetic tests. However, some drug companies provide a patient-support program for newly diagnosed ovarian cancer at advanced stages. These companion diagnostics may be continued with a patient-support program or out-of-pocket money for patients in the near future. However, NHI has announced that small panels directly relevant to reimbursed target therapies will be partially reimbursed with copayment from May of 2024.

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