Introduction

There is consensus that two distinct histotypes of epithelial ovarian cancer, i.e. clear-cell carcinoma and mucinous adenocarcinoma, are more resistant to chemotherapy and have a worse prognosis than the papillary serous type [1, 2]. Therefore, gynecological trial groups have been conducting histotype-specific trials for these two entities. In this article, we discuss the updated status of trials that are ongoing, or being planned worldwide on nonserous ovarian cancer, in particular the clear-cell carcinoma (CCC) and the mucinous adenocarcinomas of the ovary.

Clear-cell carcinoma

CCC is a rare tumor in western countries, although it represents more than 20% of tumors in Japanese ovarian cancer patients [3]. Sugiyama et al. first reported that CCC appeared to be resistant to conventional chemotherapy [3], and a retrospective meta-analysis confirmed this [1, 2]. At this moment, worldwide much effort is being made to find better strategies for the treatment of patients with CCC, including other chemotherapeutic approaches and the use of molecular targeted agents.

Chemotherapy trials

JGOG3017 trial (first line). The first histotype-specific phase III trial is the JGOG3017 study. In this trial, patients with stages Ia up to IV CCC were randomized to receive an experimental regimen of irinotecan (CPT-11, a topoisomerase-I inhibitor) and cisplatin (CPT-P) or the standard paclitaxel/carboplatin (TC) regimen. The choice of the CPT-P regimen was based on the promising findings of an earlier carried out randomized phase II with the same two regimens [4]. The TC regimen (T 175 mg/m² and C calculated for an AUC of 6 mg/ml min, both given i.v.) was administered every 3 weeks for six cycles. The CPT-P regimen (CPT-11 60 mg/m² on days 1, 8, 15 and cisplatin 60 mg/m² on day 1, both given i.v.) was administered every 4 weeks for six cycles. Primary end point of this study is progression-free survival (PFS), and secondary end points are overall survival (OS), and safety.

JGOG268 trial (first line). GOG268 trial is an open-label phase II trial for newly diagnosed stages III and IV CCC of the ovary to examine the activity of one of the mTOR inhibitors, temsirolimus. Primary tumors must contain at least for 50% the clear-cell component. Tumors should be negative for expression of WT-1 antigen and estrogen receptor (ER) antigen by immunohistochemical (IHC) staining.

The study opened in 2006 in Japan, Korea, France and UK, and closed for accrual in 2009 with 642 patients. The data will mature in 2014.

Molecular targeted agent trials

mTOR inhibitors

GOG268 trial (first line). Since more than 80% of CCC of the ovary has shown activation of the AKT-mTOR pathway, it is of great interest to explore the potential of mTOR inhibitors [5, 6]. GOG#268 trial is an open-label phase II trial for newly diagnosed stages III and IV CCC of the ovary to examine the activity of one of the mTOR inhibitors, temsirolimus. Primary tumors must contain at least for 50% the clear-cell component. Tumors should be negative for expression of WT-1 antigen and estrogen receptor (ER) antigen by immunohistochemical (IHC) staining.

Primary end point of this trial is PFS at 12 months, and secondary end points include adverse events, duration of PFS and OS, and tumor response. IHC expression of components of the mTOR signaling pathway will be explored.

Temsirolimus will be administered in combination with paclitaxel and carboplatin for 6 cycles, and then given for 11 cycles as a maintenance therapy. For the combination phase, paclitaxel at 175 mg/m² and carboplatin calculated for an AUC of 6 mg/ml min is administered i.v. on day 1. Temsirolimus at 25 mg/day is administered on days 1 and 8 i.v. This combination will be repeated every 3 weeks for six cycles. For the maintenance phase (cycle 7–17), temsirolimus at 25 mg/day will be administered on days 1, 8, and 15 every 3 weeks for 11 cycles.

In this trial, the United States will enroll 45 patients and also Japan will enroll 45 patients. This sample size will result in an 80% power to detect an improvement in median PFS from 3 to 5 months at a 10% one-sided level of statistical significance. Genetic difference between clear-cell carcinomas in both countries will be compared.

JGOG3021/EVEROCC trial. JGOG is planning a phase II trial of another mTOR inhibitor, everolimus, for recurrent CCC of the ovary. This is an open-label single-arm trial to examine
whether everolimus improves the clinical control rate. Extensive translational research will be incorporated in this trial. Eligible patients will be those diagnosed as CCC of the ovary and recurrent after at least one platinum-based chemotherapy, but no more than three prior chemotherapy regimens. Patient consent must be obtained before enrollment for the exploration of PIK3CA/KRAS mutations. Primary end point is the clinical control rate (CR, PR, SD>8 weeks). Secondary end points are OS, PFS, response rate, adverse events, and the relationship between tumor biomarkers and antitumor efficacy. Everolimus at 10 mg will be orally administered daily until disease progression or unacceptable toxicity is observed. As one of the translational research components, correlation between the change of SUV of the PET scan and antitumor effect of everolimus will be examined to investigate whether change of SUV is a useful biomarker to predict the efficacy of mTOR inhibitor.

This trial is ready to open soon, but is pending Japanese government funding approval.

antiangiogenic drugs
GOG254 (recurrant). GOG is now conducting a single-arm phase II trial to evaluate the efficacy of sunitinib malate in recurrent or persistent CCC of the ovary. Sunitinib malate is an oral agent and an inhibitor of vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR) tyrosine kinase. Primary tumors must be of at least 50% clear-cell histology and negative for expression of WT-1 antigen and ER antigen by IHC staining. Sunitinib malate 50 mg/day for 4 weeks followed by 2 weeks off is administered in repeated 6-week cycles until disease progression or unacceptable adverse effects that prohibit further therapy occurs. Primary objectives are to evaluate the antitumor activity of sunitinib malate in patients with persistent or recurrent CCC and to examine the nature and degree of toxicity in this cohort of patients treated with this regimen. Secondary end points are duration of PFS and OS in this patient population. This trial opened April 2010 and accrual of the first stage (24 patients) was completed in October 2012.

nintedanib (recurrant). Scottish Gynaecologic Cancer Trial Group, National Cancer Research Institute, and Nordic Society of Gynecologic Oncology are planning a randomized phase II study of nintedanib (BIBF1120) versus chemotherapy in recurrent CCC. Nintedanib is a novel triple angiotinase inhibitor that inhibits VEGFR, PDGFR, and FGFR. In this trial, platinum-resistant recurrent CCC will be randomized either to nintedanib 200 mg b.i.d. until progression or one of the single chemotherapy agents, PLD, weekly paclitaxel, or weekly topotecan. The primary end point of this study is PFS, and secondary end points include OS, toxicity, response rate, and QoL.

mucinous adenocarcinoma
Mucinous adenocarcinoma is another rare entity of ovarian cancer, which has been known to be resistant to chemotherapy, when found in primary advanced-stage disease or recurrent disease [7]. It has been hypothesized that mucinous adenocarcinoma is similar to colon cancer [8]. In fact, there are a number of trial proposals using chemotherapy regimen or molecular agents suitable for colorectal cancer. However, due to the rarity of the tumor, it is extremely difficult to conduct such trials even with international collaboration.

mEOC trial
To the best of our knowledge, mEOC/GOG241 is the only ongoing prospective clinical trial for mucinous adenocarcinoma. This is a GCIG intergroup trial, in which paclitaxel/carboplatin ± bevacizumab is being compared with capecitabine/oxaliplatin ± bevacizumab as first-line chemotherapy in patients with mucinous epithelial ovarian cancer (mEOC). Eligible patients are newly diagnosed stage II–IV mucinous carcinoma of the ovary or fallopian tube, or recurrent stage I. Target sample size is 332, but the accrual is slow not only because of the rarity of the disease but also because of the nonavailability of oxaliplatin and capecitabine for ovarian cancer in the United States.

There is currently no ongoing trial or even one close to being opened for recurrent mucinous adenocarcinoma. Again, this is due to the small numbers of patients that would be available for such a trial. International collaboration is undoubtedly needed. However, the existing cross-border differences regarding regulatory mechanisms and/or drug availability are the real barriers to overcome in the near future. Moreover, overtaking the hurdle of drug (non)availability in each country should get high priority.

disclosure
The authors have declared no conflicts of interest.

references