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ORIGINAL ARTICLE

Continuing Therapy beyond Adjuvant Chemotherapy to Optimise Cure in Advanced Ovarian Cancer: a Dream Coming True?

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ABSTRACT

The GOG111 and OV-10 were pivotal studies published in 1996 and 2000 respectively which established paclitaxel / cisplatin as standard postoperative adjuvant chemotherapy for advanced epithelial ovarian cancers. A second major breakthrough in the ensuing past decade has yet to be witnessed. Carboplatin has been proven to confer similar efficacy when combined with paclitaxel with much less neurotoxicity in the GOG158 and AGO studies that were reported in 2003, and have since been adopted as standard clinical practice. Replacing paclitaxel with docetaxel, delivery of cisplatin intraperitoneally, or adding a third agent to form triplets have not produced impressive improvements. Moreover, they were not widely accepted due to technical difficulties and unacceptable toxicities. For stage III/IV cancers, despite a high clinical response rate of 70 to 80% and a pathological complete response rate of ~30% after 6 to 8 cycles of paclitaxel / carboplatin following primary cytoreductive surgery, the median overall survival remains relatively low at ~26 months for those with bulky residuum, and ~60 months for those with optimal cytoreduction, translating into a 5-year overall survival of ~30 to 40%. The median progression-free survival remains at around 16 months only for patients with stage IV and stage III disease after suboptimal cytoreduction, and at 24 months only even for those with stage III after optimal cytoreduction. The resulting low 5-year progression-free survival of approximately 20% indicated continuous disease relapses or progression following postoperative chemotherapy and hence the concept of effective consolidation or maintenance therapy appeared attractive. Over the years, studies involving sequential / consolidation standard-dose oral or intravenous 'second-line' chemotherapy, intraperitoneal chemotherapy, high-dose chemotherapy with stem cell transplantation, external beam radiotherapy or intraperitoneal radiotherapy with radioactive phosphorus or radioactive monoclonal antibody have largely failed to improve outcomes. More recently, results of randomised studies testing biological therapies such as interferon, CA125-specific monoclonal antibody, multi-targeting agents and anti-angiogenesis targeted therapy have also been reported, but yielded variable results. Early results from 2 recent randomised studies suggest progression-free survival benefit by adding bevacizumab concurrently with, and then as prolonged maintenance therapy following postoperative adjuvant paclitaxel / carboplatin chemotherapy.

Key Words: *Antineoplastic combined chemotherapy protocols; Cisplatin; Disease-free survival; Ovarian neoplasms; Paclitaxel; Treatment outcome*

中文摘要

治療晚期卵巢癌後的輔助化療以外再施以持續療法為病人帶來最佳效果：夢想是否可以成真？

顏繼昌

分別發表在1996及2000年的兩項關鍵性研究（GOG111及OV-10）確立了用紫杉醇（paclitaxel）/順鉑（cisplatin）作為晚期上皮性卵巢癌的標準術後輔助化療，在其後十年卻再沒有突破。在2003年發表

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的GOG158及AGO研究指出，卡鉑（carboplatin）加紫杉醇和以往的順鉑加紫杉醇效果相若，而且神經毒性大幅度減少，自此被引入作為標準臨床使用。把多西他賽（docetaxel）替代紫杉醇，並在腹腔內注入順鉑，或加入第三種製劑，療效並不顯著增加；而且由於技術上的困難和毒性反應有所增加，這些方法不被廣泛接受。第三/四期卵巢癌患者在進行第一次卵巢癌減積手術並接受6至8周期紫杉醇加卡鉑的化療後，儘管有70至80%的高反應率及30%的病理完全反應率，總存活率中位數仍處於低水平。有大型殘餘腫瘤的病人，中位生存期約為26個月；而腫瘤減積達至最佳效果的病人，中位生存期則約為60個月；相當於30至40%的五年生存率。腫瘤減積未達至最佳效果的第三/四期病人，其無惡化生存期的中位數只有大約16個月。就算是腫瘤減積達理想效果的第三期病人，其無惡化生存期中位數亦只有24個月。只有20%的五年總生存率，顯示癌病在接受化療後會不斷復發或繼續惡化，因此進行有效的鞏固治療或維持治療的概念顯得很吸引。多年來，有很多研究關於序貫或鞏固性的治療，如用標準劑量的口服或靜脈注射的二線化療、腹腔化療、高劑量化療併幹細胞移植、體外放射治療、或以放射性磷及放射性單克隆抗體作腹腔內放射治療，可是它們大多數都未能提升療效。最近有一些測試生物治療的隨機對照研究，如使用干擾素、CA125單克隆抗體、多靶向製劑及抗血管生長標靶治療等，但報導的療效並不一致。兩個近期發表的隨機對照研究中，其早期結果顯示術後紫杉醇加卡鉑輔助化療中加入同步貝伐珠單抗（bevacizumab），及以其作為維持療法有助延長無惡化生存期。

INTRODUCTION

Ovarian cancer is the 6th commonest to affect females in Hong Kong and the second commonest arising from the female genital tract; 469 new cases were diagnosed in 2008.[1] In the US, 112,541 newly diagnosed ovarian cancers were reported in the 10-year period of 1995 to 2004 based on cancer registries that covered 64% population, which gave an age-adjusted incidence rate of approximately 112 per million.[2] The majority of the ovarian cancer patients presented with late-stage disease, with a 10-year overall survival (OS) of only 40%, even for those achieving a pathologically complete response (pCR) after chemotherapy. By contrast, 70 to 90% of the 20 to 25% of patients presenting with stage I and II disease survived 10 years.[3]

TREATMENT MILESTONES FOR ADVANCED OVARIAN CANCERS

Since McGuire et al's landmark GOG 111 study in 1996[4] that demonstrated the superiority of combination paclitaxel and cisplatin over the then standard regimen of cyclophosphamide and cisplatin, there have been few further breakthroughs. This pivotal randomised study entailed 386 patients with stage III and IV ovarian cancers treated with 6 cycles of either paclitaxel and cisplatin or cyclophosphamide and cisplatin, after primary cytoreductive surgery.[4] There was a significant difference in both progression-free survival (PFS) and OS in favour of the former treatment, with a hazard ratio (HR; it refers to the risk of adversity relative to the comparator) of 0.7 and 0.6, respectively; although the absolute 4-year PFS of 30% and OS of approximately 20% were neither impressive. In the study, paclitaxel was infused as 135 mg/m^2 over 24 hours. In 2000, the superiority of paclitaxel and cisplatin over cyclophosphamide and cisplatin was also confirmed by a European / Canadian Intergroup Study OV-10, in which paclitaxel was infused at 175 mg/m^2 over 3 hours.[5]

Due to the shorter infusion schedule and the probability of fewer neurological complications, carboplatin (instead of cisplatin) in combination with paclitaxel was soon investigated in 2 randomised studies reported in 2003.[6,7] The German AGO study enrolled 798 patients with stage IIb-IV cancers.[6] In the study, 68% and 81% of those with measurable residual disease after primary cytoreductive surgery treated by paclitaxel / carboplatin and paclitaxel / cisplatin respectively achieved a clinical response, whereas 37% and 43% of those undergoing second-look laparotomy achieved pCR.[6] The differences were not statistically significant. There was also no significant difference in actuarial PFS and OS between the 2 arms. As a whole group, an overall clinical response rate of around 70 to 80%, a 5-year OS of around 35% and a 5-year PFS of around 20% were observed for stage IIb-IV cancers. The GOG-158 study,[7] on the other hand, enrolled only patients with optimally cytoreduced (residuum <1 cm) stage III disease. Again no statistically significant difference was observed

between those receiving paclitaxel / carboplatin versus paclitaxel / cisplatin. Conceivably, the more favourable patients recruited in the GOG-158 study showed better overall outcome when compared with the AGO study, as pCR was demonstrated in 46 to 53% patients undergoing second-look laparotomy, and the 5 year OS and PFS were ~45% and 25% respectively. Nevertheless, those with no gross residuum after primary cytoreductive surgery had a superior 5-year PFS of around 40% compared to around 15% for those with any gross residuum (but <1 cm), and this was irrespective of the chemotherapy regimen to which they were assigned.[7] Taken together, these 2 randomised studies established the paclitaxel / carboplatin regimen as standard adjuvant chemotherapy for advanced ovarian cancers after primary cytoreductive surgery.

Over the past couple of years, randomised studies were performed to challenge the supremacy of paclitaxel / carboplatin. The ICON 3 study[8] compared paclitaxel / carboplatin with other time-honoured regimens like CAP (cyclophosphamide / adriamycin / cisplatin), single-agent cisplatin, or single-agent carboplatin, but observed no significant survival difference. The other taxane of docetaxel was also partnered with carboplatin and compared with the standard paclitaxel / carboplatin regimen in the SCOTROC study reported in 2004.[9] It too showed no significant difference with respect to the various outcomes studied. The intraperitoneal delivery of paclitaxel / csiplatin was also compared with intravenous paclitaxel / cisplatin in the GOG 114 and 172 studies.[10,11] Although improvements in OS were observed, the restricting recruitment only to optimally cytoreduced patients, and the demanding technical expertise needed for intraperitoneal drug delivery have not endeared these regimens to clinical practice. Overall, paclitaxel / carboplatin remains the gold standard of chemotherapy, against which all new regimens should be benchmarked.

With the advent of new chemotherapy agents showing promise in second-line therapy and recurrent disease settings, the ambitious GOG0182-ICON5 study enrolled more than 4300 previously untreated stage III or IV patients to compare 4 new chemotherapy regimens with the standard control arm of 8 cycles of paclitaxel / carboplatin.[12] The 4 experimental arms consisted of 8 cycles each of 2 new triplets of paclitaxel / carboplatin / gemcitabine and paclitaxel / carboplatin / doxil, and 2 other regimens with sequential doublets (4 cycles of carboplatin / topotecan or carboplatin / gemcitabine) followed by 4 cycles of paclitaxel / carboplatin. The study results were reported in 2009, and demonstrated no significant superiority with respect to PFS or OS with the newer approaches (Figure).[12] Again, when patients were stratified by the amount of residual disease after primary cytoreductive surgery, those with only microscopic residuum fared significantly better than those with macroscopic residuum, which

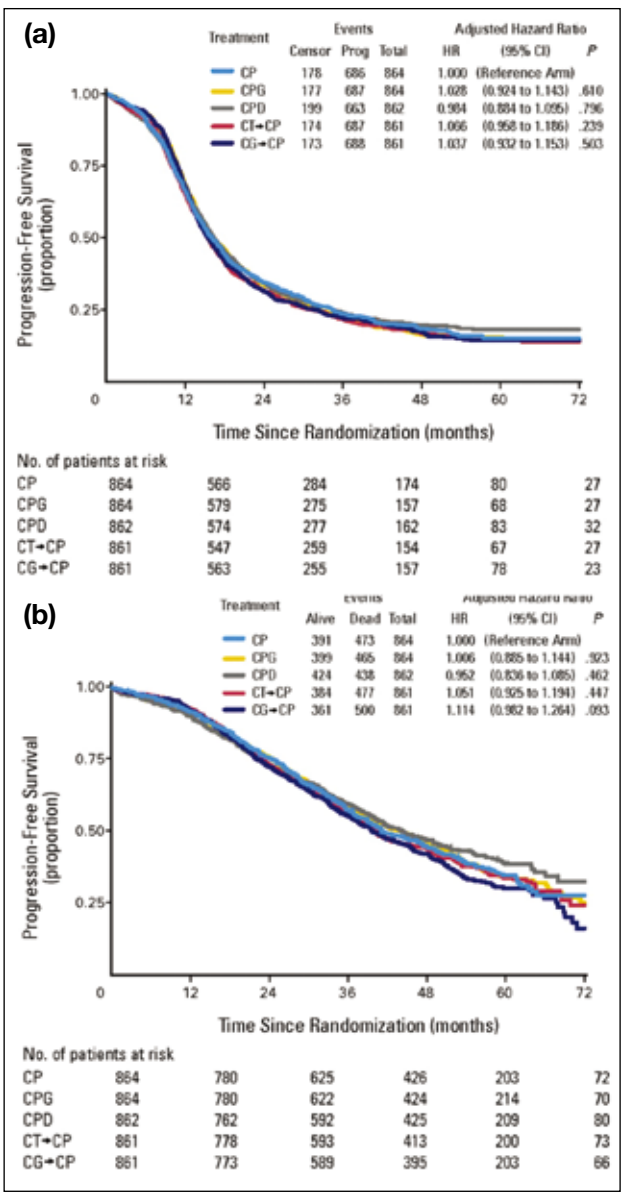

Figure. Estimates of (a) progression-free survival and (b) overall survival for each treatment arm in the GOG0182-ICON5 study.[12] Abbreviations: HR = hazard ratio. CP = carboplatin and paclitaxel; CPG, carboplatin, paclitaxel, and gemcitabine; CPD, carboplatin, paclitaxel, and doxorubicin; CT→CP, carboplatin plus topotecan, then carboplatin plus paclitaxel; CG→CP, carboplatin plus gemcitabine, then carboplatin plus paclitaxel. (Reprinted with author permission).

re-emphasised the importance of complete primary cytoreductive surgery, as well as the inability of aggressive chemotherapy alone to redeem those patients with a poor prognosis due to gross residual tumour after primary cytoreductive surgery.[12]

STRATEGIES TO IMPROVE OUTCOME IN PATIENTS WITH ADVANCED OVARIAN CANCERS

Early diagnosis has always been the key to improving patient outcome. As alluded to earlier, those with early stages have much better outcomes than those with advanced stage III or IV cancers. Short of a robust and cost-effective population-based screening programme, promulgating population education through mass media, and exploring sensitive serological tumour markers might be helpful. Recently the tumour marker of HE-4 (human epididymis protein 4) has been widely studied and proven to add sensitivity and specificity to CA-125 in distinguishing benign from malignant pelvic or adnexal masses.[13] Further studies to refine its adoption in diagnostic algorithms may provide clinicians a better tool to work towards an earlier diagnosis of ovarian cancer. Secondly, aggressive primary cytoreductive surgery by dedicated gynaecological specialists is critical in determining the prognosis of patients with advanced ovarian cancers, irrespective of the subsequent chemotherapy employed. More recently, neoadjuvant chemotherapy followed by 'interval' cytoreductive surgery has been reported to provide patients with stage IIIc or IV ovarian cancers an alternative option with equivalent outcomes.[14] Irrespective of the caveats and skepticism about the study, patients with marginal performance status or anticipated difficult primary surgery may be considered candidates for such an approach, so as to avoid significant postoperative complications.

Apart from the amount of residual tumour after primary cytoreductive surgery, the pathological response status obtained at second-look laparotomy after postoperative adjuvant chemotherapy is another significant predictor of outcome. Outside clinical studies, the second-look laparotomy or laparoscopy with or without interval cytoreductive surgery is no longer performed. If positron emission tomography (PET) / computed tomography (CT) scan findings can represent surrogates of pathological responses, we will have an additional tool for formulating further customised therapies for individual patients after chemotherapy, and denounce second-look laparotomy once and for all as the value of additional interval cytoreductive surgery is still the bone of contention. Obviously, an even more efficacious chemotherapy regimen is desirable, especially if it can be confirmed to confer more durable pCRs than after the current standard paclitaxel / carboplatin chemotherapy. A closely related approach is to add sequential consolidation or maintenance therapy after completing adjuvant chemotherapy, particularly for those who achieved complete clinical and / or pathological responses. Through further chemotherapy delivered either orally, intravenously, intraperitoneally, or in a high-dose fashion, or through further radiotherapy or biological therapy, avoidance or delay of relapse will hopefully be achieved resulting in a parallel improvement in PFS. The strategy makes profound clinical sense as the typical actuarial PFS curve of patients with advanced ovarian cancer shows continuous progression throughout the 4 to 5 years after surgery, as exemplified in the GOG0182-ICON5 study (Figure).[12] There was comparatively less progression (around 10%) in the first 6 months when patients were receiving chemotherapy and also modest progression (around 20%) after 18 to 24 months. However, there was a precipitous drop in PFS (up to 50%) in the 12-month period from around 6 to 18 months after primary cytoreductive surgery. Instituting effective maintenance therapy during this 'vulnerable' period is therefore scientifically sound to shift the PFS curve upwards and to the right.

CONSOLIDATION AND MAINTENANCE CHEMOTHERAPY

Prolonging further intravenous chemotherapy beyond 6 or 8 cycles is the logical option to consider as a means of consolidation or maintenance therapy. In the 1990s, 3 randomised studies reported outcomes after comparing 5 or 6 cycles of adjuvant chemotherapy with no more treatment or 3 to 6 cycles of the same chemotherapy after primary cytoreductive surgery.[15-17] The chemotherapy regimens used in the 3 studies (all initiated before the GOG 111 report) were non-taxane containing, and included: CAP, single-agent carboplatin or single-agent cisplatin. None of these studies entailing prolonged chemotherapy reported any improvement in OS.[15-17] The Mito-1 study (Multi-center Italian Trials in Ovarian Cancer) explored the use of topotecan, which was considered non–cross resistant with taxane, as sequential consolidation / maintenance therapy.[18] A total of 273 stage Ic-IV patients were recruited and randomised to either 4 cycles of topotecan or no further treatment after achieving clinical complete or

partial response after 6 cycles of paclitaxel / carboplatin chemotherapy following primary cytoreductive surgery. The study did not report any significant difference in PFS with the addition of 4 cycles of topotecan.

On the other hand, the GOG 178 study[19] randomised 277 patients (of whom 222 were evaluable) who achieved clinical complete response (CR) after 5 to 6 cycles of paclitaxel / carboplatin chemotherapy to either 3 or 12 cycles of maintenance intravenous paclitaxel. Patients receiving 12 cycles had statistically superior median PFS (28 months vs 21 months, p = 0.0023) at the expense of more grade 3 sensory neuropathy. However, data on the pattern of disease progression showed clustering of progression around the 9-month period after completion of maintenance paclitaxel, namely during the 3-12–month period for the patients with shorter and during the 12-21–month period for those with longer maintenance paclitaxel respectively.

Patients with stage III disease achieving either pCR or with minimal macroscopic disease (<1 cm) in an adhesion-free abdomen after primary adjuvant chemotherapy should be the best candidates for exploring the benefit of consolidation intraperitoneal chemotherapy. This was the inference from the sequential GOG studies comparing primary intraperitoneal chemotherapy with intravenous chemotherapy after primary cytoreductive surgery, in which the former showed superior outcomes.[10,11,20] Patients with stage IIb-III achieving pCR at second-look laparotomy after primary adjuvant platinum-based chemotherapy were recruited in the EORTC 55875 study.[21] A total of 153 patients were randomised between 1988 and 1997 to either 4 cycles of intraperitoneal cisplatin at 90 mg/m^2 once every 3 weeks, or observation, but the study was terminated prematurely due to slow patient accrual. At a median follow-up of 8 years, there was no statistically significant difference between treatments in either PFS (HR = 0.89; 95% confidence interval [CI], 0.6-1.3) or OS (HR = 0.82; 95% CI, 0.5-1.3).

During the 1990s, enthusiasts of the strategy of high-dose chemotherapy followed by autologous stem cell transplantation held high hopes for curing ovarian cancer using this approach, as it was one of the most chemo-sensitive solid tumours with well-established sensitivity to alkylating agents. Moreover, the dose-response relationship and dose-intensity data on ovarian cancer for a number of chemotherapy drugs had been available for many years.[22,23] The minimal risk of being contaminated by cancer cells from using bone marrow or peripheral stem cells also lent collateral support to this approach. The only randomised study was reported in an abstract form in ASCO in 2004.[24] The GINECO-FNCLCC-SFGM-TC study randomised patients with stage III or IV cancers to either 3 cycles of conventionally dosed chemotherapy with carboplatin and cyclophosphamide, or high-dose chemotherapy using the same drugs followed by peripheral stem cell transplantation. Among the 110 patients enrolled from 1995 to 2000, 39% achieved pCR, 20% had residual microscopic disease and 41% had residual macroscopic tumour noted at second-look laparotomy after primary adjuvant chemotherapy. In the high-dose treatment arm, 20% of the patients did not receive high-dose chemotherapy and there were 2 deaths from drug toxicity. After a median follow-up of 60 months, there was a numerical advantage for high-dose treatment in terms of median PFS (17.5 vs 12.2 months) and OS (49.7 vs 42.5 months), both of which were not statistically significant.

CONSOLIDATION AND MAINTENANCE RADIOTHERAPY

Since radiotherapy had been the established standard therapy after primary cytoreductive surgery before the platinum era, the role of consolidation radiotherapy has also been vigorously studied over the past 10 to 20 years. Sorbe et al[25] reported the randomised study from the Swedish-Norwegian Ovarian Cancer Study Group in 2003. A total of 172 patients with either pCR or pathological partial response (pPR) after 4 cycles of postoperative adjuvant chemotherapy with cisplatin and adriamycin (both at 50 mg/m^2) were recruited between 1988 and 1993. Those with pCR (n = 98) were randomised to either observation, 4 more cycles of the same chemotherapy, or whole abdomen-pelvic radiotherapy, whereas those with pPR (n = 74) were randomised to chemotherapy or radiotherapy. The PFS of patients with pCR was superior after adjuvant radiotherapy when compared to those on chemotherapy (p = 0.032) and the OS difference favoured radiotherapy although the difference was not statistically significant (p = 0.084). The benefit, however, was partially offset by an increased incidence of grade 3 bowel toxicity (10% vs 4%), with some patients having an ileostomy or colostomy for the bowel complications.

Conversely, in 1993 the North Thames Ovary Group Study reported similar PFS and OS values for patients receiving either consolidation radiotherapy or

chemotherapy after primary adjuvant chemotherapy.[26] From 1985 to 1989, 117 patients with stage IIb-IV cancers achieving either pCR or macroscopic residual tumour of <2 cm after 5 cycles of carboplatin were randomised to 5 more cycles of carboplatin or abdominal-pelvic radiotherapy. There was no difference in outcome in the subgroups of patients with pCR status or residual macroscopic tumour.

Arguably, more targeted radiation to the high-risk peritoneal surface harbouring microscopic disease could achieve a better therapeutic ratio. In a randomised study, 202 stage III patients who achieved pCR after chemotherapy were recruited from 1987 to 1996.[27] They were randomised to either 15 mCi of radioactive phosphorus-32 or observation. The radioactive phosphorus-32 in colloid suspension produced pure beta radiation with a short radiation range of 4 mm, which decayed at a half-life of 14.3 days. The radioactive phosphorus-32 was delivered intraperitoneally in 500 cc normal saline, preceded and followed by 250 cc normal saline. At a median follow-up period of 63 months, there was no difference in relapse rate or OS. The relapses after intraperitoneal radioactive phosphorus treatment were mostly in retroperitoneal sites, liver parenchyma, and at peritoneal sites to where distribution was suspected to be suboptimal.

Targeting precision can be enhanced by using a murine monoclonal antibody tagged with yttrium-90, which targets the epitope of *MUC1* gene product expressed on the apical surface of 90% of adenocarcinoma cells. From 1998 to 2003, 447 patients with stage Ic-IV cancers with negative second-look laparoscopy after platinum-based adjuvant chemotherapy were randomised to 25 mg of the radioactive antibody with or without institutional standard therapy, or observation with or without institutional standard therapy alone.[28] There was no difference between groups in OS, relapse-free survival, or time-to-relapse. However, the lack of benefit may be due to the following reasons: the proportion of patients receiving consolidation chemotherapy initiated as institutional standard therapy was not balanced, radiation doses achieved through one single intraperitoneal instillation were possibly suboptimal, and the expression of the *MUC1* gene in tumours located in sanctuary subserosal sites may have been obscured. Nevertheless, the study demonstrated a proof of concept, in that the lack of overall benefit could have resulted from an increased incidence of extraperitoneal relapses offsetting the reduction of intraperitoneal relapse in those receiving radioactive monoclonal antibody.[29]

CONSOLIDATION AND MAINTENANCE BIOLOGICAL THERAPY

Prolonged biological therapy is an attractive option for maintenance therapy, as when given alone such therapy may be effective for small volume cancers and give rise to fewer side-effects than cytotoxic agents. Maintenance alpha-2 interferon was given subcutaneously until disease progression or significant toxicity in a randomised study in patients who did not progress after postoperative chemotherapy.[30] A total of 300 patients with stage Ic-IV were enrolled from 1990 to 1997 and randomised to either maintenance interferon or observation. Both OS and event-free survival in the 2 arms did not differ when the study was reported in 2004. Another study with similar design was reported by SWOG in 2006.[31] From 1988 to 1999, 74 patients with documented disease-free status at second-look laparotomy after at least 4 cycles of platinum-based chemotherapy were randomised to either observation or intraperitoneal interferon given once weekly for 6 cycles. The study was terminated prematurely and reported no difference in both OS and PFS.

With the ubiquitous prevalence of CA-125 (the surface mucin-like glycoprotein antigen present in almost 95% of all non-mucinous cancers), a monoclonal antibody targeting the antigen eliciting T-cell dependent autoimmune cytotoxic properties seemed a most desirable treatment option. The murine antibody oregovomab was used in a randomised study for 147 patients with stage III or IV ovarian cancer achieving CR after postoperative chemotherapy.[32] Patients were randomised to either observation or oregovomab; the latter was given intravenously once at a dose of 2 mg in 50 ml of normal saline over 20 minutes. The 2 arms had similar time to relapse (TTR). However, there was an improvement of TTR in certain subgroups, namely those having a low CA-125 level, a low volume of residual tumour, and a robust immune response after monoclonal antibody treatment.

More recently, agents targeting vascular endothelial growth factor (VEGF) and tyrosine kinase (TK) receptors, as well as multiple downstream cellular signalling pathways have emerged as possible effective therapies in certain cancers. Both sorafenib and pazopanib are being investigated in ongoing randomised

clinical studies in which such multi-targeting agents were tested as maintenance therapies. Bevacizumab, another monoclonal antibody targeting circulating VEGF (shown to be effective in breast, colorectal, and lung cancers) has also been studied in 2 large randomised studies.[33,34] Both the GOG0218 study[33] and the ICON7 study[34] had similar designs for treating advanced ovarian cancers, and have been reported in an abstract form in 2010 ASCO and ESMO meetings, respectively.

In the GOG0218 study, patients with stage III (both optimally or suboptimally cytoreduced) or stage IV ovarian cancers were randomised after primary cytoreductive surgery to one of the 3 following arms: carboplatin (area under the curve [AUC] = 6) and paclitaxel (175 mg/m^2) for 6 cycles, similar chemotherapy for 6 cycles with concomitant bevacizumab (15 mg/kg) for 5 cycles from cycle II onwards, and chemotherapy plus concomitant bevacizumab as in the 2nd arm and 15 more cycles of maintenance bevacizumab to be given at the same dose and interval as the concomitant treatment.[33] Altogether 1873 patients were randomised with stratification for performance status and stage / residual tumour bulk. About two-thirds of the patients had either suboptimally cytoreduced stage III or IV cancers, and more than 80% had serous carcinoma. The protocol's primary endpoint was PFS and was reported to favour treatment with bevacizumab both concomitant with and as maintenance therapy after chemotherapy (arm 3). The median PFS was 14 months, which was statistically superior to the values in treatment arms 1 and 2 (10 and 11 months, respectively), with a HR of 0.72 (95% CI, 0.63-0.82). Interestingly, concomitant bevacizumab without maintenance did not confer benefit compared to chemotherapy alone. In the forest plot, the benefit in PFS was found across all subgroups. At a median follow-up of 17 months at the time of the report, there was no difference in OS. The investigators reported no excess of adverse events including gastrointestinal perforation in those treated with bevacizumab and the anti-VEGF therapy was generally well tolerated. They concluded that after primary cytoreductive surgery, adding concomitant and maintenance bevacizumab to standard paclitaxel / carboplatin chemotherapy should be considered a standard option in patients with advanced ovarian cancer.

The ICON7 study had a similar study design.[34] In all, 1028 patients with stage I-IV ovarian cancers were randomised to either 6 cycles of paclitaxel / carboplatin chemotherapy, or similar chemotherapy with concomitant and maintenance bevacizumab. The bevacizumab was given at 7.5 mg/kg (half the dosage employed in GOG0218 study). It could be started together with the first cycle of chemotherapy at the discretion of the investigators, and be given as maintenance treatment for a total of 12 additional cycles after completion of chemotherapy (vs 15 cycles in GOG0218 study). Due to the difference in inclusion criteria regarding the cancer stage (stage I and II allowed), only one-third of the patients in the ICON7 study had an unfavourable status (suboptimally cytoreduced III or IV stage disease). In this study too the protocol-defined primary endpoint was PFS. The bevacizumab-treated arm had a superior median PFS at 18.3 months, which was 2.3 months longer than those treated with chemotherapy alone. The difference was statistically significant, with a HR of 0.79 (95% CI, 0.68-0.91). Although there was a general trend of benefit in all subgroups according to the forest plot, unfavourable status patients (with suboptimally cytoreduced stage III or stage IV cancers), which formed the majority of patients in the GOG0218 study, benefited more. In the unfavourable subgroup, the median PFS at 16 months was 5.4 months longer than that in the controls, with a HR of 0.68 (95% CI, 0.55-0.85), which was similar to the median PFS (14 months) in arm 3 patients of the GOG0218 study. Conceivably, there were more grade 3 or higher adverse events related to hypertension and thrombo-embolism in this study, but no new safety concerns. The ICON7 study was the second positive randomised phase III study showing a PFS benefit for concomitant and maintenance bevacizumab when added to chemotherapy. Eagerly awaited data on longer-term PFS, mature OS, and translational research should be available in 2012.

Superimposing and reading carefully the PFS curves of the 2 studies confirmed that addition of bevacizumab treatment prevents some of the expected progression during the maintenance phase, beginning at around 9 months to 1 year following chemotherapy. This is the most 'vulnerable' period after postoperative adjuvant chemotherapy alone,[33,34] and the addition of bevacizumab therapy shifts the PFS curves to the right. Due to the difference in the proportion of more favourable optimal stage III patients (two-thirds vs one-third), the PFS curves of both arms of the ICON7 study stayed above those in the GOG0218 study counterparts. Irrespective of the difference in dose and maintenance

duration of bevacizumab, there was an improvement in PFS with addition of concomitant and maintenance bevacizumab to paclitaxel / carboplatin chemotherapy. Judging from the slowly closing gap between PFS curves beyond 2 years, it may be reasonable to explore continuing prolonged maintenance bevacizumab beyond 12 to 15 cycles, provided that significant adverse events are not a problem. If longer follow-up does not demonstrate an overall survival benefit, a vigorous cost-benefit analysis needs to be conducted to justify the adoption of such costly maintenance therapy. Overall, the results of both studies indicate encouraging improvement in PFS, but still fall short of fully realising the dream of curing advanced ovarian cancers.

CONCLUSION

Advanced ovarian cancer is definitely treatable but still not a commonly curable cancer after standard cytoreductive surgery and adjuvant paclitaxel / carboplatin chemotherapy. Aggressive primary cytoreductive surgery before adjuvant chemotherapy, or aggressive interval surgery after neoadjuvant chemotherapy, is crucial, as the ability to remove all macroscopic tumours predicts a favourable prognosis. Delivering chemotherapy intraperitoneally may offer better outcomes for suitable patients with optimally cytoreduced stage III disease,[10,11,20] while additional concomitant and maintenance bevacizumab has been shown to prolong PFS, especially for advanced cancers.[33,34] More novel multi-targeting biological agents, validated serum markers for early cancer detection, and discovery of specific gene signatures that can predict outcomes should be further explored.

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