available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Editorial Comment

Having progress with upfront chemotherapy in ovarian cancer. Is it still a possible goal?

*Sandro Pignata**

Department of Urology and Gynecology, National Cancer Institute of Naples, via M. Semmola 80131, Naples, Italy

ARTICLE INFO

Article history:
Received 6 April 2010
Accepted 6 April 2010
Available online 6 May 2010

Epithelial ovarian cancer is the fourth cause of cancer-related death in women. More than 25,000 new cases are diagnosed each year in the United States alone[1] and approximately 75% of these are found in an advanced stage.[1,2] The standard of care for these patients is maximal surgical cytoreduction followed by systemic carboplatin/paclitaxel chemotherapy and, actually, is reasonable to expect a five-year survival for 40% and 20% of women diagnosed with ovarian cancer at stages III and IV, respectively.[2]

Ovarian cancer is considered as one of the most chemosensitive solid tumours. Platinum and paclitaxel reached the ovarian cancer scenario more than 20 years ago. In the early 1980s, cisplatin was recognised as a new and potent drug in the management of ovarian cancer with its efficacy related to the peculiar capacity of interaction with DNA. Paclitaxel, originally derived from the bark of the Pacific Yew tree, Taxus brevifolia, was identified as the active constituent in 1971. Two randomised trials (Gynecologic Oncology Group (GOG) 111, OV-10), comparing cisplatin/paclitaxel with cisplatin/cyclophosphamide, showed additional clinical benefit, in terms of progression free survival (PFS) and overall survival (OS) when cyclophosphamide was replaced by 3-weekly paclitaxel in the first line setting.[3,4] Due to the significant toxicity of the cisplatin–paclitaxel combination, three trials in the following years have investigated the equivalence of carboplatin and cisplatin in combination with paclitaxel in the first-line setting. The principle on the basis of these trials is that carboplatin is associated to significantly lower neurotoxicity and renal toxicity and that the combination of carboplatin and 3-h infusion paclitaxel can be given as an outpatient schedule.[5–7] All these trials showed a more favourable toxicity profile for the carboplatin/paclitaxel arm while no difference was observed in PFS and OS. Based on these data and due to the easiness of delivery, the carboplatin–paclitaxel combination has become an almost universal choice in the management of ovarian cancer, and it is the standard comparator in all the recent trials performed in this disease.

With carboplatin–paclitaxel it is possible to obtain a response rate of about 65%, PFS of 16–21 months and an OS of 32–57 months. However, although the majority of the patients respond to first line chemotherapy, most of them recur and require a salvage treatment. Thus, a very important priority for gynaecologic oncology research is to try to improve the outcome of the first line treatment.

In this issue of the European Journal of Cancer, Agarval et al.[8] on behalf of the SCOTROC group presents the data of a phase II study investigating a schedule of chemotherapy including four cycles of carboplatin followed by four cycles of gemcitabine and paclitaxel. This is the sixth of 6 consecutive trials with the same inclusion criteria evaluating the role

* Address: Division of Medical Oncology, Department of Urology and Gynecology, National Cancer Institute of Naples, Via Mariano Semmola, 80131 Naples, Italy. Tel.: +39 081 5903637; fax: +39 081 5903822.
E-mail address: sandro.pignata@gmail.com
0959-8049/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2010.04.005

of sequential chemotherapy with carboplatin followed by docetaxel (SCOTROC2A armA), gemcitabine/3-weekly docetaxel (SCOTROC2A armB), gemcitabine/weekly docetaxel (SCOTROC2A armC), irinotecan/docetaxel (SCOTROC2B armB), gemcitabine/3-weekly paclitaxel (SCOTROC2C) and gemcitabine/weekly paclitaxel (SCOTROC5). The aim of these phase II trials was to select the best comparator for phase III trials.

The SCOTROC consortium is one of the most important groups in gynaecologic oncology and the authors have to be complimented for their projects, including this, enrolling overall more than 300 patients.

In this paper the sequential schedule with four cycles of carboplatin followed by four cycles of 3-weekly paclitaxel/gemcitabine showed to be feasible and active with a 73.7% of response rate and a PFS of 14.2 months.[8] Taken overall, the data suggest that this sequential schedule does not perform better than the standard treatment and that should not be investigated in a phase III study. The results are in agreement with what is known from the literature: the addition of a third drug to carboplatin and paclitaxel is not able to improve the outcome of patients with ovarian cancer.

In the last 10 years gemcitabine, topotecan and pegylated liposomal doxorubicin (PLD) have shown significant activity in platinum-resistant and platinum-sensitive recurrent ovarian cancer and have been investigated also in the first line setting in addition to carboplatin/paclitaxel either with triplets of drugs or with sequential doublets.

The largest of these studies, and also the largest prospective treatment trial in advanced ovarian cancer is the GOG 182-ICON 5,[9] an international, 5-arm trial designed with the aim to evaluate four different experimental arms against carboplatin–paclitaxel. More than 4000 patients were randomly assigned to receive one of the following schedules of treatment: carboplatin and paclitaxel (control arm) or gemcitabine plus carboplatin plus paclitaxel (Arm 2); PLD plus carboplatin plus paclitaxel (with PLD given every other cycle) (Arm 3); topotecan plus carboplatin, given on Day 3 for 4 cycles followed by four cycles of carboplatin–paclitaxel (Arm 4); gemcitabine plus carboplatin for 4 cycles followed by four cycles of carboplatin–paclitaxel (Arm 5). Remarkably, none of the experimental arms showed a statistically significant improvement in the PFS or OS, compared with the standard treatment, which achieved a median PFS of 16.0 months and a median OS of 44.1 months for the entire study population, including both patients with optimal and suboptimal residual diseases. As expected, the triplets and sequential doublets were characterised by an increased haematologic toxicity.[9]

In accordance with these results, the NCIC-CTG has presented at ASCO (American Society of Clinical Oncology) 2008 the preliminary results of the phase III trial comparing carboplatin–paclitaxel with cisplatin–topotecan (four cycles), followed by carboplatin–paclitaxel (four cycles). Along with the GOG 182 results, the sequential doublet containing topotecan was not able to improve PFS and OS compared to the standard triplet.[10]

Other phase III studies have investigated the role of triplets with carboplatin–paclitaxel and the addition of a new drug compared to the standard. Recent data from an AGO randomised study with 1742 patients enrolled to demonstrate a survival advantage for the administration of a triplet containing paclitaxel, carboplatin and gemcitabine, compared with carboplatin–paclitaxel, in ovarian cancer patients, both in early and advanced stages.[11]

Similar data were obtained by the triple combination of paclitaxel, carboplatin and epirubicin,[12] and the concurrent combination of carboplatin, paclitaxel and topotecan.[13]

In conclusion, the SCOTROC phase II trial contributes to knowledge in this field confirming the available data: the addition of a third drug to carboplatin and paclitaxel does not improve the outcome of first line chemotherapy in ovarian cancer.

Thus, unfortunately all the trials performed in the last decade failed to show any improvement over carboplatin–paclitaxel with the new chemotherapy agents available for ovarian cancer.

However, a very important point of discussion was raised in the paper by the authors: a comparative analysis of the four SCOTROC trials with different sequential schedules of chemotherapy was performed with a solid historical control represented by 1000 patients enrolled in the SCOTROC1 study. Using a HR of 0.75 relative to the SCOTROC1 (33% increase in PFS or OS), only the SCOTROC2C, with carboplatin followed by weekly paclitaxel and gemcitabine, had HR compatible with this figure both for PFS and OS. The authors conclude that the superior PFS observed in the SCOTROC2C is probably related to the use of weekly paclitaxel rather than the addition of sequential gemcitabine.[8] Although the indirect comparison among different trials is exposed to the risk of biases, the observation is very interesting and support some evidences recently published in the literature in favour of the weekly administration of paclitaxel.

Several reports, in the setting of solid tumour such as lung cancer and breast cancer, have suggested a more favourable toxicity profile,[14] and an increased activity with the weekly administration of paclitaxel compared with the usual 3-weekly schedule.[15] In fact, it has been proposed that the weekly administration of paclitaxel may increase the activity of the drug conjugating its antimitotic activity with an anti-angiogenesis effect.[16]

In the scene of ovarian cancer, there are many trials showing that weekly paclitaxel is very active in the setting of recurrent platinum-resistant ovarian cancer[16] but recently weekly paclitaxel has been also investigated in the first line setting. Katsumata et al.[17] have recently published the results of the Japanese Gynecologic Oncology Group (JGOG) phase III trial comparing the standard 3-weekly carboplatin–paclitaxel schedule with an experimental arm containing 3-weekly carboplatin and a dose dense administration of paclitaxel at the dose of 80 mg/m^2 on days 1, 8 and 15, q21. Among the 631 stages II–IV epithelial ovarian, fallopian tube or primary peritoneal cancer eligible patients, after a median follow-up of 29 months they found that median PFS was of 17.2 and 28 months for the conventional and the experimental group, respectively ($P = 0.0015$). Accordingly, OS at 3 years was 72% and 65%, respectively ($P = 0.03$). Except for severe anaemia, more frequent in the experimental group, other toxicity rates were similar in both groups.

This is the first study with chemotherapy showing a positive result in the recent years and suggests that a dose-dense

weekly administration of paclitaxel could have a great potentiality in the first-line treatment of patients with ovarian cancer. However, given the different genetics in the Japanese population (i.e. higher proportion of patients with clear cell histology) confirmatory trials in the western population are urgently needed. On these fundaments, the MITO group has started a phase 3 open-label multicentre trial (MITO-7) that is ongoing in Italy and the ICON 8 is planned in Europe. These two trials will definitely clarify the role of weekly paclitaxel in first line ovarian cancer. With an old drug as paclitaxel, with an expired label and no specific interest of pharma company, these trials are the demonstration that academic research is still needed in this field to address very important clinical questions.

The deeper knowledge of ovarian cancer's biology has led to the identification of multiple molecular targets, such as growth factor receptors, signal transduction pathways, cell cycle regulators and angiogenic mechanisms. Therefore, the last years have seen an explosive development and availability of novel targeting agents and the first results of the first phase III trials will be available in the 2010–2011. However, waiting for the results of the biological agents the international cooperation in Gynaecologic Oncology should not abandon the attempts of improving chemotherapy.

A simple example is the treatment of ovarian cancer with different histology. Is it still acceptable that in the year 2010 carboplatin/paclitaxel is the standard treatment in all ovarian cancers independently from the histology and of the biology of the tumours? Clear cells, mucinous, serous low grade adenocarcinoma are clearly different entities that may require different drugs and treatment. Cooperation in this field is urgently needed.

Based on these considerations I believe that there is still room for trials designed with the aim of improving first line chemotherapy. Weekly paclitaxel and rare histotypes are only an example of this.

SCOTROC and the other European Gynaecologic Oncology groups will do their part.

Conflict of interest statement

None declared.

REFERENCES

1. Jemal A, Tiwari RC, Murray T, et al. American Cancer Society Cancer statistics, 2004. *CA Cancer J Clin* 2004;**54**:8–29.
2. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006;**95**(Suppl. 1): S161–92.
3. McGuire WP, Ozols RF. Chemotherapy of advanced ovarian cancer. *Semin Oncol* 1998;**25**:340–8.
4. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin–paclitaxel versus cisplatin–cyclophosphamide in women with advanced epithelial ovariancancer: three-year results. *J Natl Cancer Inst* 2000;**92**:699–708.
5. Neijt JP, Engelholm SA, Tuxen MK, et al. Exploratory phase III study of paclitaxel and cisplatin vs paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol* 2000;**18**:3084–92.
6. du Bois A, Lück H, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel vs carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2000;**95**:1320–9.
7. Ozols RF, Bundy BN, Greer BE, et al. Gynecologic oncology group phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;**21**:3194–200.
8. Agarval R, Gourley C, Perren TJ, et al. First line therapy for ovarian cancer with carboplatin followed by paclitaxel–gemcitabine (SCOTROC5): a feasibility study and comparative analysis of the SCOTROC series. *Eur J Cancer* 2010;**46**(11):2020–6.
9. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol* 2009;**27**:1419–25.
10. Hoskins PJ, Vergote I, Stuart G, et al. A phase III trial of cisplatin plus topotecan followed by paclitaxel plus carboplatin versus standard carboplatin plus paclitaxel as first-line chemotherapy in women with newly diagnosed advanced epithelial ovarian cancer (EOC) (OV.16). A Gynecologic Cancer Intergroup Study of the NCIC CTG, EORTC GCG, and GEICO. *J Clin Oncol* 2008:26 [abs LBA5505. ASCO 2008].
11. Herrstedt J, Huober J, Priou F, et al. A randomized, phase III study (AGO-OVAR-9, GINECO-TCG, NSGO-OC-0102): gemcitabine–paclitaxel–carboplatin (TCG) versus paclitaxel-carboplatin (TC) as first-line treatment of ovarian cancer (OC): survival of FIGO stage I–IIA patients. *J Clin Oncol* 2009;**27**:18s [abs LBA5510. ASCO 2009].
12. du Bois A, Lück HJ, Bauknecht T, et al. First-line chemotherapy with epirubicin, paclitaxel, and carboplatin for advanced ovarian cancer: a phase I/II study of the Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group. *J Clin Oncol* 1999;**17**:46–51.
13. Scarfone G, Scambia G, Raspagliesi F, et al. A multicenter, randomized, phase III study comparing paclitaxel/carboplatin (PC) versus topotecan/paclitaxel/carboplatin (TPC) in patients with stage III (residual tumor >1 cm after primary surgery) and IV ovarian cancer (OC). *J Clin Oncol* 2006;**24**:18S [abs 5003 ASCO 2006].
14. Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. *J Clin Oncol* 2008;**20, 26**(3):468–73.
15. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008;**358**:1663–71.
16. Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006;**101**:436–40.
17. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomized controlled trial. *Lancet* 2009;**374**:1331–8.