Ovarian cancer: State of the art and future directions

A. Awada, *M.D., Ph.D.*, **J. Klastersky,** *M.D., Ph.D.*

Department of Internal Medicine and Medical Oncology, Institut Jules Bordet, Brussels (Belgium)

Summary

The median survival of patients with ovarian cancer has increased steadily, mainly due to a multidisciplinary approach including surgery and chemotherapy. This editorial article summarizes the important messages taken from clinical research performed in this field over the last 15 years. It deals with the following issues: screening, prevention, management of early and advanced disease, maintenance/consolidation therapies and the treatment of relapsing patients. It also gives some future directions with the hope to improve the management and the outcome of this highly lethal disease.

Key words: Ovarian cancer; Disease management; Chemotherapy.

Introduction

The median survival of patients with ovarian cancer has increased steadily the last 20 years. This has been the result of a multidisciplinary approach including surgery and the introduction of platinum and more recently taxane-based chemotherapy. Nevertheless, five-year survival remains poor and consequently new approaches are needed in the management of this disease.

The cornerstones for the management of ovarian cancer are a comprehensive staging and therapeutic laparotomy (optimal primary or interval debulking) and chemotherapy. However, several controversies remain as to screening, prevention and the treatment of patients with both early and advanced-stage ovarian cancer. These issues will be reviewed in this paper. Future directions will also be presented.

Screening

Transvaginal ultrasound and CA-125 levels are among the means used to screen women for ovarian cancer. Overall, both techniques have been considered scientifically unsatisfactory to be used routinely. The recent development of proteomic profiling could be a strategy forward. Petricoin *et al.* [1] developed a bioinformatic tool to identify proteomic patterns in serum that distinguish neoplastic from non-neoplastic disease. They considered that pathological changes within the ovary might be reflected in proteomic patterns in serum and identified a cluster pattern that completely segregated cancer from non-cancer. As the authors concluded, these findings justify a prospective evaluation of proteomic pattern technology in high-risk women as well as general populations.

Prevention

The mutations on BRCA1 and BRCA2 genes give an increased cumulative ovarian cancer risk and that risk increases during aging. Kauff *et al.* [2] reported that prophylactic salpingo-oophorectomy (in women 35 years of age or older) reduced the risk of ovarian cancer in women who had BRCA1 or BRCA2 mutations. So far, there are no agents that might be used as preventive measures in high-risk women for ovarian cancer, but the recent progress of molecular biology and consequently a better understanding of ovarian carcinogenesis might result in the identification of important mechanisms and pathways in tumors, which could be targeted by using the new molecular therapies.

Early-stage disease

There is an agreement that no adjuvant therapy is necessary for patients who have FIGO Stage I disease with well-differentiated disease and optimal surgical staging. Patients with high-risk early stage ovarian cancer (Stages IA or IB with poorly differentiated or grade 3, Stage IC or clear cell cancers and all Stage II) and incompletely staged disease are currently, based on several randomized trials (GOG trials, ICON 1 and ACTION), treated with three to six cycles of platinum ± paclitaxel based chemotherapy [3, 4]. However, for pa-

tients who are optimally staged and have Stage I and high-risk features, there is a controversy whether they should be treated with immediate chemotherapy and thus it is essential that future trials attempt to prospectively confirm that adjuvant chemotherapy in early-stage ovarian cancer is not effective after optimal surgical staging.

Advanced-stage disease

The median survival of advanced ovarian cancer improved from 12 months in the 1970's to approximately 30 months in 2000. There is a high response rate in ovarian cancer (80%) but unfortunately there is also a high recurrence rate.

The most important drugs in the treatment of advanced ovarian cancer are platinum compounds and taxanes. Based on several randomized trials and available data, there is a general agreement among investigators in this field that six cycles of platinum/taxane-based combination chemotherapy is a good therapeutic standard [5]. Carboplatin alone (minimum AUC6) is a good alternative mainly in patients at high risk for neurotoxicity or unable to tolerate combination chemotherapy [6]. GOG 182 (ICON V trial in the UK and Europe) is an ongoing trial across the continent comparing, as a control arm, carboplatin and paclitaxel and, as experimental arms, the triplet of carboplatin, paclitaxel and gemcitabine, the triplet of carboplatin, paclitaxel and every other cycle pegylated liposomal doxorubicin (Caelyx), the doublet of carboplatin and topotecan in sequence with carboplatin and paclitaxel and similarly the doublet of carboplatin and gemcitabine in sequence with carboplatin and paclitaxel. A total of eight cycles of chemotherapy are given and 4,000 patients will enter this important randomized trial.

A limited number of randomized trials compared intraperitoneal chemotherapy versus intravenous chemotherapy and were reviewed recently [5]. The important messages from the intraperitoneal approach are the following: 1) the toxicity of the intraperitoneal arm was significant, in part due to higher doses of cisplatin administered in these trials (100 mg/m^2) 2) the technique related to this treatment is cumbersome for both patient and clinician and 3) there is a trend for a better disease-free survival and survival in favor of the intraperitoneal arm. Despite these positive results in relation to outcome, the EORTC is not performing any randomized trials of intraperitoneal chemotherapy and preferred to study other concepts and new cytotoxics or molecular-targeted therapies.

Epothilone drugs, taxanes analogues, new formulations of antimetabolites, topoisomerases inhibitors, new generations of platinum compounds and ET-743 are among the new cytotoxics under clinical investigation. It is important to continue this research in order to find new agents mainly active in resistant disease to standard therapies. In addition, the focus should be on the development of other classes of agents based on the progress of molecular biology, which have a selective activity on tumor cells or the microenvironment and less systemic toxicity than conventional chemotherapy. Examples of these classes include inhibitors of signal transduction pathways, growth factors and receptors of growth factors in both cancer cells and endothelial cells, which are involved in tumor angiogenesis. So far, and even in the presence of active clinical investigation in this field, there is no breakthrough by using the molecular targeted therapies alone or in combination with cytotoxic agents but this kind of research is still in its early steps.

Maintenance/consolidation therapy

Most patients with advanced ovarian cancer achieve complete clinical response after debulking surgery and chemotherapy. However, sooner or later the majority present disease recurrence. Maintenance/consolidation therapies have focused on several approaches including high-dose chemotherapy, whole abdominal radiotherapy, intraperitoneal administration of chemotherapy, P32 or antibodies conjugated with a variety of radioisotopes, intravenous chemotherapy (such as topotecan, paclitaxel), immunotherapy and more recently molecular-targeted therapies [5]. At this time, no form of maintenance/consolidation therapies has been shown to statistically improve overall survival, although several studies are still ongoing.

Relapsing disease

The usual course of relapsing ovarian cancer is the following: after the operation a patient has at the time the primary tumor is diagnosed, she receives adjuvant chemotherapy with platinum derivatives and taxanes. When the relapse occurs, the patient is usually asymptomatic or has few symptoms. Nevertheless, the cure at

this stage has become difficult, or even impossible, and the evolution of the disease and the response to any treatment cannot be optimally predicted (although it can be predicted to a limited extent, based namely on the time interval that has elapsed since her last course of adjuvant chemotherapy). Several chemotherapeutic agents are available that can treat this relapse: topotecan, VP-16, gemcitabine, weekly taxane, a platinum compound again and a pegylated liposomal form of doxorubicin (Caelyx). All the chemotherapeutic agents have a more or less equivalent activity; the major difference is found in the administration schedules and safety profile, as well as in the cost.

The following table summarizes several important pieces of information about these chemotherapeutic agents.

	Topotecan	Gemcitabine	VP-16 oral	Oxaliplatin	Caelyx
Availability of randomized comparative studies	Yes	Yes	No	Yes	Yes
Administration schedule (IV)	Day 1 to 5 3-week cycle	D1-D8-D15 4-week cycle	Oral	Day 1 3-week cycle	Day 1 4-week cycle
Hematological toxicity	Major	Moderate	May be major	Moderate	Minor to moderate
Alopecia	Yes	Minor	Yes	Minor	Minor
Cutaneous toxicity	No	Occasional rash	No	No	Hand-foot syndrome
Need for G-CSF	Sometimes	No	No	No	No
Neuropathy	No	No	No	Yes	No

A randomized study comparing Caelyx with topotecan in patients that have already been treated with platinum derivatives showed that Caelyx was as effective as topotecan. In that study, a retrospective analysis of the subgroups suggested that Caelyx was superior in terms of survival to topotecan in the group of patients considered responsive to platinum derivatives, but not in the group considered resistant to platinum derivatives [7]. In addition, the combination of Caelyx plus carboplatin was investigated by a French team in 105 patients with relapsing ovarian cancer who were sensitive to platinum derivatives. The response rate was remarkable (63%) [8]. Moreover, the ICON 4/AGO-OVAR-2.2 trial [9] showed also that paclitaxel in combination with a platinum improves survival and progression-free survival in patients with "platinum sensitive" relapsed ovarian cancer compared to platinum-based chemotherapy. Based on these results and other available data, a platinum-based combination therapy (mainly carboplatin combined with paclitaxel or Caelyx or gemcitabine) could be considered at this time an optimal therapy in this group of relapsing patients considered sensitive to platinum therapy. Since the treatment at relapse is most often not curative, the side-effects described in the above table should be considered when choosing the therapy and their relevance to the particular patient (e.g., age), the tumor (e.g., presence or absence of widespread peritoneal carcinomatosis) and the previous treatment (e.g., which therapy used and how long the platinum-free interval). Finally, it is important to remember that some of these drugs (e.g., Caelyx, topotecan, gemcitabine) have already been included in investigational therapeutic protocols in a first-line setting and that, in the near future, it will be necessary to modify the treatment at the time of relapse depending on the results coming from these studies.

Conclusion

There have been modest but significant advances in the treatment of ovarian carcinoma. Understanding the resistance mechanisms and continuing to develop new cytotoxic agents active in resistant disease are of utmost importance. With the progress of molecular biology, genomics and proteomics, we could expect further progress based on the discovery of prognostic and predictives signatures, as well as the development of molecular-targeted therapies, which should fight in particular the anti-apoptotic pathways and tumor angiogenesis. The latter therapies might be of particular interest as maintenance/consolidation treatments, since available cytotoxic agents have major antitumor effects, leading to a significant shrinking of the tumor in a substantial number of patients, but unfortunately they are not able to completely eradicate the cancer cells or to avoid the development of resistance and tumor progression.

Acknowledgements

The authors would like to thank Miss Isabelle François for her secretarial assistance.

References

[1] Petricoin E.F., Ardekani A.M., Hitt B.A. *et al.*: "Use of proteomic patterns in serum to identify ovarian cancer". *Lancet,* 2002, *359*, 572.
[2] Kauff N.D., Satagopan J.M., Robson M.E. *et al.*: "Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation". *N. Engl. J. Med.*, 2002, *346,* 1609.
[3] Ozols F.: "Controversies in ovarian cancer". Proceedings of the 15th International Congress on Anti-Cancer Treatment, Paris, France, 09-12/02/2004 (educational lecture, 83).
[4] Trimbos J.B., Parmar M., Vergote I. *et al.*: "International collaborative ovarian neoplasm trial I and adjuvant chemotherapy in ovarian neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma". *J. Natl. Cancer Inst.,* 2003, *95*, 105.
[5] Mano M., Awada A., Minisini A. *et al.*: "Remaining controversies in the upfront management of advanced ovarian cancer". *Inter. J. Gynaecol. Cancer,* 2004 (still in press).
[6] "Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomized trial". *Lancet*, 2002, *360,* 505.
[7] Gordon A.N. *et al.*: "Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan". *J. Clin. Oncol.,* 2001, *19*, 3312.
[8] Ferrero J.M. *et al.*: "Caelyx and paraplatine in patients with advanced ovarian cancer in late relapse: a gineco phase II trial". Abstract, 828, ASCO, 2002.
[9] Parmar M.K., Ledermann J.A., Colombo N. *et al.*: "Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial". *Lancet*, 2003, *361*, 2099.

Address reprint requests to:
A. AWADA, M.D., Ph.D.
Institut Jules Bordet
Unité de Chimiothérapie
Rue Héger-Bordet, 1
1000 Bruxelles (Belgium)