

## CHEMOTHERAPY FOR EPITHELIAL OVARIAN CANCER

VIŠNJA MATKOVIĆ

Gynecologic Cancer Center, Zagreb University Hospital, Zagreb, Croatia

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### Summary

Systemic chemotherapy following the appropriate surgical procedure is the cornerstone of first – line treatment of epithelial ovarian malignancy.

Ovarian carcinoma is the leading cause of cancer deaths of the female reproductive system. Early – stage ovarian carcinoma is generally asymptomatic; therefore , the majority of women are diagnosed with advanced – stage disease ( FIGO stage III or IV). Five – year survival rates for women with stage III or IV disease range from less than 5% to 20%.

Current systemic therapy for ovarian cancer consists of combination of carboplatin and paclitaxel. While the majority of patients achieve clinical complete remission after six cycles of chemotherapy , the relapse rate stands at over 50%. Median survival time for patients after recurrence is approximately 2 years. New treatment approaches for patients with advanced ovarian cancer include consolidation and maintenance therapy, intraperitoneal administration of cytotoxic agents, new combination chemotherapy regimens, the development of new cytotoxic agents, and molecular-target therapies.

Palliation and optimizing quality of life as the primary treatment goals for patients with recurrence, as the probability of cure for this population is remote. Patients with recurrent ovarian carcinoma are typically divided into two groups with differing prognoses. Patients with progression on primary therapy or after a treatment-free interval of less than 6 months are considered platinum-resistant; those who relapse or develop progression after a treatment-free interval of greater than 6 months after chemotherapy are platinum sensitive. Platinum sensitive patients are more likely to demonstrate a response to subsequent chemotherapy: therefore, they have a more favorable prognosis.

KEY WORDS: *epithelial ovarian cancer, chemotherapy*

### KEMOTERAPIJA U LIJEČENJU EPITELNOG RAKA JAJNIKA

#### Sažetak

Sistemska kemoterapija nakon odgovarajućeg kirurškog zahvata temelj je terapije prvoga reda u liječenju epitelnog raka jajnika. Karcinom jajnika je glavni uzrok smrti od raka ženskog spolnog sustava. Početni stadij raka jajnika obično je bez simptoma pa se stoga u većine žena dijagnosticira tek u uznapredovalom stadiju (FIGO stadij III. ili IV.). Petogodišnje stope preživljenja u žena sa stadijem bolesti III. ili IV. kreću se od manje od 5% do 20%.

Sistemska terapija koja se trenutačno primjenjuje u liječenju raka jajnika, sastoji se od kombinacije karboplatina i paklitaksela. Premda većina bolesnica postiže kliničku potpunu remisiju nakon šest ciklusa kemoterapije, stopa relapsa i dalje je veća od 50%. Medijan preživljenja za bolesnice nakon ponovne pojave bolesti je otprilike 2 godine. Novi pristupi u liječenju za bolesnice s uznapredovalim rakom jajnika uključuju konsolidaciju i terapiju održavanja, intraperitonejsku primjenu citotoksičnih lijekova, nove kombinacije kemoterapijskih shema, razvoj novih citotoksičnih lijekova i lijekova koji djeluju na ciljane molekule.

Palijacija i postizanje optimalne kvalitete života postavljeni su kao primarni ciljevi u liječenju bolesnica u kojih se bolest ponovno pojavila jer su za tu populaciju izgledi za izlječenje slabi. Bolesnice u kojih se rak jajnika ponovno pojavio obično se dijele u dvije skupine koje se razlikuju prema prognozi bolesti. Bolesnice u kojih je došlo do progresije dok su primale primarnu terapiju ili nakon razdoblja od manje od 6 mjeseci u kojemu nisu primale terapiju, smatraju se otpornima na platinu; one u kojih se bolest pogoršala ili u kojih je došlo do progresije nakon što više od 6 mjeseci nakon kemoterapije nisu primale nikakvu terapiju, osjetljive su na platinu. Veća je vjerojatnost da će bolesnice osjetljive na platinu reagirati na sljedeću kemoterapiju: prognoza je za njih stoga povoljnija.

KLJUČNE RIJEČI: *epitelni rak jajnika, kemoterapija*

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## INTRODUCTION

Ovarian cancer is the second most common gynecological cancer and the leading cause of death from gynecological malignancies. Since accurate methods for early detection are lacking, only 25-30% of these cancer are diagnosed at an early stage. The prognosis of patients with stage I and II disease is good compared with that of patients with advanced stages. Currently, survival of women with early stage ovarian cancer properly staged ranges between 80-95%. The surgical treatment of choice for women with early stage ovarian carcinoma is radical and includes hysterectomy with bilateral salpingo-oophorectomy (1,2).

Primary radical tumor debulking surgery followed by systemic platinum/taxane-based chemotherapy is considered standard in the management of advanced stage ovarian carcinomas. Five-year survival rates for women with stage III-IV disease range from less than 5% to 20% (2).

## PRIMARY CHEMOTHERAPY FOR EPITHELIAL OVARIAN CANCER

Epithelial ovarian cancer (EOC) is considered to be a chemosensitive neoplasm, with initial overall response rates to systemic therapy exceeding 80% when integrated with cytoreductive surgery. However, among women with advanced-stage disease at diagnosis, long-term survival remains poor due to potential tumor recurrence and emergence of drug-resistant disease. Primary chemotherapy has evolved from single alkylating agents such as cyclophosphamide, melphalan to cisplatin and cisplatin-based combinations, followed by incorporation of paclitaxel. The further step has been substitution of carboplatin for cisplatin. In particular, although mature results from GOG 111 clearly established the superiority of cisplatin-paclitaxel compared to cisplatin-cyclophosphamide. The GOG 158 and AGO also clearly established that carboplatin-paclitaxel was at least as effective as cisplatin-paclitaxel (2-4). Other phase III trials, including GOG 132 and ICON3, have suggested that sequential therapy with single-agent platinum followed by paclitaxel at progression can achieve equivalent long-term outcomes in pa-

tients with advanced disease. In addition, while some trials have demonstrated significant improvements in median survival, long-term survival and overall disease mortality have remained largely unchanged (5).

Until now, platinum remains the most important conventional cytotoxic agent used in the treatment of ovarian carcinoma. There is a general acceptance that carboplatin is at least as effective as cisplatin. Thus far, newer platinum analogues, including oxaliplatin, have not demonstrated superiority over carboplatin in terms of either efficacy or tolerability (6).

The second most important class of cytotoxic agents to emerge has been the taxanes. Although the majority of clinical experience has been established with paclitaxel, a series of studies, including a phase III randomized trial, have established that incorporation of docetaxel is an acceptable alternative with a different toxicity profile. There are no data to indicate superiority of docetaxel compared to paclitaxel in the management of newly diagnosed or recurrent disease.

After more than fifteen years of investigation, there is still controversy regarding the role of intraperitoneal platinum-based therapy. While some studies with intraperitoneal cisplatin have documented a modest improvement in median survival, this has been at the expense of increased non-hematologic toxicity and treatment complexity.

Another area of controversy is maintenance (or consolidation), which could include high-dose treatment with hematopoietic progenitor cell support, intraperitoneal cisplatin for small-volume residual disease, conventional-dose extended therapy with taxanes (weekly paclitaxel, 8 cycles instead of 6 cycles of conventional chemotherapy), supplemental therapy with other cytotoxic agents (topotecan), and hormonal interventions. Only a limited number of phase III trials have been completed, and none have documented a survival advantage.

In this setting, short-term improvements in progression-free survival are not sufficient to recommend a change in the standard of care (carboplatin AUC 5-7+paclitaxel, 175m/2), and maintenance therapy has not been widely

adopted for patients in clinical complete remission at conclusion of primary therapy (4).

## CHEMOTHERAPY OF RECURRENT EPITHELIAL OVARIAN CARCINOMA

Although most patients demonstrate a complete response to surgery and first-line chemotherapy, 50-75% of advanced-stage patients have persistent or recurrent disease. Unfortunately, recurrence is incurable in almost all patients. For this reason, the main objectives of the treatment should be to ameliorate the symptoms and to maintain the quality of life of the patients. Chemotherapy is the therapy of choice for most of these patients (7).

Clinical data from individual patients, such as a time interval from the end of the first line chemotherapy and the response previously observed, permit us to divide patients into platinum-sensitive and platinum-resistant. Moreover, other clinical data such as serous histology, number of sites involved and the maximum diameter have been shown to have a prognostic significance (8).

Platinum-resistant disease includes patients without response to front line platinum-based chemotherapy or relapsing before 6 months after the end of the first line. These patients have usually a worse performance status and prognosis. In fact, the expected median survival is less than 10 months (9).

In the last 15 years, several single agents have shown a modest but unequivocal activity in the platinum-resistant disease. Response rates of 10-15% and median survival of 9 months have been reported with paclitaxel, topotecan, pegylated liposomal doxorubicin, oxaliplatin, gemcitabine, docetaxel, etoposide, tamoxifen (10-12).

In conclusion, there is no randomized clinical trial which have demonstrated any single or combination chemotherapy to be superior in platinum-resistant ovarian cancer. For this reason, sequential single agent should be considered the treatment of choice. Patient performance status, toxicity, mode of administration and quality of life should be the principal factors to be considered in the election between the available alternatives (13,14).

On the other hand, platinum-sensitive recurrence includes a better prognosis group of patients in which longer platinum-free interval is associated with a higher probability of response and prolongation of disease-free survival to re-treatment with the platinum schedule. Nowadays, we have several randomized clinical trials which consistently have demonstrated the superiority of platinum-based combination over platinum single agent (15-17).

## CONCLUSION

The median survival of women with epithelial ovarian cancer, especially those with advanced stages has increased steadily since the late 1970's. Advances in surgical techniques, chemotherapy and supportive care have all contributed to this improvement. The integration of new drugs into the treatment resulted in quantum leaps in survival when highly active drugs like cisplatin/carboplatin and paclitaxel were added to primary therapy. Less active drugs have probably led to more subtle improvements when added to the management of recurrent and resistant disease (topotecan, pegylated liposomal doxorubicin, oxaliplatin, gemcitabine, docetaxel and etoposide). Hundreds of new drugs are in clinical development and a large number are in active preclinical development (antiangiogenic reagents, humanized monoclonal antibodies, selective hormonal agents).

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*Author's address: Višnja Matković, M.D., Gynecologic Cancer Center, Zagreb University Hospital, Petrova 13, 10 000 Zagreb, Croatia; e-mail: imatko@net4u.hr*