Portsmouth Regional Hospital
Cancer Care Center

ROLE OF CHEMOTHERAPY FOR ADVANCED OVARIAN CANCER

Data analyzed by Robert McLellan, MD, Gynecologic Oncology Surgeon

In the United States, epithelial ovarian cancer is the second leading cause of malignancy affecting the female reproductive tract. As ovarian cancer presents with advanced disease in the majority of patients, there are more deaths from ovarian cancer than from all the other gynecologic malignancies combined. The American Cancer Society estimates that in 2013 there will be 22,240 new cases of ovarian cancer in the U.S. and 14,030 deaths.

In combination with cytoreductive surgery, the current standard chemotherapy for patients with advanced-stage epithelial ovarian cancer consists of combination treatment with a platinum based agent and a taxane. This approach has been established through a series of randomized clinical trials comparing various chemotherapeutic agents alone and in combination. A subset of studies also suggests that a combination treatment program including an intraperitoneal component of therapy should be considered for patients with small-volume residual Stage III disease.

The importance of platinum-based chemotherapy for advanced-stage epithelial ovarian cancer was established in the late 1980. In 1986, the Gynecologic Oncology Group (GOG) published the largest comparative trial of a platinum-containing regimen versus a non-platinum-containing regimen, comparing doxorubicin plus cyclophosphamide with or without Cisplatin. Treatment with the Cisplatin-containing regimen was associated with a statistically superior response rate, progression-free survival, and overall survival. Subsequently, paclitaxel was established as a highly active agent in ovarian cancer. In 1996, the GOG reported results of a comparative trial of Cisplatin plus cyclophosphamide versus Cisplatin plus paclitaxel (GOG #111) in which the Cisplatin plus paclitaxel treatment arm was associated with statistically superior progression-free survival (18 months versus 13 months, $p=0.01$) and overall survival (38 months versus 24 months, $p<0.001$). These results were confirmed by a European study (OV-10), in which overall survival again favored the Cisplatin plus paclitaxel treatment arm (35.6 months versus 25.8 months, $p=0.002$).

Because carboplatin has a more favorable toxicity profile than Cisplatin, the GOG initiated a study comparing carboplatin (AUC 7.5) and 3-hour paclitaxel (177mg/m^2) versus Cisplatin

(75mg/m²) plus 24 hour paclitaxel (135 mg/m²) (GOG #158). A concurrent European study (AGO-OVAR3) compared paclitaxel (185mg/m²) plus carboplatin (AUC 5) with paclitaxel (185mg/m²) plus Cisplatin (75mg/m²). Both studies revealed equal therapeutic efficacy between the two treatment arms but a more favorable toxicity profile of the carboplatin arm. Gastrointestinal, renal, metabolic, and leukopenic toxicities were significantly more common in the Cisplatin arm, whereas thrombocytopenia was more frequent in the carboplatin arm. Patients receiving carboplatin plus paclitaxel had significantly better quality of life compared to those treated with Cisplatin plus paclitaxel.

The primary analysis of the JGOG 3016 trial showed that a dose-dense paclitaxel and carboplatin regimen significantly improves progression-free and overall survival compared with the conventional regimen as first-line chemotherapy for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer.
Patients with stage II-IV ovarian cancer were randomly assigned to receive conventional treatment (carboplatin area under the curve [AUC] 6 mg/mL per min and paclitaxel 180 mg/m² on day 1) or dose-dense treatment (carboplatin AUC 6 mg/mL per min on day 1 and paclitaxel 80 mg/m² on days 1, 8, and 15). The treatments were **repeated every 3 weeks** for six cycles; responding patients had received three additional cycles.

637 patients were enrolled, of whom 631 were analyzed (312 assigned to the dose-dense regimen, 319 to the conventional regimen). Median follow-up was 76.8 months (IQR 68.9 - 85.6). Median progression-free survival was significantly longer in the dose-dense treatment group than in the conventional treatment group (28.2 months [95% CI 22.3 - 33.8] *vs* 17.5 months [15.7 - 21.7]. Median overall survival was 100.5 months (95% CI 65.2 - ∞) in the dose-dense treatment group and 62.2 months (52.1 - 82.6) in the conventional treatment group (HR 0.79, 95% CI 0.63 - 0.99; p=0.039).

The Society of Gynecologic Oncology recently suggested that the dose-dense regimen may offer a new standard of care for first-line chemotherapy in patients with advanced epithelial ovarian cancer based on long-term follow-up data from the JGOG 3016 trial.

In 2006, the GOG published results of a randomized prospective trial comparing intraperitoneal Cisplatin (100mg/m²) plus intravenous (135mg/m²) and intraperitonal (60mg/m²) paclitaxel against the standard regimen of intravenous Cisplatin (75mg/m²) plus intravenous paclitaxel (135mg/m²) (GOG #172) in patients with optimally resected Stage III ovarian cancer. In this study, 42% of patients in the intraperitoneal therapy group completed all 6 cycles of treatment, and patients who were randomized to this arm had a 16-month advantage in medial survival time (65.6 months) compared to women who received intravenous chemotherapy alone (49.7 months, p=0.03). Intraperitoneal chemotherapy was associated with significantly more toxicity and lower quality of life scores up to 12 months after initiating therapy. Subsequently, the Cochrane collaboration conducted a meta-analysis of eight randomized clinical trials of intraperitoneal chemotherapy for advanced-stage ovarian cancer, including 1,819 subjects, and

reported a statistically significant hazard ratio of 0.79 for both time to progression and time to death for intraperitoneal chemotherapy compared to standard intravenous chemotherapy. Based on these findings, the National Cancer Institute issued a recommendation that clinicians give strong consideration toward using intraperitoneal chemotherapy for patients with advanced-stage ovarian cancer and minimal residual disease following primary surgery. It is important to recognize that patients with optimally resected small-volume disease appear to be the best candidates for intraperitoneal chemotherapy. Patients with suboptimal residual disease or contraindications for intraperitoneal chemotherapy should receive intravenous carboplatin plus paclitaxel. In addition, a standard intraperitoneal chemotherapy regimen, in terms of minimizing toxicity and optimizing treatment completion rates, has yet to be determined.

Primary cytoreductive surgery followed by adjuvant chemotherapy has traditionally been considered the standard for patients with ovarian cancer. Vergote et all reported the results of a randomized trial examining neoadjuvant chemotherapy with interval cytoreduction in women with Stage IIIC to IV ovarian cancer. Neoadjuvant chemotherapy was not inferior to primary cytoreduction followed by adjuvant chemotherapy. Surgical morbidity, mortality and rate of optimal cytoreduction tended to be improved in the neoadjuvant arm of the study.

In summary, three patients presented with Stage IA ovarian cancer, each treated with surgery. One patient presented with Stage IIA, underwent surgery but declined chemotherapy. There were five Stage III/IIIC cancers, each undergoing surgery, three of whom were treated with chemotherapy at PRH, one of whom treated with chemotherapy elsewhere, and one patient who declined chemotherapy. Of the three Stage IV cancers, both surgery and chemotherapy were given for the one patient receiving treatment at PRH. The one additional patient had recurrent ovarian cancer, initially and subsequently treated with surgery and chemotherapy.

Data analysis: 100% of patients with Stage III ovarian cancer were treated according to national guidelines.

Literature

1. Omura G, Blessing JA, Ehrlich CE, Miller A, Yordan E, Creasman WT, et al. A randomized trial of cyclophosphamide and doxorubicin with or without Cisplatin in advanced ovarian carcinoma: A Gynecologic Oncology Group study. Cancer 1986; 57:1725-30
2. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and Cisplatin compared with paclitaxel and Cisplatin in patients with state III and stage IV ovarian cancer. N Eng J Med 1996; 334:1-6
3. Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, et al. 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

4. Armstrong DK, Bundy B, Wenzel L, Juang HQ, Baergen R, Lele S, et al for the Gynecologic Oncology Group. Intraperitoneal Cisplatin and paclitaxel in ovarian cancer. N Eng J Med 2006;354:34-43
5. Noriyuki Katsumata, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG3016): a randomized, controlled, open-label trial. Lancet Oncol 2013;14:1020-26
6. Ignace Vergote, MD, PhD, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Eng J Med 2010;363:943-53

Data analyzed by Robert McLellan, MD, Gynecologic Oncology Surgeon and Dr. Christine Wasilewski, Medical Oncology.

Data prepared by Marni Piper, Certified Tumor Registrar and Bonnie Fossett RN, Quality Management.