

# SEARCHING FOR THE BEST TREATMENT FOR OVARIAN CANCER

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Searching for the best ovarian cancer treatment has become a complex and somewhat territorial issue.

In the United States, the predominant treatment for ovarian cancer is surgery followed by chemotherapy. In other countries, radiation plays a dominant role. Physicians in the United States have yet to find radiation's place but it certainly has a position based on extensive data.

A recently published paper by David Alberts et al in the prestigious New England Journal of Medicine evaluated intravenous chemotherapies only compared to intravenous plus chemotherapy directly into the abdominal cavity. This is called intraperitoneal treatment.

While most chemotherapies are administered intravenously (through the veins), the role of putting chemotherapy where tumors are is, in general, to increase the dose of chemotherapy deliverance to the tumor. The higher the dose that can be safely administered, the more likely a response will be had - in general. Placing chemotherapy into the abdomen or intraperitoneal has been the subject of study over parts of the last two decades.

Why is this issue important? Ovarian cancer remains the number one malignant killer in the gynecologic category in the United States. Most women with advanced ovarian cancer die of the disease. It is for that reason that research to determine the best treatment and combining treatments such as chemotherapy, surgery and radiation are most crucial.

The recently reported protocol is a Phase III meaning it compares two highly esteemed regimens for previously untreated patients. These patients, as well, could not have residual tumor larger than 2 centimeters (cm) in greatest diameter left after surgery. All patients had an exploratory laparotomy (surgical opening of the abdomen) with removal of the uterus, ovaries and all tumor nodules greater than 2cm.

Patients were then randomly assigned, after the Informed Consent Process, to receive intraperitoneal Cisplatin plus intravenous Cyclophosphamide or intravenous Cisplatin and intravenous Cyclophosphamide.

The treatments were continued every three weeks for six cycles. After treatment, physical examination was repeated with blood testing performed as well as chest x-ray. Patients who had no obvious evidence of disease had a second operation to determine the exact response to therapy. A complete pathologic response was "defined as no pathologic evidence of disease on second-look surgery and biopsy of the upper abdomen and para-aortic and retroperitoneal lymph nodes as well as any other site previously involved with tumor."

Over a six-year period ending in 1992, 654 women were randomly allocated to one treatment or the other. Because of patient refusal, death or protocol violation, 546 eligible patients remained in the study. Of 546 actual patients, 20 never received any treatment, 81 did not complete treatment and 45 had tumors that progressed before completion of treatment. "Second-look surgery was not performed in these patients for obvious reasons. In 103 of the remaining 400 patients, surgery was not performed because it was felt to be contra-indicated or patient refusal."

Two-hundred-ninety-seven patients with no obvious clinical disease underwent second-look surgery. The rate of complete pathologic response was 36% in the intravenous group and 47% in

the intraperitoneal group. The median survival was 41 months in the intravenous group and 49 months in the intraperitoneal group.

Patients after surgery who had microscopic disease did better than those who had bulky disease. Patients who had microscopic disease had a median survival of 76 months compared to 42 months in patients who had tumors less than 0.5 cm. after surgery. Patients who had tumors measuring 0.5 to 2 cm. had a median survival of 32 months.

The authors noted, "The effect of the treatment intravenous or intraperitoneal Cisplatin was not influenced by the extent of residual disease before the interaction of treatment and residual disease. There were two treatment-related deaths in the intraperitoneal group and none in the intravenous group although more patients in the intravenous group had marked lowering of blood counts. Other side effects as well were noted."

The authors noted, "The median survival of the patients treated intraperitoneally was eight months longer than that of patients given intravenous Cisplatin."

The authors go on to state, "These results represent a 20% improvement in median survival and a 24% reduction in the risk of death during the entire follow-up period among the eligible patients in the intraperitoneal group." Furthermore they note that side effects like "neutropenia, tinnitus, hearing loss and neuromuscular toxic effects were significant less frequent in the intraperitoneal group than in the intravenous group." However, abdominal pain was more common in the intraperitoneal group.

Why did women with ovarian cancer who received intraperitoneal Cisplatin live longer? The authors speculated that, "Our patients had never before received chemotherapy and their tumors may therefore been highly sensitive to Cisplatin. Moreover, the precision in measuring intraperitoneal tumor masses during an initial exploratory laparotomy is limited and the total volume of mass may have more prognostic value than the maximum dimension."

Where do women now go with this data? Recently presented data has shown benefit for Taxol administration. The authors comment, "The combination of intravenous Paclitaxel (Taxol) plus intraperitoneal Cisplatin may prove to be more effective than intravenous Cyclophosphamide plus intraperitoneal Cisplatin in patients with Stage III ovarian cancer and minimal residual disease. The gynecologic oncology group recently reported that Paclitaxel plus Cisplatin significantly increased survival (median 38 months versus 24 months with Cyclophosphamide plus Cisplatin) when administered as a primary chemotherapy with incompletely resected Stage III or Stage IV ovarian cancer. Ongoing Phase III studies by the gynecologic oncology group and the Southwest Oncology group will further define the role of intraperitoneal Cisplatin (and intravenous Paclitaxel) in the treatment of Stage III ovarian cancer that has been optimally resected."