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CA125 Regression in Ovarian Cancer Patients Treated with Intravenous versus Intraperitoneal Platinum-Based Chemotherapy – A Gynecologic Oncology Group Study

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In January 2006, the results of the most recent randomized control trial utilizing intraperitoneal (IP) chemotherapy were released and spurred an NCI clinical alert and the Society of Gynecologic Oncology Clinical Practice statement on the use of IP chemotherapy for newly diagnosed optimally debulked ovarian cancer patients [1]. The impressive 16-month overall survival advantage demonstrated by Gynecologic Oncology Group (GOG) protocol 172 led many clinicians to increase the use of IP chemotherapy in their practice; however, there are limited data regarding the appropriate CA125-based measure of response during the therapeutic monitoring for patients undergoing IP treatment.

CA125 levels are routinely used to follow response to chemotherapy in women with epithelial ovarian cancer. CA125, however, is a non-specific marker and is known to rise in the presence of peritoneal irritation. Administration of IP cytotoxic chemotherapy, therefore, has the potential to cause a false elevation in CA125 levels. For this study, we evaluated CA125 levels among patients enrolled on GOG 114, as this protocol represents a randomized trial of IP vs IV treatment, and includes a high frequency of CA125 monitoring.

Patients on this study received IV cisplatin and paclitaxel for 6 cycles or IV carboplatin for 2 cycles followed by IP cisplatin and IV paclitaxel for 6 cycles. The protocol was designed to acquire CA125 levels weekly for 12 weeks or until the level reached a value of ≤ 35 units on two successive weekly samples. CA125 data were available for 223 patients who received IV cisplatin/paclitaxel and for 231 patients who received IV carboplatin followed by IP cisplatin/paclitaxel. All patients were optimally debulked to ≤ 1 cm prior to study entry. The treatment groups were well matched for age, performance status, histologic cell type, and debulking to microscopic disease. There was no statistically significant difference in baseline CA125 between the treatment groups.

During cycles 1 and 2, no difference in CA125 response occurred for patients receiving IV high-dose carboplatin versus IV cisplatin/paclitaxel. During all subsequent treatment cycles, there was no statistically significant difference in CA125 levels or in rate of CA125 normalization between IV- and IP-treated patients (Figure 1). The time for 80% of patients to

demonstrate CA125 normalization was 98 days from the day of surgery for patients receiving IV treatment and 106 days for those receiving IP treatment.

Recently, Richardson et al reported a single-institution retrospective analysis on CA125 decline among IP- and IV-treated patients [2]. There was no statistically significant difference in CA125 regression among the groups. In fact, the authors found a trend toward a shorter time to CA125 normalization and time to CA125 nadir for IP-treated patients. However, there were only 17 patients in the IP treatment arm, and this treatment group had a significantly higher rate of primary debulking to microscopic residual disease (71%) compared to IV-treated patients (25%), a difference that could have contributed to a more favorable CA125 normalization among the IP-treated group.

A separate single-institution evaluation of 38 IP-treated patients presented by Richard et al indicated that IP catheters may prolong the time to CA125 normalization [3]. Elevated CA125 levels upon completion of IP treatment were identified and appeared to be largely due to the presence of the IP catheter. Sixty-eight percent of IP-treated patients achieved CA125 normalization upon completion of IP chemotherapy, whereas 87% of these patients normalized their CA125 values following removal of the IP catheter. This is an important observation, as a spurious elevation in CA125 when the patient otherwise appears to have had a complete clinical response may be resolved by removal of the IP catheter. However, the data in our current study suggest that across randomized treatment groups in a larger patient population, this is not a frequent occurrence. IP-treated patients demonstrated normal CA125 levels at a rate similar to that of patients receiving IV-only treatment, including levels drawn upon completing adjuvant therapy.

Importantly, analysis of CA125 decline among patients treated on protocol GOG 172 performed by Krivak et al identified a similar regression of CA125 levels in both IV- and IP-treated patients [4]. The CA125 analysis from GOG 172 and the

current evaluation of patients in GOG 114 both demonstrate a similar rate of CA125 normalization among well-matched patients undergoing IV chemotherapy or an experimental regimen containing a component of IP drug delivery. These data support the utilization of standard CA125 response criteria in the therapeutic monitoring of patients receiving IP treatment.

The frequency of CA125 measurements in this study was a median of 11 days, more frequent than the 21-day interval that is standard for most protocols, and often used in clinical practice. The high frequency of CA125 measurement in this study targets the window within which an intra-cycle and potentially tran-

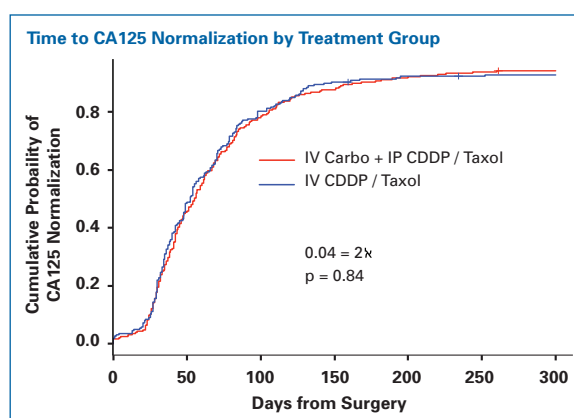


Figure 1. Time to CA125 normalization from date of surgery by treatment arm. IV, intravenous; IP, intraperitoneal; CDDP, cis-diamminedichloro-platinum(II) or cisplatin; Taxol, paclitaxel; Carbo, carboplatin

sient non-specific elevation of CA125 from IP drug delivery would be identified. This is the largest evaluation of CA125 regression among IP- versus IV-treated patients to date. No difference in CA125 response was seen in patients receiving IP vs IV treatment. This study supports the utilization of standard CA125 response criteria in therapeutic monitoring for patients receiving IP treatment. The high frequency of CA125 measurement until normalization of values and the large size of the patient cohort are unique to this study.

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