



Invited Commentary | Oncology

Are We Ready for Hyperthermic Intraperitoneal Chemotherapy in the Upfront Treatment of Ovarian Cancer?

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Advanced epithelial ovarian cancer (EOC) has a well-characterized pattern of spread; the cancer cells tend to stay within the peritoneal cavity, attaching to organ surfaces and only invading superficial layers.¹ This pattern makes intraperitoneal chemotherapy an attractive alternative to conventional systemic chemotherapy in select patients with EOC, although it can be poorly tolerated. Hyperthermic intraperitoneal chemotherapy (HIPEC) performed at the time of cytoreductive surgery is a method of delivering intraperitoneal chemotherapy that can mitigate the concerns of patient tolerance and catheter-related issues seen in normothermic intraperitoneal chemotherapy. Hyperthermia is thought to synergize with chemotherapy by increasing activity of the agent, as well as promoting deeper penetration of the drug into tumor implants.² Previous studies of HIPEC in advanced EOC have generally examined its use in the interval or recurrent setting. The first randomized trial, published by Spiliotis et al³ in 2015, found 13-month improvement in survival with the addition of HIPEC to secondary cytoreductive surgery, a benefit found in both platinum-sensitive and platinum-resistant cohorts. More recently, van Driel et al⁴ randomized women with stage III EOC undergoing neoadjuvant chemotherapy to interval debulking surgery (IDS) with and without HIPEC with cisplatin at a dose of 100 mg/m². The women who underwent IDS with HIPEC demonstrated a 3.5-month improvement in progression-free survival and a 12-month improvement in overall survival.⁴ These findings support the use of HIPEC in this setting, although the trial had significant limitations, including the lack of stratification by International Federation of Gynecology and Obstetrics or *BRCA* mutation status, imbalance in the 2 groups, and randomization prior to surgery. Despite these limitations, we now routinely discuss HIPEC with cisplatin at a dose of 100 mg/m² in the interval setting with the subset of patients with abdominally confined disease, whom we anticipate will experience optimal IDS (the removal of all tumor to microscopic disease).

Lei et al⁵ report a new study including patients with EOC undergoing primary cytoreductive surgery (PCS) with or without the addition of HIPEC. This well-designed retrospective study includes data from 5 high-volume surgical centers in China with strict inclusion criteria. Within the cohort of 584 patients, 425 underwent PCS plus HIPEC and 159 underwent PCS alone. At a median follow-up of 42.2 months, the addition of HIPEC led to a nearly 16-month increase in survival for the PCS-HIPEC group (median, 49.8 months; 95% CI, 45.2-60.2 months) compared with the PCS group (median, 34.0 months; 95% CI, 28.9-42.3 months). The 3-year overall survival was also increased by nearly 11 percentage points for the PCS-HIPEC group (60.5%; 95% CI, 55.5%-65.2%) vs the PCS group (49.6%; 95% CI, 41.2%-57.5%). Remarkably, the improvement in survival was found in patients who underwent both optimal (<1 cm) and suboptimal cytoreduction, although the improvement in median survival time did not reach significance in the suboptimal cohort. Because HIPEC only superficially penetrates tumors, patients with large residual tumors are not thought to be ideal candidates for the procedure; however, the findings of Lei and colleagues suggest that there might be an oncological effect even in this cohort.

The HIPEC regimen used by Lei et al⁵ was cisplatin at a dose of 50 mg/m² delivered on days 1, 3, and 5,⁵ which is very different from the regimens used by either Spiliotis et al³ or van Driel et al.⁴ Considering the unusual multiday HIPEC protocol, one would anticipate a higher level of grade III and IV toxicities, but Lei et al⁵ noted an increase only in the frequency of electrolyte disturbances. This

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toxicity profile is in line with previously reported HIPEC studies, suggesting that this iterative HIPEC with PCS may be well tolerated and efficacious.

Although there are data to support the use of HIPEC with cisplatin at a dose of 100 mg/m² in the recurrent or interval setting, there are scant data on the use of HIPEC in the PCS setting.⁶ The study by Lei et al,⁵ with the largest cohort of patients treated with HIPEC in the upfront setting, supports its use in the primary cytoreductive setting. There are, however, some important limitations to this study. The retrospective nature of the study contributes significantly to selection bias, which might be reduced, but not eliminated, by propensity score matching as performed by the authors. There is imbalance in the 2 cohorts, and patients with PCS-HIPEC underwent more systemic chemotherapy cycles than the PCS group (≥6 cycles; 51.8% vs 35.2%). These patients represent a heterogeneous group with low-grade serous cancers, and the decision to perform HIPEC ultimately was decided on a case-by-case basis. The unusual method of multiday HIPEC with lower-dose cisplatin (50 mg/m²) used in the study is not founded on strong phase 1 trial data and is difficult to generalize to other institutions that use single-time HIPEC during cytoreductive surgery. Also, without tumor genomic data (especially *BRCA1* or *BRCA2* mutation information), surgical outcomes, and patterns of recurrence, it is difficult to draw more conclusions on the safety and efficacy of HIPEC in this setting. Finally, this cohort may not be generalizable to other populations in which adjuvant chemotherapy compliance is better. It is concerning that only 47.3% of patients completed at least 6 cycles of postoperative intravenous chemotherapy in the study by Lei et al.⁵

Nevertheless, the study by Lei et al⁵ adds to recent evidence indicating that the addition of intraperitoneal chemotherapy with HIPEC, whether upfront or at interval debulking, might improve overall survival. It would appear to us, after reviewing the available published evidence supporting the use of HIPEC, that one should discuss the use of HIPEC preoperatively with patients with stage III, low-volume disease who are thought to likely experience optimal (RO) cytoreduction. From the data presented by Lei et al,⁵ one could argue that even patients with large volumes of residual disease could benefit from HIPEC with PCS, but the data are less convincing and need further investigation. We expect that remaining questions will be conclusively answered by a phase 3 randomized trial that just opened this year.⁷ In the international OVHIPEC-2 trial, patients with stage III disease who achieve cytoreduction to less than or equal to 2.5 mm will be randomized to either receive HIPEC or not receive HIPEC, followed by adjuvant chemotherapy. It is anticipated that results will be available in 2026. Until then, we expect that more institutions will publish their experiences with HIPEC to help guide decision-making on its use in the upfront treatment of ovarian cancer.

ARTICLE INFORMATION

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