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Expert Opinion

CHIPOR, HORSE, and beyond: unraveling the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer

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The advantage of hyperthermic intraperitoneal chemotherapy (HIPEC) is that it maintains direct exposure of anticancer drugs to the tumor while avoiding the use of intraperitoneal ports, which makes less complication from intraperitoneal chemotherapy while maintaining the survival benefit [1]. An additional advantage is that the chemotherapeutic agent can be exposed to the entire visceral and parietal peritoneum before adhesions occur after surgery. In addition, hyperthermia can be added, which is a great advantage in that it makes the tumor more BRCAness-like and increases its response to anticancer drugs [2].

In 2018, the OVHIPEC-01 trial, the first phase III randomized trial in ovarian cancer performed by van Driel et al. [3], reported that HIPEC increases progression-free survival (PFS) and overall survival (OS) when interval cytoreductive surgery is performed after neoadjuvant chemotherapy in stage III ovarian cancer. In 2022, Lim et al. [4] reported that there was no survival benefit of HIPEC during upfront surgery in the KOV-HIPEC-01 trial, but as in the OVHIPEC-01 trial, HIPEC increased PFS and OS when interval cytoreductive surgery was performed after neoadjuvant chemotherapy.

A meta-analysis later demonstrated that HIPEC is beneficial for survival in cases of recent exposure to chemotherapy within 6 months [5]. In the recent chemotherapy exposure group (<6 months), HIPEC was associated with improvement of both PFS (hazard ratio [HR]=0.585; 95% confidence interval [CI]=0.422–0.811) and (≥6 months) OS (HR=0.519; 95% CI=0.346–0.777), while in the non-recent chemotherapy exposure group, HIPEC failed to significantly affect PFS (HR=1.037; 95% CI=0.684–1.571) or OS (HR=0.932; 95% CI=0.607–1.430).

The CHIPOR and HORSE studies further contributed to the understanding of HIPEC's role in ovarian cancer [6,7]. The HORSE trial evaluated HIPEC in the first-recurred platinum-sensitive recurrent ovarian cancer during secondary cytoreductive surgery but found no significant benefit in either PFS (median PFS: 16.9 vs. 15.7 months; HR=0.97, p=0.863) or OS (median OS: 53.8 vs. 52.6 months; HR=0.96, p=0.870) [6]. However, the CHIPOR trial demonstrated a significant survival benefit by administering 6 cycles of platinum-based chemotherapy to patients with platinum-sensitive recurrent ovarian cancer, followed by consolidation HIPEC after cytoreductive surgery [7]. It showed a significant improvement in OS with HIPEC (median OS: 54.3 vs. 45.8 months; HR=0.73, p=0.024), supporting its application in selected cases.

These 2 findings further support the hypothesis that HIPEC might offer clinical benefits in cases where recent chemotherapy exposure has occurred, and the tumor is resectable. Their findings may be explained by previously proposed hypotheses that hyperthermia can render chemo-resistant cancer cells more susceptible to chemotherapy. The rationale for this effect lies in heat-induced inhibition of HSP90, which disrupts DNA damage repair pathways and promotes the degradation of BRCA1/2 proteins, thereby sensitizing cells to the DNA damage caused by platinum-based chemotherapy [8,9].

In this consistent context, HIPEC is expected to provide a survival benefit in platinum-resistant recurrent ovarian cancer. However, since the role of cytoreductive surgery is unclear in this setting, we can look forward to the results of the KOV-HIPEC-02R (RECOVER) trial, which is currently registered in more than 80% and is expected to produce results within 2–3 years (NCT05316181). In primary ovarian cancer, the OVHIPEC-02 trial has been registered for more than 3-quarters of targeted number of the stage III patients after upfront surgery (NCT03772028). The role of HIPEC during interval cytoreductive surgery after neoadjuvant chemotherapy in stage III and IV patients with maintenance therapy with poly(ADP-ribose) polymerase inhibitors or bevacizumab is evaluated in the ongoing KOV-04, FOCUS (enrollment >50%, target number: 520) (NCT05827523). In near future, the role of HIPEC in the management of ovarian cancer could be clearly identified with these ongoing clinical trials of HIPEC.

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