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Editorial

Saved by the evidence: Hyperthermic intraperitoneal chemotherapy still has a role to play in ovarian cancer

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We read with interest the article by Serve Evrard on the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal peritoneal carcinomatosis [1]. Evrard's analysis is highly relevant and draws attention to the limitations of recommendations based on expert consensus. An expert consensus report may advocate a treatment approach based on convictions rather than evidence, with results from one disease being extrapolated to other indications without the necessary evaluation. While these convictions may seem reasonable, they do not stand the test of evidence from well-conducted studies. As pointed out by Evrard, it took 15 years for HIPEC combined with complete cytoreductive surgery (CRS) to lose its status as standard of care for colorectal carcinomatosis. In 2003, the findings of the Dutch trial [2,3] comparing aggressive CRS plus HIPEC with palliative chemotherapy earned HIPEC recognition as part of the standard treatment for colorectal carcinomatosis, but just last year, the publication of the PRODIGE 7 trial [4] results comparing maximal CRS surgery plus HIPEC with oxaliplatin for 30 minutes at 43 °C versus CRS plus systemic chemotherapy, effectively put an end to the use of HIPEC in this setting or at least the use of HIPEC with the trial protocol. However, unfavorable outcomes with systemic chemotherapy have never meant that the chemotherapy is ineffective *per se*, but rather that the particular regimen employed (drug, dosage, frequency, and duration) may need to be modified.

Evrard's points regarding the limitations of HIPEC are nonetheless worth discussing [1]. Extensive peritoneal stripping in CRS renders HIPEC ineffective as the target surface is removed leaving only the underlying muscle to interact with the chemotherapy agent. However, when diaphragmatic and pelvic peritonectomy are performed, it is impossible to remove the entire peritoneum. In addition, some authors have postulated that HIPEC could have a prophylactic effect on parts of the peritoneum unaffected by carcinomatosis. CRS, regardless of the technique used, involves the removal of macroscopic, not microscopic, disease. Little to nothing can be done about microscopic disease during surgery, and subsequent histologic examination of peritoneal biopsy specimens frequently reveals microscopic disease in areas deemed healthy by the surgeon. HIPEC would therefore appear to be an attractive option for treating residual microscopic disease that cannot be surgically managed, as the chemotherapy agent is delivered to a depth of 3 mm (i.e., 20 layers of cells), where it can act on undetectable disease.

Numerous protocols describing different drugs, intraperitoneal temperatures, and exposure times are all grouped under the term *HIPEC*, and variations in these factors can all affect survival and toxicity outcomes. Evrard rightly draws attention to potential pitfalls associated with variations to optimal intraperitoneal conditions based on a homogeneous temperature of 43 °C and short exposure. Trial and error and constant readjustments, however, are only to be expected in surgery, and current practice seems to be moving towards the use of lower temperatures (41°C-42 °C)—aimed at reducing toxicity—and longer exposure times (90 minutes)—aimed at increasing effectiveness [3].

No survival benefits have been demonstrated for HIPEC in the setting of colorectal carcinomatosis. One problem with evaluating HIPEC is that histology results are typically reported as a whole [5,6], even though overall survival is affected differently by the natural history of each disease. In colorectal cancer, malignant cells breach the basement membrane and spread to another part of the body via the lymphatic system, the bloodstream or both, resulting in metastasis. The natural history of ovarian, fallopian tube, or primary peritoneal cancer, however, is very different, as there is no breach of the basement membrane and no lymphatic or hematogenous spread. In this case, the cancer appears to spread by contiguity as part of a process in which the tumor cells become mobile and attach themselves to the peritoneum within this single cavity. The ovaries and the fallopian tubes are therefore “exposed” as there is no basement membrane to act as a physical barrier. Most patients with ovarian cancer die of peritoneal recurrence, which has a greater impact on overall survival than recurrence at other sites. Data from Ceresoli et al. indicate that treatment with CRS plus HIPEC modifies the natural history of ovarian cancer by “sterilizing the peritoneum”. The authors observed a much lower rate of peritoneal recurrence only (i.e., peritoneal recurrence without systemic spread) in patients who underwent CRS plus HIPEC compared with CRS alone (14% vs. 43%) [7,8]. What these results show is that patients with ovarian cancer treated with HIPEC do not die of early peritoneal disease, but of distant metastases that form part of the natural course of disease. This survival benefit was perfectly demonstrated by Van Driel and his team in the phase III randomized controlled OVHIPEC trial (evidence level 1) [3,9]. This trial evaluated the effects of HIPEC in patients with ovarian cancer who had undergone previous chemotherapy and complete CRS (no residual disease) or optimal CRS (residual tumor <1 cm).

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Interval CRS was performed after three cycles of intravenous chemotherapy with carboplatin (area under the curve, 6 mg/mL/min) and paclitaxel (175 mg/m^2). The patients were randomized to the CRS-only arm (123 patients) or the CRS plus HIPEC arm (122 patients) at the time of surgery. The median age of the patients was 63 years in both arms. The percentage of patients with and without residual disease after surgery was also identical in the two groups: 30% of patients had tumor nodules $\leq$10 mm and 67% had no visible tumor. The primary endpoint was recurrence-free survival calculated from the time of randomization. Secondary endpoints were overall survival, adverse effects, and quality of life. Recurrence was diagnosed on the basis of imaging studies (Response Evaluation Criteria in Solid Tumors 1.1 criteria) in 83% of patients and increased serum cancer antigen 125 levels in the remaining 17%. Median follow-up time was 4.7 years. Median recurrence-free survival was 10.7 months in the CRS-only arm and 14.2 months in the CRS plus HIPEC arm ($p = 0.003$). The respective median overall survival times were 33.9 months and 45.7 months ($p = 0.02$). Adverse effect rates were similar in both arms (25% for CRS vs. 27% for CRS + HIPEC, $p = 0.74$). Time from surgery to re-initiation of chemotherapy was 30 days in the CRS-only group and 33 in the CRS plus HIPEC group; 90% and 94% of patients respectively received the three cycles of postoperative chemotherapy originally envisaged (Level of evidence 1). The clear overall survival benefit observed in patients who underwent HIPEC in addition to CRS position HIPEC as a relevant treatment for patients with FIGO stage III ovarian cancer.

Several authors have published criticisms of the OVHIPEC trial and its results in the *New England Journal of Medicine*. The main criticisms were related to the higher costs associated with the use of HIPEC (e.g., longer operating times and hospital stays), concerns regarding the reproducibility of the technique (and results) at less experienced centers (particularly from the perspective of increased morbidity), lower median survival rates compared with initial optimal surgery before adjuvant chemotherapy, and a failure to screen for *BRCA* mutations (patients with these mutations have a better prognosis and can also benefit from maintenance olaparib treatment). Because of these criticisms, numerous authors concluded that HIPEC, at least for now, should only be performed within the setting of a clinical trial. International guidelines, and most notably the European Society of Gynaecological Oncology guidelines, do not recommend the use of HIPEC in ovarian cancer. French national recommendations published in December 2018 [10], however, state that HIPEC, performed in the same conditions as in the OVHIPEC trial, can be contemplated as a treatment option after interval CRS in patients with FIGO III stage ovarian cancer.

The OVHIPEC trial also provides a long-awaited requirement to standardize the HIPEC protocol. The survival benefits observed in the trial were achieved with the following protocol: cisplatin at a total dose of 100 mg/m^2 administered as 50 mg/m^2 at the beginning of the procedure, 25 mg/m^2 at 30 minutes, and 25 mg/m^2 at 60 minutes. The perfusion lasted for 90 minutes and the intra-abdominal temperature was 40°C–41 °C. Sodium thiosulfate administered as an intravenous bolus at a dose of 9 g/m^2 at the start of perfusion followed by continuous infusion at a dose of 12 g/m^2 for 6 hours was used to prevent nephrotoxicity. This protocol appears to minimize the adverse effects associated with HIPEC while maintaining efficacy. Other protocols would need to be evaluated in prospective studies.

In short, HIPEC has suffered from a lack of evidence-based evaluation in different disease settings and a need to standardize the treatment protocol. Such “lapses” have resulted in expert opinions which are poorly grounded in the evidence. Today, after 20 years of development spearheaded by the creators of the technique, HIPEC has reached a certain level of technical and “oncological” maturity. While it was not shown to offer additional benefit in colorectal cancer according to the PRODIGE 7 protocol, it is effective in ovarian cancer according to the OVHIPEC protocol. Furthermore, the OVHIPEC trail provides a standardized protocol which should overcome the hitherto limited uptake of HIPEC in ovarian cancer.

Conflict of interest

Authors have no conflict of interest.

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