Editorial

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Hyperthermic intraperitoneal chemotherapy for ovarian cancer: is there a role?

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See accompanying article by Coccolini and colleagues on page 54.

Epithelial ovarian cancer (EOC) remains a major killer of women despite the fact that, paradoxically, it has innate characteristics which should facilitate effective treatment: it begins, and frequently remains, confined within the peritoneal cavity for much of its natural history (apart, most notably) from retroperitoneal lymph node involvement, it is relatively 'non-invasive' and thus amenable to surgical resection, and it responds well to initial chemotherapy. In addition, the peritoneal barrier enables the targeted delivery of chemotherapy directly to the peritoneal tumors [1]. These factors underpin the treatment modalities that can deliver the best outcomes for patients.

In advanced disease, the importance of surgical resection of all visible disease together with the use of platinum and taxane chemotherapy is widely recognized [2]. In randomized trials, intraperitoneal (IP) therapy following front-line surgery has a significant impact on survival [3]. For those patients in Gynecologic Oncology Group 172 [4] with no residual disease following front-line surgery who were randomized to the IP arm, the median overall survival was 128 months [5]. This is the current high-water mark for survival in advanced ovarian cancer.

Despite all these facts, virtually the only agreement about treatment for advanced disease is that surgery and chemotherapy play a role, and that current treatment is ineffective in far too many. Could hyperthermic intraperitoneal chemotherapy (HIPEC), which incorporates all of the above, with the addition of heat, and delivery at the time of surgery when disease volume is at its lowest and all peritoneal surfaces and tumors are exposed, play a role in improving outcomes?

In this edition of the journal, Coccolini et al. [6] report the application of an IP perfusion of cisplatin (100 mg/m^2) and paclitaxel (175 mg/m^2) for up to 90 minutes at a 'thermal plateau' of 41.5°C following cytoreductive surgery (CRS) for EOC. Fifty-four patients were treated in three different centers (one contributing only two patients) with different chemotherapy treatments at several different natural history time-points.

The report adds to the general pool of data that has been accumulating with regards to the use of HIPEC in EOC and, more specifically, information on the morbidity associated with CRS and HIPEC with combination cisplatin and paclitaxel. The use of combination cisplatin and paclitaxel with hyperthermia, at exactly the same dosages, has been reported previously [7] and more recently [8]. The choice of paclitaxel is of note because although there is doubt about whether there is any significant enhancement of paclitaxel cytoxicity by hyperthermia [9,10], there is a report of prolonged exposure of the peritoneal surfaces to concentrations of paclitaxel above the cytotoxic threshold for a mean of 2.7 days (range, 1 to 4 days) following HIPEC and drainage of the peritoneal cavity [10].

The morbidity and mortality rates of HIPEC following CRS using other chemotherapy agents are much clearer following well-conducted studies at different time-points [11-16]. Much of any additional morbidity is caused by the addition of chemotherapy. The figures stand up well in comparison to those from patients undergoing extensive CRS without HIPEC, especially with regard to perioperative mortality [17].

This report would be more enlightening if it included detail on such questions as the time from HIPEC to subsequent chemotherapy, the histological grade of the tumors, whether borderline tumors were excluded, the spectrum and numbers of patients treated for EOC at the participating institutions, including the overall numbers initially treated with neoadjuvant chemotherapy or surgery and the number of patients with 'suboptimal' CRS precluding them from HIPEC. Also beneficial would have been additional clarity on the definitions of platinum sensitivity and 'recovery time,' the carboplatin-taxane combination mentioned in the discussion, the unreferenced

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previous report using the same combination of drugs at the same dose [7], and explanation of the range of median overall survival reported for patients undergoing CRS and HIPEC in the literature, stated as 24 to 106 months, the upper range of which has only been reported with CRS followed by systemic and normothermic IP chemotherapy [18].

At this point, the question is whether HIPEC can improve survival for women with EOC and positively affect quality of life at any of the natural history time-points. Recently, a randomized trial of CRS and HIPEC with cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 for recurrent International Federation of Gynecology and Obstetrics (FIGO) stage IIIC and IV EOC reported a significantly improved mean survival in the HIPEC arm, 26.7 versus 13.4 months [8]. Unfortunately, the randomization was performed before the CRS, but nevertheless this is the start of the accrual of more definitive data, particularly from ongoing randomized controlled trials around the world, of which there are at least 6 currently registered at ClinicalTrials.gov of US National Institutes of Health (http://www.clinicaltrials.gov).

Will these trials be enough to answer all the questions? Almost certainly not. More will need to be done, with future challenges including defining the possible roles of HIPEC within the spectrum of other treatments for OC including repeated normothermic IP chemotherapy, early postoperative IP chemotherapy, and novel and biological agents.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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