Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer: Where Do We Go From Here?

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In the view of this commentator, the ongoing debate regarding a potential role for hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of ovarian cancer represents an excellent example of the rarely publicly discussed fundamental clash between the requirements of so-called evidence-based (e.g., randomized phase III trial data) medicine versus the roles of both clinical innovation in advancing therapeutic paradigms and a focus on optimizing care for the individual patient. Furthermore, the discussion emphasizes the genuine difficulty associated with distinguishing excellent clinical judgment from selection bias in the conduct of prospective nonrandomized clinical trials or the analysis of retrospective reports of institutional experiences.

A Very Brief Review and Discussion of the Background of This Debate

HIPEC

Although it is not the specific purpose of this particular commentary, it is essential to formally acknowledge the existence of both a robust preclinical literature that provides support for the potential clinical utility associated with the intraperitoneal delivery of “heated” chemotherapy in the management of neoplasms whose natural history appears to be principally confined to this body cavity, as well as a growing clinical literature (e.g., retrospective series, prospective clinical trials) that suggests patients with several cancer types (e.g., metastatic appendix, peritoneal mesothelioma, colon, ovarian) experience benefit (as measured by length of survival from the date of the procedure) [1–5].

Various authors have attempted to compare the outcomes observed following HIPEC with those observed after alternative experiences, including those in patients managed with cytoreductive surgery only, systemic chemotherapy only, supportive care only, or some combination of these strategies. Unfortunately, there are several major issues that prevent a firm conclusion regarding the validity of the utility of this aggressive, expensive, and potentially morbid strategy in the management of any cancer type. These concerns are briefly summarized in the following paragraphs.

First, with the extensive reported experience with HIPEC, it is reasonable to conclude the procedure can be successfully undertaken by well-trained surgical/gynecologic oncologists and at institutions experienced in the approach, with a generally acceptable risk for serious treatment-related morbidity and mortality [1–5]. Furthermore, the reports have clearly documented that many patients with advanced, progressive, and previously treated cancer (including “standard-of-care” systemic antineoplastic therapy) involving the peritoneal cavity have been able to experience prolonged survival (measured in “many years”) following the performance of this procedure [1–5].

Second, what cannot be concluded, however, based on the existing evidence is the critical question of the relative roles played by a number of highly relevant patient-related features as well as several factors associated with the technique itself (Panel 1).

Third, in ovarian cancer, the problems identified in Panel 1 are compounded by the truly striking absence of randomized trial data demonstrating the clinical utility of the “package” of successful aggressive cytoreductive surgery followed immediately by heated intraperitoneal chemotherapy versus successful aggressive cytoreductive surgery alone, or such surgery combined with more standard intraperitoneal chemotherapy (i.e., without heat and over multiple courses following recovery from surgery), or aggressive surgery combined with current standard-of-care systemic antineoplastic therapy (possibly in the near future to include immunotherapy). In fact, a study in colon cancer that is often cited as a landmark randomized trial supporting HIPEC was, unfortunately, a profoundly misguided effort, as it compared only a minimal (or no) attempt at surgical cytoreduction plus systemic chemotherapy with aggressive surgical cytoreduction plus HIPEC [3]. As a result, the impact of the aggressive cytoreductive surgery alone in this trial is completely unknown.

Fourth, the reported prospective and retrospective experiences with HIPEC fail to acknowledge the critical issue of the decision-making routinely used by experienced expert clinicians in the daily management of individual patients and how this absolutely essential process in defining optimal
The Role of Surgical Cytoreduction in Ovarian Cancer

It is perhaps more than a little ironic that the question of the level of evidence supporting HIPEC in the management of ovarian cancer should be so prominently discussed when the gynecologic oncology community continues to struggle with the fundamental nature of the existing level of evidence that currently supports the role of aggressive primary surgical cytoreduction in the malignancy. One would be hard pressed to find a guideline produced by any group of gynecologic oncologists that did not insist the standard of care in disease management of newly diagnosed epithelial ovarian cancer should be an attempt at maximal surgical cytoreduction, followed by antineoplastic chemotherapy (systemic or, it appears uncommonly, intraperitoneal).

Yet it would be equally difficult to find randomized phase III trial evidence that unequivocally supports the superiority of this strategy compared, for example, with the administration of several cycles of platinum-based cytotoxic chemotherapy followed by surgery [6, 7]. Although the existing phase III trial data do not suggest a different survival outcome associated with the neoadjuvant approach, the population-based overall surgical morbidity associated with primary surgery is reduced [6, 7].

The intent in making this statement is not to debate the relative merits of primary surgical cytoreduction versus delayed surgery (following a response to effective neoadjuvant therapy) but rather to highlight the absence of highest quality evidence supporting the former approach. Of course, extensive retrospective experiences provide evidence for both the utility and safety of primary surgical cytoreduction in the majority of women presenting with advanced stage ovarian cancer, but that is not the question being addressed in this commentary. The issue is whether phase III randomized trial data are required to use a strategy when, in the experience of appropriately trained gynecologic/surgical oncologists, an approach is shown to be reasonably safe and results in outcomes that appear to be superior to that resulting from alternative strategies.

Intraperitoneal Chemotherapy in the Management of Ovarian Cancer

Finally, we come to the difficult issue of the intersection between reported experience (even if “extensive,” as in the case of primary surgical cytoreduction in ovarian cancer), clinical judgment (which characterizes the excellent physician), and solid evidence-based randomized phase III trial data.

Three phase III randomized trials have demonstrated the favorable impact of platinum-based primary intraperitoneal chemotherapy following an attempt at maximal surgical cytoreduction in advanced epithelial ovarian cancer [8–13]. Again, the intent here is not specifically to debate the role of intraperitoneal chemotherapy or to comment on the rather disquieting observation that a surprisingly small percentage of patients who appear to be candidates for this approach actually receive regional therapy following surgery [13]. Rather, the point to be made is that this evidence stands in sharp contrast to both that existing with the novel approach of immediately delivering a heated cytotoxic agent directly into the peritoneal cavity following aggressive cytoreductive surgery or to the claimed benefits of a requirement that the standard of care in the management of ovarian cancer should be primary cytoreductive surgery.

CONCLUSION

The preceding discussion has highlighted both the status of the debate regarding the potential role of HIPEC in the management of ovarian cancer and what may appear at times to be less than an openly honest assessment as to the requirements for this, or other innovative approaches, to be considered as important.
acceptable standard-of-care strategies in the management of ovarian cancer.

Why is it mandated that HIPEC be supported by phase III trial evidence when this requirement has never been satisfied for the role of primary cytoreductive surgery in this malignancy [6, 7]? And what is the relevance of phase III trial data anyway if such data demonstrating a favorable impact on survival in ovarian cancer appear to not be embraced by the community of practicing oncologists (gynecologic and medical) [13]?

And even if a phase III trial of HIPEC were successfully initiated, completed, and reported in the peer-reviewed literature in a specific clinical setting (e.g., heated intraperitoneal carboplatin immediately following primary cytoreductive surgery of advanced ovarian cancer compared with a standard, 6-cycle, every-3-weeks regimen of intraperitoneal cisplatin) this experience would not answer the question of the utility of alternative regional drug delivery approaches. For example, perhaps platinum is not the ideal drug to use in this manner, because the concentration differences between cavity and systemic compartment exposures are highly likely to be substantially lower than with alternative drugs (e.g., paclitaxel, mitomycin, anthracyclines).

And perhaps it is not in the primary setting where the greatest benefit of HIPEC will be seen, because of the already favorable impact of primary systemic platinum-based treatment in ovarian cancer. In fact, it may conceivably be in the platinum-resistant setting, where therapeutic options are far more limited, where the maximum impact on an ultimate survival outcome may be observed.

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