Cytoreductive Surgery and Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) for Gastric Adenocarcinoma: Why Haven’t We Reached the Promised Land?

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Gastric adenocarcinoma (gastric cancer, GC) is the fourth most common cancer and the second leading cause of cancer death worldwide. There are major differences in the incidence of GC across countries and continents. Global incidence, as well as primary tumor location and histological type are constantly changing. In the US and most of Western Europe, there has been a marked decline in distal, intestinal type GC, while the incidence of proximal and Barrett’s type adenocarcinoma of the gastric cardia and esophago-gastric junction has been increasing. The incidence of diffuse type adenocarcinoma, on the other hand, is largely unchanged [1]. Adenocarcinoma of the body and antrum predominates in developing countries, among African-Americans, and in lower socio-economic groups, whereas proximal tumors are more common in developed countries, among Caucasians, and in higher socio-economic classes. The main risk factors for adenocarcinoma of the body and antrum include Helicobacter pylori infection and predisposing dietary factors, whereas gastroesophageal reflux disease and obesity play important roles in the development of proximal stomach cancer.

The current treatment paradigm includes surgical resection with D1+ or D2 lymphadenectomy for non-metastatic GC, and palliative systemic therapy for disseminated tumors. In patients with locally advanced GC demonstrating serosal invasion, lymph node metastasis or positive peritoneal washing cytology, the prognosis following surgical therapy alone is poor. In an attempt to improve survival, various innovative therapeutic approaches have been studied. In the US, the Intergroup 0116 study showed a survival advantage for post-operative combined modality using chemoradiation [2]. Despite the lack of surgical quality assurance, resulting in poor quality surgery for most patients participating in the trial, this approach is now widely adopted throughout Northern America. A different approach was studied in Europe in large prospective randomized clinical trials. In the MAGIC trial conducted by the Medical Research Council in the UK, chemotherapy [Epirubicin, Cisplatin, and 5-Fluourouracil (ECF)], delivered before and after surgery was compared to surgery alone [3]. The 13% (36% vs. 23%) benefit in 5-year overall survival shown for the multi-modality (chemotherapy + surgery arm) is the main reason this approach adopted throughout Europe. A less toxic regimen [Epirubicin, Oxaliplatin, and Capegitabine (EOX)] having comparable efficacy was demonstrated in the REAL-2 study and has supplanted the more toxic ECF regimen as standard of practice in Europe [4].

The prognosis of metastatic GC is dismal. Multiple clinical trials evaluating the efficacy and toxicity of cytotoxic agents have shown disappointing response rates, low therapeutic ratio, with disappointing median survivals of 6–16 months [5]. Despite major advances in the development of biologic agents for the treatment of gastrointestinal cancers, such as Bevacizumab and Cetuximab for metastatic colorectal cancer, there are currently no available efficacious biological agents approved for the treatment of advanced GC. Recently, Trastuzumab, a recombinant humanized anti-HER-2 monoclonal antibody, demonstrated absolute survival improvement of nearly 3 months in patients with metastatic GC overexpressing HER-2. Unfortunately, HER-2 is overexpressed in only ~20% of GC patients [6].

The lack of efficient systemic therapy combined with the fact that the peritoneum is a preferential site for GC dissemination, has been the impetus for many investigators to study intra-peritoneal administration of cytotoxic agents in both therapeutic and adjuvant setting for metastatic GC. Most studies evaluating the incremental value of intra-peritoneal chemotherapy when added to systemic therapy or surgery were conducted in the adjuvant setting. Yan et al. [7] reviewed all clinical trials studying intra-peritoneal chemotherapy in resectable GC. They found 106 published peer-reviewed articles, of which 14 were prospective randomized clinical trials. One trial was excluded from the analysis because it compared hyperthermic to normothermic intra-peritoneal chemotherapy. In the 13 randomized clinical trials analyzed, 1,648 patients were randomly assigned to receive either intra-peritoneal chemotherapy (n = 873) or other form of therapy (n = 775). Only one clinical trial evaluated the role of hyperthermic intra-peritoneal chemotherapy (HIPEC) in GC, which compared surgery + HIPEC to surgery alone. In this met-analysis, surgery + HIPEC was associated with significantly improved survival compared to surgery alone.

In this issue of the Journal of Surgical Oncology, Li et al. [8] report their results with 10 patients treated with cytoreductive surgery (CRS) and HIPEC in GC patients with limited peritoneal dissemination. In a cohort of 127 patients, 54 patients underwent surgical resection, 40 patients underwent CRS, and 33 patients received HIPEC. The median survival of the patients was 9 months, and the 5-year survival of the patients was 20%.

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of which 10 patients underwent resection with HIPEC. The median survival in the unresected group was 6.0 months compared to 11.8 months in the resected patients. The patients that were treated with surgery + HIPEC had a significantly improved survival compared to the patients that were treated with surgery alone. This report demonstrates the current status of therapy for peritoneal dissemination of GC. Despite Level I evidence supporting surgery + HIPEC over surgery alone or palliative chemotherapy, only a minority of all patients in this cohort was offered HIPEC.

Currently, CRS combined with HIPEC and/or early post-operative intra-peritoneal chemotherapy (EPIC) has gained acceptance worldwide as the treatment of choice in several tumor types: Pseudomyxoma peritonei, carcinoma of the vermiform appendix, colorectal cancer and diffuse malignant peritoneal mesothelioma. It is only logical that the growing evidence supporting this form of therapy would encourage more centers to practice CRS + HIPEC for a disease in which peritoneal dissemination remains a major form of treatment failure and ultimate patient demise. However, only few centers offer CRS + HIPEC to GC patients with peritoneal dissemination. One of the leading groups in this field, the Yonemura group from Japan, has shown favorable outcomes in several Phase II and Phase III clinical trials utilizing CRS + HIPEC both in the adjuvant setting and in the treatment of established peritoneal metastasis. It is perhaps because of this groups understanding of the biology and clinical implications of peritoneal dissemination, combined with their vast experience in and commitment to advancing the treatment of patients with GC that their encouraging results have yet to be reproduced by others. The main reason for the lack of wide acceptance of CRS + HIPEC in GC remains the poor overall oncological outcome. Many surgeons take a nihilistic approach to this challenging disease and have reluctance in treating patients with a multi-modality approach such as CRS + HIPEC, which can be associated with high morbidity and mortality where gain in survival is marginal.

If newer systemic agents could show response rates in GC similar to those attained in metastatic colorectal cancer with modern cytotoxic and targeted therapy, then more surgical and medical oncologists would favor the use of CRS + HIPEC as part of a multi-modality treatment paradigm, which would in all likelihood result in a proportionally larger cohort of patients with long-term survival. In the meantime, the vexing question remains, what is the added value of HIPEC in GC patients at high risk for peritoneal recurrence following D2 surgery? Clearly, preventing and/or delaying the development of peritoneal carcinomatosis would have further clinical implications than treating established carcinomatosis. This particular question has been addressed by The European Union Network of Excellence on Gastric Cancer (EUNE). The EUNE protocol will study the added value of HIPEC to the current European paradigm in the treatment of GC established by the MAGIC trial [3]. Patients with serosal invasion (T3–T4), lymph node metastasis (N1) or patients with positive peritoneal cytology will be enrolled in the trial. All patients will receive three cycles of platinum-based therapy as defined by the MAGIC trial, followed by D2 resection of primary tumor and regional lymph nodes. Patients will then be randomized to undergo surgery with HIPEC using Oxaliplatin or surgery alone. We remain hopeful that this study will provide practice-altering data—the admission ticket into the promised land of CRS + HIPEC for GC.

REFERENCES