Evolving Treatment Strategies and Outcomes in Advanced Gastric Cancer with Peritoneal Metastasis

Fadi S. Dahdaleh, MD[a], Kiran K. Turaga, MD, MPH[b,*]

KEYWORDS

• Advanced gastric cancer • Peritoneal metastasis • Chemotherapy
• Targeted therapy • Regional intraperitoneal chemotherapy • Cytoreductive surgery
• HIPEC

KEY POINTS

- Gastric cancer carries a high malignant potential compared with other epithelial malignancies and has a particular tendency to involve the peritoneum in its advanced stages.
- An important distinction must be made between macroscopic and microscopic peritoneal metastasis given the differences in treatment and prognosis.
- Effective systemic approaches for the treatment of advanced gastric cancer include cytotoxic chemotherapy and targeted therapies; however, their effect on peritoneal metastasis is not well-documented.
- The success of an approach that combines cytoreductive surgery with intraperitoneal chemotherapy in other epithelial malignancies has led investigators to explore this strategy in gastric cancer, with the ultimate goal of attaining long-term survival.
- The burden and extent of disease, as well as tumor biology, are important prognostic factors in determining candidates for peritoneal-directed therapies.

INTRODUCTION

Gastric cancer (GC) is the fourth most common malignancy and the second leading cause of cancer-related deaths worldwide, with only a quarter of patients surviving at 5 years.[1,2] Free tumor cells on cytologic-negative examination and macroscopic peritoneal metastasis (PM) are common manifestations of advanced GC because

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[a] Complex General Surgical Oncology, Section of General Surgery/Surgical Oncology, The University of Chicago Medicine, 5841 South Maryland Avenue, Room S214, MC 5094, Chicago, IL 60637, USA; [b] The University of Chicago Medicine, Section of General Surgery/Surgical Oncology, 5841 South Maryland Avenue, Room G207, MC 5094, Chicago, IL 60637, USA
* Corresponding author.
E-mail address: kturaga@surgery.bsd.uchicago.edu

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they are clinically evident in 11% of patients on initial presentation, are radiologically occult in 35% of cases intended for curative resection, and constitute recurrences in 30% of patients.[3–5] A distinction is made in the literature with regard to the treatment and prognosis of cytologic-negative disease and PM. When diagnosed, PM predicts a dismal prognosis, with median survival times of 3 to 4 months when left untreated and 10 months with conventional chemotherapy.[5–7] In contrast, cytologic-negative disease seems to respond to systemic therapy more readily with a reported median survival of up to 36 months in selected cases.[8–10] Importantly, long-term survival has rarely been reported in advanced GC with either cytologic-negative or PM when systemic approaches are used, which underscores the miniscule prospect for cure for those patients.[7,11,12] There have been major advances in the treatment of advanced GC with the introduction of novel cytotoxic chemotherapeutic regimens, molecular targeting agents, and immune checkpoint inhibitors.[13–15] In most published studies, however, peritoneal involvement is grouped with other forms of advanced GC, rendering the specific effect of these treatments on PM and cytologic-negative disease difficult to ascertain. The success of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of PM in other epithelial malignancies has led investigators to explore this approach in GC and, perhaps encouragingly, survival beyond 5 years has been sporadically reported in highly selected patients.[16,17]

PATHOPHYSIOLOGY OF PERITONEAL INVOLVEMENT

It is commonly believed that PM occurs through the deposition of tumor cells either by the direct extension and subsequent cellular exfoliation, or through the traumatic dissemination of cancer cells during surgery.[18,19] Clinical validation of the concept of direct extension is perhaps provided by observing the higher rate of PM seen with increasing tumor stages (T-stages) and with the incidence of serosal invasion.[3] It is also hypothesized that during gastrectomy, cancer cells present within the lymphatic channels and blood vessels are shed, thereby contaminating the peritoneum.[20] In a study by Yu and colleagues,[21] cytologic-negative rates increased from 24% to 58% in lavage samples obtained at the beginning and end of gastrectomies. Free cancer cells then attach to the peritoneal surface; a process facilitated by the action of cytokines, which further aid in the deposition of fibrin layers, entrapping those cells. This new restrictive milieu is thought to hinder the penetrance of drugs delivered systemically and provides grounds for the early administration of intraperitoneal (IP) treatments.[22,23]

SYSTEMIC THERAPIES

The National Comprehensive Cancer Network recommends either systemic chemotherapy with fluoropyrimidine and platinum-based agents or best supportive care (BSC) for patients with metastatic GC, including PM and cytologic-negative disease.[24] Learning about specific practice patterns is challenging, however, given the sparsity of descriptive population studies. One study reported that 24% of patients with GC and PM underwent resection of their primary tumor, and only 23% of those received systemic chemotherapy.[5] Conversely, palliative chemotherapy was the treatment of choice in 65% of patients in another study, of which 80% had PM as their only documented site of metastasis.[25] Furthermore, the outcomes of patients with PM or cytologic-negative disease treated with systemic chemotherapy alone are difficult to determine because the literature typically groups patients with advanced GC in its different forms of metastasis into a single encompassing entity.[2,26,27] Finally, as the understanding of the biology and molecular profiling of GC advances, other treatments