Future Directions in Improving Outcomes for Patients with Gastric and Esophageal Cancer

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KEYWORDS

• Molecular profiling • Epidemiology • *Helicobacter pylori* • Targeted therapy
• Locally advanced disease

KEY POINTS

- Over the past 10 years, we have witnessed dramatic changes in both our understanding of gastric and esophageal cancer, in particular that disease subtypes exist and now applying this knowledge to clinical utility, as well as its management, in particular with the use of adjuvant therapy for locally advanced disease and multiple lines of treatment of patients with metastatic disease.
- We are no longer limited to cytotoxic systemic therapy, as we have 2 new biological agents approved to treat advanced disease, with several more promising prospects under development.
- In this article, the author looks to the future, attempting to answer the question of which advancements will play the biggest role in improving patient outcomes in this still-devastating disease.

INTRODUCTION

As this issue of *Hematology/Oncology Clinics of North America* has outlined, there have been many advances in understanding the molecular underpinnings of gastric and esophageal cancer and how these cancers are now managed. However, despite the many advances in the management of gastric and esophageal cancers discussed herein, the reality remains that most patients diagnosed with gastric or esophageal cancer will ultimately die of their disease, most living for less than 1 year once their disease has metastasized. In countries apart from Japan and Korea, for example, those without an active gastric cancer screening program, most patients with gastric and esophageal cancer will be diagnosed with locally advanced or metastatic disease.[1]

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Patients with locally advanced disease are more likely to have micrometastatic disease that results in higher rates of recurrence, usually within 2 years, following resection of the primary disease. These sobering data likely explain some of the differences in the epidemiology and natural course between cancers identified on screening and sporadic gastric cancers. Indeed, in the United States, the fatality/case ratio for gastroesophageal cancers is 0.66,[2] suggesting that approximately two-thirds of newly diagnosed patients will have metastatic disease at some point during the course of their illness and will require systemic therapy.

Many drugs are considered active in the treatment of gastric and esophageal cancer, including platinum (cisplatin and oxaliplatin), fluoropyrimidines, irinotecan, taxanes, and targeted therapies (ie, trastuzumab and ramucirumab).[3] It is compelling that we have approval of 2 new targeted antibody approaches to the disease in the past several years. However, despite the many treatment options available, median survival for advanced gastric cancer remains 8 to 10 months for most patients.[4,5] There are several areas where the author thinks that advances can possibly alter these harsh realities.

DISEASE PREVENTION

Gastric cancer is responsible for approximately 952,000 new diagnoses (6.8% of new cancer cases worldwide) and 723,000 deaths annually (8.8% of total).[6] In the United States in 2009, an estimated 21,130 new cases (14th most common) of gastric cancer were diagnosed with 10,620 deaths (13th most common). In Europe, gastric cancer ranks fifth with an estimated 159,900 new cases per year in 2006 and 118,200 deaths (fourth most common cause of cancer-related death).[7] Nearly two-thirds of all cases globally occur in developing countries in Eastern Europe, South America, and Asia, with 42% of all new cases developed in China alone.[8]

Gastric cancer is a heterogeneous disease with several established risk factors (summarized by Shah[5]). Gastric cancer subtypes (proximal nondiffuse, diffuse, and distal nondiffuse)[5] defined by these risk factors have been molecularly classified as unique entities.[9] The most relevant hereditable causes of gastric cancer include constitutional mutations in *CDH1* (causing hereditary diffuse gastric cancer[10]) and DNA repair enzyme deficiency in Lynch syndrome.[11] Individuals carrying a *CDH1* mutation have an 80% lifetime risk of developing gastric cancer and are, therefore, recommended to undergo a risk-reducing prophylactic gastrectomy.[12] However, environmental or modifiable factors are also major contributors to the development of this disease.[5,13] For example, in a study of cancer risk in monozygotic and dizygotic twins, the estimated proportion of nonshared environmental factors contributing to gastric cancer risk is 62%, whereas the contribution from heritable risk is estimated at only 28%.[14]

The most significant environmental risk factor is infection with *Helicobacter pylori*, a gram-negative bacillus identified in 1983 as the pathogen responsible for gastric ulcers and peptic ulcer disease. *H pylori* is the most common chronic bacterial pathogen in humans,[15] with a high prevalence in both developing and industrialized countries. In 1994, the World Health Organization and the International Agency for Research on Cancer consensus group classified *H pylori* as a class I carcinogen.[16] Notably, however, less than 1% of infected patients develop gastric cancer during their lifetime.[17] The bacterium is present in the stomachs of at least half of the world's population and is usually acquired in childhood. When left untreated, the pathogen generally persists for the individuals' lifetime. Therefore, exposure to *H pylori* is chronic and long-standing. This long latency period between infection and the development of