The Gastric Cancers: Targeted for Personalized Medicine

The blunt instrument of cancer chemotherapy, as wielded against gastric cancer, is likely to get considerably more precise and effective. There are many to thank for this development, not least of which are researchers at NewYork-Presbyterian Hospital, who have advanced our understanding of the family of oncologic disorders whose group name—gastric cancer—belies significant variability. The emerging understanding of gastric cancer as a group of subtypes whose susceptibility to chemotherapeutic intervention is not monolithic is set to have a significant effect on clinical drug trials and cancer therapy.

Introduction

The Lauren classification scheme,1 the nearly half century-old system that separates gastric adenocarcinomas into either intestinal or diffuse type based on histopathology, does not adequately reflect the latest understanding of gastric cancer.

Manish A. Shah, MD, Director of Gastrointestinal Oncology at NewYork-Presbyterian/Weill Cornell Medical Center, where he is also Co-director of Research at the Center for Advanced Digestive Care, noted that chemotherapy for gastric cancer has been poorly defined for decades. “Whether the patient had diffuse- or intestinal-type gastric cancer didn’t really matter too much in these studies; the patient would receive the chemotherapy that was available for gastric cancer as a whole.”

Dr. Shah, who is also Associate Professor of Medicine at Weill Cornell Medical College, added, “In clinical trials, a chemotherapy’s effectiveness was reported generally, not broken down into subtypes. The patients had stomach cancer, and this trial showed how well the chemotherapy worked against it. This is how research on gastric cancer has been performed for decades.”

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Additionally, a rising tide of research on biomarkers has begun to differentiate susceptibilities to chemotherapy.

Mouse Models

Timothy C. Wang, MD, Division Chief, Digestive and Liver Diseases, NewYork-Presbyterian/Columbia University Medical Center, who is the Silverberg Professor of Medicine at Columbia University College of Physicians and Surgeons, is a world leader in the creation of mouse models for gastric cancer. The mouse models from Dr. Wang’s laboratory help further understanding of how these cancers develop, including their genetic requisites. The mouse models are crucial because a fuller picture of how these cancers develop will offer the opportunity to intervene at an earlier stage, or perhaps prevent the cancer entirely.

Dr. Wang has extensive experience with mouse models of Helicobacter felis and H. pylori infection, and his lab was the first to fully describe a murine model of Helicobacter-dependent gastric carcinogenesis.2 “What we have been doing over the past several decades is combining Helicobacter infection with genetic modifications in transgenic mice that overexpress growth factors or cytokines, or with various diets, or with other types of infections. We are trying to determine what are the important cofactors that bring about the induction of stomach cancer. Only about 1% of individuals infected with Helicobacter go on to develop stomach cancer, so why is that? We are researching genetically determined host factors that predispose to stomach cancer.”

Dr. Wang has found that certain coinfections can accelerate, whereas others can impede the development of cancer. Surprisingly, helminth worms slow gastric cancer in those infected with H. pylori,3 a fact that is likely reflected in the low prevalence of these cancers in low-lying, wet areas of Africa where the worm is common, despite the locally high rate of H. pylori infection.

Dr. Wang has used his mouse models to confirm human observations. A report by El-Omar et al in Nature found that specific genetic polymorphisms in the gene for the cytokine interleukin-1beta (IL-1β) seemed to correlate with the susceptibility of gastric cancer in the presence of infection with H. pylori.4 Dr. Wang’s lab was able to overexpress IL-1β in the stomach of mice, which went on to spontaneously develop stomach cancer. When infected with H. felis, the mice developed stomach cancer very rapidly, suggesting that Helicobacter infection together with high amounts of IL-1β create an excellent environmental milieu in which stomach cancer develops. These findings validated the human observations of El-Omar et al.5 “What we have learned from our H. pylori mouse models is that the particular type of immune response is what drives the development of cancer. But it is clear that other infectious agents or bacteria can modulate the response. In the gut there are trillions of bacteria—in fact, there are more bacteria in the gut of a mammal than there are cells in its body. For that reason this is a complicated question.”

Heterogeneity

The more one explores the differences in gastric cancers, the more variations present themselves. Most obvious, perhaps, are the geographical differences in prevalence. In the United States, and in the developed West generally, proximal tumors, cancers of the gastroesophageal (GE) junction, distal esophagus, and cardia tumors are significantly more prevalent than in Korea, where middle and lower gastric cancers predominate.6 Staging at diagnosis differs, too, with earlier staging more likely in Korea, which enjoys higher overall survival. Gastric cancer is most common in China and Japan, where intestinal-type cancer predominates.

Epidemiologies vary. Cardia and GE junction cancers, more common in the industrialized West, are 5 times more likely in men than women and twice as likely in blacks than whites. Distal noncardia cancers are twice as likely in men than women and 4 times more likely in blacks than whites. The main risk factors for gastric cancers are H. pylori, tobacco use, and genetic predisposition. But the relationships are not straightforward. “Stomach cancer is in part disappearing because of the decline in H. pylori, but there is a disconnect between its prevalence in some countries and the rate of cancer. For one thing, it seems that there are differences in bacteria strains, so researchers talk about the African, Asian, and European strains, for example,” Dr. Wang said. “Stomach cancer is most common per case of H. pylori infection in Japan, so it might be that the Japan strain is the most virulent. There are regions in China and Korea that nearly match Japan in terms of virulence.” Diet may be another factor, although dietary studies have been difficult to replicate.

The role of H. pylori varies among subtypes of gastric cancer. The pathogenesis of noncardia gastric cancer is initiated by chronic inflammation (eg, from H. pylori), progressing from chronic gastritis, intestinal metaplasia, to dysplasia.7,9 And yet the presence of H. pylori gastritis may be protective against proximal adenocarcinomas.10,11 Thus, as H. pylori infection has decreased in the industrialized West, a “proximal shift” has been noted, with more proximal GE junction tumors, as well as esophageal cancers, occurring. “There is this idea that gastric cancers are decreasing when, in fact, if you look at individual subtypes, you see quite a lot of variation,” Dr. Shah said.

These geographic differences affect clinical trials. “If you look at a clinical trial done in Europe or North America, perhaps 25% of the patients with stomach cancer will have GE
junction tumors, maybe 30% will have diffuse cancers, and the rest will be intestinal antral tumors,” Dr. Shah explained.

“If you did the same clinical trial in Japan, 5% would have GE junction tumors, and the rest would be evenly split between diffuse and intestinal antral tumors.

“And the question is,” Dr. Shah added, “does that matter?”

**Tomorrow’s Therapy**

Increasingly, as targeted pharmacologic intervention for gastric cancer is tested in clinical trials, the heterogeneity of gastric cancer will indeed matter. “There are many new drugs for gastric cancer being tested now or that will be soon,” Dr. Shah said. “There are MET inhibitors, antiangiogenic agents, EGFR [epidermal growth factor receptor] inhibitors, and others. The more targeted the drug and specific the effect, the greater the chance the drug is subtype-specific.”

Dr. Shah offered an example. “Trastuzumab (Herceptin, Genentech) is approved for HER2-positive gastric cancer, for instance, but diffuse gastric cancer is rarely HER2-positive. GE junction tumors are HER2-positive about 30% of the time, and distal intestinal gastric cancers are HER2-positive about 20% of the time. So the target differs among subtypes,” thereby demonstrating their relevance.

Dr. Shah and his colleagues participated in a trial of bevacizumab (Avastin, Genentech/Roche) when added to capetibamine plus cisplatin for first-line treatment of gastric cancer; the primary end point was overall survival. Results showed that bevacizumab, while increasing progression-free survival and overall response rate, did not improve overall survival. A follow-up study evaluated the efficacy of bevacizumab using a comprehensive prospective biomarker analysis, and found that baseline plasma levels of vascular endothelial growth factor A (VEGF-A) and tumor expression of neuropilin-1 are candidate biomarkers of efficacy. It also was noted that plasma VEGF-A levels were predictive of efficacy in non-Asian patients.

In a separate study, Dr. Shah and his colleagues found that when bevacizumab was added to chemotherapy in patients with metastatic GE adenocarcinoma, intuiting differences according to gastric cancer subtype were revealed. The response rate was 85% in patients with proximal/GE junction tumors, 56% in patients with distal/intestinal tumors, and only 38% in patients with diffuse tumors. Dr. Shah and his colleagues are now examining the influence of gastric cancer subtype on taxane sensitivity, with preliminary data suggesting that the ability of the drug to engage with microtubules (the drug target) may be subtype-dependent (Figure). This finding is now being pursued in a prospective clinical trial in gastric cancer.

In the future, oncologists treating patients with gastric cancer will note the subtype of gastric cancer and treat accordingly, using a drug or drugs that are specifically effective for that group. “By doing this we will be able to increase survival for the whole group of gastric cancers,” Dr. Shah said. “It is still a very deadly disease. This type of research will improve patient outcomes.”

**References**


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