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Gastric Adenocarcinoma in Children and Adolescents

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Abstract

Gastric adenocarcinoma (GAC) is an extremely rare cancer in children with very limited information on the clinical presentation and outcome. We report 5 pediatric patients with GAC treated between 1990–2008 at our institution. Median age at diagnosis was 17 years (range 8–17). Our case series suggests that pediatric GAC patients present with diffuse metastatic disease (4 patients) and with patterns of spread similar to adult GAC. Initial chemotherapy was mainly platinum-based. Median time to progression was 4 months. The only long-term survivor was a patient with localized disease who had complete surgical removal of primary tumor.

Keywords

Gastric Adenocarcinomas; gastric cancer; gastric carcinoma; Children; Adolescents

Introduction

The median age at diagnosis for gastric adenocarcinoma (GAC) is 50+ years, and these cancers are extremely rare in children. Gastrointestinal malignancies in children comprise just 5% of all pediatric neoplasms, and primary GAC represents 0.05% of all childhood cancers [1]. This is in contrast to the adult population wherein in the United States there will be an estimated 21,000 new cases of gastric cancer with more than 10,000 deaths in 2010 alone [2]. With a median survival time of 7–10 months, metastatic GAC is an aggressive malignancy in adults, and the 2-year survival is approximately 10%–15% with conventional chemotherapy [3].

There are limited data on the clinical presentation and outcomes in pediatric GAC. Staging and therapy in children is based on the adult oncology experience [4,5]. Herein, we report the clinical experience of GAC in children and adolescents treated at The University of Texas M. D. Anderson Cancer Center (MDACC).

Patients and Methods

This study was approved by MDACC Institutional Review Board. We identified all pediatric patients from the MDACC tumor registry (less than 18 years of age) diagnosed and treated

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None

for GAC at MDACC between January 1, 1990 to December 31, 2008. Medical records were reviewed for demographic and clinicopathologic information. Time to disease progression (TTP) was defined as duration of time from diagnosis date (defined as date of tissue biopsy) to date of noted radiographic disease progression. Duration of clinical follow-up was defined as duration of time from diagnosis date to last documented clinical follow-up or date of death. All evaluated patients had histologic specimens that had been reviewed by an experienced pathologist at MDACC.

Results

Patient Characteristics

Among 292,621 cancer patients (6,134 less than 18 years of age) who presented to MDACC between 1990–2008, 4204 patients had gastric cancer. Five patients were identified (3 females) with gastric cancers who were less than 18 years of age which is 0.0017% of all patients with cancer, 0.11% of all patients with gastric cancer, and 0.08 % of all cancer patients less than 18 years of age treated in this time period. The median age at diagnosis was 17 years (range 8–17 years). Three patients were Hispanic/Latino, 1 was African-American, and 1 was of Arabic ethnicity. Initial clinical presentations were mostly nonspecific; the most common symptoms were vomiting/hematemesis, abdominal pain, anemia, and weight loss. One patient presented in shock with pulmonary hypertension and hemolytic anemia. Median duration of symptoms prior to diagnosis was 3 months (range 0.5–24 months). One patient had a family history of GAC while another patient had family history of colorectal carcinoma. Four patients presented with metastatic disease. Sites of involvement included 3 patients with peritoneal carcinomatosis, 3 with liver metastases, and 1 with lung metastases (Table I). Histology of tumor was poorly differentiated adenocarcinoma for all patients, and in 3 of the tumors signet ring cells were identified. One of the 2 patients tested for *Helicobacter pylori* was positive. Immunohistochemical analysis was performed in 2 patients. One patient had tumor that was positive for cyclo-oxygenase -2 (COX-2) and negative for epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER-2/neu), and c-kit, while another patient had tumor positive for Her-2/neu by immunohistochemistry and negative for estrogen receptor (ER) and progesterone receptor (PR).

Treatment

Chemotherapy regimens were varied, but all patients received platinum-based chemotherapy (3 patients with cisplatin and 2 with oxaliplatin) and 5 fluoro-uracil (5FU) with leucovorin rescue during the course of their treatment, and 2 patients also had surgical treatment. In one patient bevacizumab was added to cisplatin plus irinotecan after 2 cycles [3]. One patient had definitive pre-operative radiation treatment to a total of 45 Gray in 25 fractions. The multimodality treatments are outlined in Table II.

Clinical Outcomes

All patients experienced progression of disease, and median TTP was 4 months (range 2–7 months). Four patients died of disease, and mean time to death from initial progression was 2.8 months (range 1–5 months). The one patient who presented without metastasis remains alive at last clinical follow-up 8.5 years after diagnosis and 7.5 years since last evidence of disease. This patient underwent a total gastrectomy for initial local tumor control, and her tumor tested positive for *Helicobacter pylori* and COX-2.

Discussion

We describe our institutional experience with 5 pediatric GAC patients. Most of the literature in pediatric GAC is limited to isolated case reports [6]. Our case series suggests that pediatric GAC patients clinically present with a pattern of disease similar to adult GAC patients indicating the aggressive nature of the disease. Our lone long-term survivor did not have metastatic disease at presentation and was able to achieve complete local tumor therapy.

The etiology of GAC in adults seems to stem from multifactorial interaction [7]. Lifestyle factors such alcohol consumption, smoking, and dietary factors, such as very high salt diet, low vegetable diet, nitroso compound content in food, and infectious factors, such as Epstein-Barr virus infection have been associated with GAC [7]. *Helicobacter pylori* infection, especially with the vacAs1-, vacAm1-, and cagA-positive genotypes, have also been linked to GAC [7]. The role of these factors appear to be accentuated in patients who already possess certain types of genetic cytokine polymorphisms like IL-1B-511*T/*T or IL-1B-511*T/*C [8]. Also individuals with blood group A have been known to have an increased risk for gastric cancer than other blood groups [9]. However, the role of these factors in the pediatric population is unknown. In children GAC develops either as *de novo* occurrence, as part of the hereditary polyposis syndromes, or after treatment of gastric lymphomas [1,10]. In our case series, none of the children had polyposis or a prior history of lymphoma, thus they are likely *de novo* occurrences. One Arabic patient tested positive for *Helicobacter pylori*, a known risk factor for GAC and commonly found in the Middle East [8–10]. The differential diagnosis of pediatric gastric tumors should include gastrointestinal stromal tumors [11], and although rare, other tumors, such as hemangioma, lymphoma, squamous cell carcinoma, carcinoids, leiomyoma, Peutz-Jeghers-type polyps of the stomach, leiomyosarcoma, lipoma, and teratoma should be considered [12].

Germ line mutation in E-Cadherin (CDH-1) has been reported in patients with hereditary diffuse gastric cancer [13]. These patients were described as having a highly penetrant susceptibility to diffuse gastric cancer with an autosomal dominant pattern of inheritance. Unfortunately, none of our patients were tested for this mutation. However, these mutations may need to be tested in young patients as these may have major implications for survival. Akin to prophylactic mastectomy in BRCA1/2 patients [14,15] there are recommendations to consider prophylactic gastrectomy in young, asymptomatic carriers of germ-line truncating *CDH1* mutations in families with highly penetrant hereditary diffuse gastric cancer [13].

Clinical presentations also varied with mostly non-specific abdominal symptoms. One patient had a history of recent pregnancy when she presented with epigastric pain, hematemesis and a septic shock like syndrome. On evaluation she had cholecystitis, pancreatitis, pulmonary hypertension, hemolytic anemia, coagulopathy and diffuse metastatic signet ring carcinoma. Most of these symptoms and the paraneoplastic syndromes resolved after she received 2 cycles of chemotherapy consisting of cisplatin with irinotecan. There are reports elucidating the potential role of pregnancy and related hormonal stimuli in the progression of gastric cancer especially in younger patients [16,17].

Adult GAC is a very challenging cancer and most patients present with advanced disease at diagnosis [18]. Patients with localized disease are candidates for multimodality approach which clearly offers a survival benefit compared to surgery alone [19]. Complete surgical resection offers a potential cure though recurrences within 2 years are still common. In the United States, preoperative chemoradiation or post-operative adjuvant chemoradiation is commonly practiced and has shown to improve survival [18]. The UK Medical Research

Council (MRC) Adjuvant Gastric trial showed survival benefit with perioperative chemotherapy alone, and this approach is common in Europe. In the metastatic setting, chemotherapy can provide palliation and provide some survival benefit. The 5FU with cisplatin regimen has been the standard frontline regimen for many years [18]. Irinotecan plus cisplatin has also been studied as both a frontline and salvage regimen. Subsequent clinical trials have also demonstrated docetaxel and capecitabine as being active agents. Another novel fluoropyrimidine, S1, has shown promise and is currently being evaluated in adult trials paired with cisplatin [20].

Targeted agents are currently being evaluated, but the outcomes have been mixed. One prospective, randomized, multicenter phase III trial demonstrated that trastuzumab plus standard chemotherapy improved survival compared to chemotherapy alone in Her-2 positive patients with gastric cancer [21]. A recent randomized clinical trial did not demonstrate a survival benefit for bevacizumab added to standard chemotherapy [22].

Because of its rarity, the diagnosis and treatment of children and adolescents with GAC remains a significant challenge. Large multi-institutional trials are not possible given that GAC is extremely rare in children. Establishing an international tumor registry and additional molecular investigations including E-cadherin testing of the tumor samples, identification of targeted genetic polymorphisms and screening of families at risk may offer more choices for these patients.

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Table 1
Clinical Characteristics of Evaluated Pediatric Patients with Gastric Adenocarcinoma

Pt no.	Age	Race	M/F	Location	Metastases	Duration of Symptom (months)	Histology	Blood Group	HP status	Genetics	Pregnancy
1	16.3	H	F	Stomach	Peritoneal carcinomato sis + Right ovary + Ascites	4	Diffuse adenoca + signet ring cell	A +	Unk	Unk	No
2	8.6	Arabic	F	Stomach	None	24	PDA+ signet ring cells	O+	+	Pos COX 2, Neg EGFR, Neg HER2 neu, Neg C-kit	No
3	17.3	H	M	Stomach/Gastro- esophagus junction	Liver	3	PDA	Unk	Unk	Unk	N/A
4	16.8	AA	M	Stomach	Liver + Peritoneal carcinomato sis + rectum	1	PDA	O +	–	Unk	N/A
5	16.9	H	F	Stomach	Diffuse +liver +lung+ i ntra- abd +vetebral	0.5	PDA+ signet ring	A+	Unk	Her 2 neu Neg, ER, Neg PR	Yes

* HP status- *Helicobacter pylori* status, H – Hispanic, AA- African American, M- Male, F- Female, PDA – poorly differentiated adenocarcinomaN/A – Not applicable, Unk- Unknown, ER- Estrogen Receptor, PR- Progesterone receptor, Pos- Positive, Neg-Negative.

Table II
Clinical presentation, Treatment and Outcome of Evaluated Pediatric Patients with Gastric Adenocarcinoma

Pt No	Clinical Presentation	Tumor Markers	XRT (dose in Gray)	Surgery	Primary Chemotherapy	Relapse Regimen	SOP	TTP In months	A/D	F/u Duration (months)
1	Nausea + Vomiting + Weight loss	LDH 508, CEA <1, CA 125- 305.3	None	No	Cisplatin + 5-FU	Irinotecan	Stomach	4.0	D	5.0
2	Anemia +Abd pain +Melena +Hematemesis	Unk	Yes (45)	Yes -total gastrectomy, partial colectomy, partial pancreatectomy and splenectomy	Irinotecan+Taxot ere+5 FU × 4 cycles - Followed by Cisplatin + 5 FU adjuvant	Radiofrequency ablation	liver	7.0	A	102
3	Dysphagia + Dyspepsia +Hemoptysis	LDH- 587, CEA <1, CA125- 47.9, CA19.9- 724.4	None	Subtotal gastrectomy +Distal esophagectomy	Epirubicin +Oxaliplatin +5 FU × 2 cycles	Irinotecan+ Cisplatin × 3 cycles	stomach	4.0	D	9.0
4	Weight loss +Pernicious anemia +Iron Deficiency anemia + Diarrhea	Unk	None	No	Oxaliplatin +5 FU +Leucovorin +Irinotecan	Gemcitabine + Imatinib	Stomach	2.0	D	6.0
5	Epigastric pain +Hematemesis+Pul HTN+ Hemolytic anemia + Coagulopathy + Cholecystitis + Pancreatitis	Unk	Yes (9)	No	Cisplatin+Irinotecan +Avastin × 5 cycles	None	Multiple	3.0	D	4.0

* A-Alive, D-Dead, XRT – Radiation treatment, SOP- Site of Progression, TTP-Time to progression in months, Unk-Unknown, 5=FU - 5 fluoro uracil, A/D – Alive/Dead