Rare but Real: Management of Small Bowel Adenocarcinoma

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OVERVIEW

Despite representing the longest segment of the alimentary tract, small bowel adenocarcinomas are rare. The diagnosis of small bowel adenocarcinoma is frequently delayed because of the nonspecific clinical symptoms and the limitations of small bowel imaging. The majority of patients will present with either lymph node or distant metastatic disease. Though the role of adjuvant therapy for resected small bowel adenocarcinoma is unclear, recent research efforts have led to an improvement in our management of advanced disease. Prospective phase II studies have successfully enrolled patients with this rare tumor type and have established the combination of a fluoropyrimidine and oxaliplatin as the most appropriate front-line chemotherapy for patients with advanced disease. Currently, five prospective clinical trials have been designed for patients with small bowel adenocarcinoma and enrollment to these clinical trials should be encouraged.

Although adenocarcinomas have historically represented the most common histologic subtype of the small intestine, the rising incidence of carcinoids has recently made this subtype the most common. The estimated number of new cases of small bowel cancer for 2012 in the United States is 8,070, with a histologic distribution of carcinoid (44%), adenocarcinoma (33%), lymphoma (15%), and sarcoma (8%).1,2 The distribution of histologic subtypes varies across the small intestine, with adenocarcinoma representing the most common cancer of the duodenum.3 One of the more interesting observations regarding small bowel adenocarcinoma relates to its 50-fold lower incidence than large bowel adenocarcinoma. This discrepancy occurs despite the small intestine representing approximately 75% of the length and 90% of the surface area of the alimentary tract.4 Although a number of hypotheses have been proposed to explain the apparent resistance of the small intestine to carcinogenesis, limited experimental evidence exists to support any one theory. General postulates include (1) Rapid turnover of small intestine epithelium which precludes the accumulation of genetic damage, (2) Increased lymphoid tissue in the small intestine, providing increased mucosal immune surveillance, and (3) The inherent nature of the small intestine and its contents, which permits less exposure to carcinogenic agents in our diet as a result of rapid transit time, a dilute alkaline environment, and a lack of bacterial degradation activity.

ETIOLOGY AND PATHOGENESIS

Because of the rarity of small bowel adenocarcinoma, limited information is available regarding risk factors and pathogenesis of this disease. The majority of cases will be sporadic in nature, although a number of inherited cancer syndromes, such as hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatosis polyposis (FAP), and Peutz-Jeghers syndrome, are associated with an increased risk of small bowel adenocarcinoma. The two most common conditions linked to sporadic small bowel adenocarcinoma, Crohn’s disease and celiac disease, are both associated with small bowel inflammation. The risk from Crohn’s disease reflects both the location of small bowel involvement, with 70% of cancers developing in the ileum, and duration of disease, with an approximate risk of small bowel adenocarcinoma of 2% after 25 years.

Although a number of molecular alterations are similar between small bowel and large bowel adenocarcinoma, such as 18q loss, p53 loss, and KRAS mutations; a dramatic difference exists in the rate of APC mutations, with one study finding a 0% rate of APC nonsense mutations in 48 patients with small bowel adenocarcinoma.5 The lack of APC mutations in conjunction with the infrequency of small bowel adenomas suggests that the incidence difference between small and large bowel adenocarcinoma may reflect a difference in the early initiation phase of carcinogenesis. A recent study comparing global DNA copy number alterations between small bowel, gastric, and colorectal cancers demonstrated that small bowel adenocarcinomas are more similar to colorectal cancers.6 In addition, small bowel adenocarcinomas demonstrate similar rates of microsatellite instability (MSI-high), 20%, and CpG island methylator phenotype (CIMP +), 27%, as seen in colorectal cancer.7 Interestingly, patients with celiac-related
small bowel adenocarcinoma have a relatively high rate of MSI-high tumors, with one study reporting a rate of 67%, all because of promoter methylation of the MLH1 gene.

PRESENTATION AND DIAGNOSIS

The median age at diagnosis for small bowel adenocarcinoma is 67, with over 85% of patients presenting after age 50. The most common symptoms are abdominal pain, nausea/vomiting, weight loss, and gastrointestinal bleeding. Stage presentation is 32% IV, 27% III, 30% II, and 10% I. This stage distribution contrasts with colon cancer, in which more patients (20%) present with stage I disease and less with stage IV disease (20%). This, in part, is likely a reflection of the lack of effective screening modalities for small bowel adenocarcinoma.

In the past, nonspecific clinical symptoms coupled with the limited sensitivity of an upper gastrointestinal series for small bowel neoplasms led to marked delays from symptoms to diagnosis. However, recent improvements in cross-sectional imaging, refinements in enteroscopy, and the development of wireless capsule endoscopy are all certain to improve the diagnosis of small bowel adenocarcinoma. For example, in a prospective study of CT enteroclysis with water in 219 patients with a clinical suspicion of a small bowel neoplasm, the sensitivity and specificity for detecting small bowel disease were 85% and 97%, respectively. Furthermore, until recently, endoscopic evaluation of the entire 7-meter-long small intestine could only be done at the time of surgical exploration. Now, both double balloon endoscopy and wireless capsule endoscopy are able to visualize the entire small bowel. Double balloon endoscopy uses two balloons in a push-and-pull technique to evaluate the entire small bowel; this requires significant expertise and is not widely available. Capsule endoscopy, first approved in the United States in 2001, has allowed markedly improved endoscopic imaging of the small intestine, although tissue acquisition is not possible with this modality and the presence of small bowel obstruction is a contraindication to this approach. In two large series of patients who underwent capsule endoscopy for a variety of reasons, small bowel tumors were identified in 76 of 978 patients (7.8%).

PROGNOSIS

In addition to stage, a number of additional factors have been associated with poor prognosis and include poor differentiation, positive margins, duodenal location, male gender, black ethnicity, and older age. Approximately 33% of small bowel adenocarcinomas present with poor differentiation, which is significantly higher than the 21% observed in colon cancer (p < 0.01). As seen with other tumor types, one of the most robust prognostic markers for resected cases is lymph node sampling. Recent data from the SEER database has demonstrated markedly improved outcomes for patients with increased nodal sampling, with one report finding eight lymph nodes and another finding 10 lymph nodes as the optimal number of sampled lymph nodes. For cases in which eight or more lymph nodes are assessed, the improvement in 5-year cancer-specific survival is 65.3% to 80.3% for stage I, 55% to 69.9% for stage II, and 40% to 45.1% for stage III disease. In a recent population-based comparison using the SEER database, even after accounting for lymph node sampling, small bowel adenocarcinoma demonstrated worse cancer-specific survival stage for stage than colon cancer. Interestingly, even when comparing stage I cases with adequate lymph node sampling, 5-year cancer-specific survival was significantly lower for adenocarcinomas of the jejunum/ileum than for colon (93.3%; p < 0.01). Such data suggest that a fundamental biologic difference exists between adenocarcinomas of the colon and small bowel.

APPROACH TO TREATMENT

Locoregional Disease

Surgical resection is the mainstay of therapy for locoregional disease. Data investigating the effect of lymph node assessment has clearly shown that small bowel adenocarcinoma, and in particular duodenal adenocarcinoma, is markedly understaged. Such data support a more extensive surgical resection in order to obtain an adequate lymph node assessment. The relapse pattern for small bowel adenocarcinomas is predominantly systemic, with one large retrospective study reporting distant and locoregional relapses accounting for 86% and 18% of all recurrences, respectively. Although a higher rate of local recurrence is seen with duodenal primaries, systemic relapse still predominates.

At present, no randomized studies have been conducted evaluating the benefit of adjuvant chemotherapy in small bowel adenocarcinoma. A number of single-institution retrospective studies have not demonstrated a clear benefit from adjuvant therapy, but these studies have all been limited by their small sample size and selection bias favoring the use of

KEY POINTS

- Despite representing the majority of the alimentary tract, the incidence of small bowel adenocarcinoma is 50-fold lower than colorectal adenocarcinoma and further research into understanding this great discrepancy is needed.
- For locoregional disease adequate lymph node assessment, 8 or more lymph nodes, strongly correlates with improved survival.
- The role of adjuvant therapy for small bowel adenocarcinoma has not been determined.
- The combination of a fluoropyrimidine and oxaliplatin represent the most appropriate front-line systemic chemotherapy.
- The role of biologic agents for this cancer are unknown, although a number of ongoing clinical trials are exploring this question.
adjuvant therapy in higher-risk patients.\textsuperscript{16,18} According to the National Cancer Database, the use of adjuvant chemotherapy has been increasing, with rates of 8.1\% in 1985 to 22.2\% in 2005 (p < 0.0001).\textsuperscript{2} In part, this likely reflects the poor outcome of high-risk patients who undergo resection, the known activity of systemic fluoropyrimidine-based chemotherapy in the metastatic setting, and extrapolation from the proven benefit of adjuvant treatment in colorectal cancer. Currently, there is an ongoing international effort as part of the Cancer Research United Kingdom/Colorectal Cancer Research Network/National Cancer Institute/European Organisation for Research and Treatment of Cancer International Rare Cancers Initiative to initiate a large prospective randomized trial evaluating the effect of adjuvant chemotherapy in resected small bowel adenocarcinoma, termed the BALLAD study (A global study to evaluate the potential benefit of adjuvant chemotherapy for small bowel adenocarcinoma).

In duodenal cancer, its retroperitoneal location and resultant higher risk for locoregional failure has led to the frequent use of adjuvant chemoradiation. Although support for this approach is limited, one recent retrospective series from Duke University found a trend toward improved 5-year overall survival for those patients with an R0 resection who received adjuvant or neoadjuvant fluoropyrimidine-based radiation therapy compared with patients who underwent surgery alone (83\% vs. 53\%; p = 0.07).\textsuperscript{19} Of further note, neoadjuvant chemoradiation for duodenal adenocarcinomas has been shown to be safe, with a number of studies reporting evidence of robust tumor downstaging in the pathologic specimens.\textsuperscript{19,20} This approach deserves further investigation as cases of locally advanced unresectable disease have been converted to resectable disease following neoadjuvant therapy.\textsuperscript{20}

### Metastatic Disease

Although no randomized studies have demonstrated a benefit of systemic chemotherapy in small bowel adenocarcinoma, a number of retrospective studies have shown a survival benefit for the use of chemotherapy.\textsuperscript{16,18} In general, the chemotherapy used for small bowel adenocarcinomas has mimicked that used for colorectal cancer, with the combination of fluoropyrimidine and oxaliplatin having consistently demonstrated the greatest activity (Table 1). Of the four prospective clinical trials reported, three studies combining a fluoropyrimidine with oxaliplatin have shown similar activity with response rates of 42\% to 50\%, and a median time to progression ranging from 7.8 to 9.8 months.\textsuperscript{21-23} Although less well studied, irinotecan has activity in small bowel adenocarcinoma. In the one study specifically evaluating its use in the second-line setting, leucovorin/fluorouracil/irinotecan (FOLFIRI) demonstrated a 20\% response rate and median progression-free survival of 3.2 months.\textsuperscript{24} At present, the role of targeted agents such as bevacizumab, regorafenib, or epidermal growth factor receptor (EGFR) inhibitors in the treatment of small bowel adenocarcinoma is not established, although ongoing studies are now underway (Table 2). Importantly, the rate of \textit{KRAS} mutations in small bowel adenocarcinoma is similar to that seen in colorectal cancer, and a handful of case reports have described responses to anti-EGFR therapy in patients with \textit{KRAS} wild-type tumors.\textsuperscript{25}

It has been suggested that duodenal adenocarcinomas have distinct chemotherapy responsiveness compared with jejunal or ileal adenocarcinomas and thus their treatment should mirror regimens for advanced gastric cancer. However, according to a recent comparative analysis of copy number alterations between small bowel, colorectal, and gastric adenocarcinomas, duodenal adenocarcinomas were more

### TABLE 1. Studies of Systemic Chemotherapy for Advanced Small Bowel Adenocarcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>Tx Line</th>
<th>N</th>
<th>Chemotherapy</th>
<th>RR (%)</th>
<th>Median OS (m)</th>
</tr>
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<tbody>
<tr>
<td>McWilliams\textsuperscript{21}</td>
<td>2012</td>
<td>Phase II (NCCTG)</td>
<td>1st</td>
<td>28</td>
<td>Capecitabine + oxaliplatin + irinotecan</td>
<td>42</td>
<td>13</td>
</tr>
<tr>
<td>Xiang\textsuperscript{22}</td>
<td>2012</td>
<td>Phase II (China)</td>
<td>1st</td>
<td>33</td>
<td>FOLFOX</td>
<td>49</td>
<td>15.2</td>
</tr>
<tr>
<td>Overman\textsuperscript{23}</td>
<td>2008</td>
<td>Phase II (MDACC)</td>
<td>1st</td>
<td>30</td>
<td>CAPOX</td>
<td>50</td>
<td>20.4</td>
</tr>
<tr>
<td>Gibson\textsuperscript{24}</td>
<td>2005</td>
<td>Phase II (ECOG)</td>
<td>1st</td>
<td>38</td>
<td>FAM</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Tsushima\textsuperscript{27}</td>
<td>2012</td>
<td>Retrospective</td>
<td>1st</td>
<td>60</td>
<td>Fluoropyrimidine monotherapy</td>
<td>22</td>
<td>13.9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22</td>
<td>FOLFOX</td>
<td>42</td>
<td>22.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td>Fluoropyrimidine + irinotecan</td>
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<td>9.4</td>
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<td>Zhang\textsuperscript{28}</td>
<td>2011</td>
<td>Retrospective</td>
<td>1st</td>
<td>28</td>
<td>FOLFIRI/CAPEX</td>
<td>32</td>
<td>14.2</td>
</tr>
<tr>
<td>Koo\textsuperscript{29}</td>
<td>2011</td>
<td>Retrospective</td>
<td>1st</td>
<td>40</td>
<td>Fluoropyrimidine based</td>
<td>11</td>
<td>11.8</td>
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<tr>
<td>Zaanan\textsuperscript{30}</td>
<td>2010</td>
<td>Retrospective</td>
<td>1st</td>
<td>48</td>
<td>FOLFOX</td>
<td>34</td>
<td>17.8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>5-FU + cisplatin</td>
<td></td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>FOLFIRI</td>
<td></td>
<td>10.6</td>
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<tr>
<td>Zaanan\textsuperscript{34}</td>
<td>2010</td>
<td>Retrospective</td>
<td>2nd</td>
<td>28</td>
<td>FOLFIRI</td>
<td>20</td>
<td>10.5</td>
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<tr>
<td>Overman\textsuperscript{31}</td>
<td>2008</td>
<td>Retrospective</td>
<td>1st</td>
<td>29</td>
<td>5-FU + platinum</td>
<td>41</td>
<td>14.8</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>51</td>
<td>Various agents</td>
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<td>12</td>
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Abbreviations: 5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; ECOG, Eastern Cooperative Group; FAM, 5-FU, doxorubicin, mitomycin C; FOLFIRI, leucovorin, 5-FU, and irinotecan; FOLFOX, 5-FU and oxaliplatin; m, months; MDACC, MD Anderson Cancer Center; N, number of patients; NCCTG, North Central Cancer Treatment Group; OS, overall survival; RR, response rate; Tx, treatment.
similar to colorectal cancers than gastric cancers. Furthermore, a number of studies have shown that HER2 amplification or overexpression is extremely rare in duodenal adenocarcinoma. In an effort to determine whether small bowel adenocarcinomas are similar to gastric cancers in terms of responsiveness to taxanes, we are conducting a phase II study of nab-paclitaxel in small bowel adenocarcinoma (Table 2).

**CONCLUSION**

Research in rare tumor types is challenging and collaborative; multi-institutional efforts are needed. Although the molecular biology of small bowel adenocarcinoma is limited, the low rate of APC mutations stands out as an intriguing molecular difference in comparison with colorectal cancer. Further elucidation of the molecular underpinnings of small bowel adenocarcinoma may provide insights as to the protective factors responsible for the dramatic 50-fold difference in incidence between small bowel and large bowel cancers. This large difference in incidence does not justify screening for small bowel cancer in the general population. However, given the increased risk of small bowel adenocarcinoma among patients with celiac disease, Crohn’s disease, or HNPCC, screening studies which utilize newer diagnostic tools deserve investigation.

Surgical resection represents the mainstay of treatment for locoregional disease. Although no data support the use of adjuvant chemotherapy, the risk of distant relapse, the reproducible activity of systemic chemotherapy in the metastatic setting, and extrapolation of results from adjuvant therapy in colorectal cancer all support investigation of adjuvant fluoropyrimidine-based chemotherapy for small bowel adenocarcinoma.

Fluoropyrimidine and oxaliplatin represent the standard front-line chemotherapy combination. Given the rarity of this cancer, enrollment in clinical trials exploring novel agents is strongly encouraged. In the last 5 years, three prospective clinical trials in this disease have been reported, which contrasts with the one clinical trial in the preceding years, and represents a positive step forward. It is hoped that an improved molecular understanding of this cancer will enable a future generation of novel studies aiming to improve the outcomes for patients with this rare cancer.

**ACKNOWLEDGMENT**

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**TABLE 2. Current Clinical Trials for Advanced Small Bowel Adenocarcinoma**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Tumor Type</th>
<th>Tx Line</th>
<th>N</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPOX + bevacizumab</td>
<td>II</td>
<td>SBA + ampullary</td>
<td>1st</td>
<td>30</td>
<td>NCT00354887</td>
</tr>
<tr>
<td>Capcitabine/oxaliplatin/irinotecan*</td>
<td>II</td>
<td>SBA</td>
<td>1st</td>
<td>33</td>
<td>NCT02043550</td>
</tr>
<tr>
<td>CAPOX + panitumumab (KRAS wild-type only)</td>
<td>II</td>
<td>SBA + ampullary</td>
<td>1st</td>
<td>20</td>
<td>NCT01204209</td>
</tr>
<tr>
<td>GEMOX + erlotinib</td>
<td>II</td>
<td>Duodenal + ampullary</td>
<td>1st</td>
<td>22</td>
<td>NCT00987766</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>II</td>
<td>SBA</td>
<td>2nd</td>
<td>10</td>
<td>NCT01710586</td>
</tr>
</tbody>
</table>

Abbreviations: CAPOX, capcitabine and oxaliplatin; GEMOX, gemcitabine and oxaliplatin; N, number of patients; SBA, small bowel adenocarcinoma; Tx, treatment.

*Chemotherapy dosing determined based upon UGT1A1 genotype.

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**Disclosures of Potential Conflicts of Interest**

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