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Commentary

Anti-EGFR Therapy in Small Bowel Adenocarcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Small bowel adenocarcinoma (SBA) is a rare disease, with an incidence rate that is approximately 50- to 100-fold less than colorectal cancer (CRC) despite the much larger surface area of the small intestine compared with that of the large intestine [1, 2]. The reasons for this striking discrepancy are unknown, but theories include the relative sterility of the small intestine, the rapid transit time in the small bowel, and the higher levels of lymphoid aggregates and IgA levels in the small intestine compared with the large bowel that might contribute to better tumor immunity and surveillance [3, 4]. Clues may also be seen in the markedly lower rate of mutations in the adenomatous polyposis coli (*APC*) gene in SBA (7%–13%) in comparison with CRC (>80%). In addition, other molecular genetic changes that predispose to SBA may be less common than those for CRC [5].

Despite the differences in incidence rates, SBA and CRC share many characteristics. Both tumors develop through the adenoma-carcinoma sequence, both are elevated in patients with familial adenomatous polyposis and hereditary nonpolyposis colon cancer, and both tend to co-occur in the same individuals [4, 6, 7]. As a consequence, in the absence of many prospective studies on SBA, the general approach has been to emulate treatment regimens used for CRC. This strategy has led to two successful trials to date for SBA, demonstrating the utility of capecitabine and oxaliplatin (CAPOX) or 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) for metastatic SBA [8, 9], analogous to CRC. A recent study from the MD Anderson group added bevacizumab to CAPOX and demonstrated significant efficacy and safety for that combination as well [10], again extending the SBA/CRC paradigm.

However, despite similar clinical management, when stratified stage-for-stage, SBA has a significantly worse outcome compared with CRC [6]. Five-year survival rates for SBA vary from 50% to 60% for stage I tumors to a dismal <5% for stage IV tumors [6]. Exactly why SBA does worse than CRC is not clear, but difficulty in detection and diagnosis for tumors in the small bowel, as compared with the large bowel, may play a role. The recent addition of capsule endoscopy to the clinical armamentarium may lead to earlier diagnoses in the small bowel and better prognoses for these patients in the future.

Our own group was the first to describe mutations in the *KRAS* oncogene in SBA [11]. Activating mutations in the *KRAS* oncogene (codons 12 and 13) have been observed in 40% to 60% of SBA, a comparable rate to that seen in CRC, suggesting the RAS/RAF/MAPK pathway may have a role in SBA carcinogenesis [12–14]. In addition, *TP53* mutations are present in 40% of SBA, suggesting a pivotal role for p53 in the adenoma-carcinoma sequence [13]. *BRAF* V600E mutations are rare in SBA [15].

The expression of the epidermal growth factor receptor (EGFR) is present in 71% of SBA [16], which is similar to the rate of expression observed in CRC, and is not associated with changes in survival [16, 17]. Cetuximab and panitumumab are monoclonal antibodies that inhibit the extracellular domain of the EGFR, thereby inhibiting ligand binding, receptor dimerization, and subsequent activation of intracellular signaling. They are approved by the U.S. Food and Drug Agency (FDA) for the treatment of *KRAS* wild-type metastatic CRC. In this issue of ***The Oncologist***, Gulhati and colleagues [18] report a phase II trial for patients with metastatic *RAS* wild-type SBA and ampullary adenocarcinoma (AAC) refractory to first-line chemotherapy. Extended *RAS* testing for *KRAS* and *NRAS* mutations was performed, and only patients with *RAS* wild-type disease were eligible. Nine patients were enrolled; one patient had AAC (pancreaticobiliary subtype), and eight patients had SBA (three duodenal, five jejunal/ileal). Two patients had a history of Lynch syndrome. The primary endpoint was response rate. Panitumumab did not yield any responses by RECIST criteria. There were two patients who achieved stable disease and seven who had progression of disease. The study was stopped early because of utility based on continuous Bayesian monitoring criteria. The median progression-free survival was 2.4 months, and the median overall survival was 5.7 months.

Despite the selection of patients based only upon the absence of any *RAS* mutations, not all such patients respond to anti-EGFR therapy, and progression of disease is inevitable even in those patients who do initially respond to treatment. Various mechanisms for resistance have been described, including *EGFR* gene mutations, activation of other receptor tyrosine kinases, such as HER2 or MET, and mutations in genes encoding key EGFR-dependent intracellular signaling transducers, such as *KRAS*, *NRAS*, *BRAF*, *PIK3CA*, *MEK*, or *ERK* [19]. Gulhati and colleagues [18] evaluated whether mutations in *BRAF*, *PIK3CA*, and *ERBB2*/HER2 genes were associated with resistance to anti-EGFR therapy. Two patients were found to have a *BRAF* G469A mutation, and one patient had a *PIK3CA* H1047R mutation. Mutations in *BRAF* are known to negatively affect anti-EGFR therapy in CRC [20]. Gulhati and colleagues argue that rather than mirroring CRC, SBA represents a distinct clinical entity.

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A recent study by Schrock and colleagues presented the first large-scale genomic profiling of SBA and comparison with CRC and gastric carcinoma (GC) [21]. This study demonstrated that SBA indeed represents a unique genomic entity. In this series, genomic profiling using hybrid capture-based next-generation sequencing on 236 or 315 cancer-related genes was prospectively performed on 317 SBAs (130 unspecified SBA and 187 duodenal adenocarcinomas), then compared with those of 6,353 CRCs and 889 GCs. The majority of SBA cases had stage IV disease (78.1%), and the majority of samples were from the primary small bowel tumor (60.3%). The most common genomic alterations in SBA were observed in *TP53* (58.4%), *KRAS* (53.6%), *APC* (26.8%), *SMAD4* (17.4%), *PIK3CA* (16.1%), *CDKN2A* (14.5%), and *ARID1A* (12.3%), findings reinforced in the work of Laforest et al [22]. There was no significant difference in rates of genomic alterations between primary and metastatic biopsy sites tested except with *BRAF*, which was more commonly mutated in metastatic lesions ($p = .047$). The authors also pointed out that the frequency of *SMAD4* and *KRAS* alterations were similar to that in CRC, whereas the frequency of genomic alterations in *TP53* and *CDKN2A* were similar to that in GC. A location-related difference in mutation pattern was recently reported between right- and left-sided colon cancer, and Gulhati and colleagues postulate that SBA may share more similarities with right-sided colon cancer, in which EGFR inhibitors have been shown to be less effective.

Microsatellite stability also differs across intestinal malignancies and site of the primary tumor. Mutation or methylation of DNA mismatch repair (MMR) genes results in MMR deficiency, microsatellite instability (MSI), and higher mutation rates. The reported incidence of MSI in SBA has been variable, ranging from 5% to 45% by microsatellite testing and from 0% to 26% by immunohistochemical staining for MMR protein loss. In a study by Overman and colleagues, MMR protein loss was seen in 35% of patients with SBA compared with approximately 15% of patients with CRC [16]. The authors suggested that this high rate may have been due to the relatively young age of the study population. In another study, when suspected Lynch syndrome patients were excluded, the frequency of MMR deficiency was 9% [15]. Testing for MMR deficiency in all patients with metastatic SBA and CRC should be performed given that it now has clinical implication in light of the FDA's 2017 approval for pembrolizumab, an immune checkpoint inhibitor, for MSI-high or MMR-deficient solid tumors irrespective of the tissue of origin.

In conclusion, SBA has some molecular features in common with CRC and GC, but overall should be considered its own unique genomic entity with several key mutational signatures. Although treatment paradigms may be initially considered based on activity in CRC, these are two distinct clinical entities and, as the MD Anderson group has ably demonstrated, careful prospective studies are necessary to confirm the efficacy of new regimens. Although the frequency of both *KRAS* mutations and EGFR expression were similar in SBA and CRC, panitumumab monotherapy demonstrated no responses in this small, single-center study. However, based on its important role in CRC, we would argue that further evaluation is needed for anti-EGFR therapy in patients with *RAS* wild-type metastatic SBA. Until such time as these studies are available, given the limited options available, it is difficult to exclude EGFR inhibitors as a therapeutic option for SBA.

Disclosures
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