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Commentary

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The UPMC Hillman Cancer Center Approach to the Management of Colorectal Cancer During the COVID-19 Pandemic Era

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In December 2019, the novel coronavirus disease 2019 (COVID-19) was first diagnosed in Wuhan, China, and had initially presented in a small cluster of patients with severe acute respiratory syndrome coronavirus-2.[1] Since its initial outbreak in the Hubei Province of China, the disease has spread throughout the world and was formally declared a global pandemic by the World Health Organization on March 11, 2020. According to the Centers for Disease Control and Prevention, as of the beginning of June 2020, nearly 6.3 million cases have been diagnosed worldwide, with 375,000 deaths. In the United States, 1.8 million cases have been reported, with nearly 110,000 deaths. It is interesting to note that the first case of COVID-19 in the United States was diagnosed on January 20, 2020, the very same date the first case of COVID-19 was reported in South Korea. However, the subsequent course of COVID-19 has taken dramatically different paths in the 2 countries, with a total of 12,003 COVID-19 cases confirmed in South Korea with only 277 deaths reported as of June 12, 2020. In sharp contrast, in the United States, nearly 2.1 million cases had been recorded as of June 12, 2020, with nearly 120,000 deaths. Without question, COVID-19 is a highly contagious disease, and it has dramatically affected the treatment of patients with cancer in the United States and countries around the world.

Cancer centers around the world have worked extensively to modify their treatment strategies to appropriately treat their patients with cancer during this pandemic. The two leading oncology associations in the United States and Europe, the American Society of Clinical Oncology and the European Society of Medical Oncology, and the National Cancer Institute of Milan, the Korean Cancer Association National Cancer Center, and an international collaborative group have reported special guidelines on how to optimally manage and treat patients with cancer during the COVID-19 pandemic.[2-8] Herein, we report the practical approach that was instituted at our cancer center, the UPMC Hillman Cancer Center of the University of Pittsburgh, as representative of the strategies that have been adopted at other major cancer centers in the United States.

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Locally Advanced Rectal Cancer

At present, 2 standard combined modality approaches are available to treat locally advanced rectal cancer. The first is to combine radiotherapy, usually administered during the course of ~5.5 weeks, with either infusional 5-fluorouracil (5-FU) or oral capecitabine. To avoid the requirement to come into the hospital for insertion of a central venous catheter and the potential complications associated with a central port, our approach during this pandemic has been to recommend oral capecitabine with radiotherapy. An alternative strategy would be to consider using short-course radiotherapy, followed by neoadjuvant chemotherapy. At the American Society of Clinical Oncology 2020 Virtual Meeting, Hospers et al[9] presented the results of the RAPIDO (rectal cancer and preoperative induction therapy followed by dedicated operation) trial. The RAPIDO trial, an international, multicenter, phase III randomized clinical trial, compared short-course radiotherapy, followed by 18 weeks of either CAPOX (capecitabine, oxaliplatin) or FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) chemotherapy before total mesorectal excision, against standard radiotherapy administered on weeks 1 to 6 combined with daily oral capecitabine for the duration of the radiotherapy course.[9] That study showed an impressive doubling of the pathologic complete response rate from 14% to 28%, a 7% reduction in disease-related treatment failure and the development of distant metastases, and an identical 3-year survival of 89% compared with standard treatment.[9] The potential advantage of this approach is that patients can significantly reduce the number of

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visits to the outpatient clinic for their daily radiotherapy sessions, thereby avoiding unnecessary exposure to other patients and medical staff who could potentially be infected with COVID-19. In addition, we would recommend the CAPOX regimen for neoadjuvant chemotherapy, instead of FOLFOX, because the use of the former would eliminate the need for a central venous catheter.

Adjuvant Therapy for Stage II-III Colon Cancer

The initiation of adjuvant chemotherapy for patients with early-stage colon cancer can be safely delayed for $\leq$ 8 weeks. However, studies from the Netherlands Cancer Institute and a group of Chinese investigators have shown that delaying adjuvant chemotherapy for $>$ 8 weeks was significantly associated with worse overall survival.[10,11] For patients with stage II colon cancer, it is important to perform microsatellite instability (MSI) testing to document the presence of MSI-high disease, because no clinical benefit has been realized from adjuvant chemotherapy for this particular patient subgroup. Thus, MSI testing can eliminate the use of ineffective treatment, the potential side effects, and unnecessary visits to the outpatient clinic that would increase the risk of exposure to COVID-19. For patients with high-risk stage II and low-risk stage III colon cancer, the IDEA (international duration evaluation adjuvant chemotherapy) study has shown that 3 months of adjuvant therapy with CAPOX should be considered as noninferior to 6 months of adjuvant therapy.[12] However, patients with high-risk stage III colon cancer will clearly derive greater benefit with 6 months of adjuvant chemotherapy, whether CAPOX or FOLFOX. During the COVID-19 pandemic, the CAPOX regimen would certainly be preferred because it eliminates the need for a central venous catheter and an infusional pump, both required for the FOLFOX regimen.

Treatment of Metastatic Colorectal Cancer

For patients who present with advanced, metastatic CRC, several important factors must be considered. These include the patient's performance status, comorbidities, tumor-related symptoms, tumor bulk, and site-limited disease, with the goal of curative surgical resection. As previously noted, during the COVID-19 pandemic, we recommend using oral capecitabine, in place of infusional 5-FU, to serve as the fluoropyrimidine backbone for combination regimens with oxaliplatin and irinotecan. The use of oral capecitabine will help reduce the frequency of in-hospital and outpatient infusional procedures. Although patient preferences for experiencing certain toxicities such as neuropathy versus gastrointestinal (GI) toxicity should be considered, during this pandemic, an oxaliplatin-based regimen could be preferred, because the potential risk of serious GI toxicities and, even, myelosuppression might be lower than those with irinotecan-based chemotherapy. For patients who are symptomatic and for whom a more immediate reduction in tumor bulk is required, an anti-EGFR antibody, either cetuximab or panitumumab, is recommended in the setting of wild-type *RAS* and *BRAF* disease. For patients with mutant *RAS* or *BRAF* disease, the anti-VEGF antibody bevacizumab is entirely appropriate. With respect to metastatic disease specifically confined to the liver or lungs and for which surgical resection is possible after conversion therapy, it is still entirely reasonable to provide aggressive treatment. Thus, the triplet regimen of FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, irinotecan), with or without cetuximab or bevacizumab, is entirely appropriate. Obviously, one concern is the potential myelosuppressive effects of this regimen, which might then place patients at increased risk of infectious complications. To address this issue, a modified schedule of FOLFOXIRI can be considered, with a reduced dose of infusional 5-FU from 3200 mg/m^2 to 2400 mg/m^2 and a reduced dose of irinotecan from 165 mg/m^2 to 150 mg/m^2. In addition, the use of granulocyte colony-stimulating factor should be considered as a prophylactic measure to reduce the risk of myelosuppression and the potential for infectious complications.

In the second-line setting, the main goal should be to maintain clinical efficacy and minimize toxicity. If a patient had been previously treated with a bevacizumab-containing regimen, continuation with bevacizumab at disease progression is entirely reasonable, and the use of alternative anti-VEGF therapies, such as aflibercept and ramucirumab, should not be considered. The rationale for avoiding these other anti-VEGF agents is that they have been clearly associated with more significant side effects, including myelosuppression and GI toxicity, compared with bevacizumab. These side effects should be avoided so as not to place patients at an increased risk for developing COVID-19 infection. In patients with *BRAF V600E* mutations, the updated results from the BEACON [study of encorafenib + cetuximab plus or minus binimetinib vs. irinotecan/cetuximab or infusional 5-fluorouracil/folinic acid/irinotecan (FOLFIRI)/cetuximab with a safety lead-in of encorafenib + binimetinib + cetuximab in patients with BRAF V600E-mutant metastatic colorectal cancer] phase III clinical trial showed that the doublet combination of encorafenib plus cetuximab yielded the same improvement in progression-free survival and overall survival compared with the triplet regimen of encorafenib, cetuximab, and binimetinib.[13] Although the overall response rate with the triplet regimen was better than that with the doublet (27% vs. 20%), this was at the expense of increased overall grade 3/4 toxicity and, in particular, GI toxicity and anemia. Therefore, we would recommend using the doublet combination of cetuximab plus encorafenib in the setting of *BRAF V600E* mutant metastatic colorectal cancer.

In the third-line, disease-refractory setting, a key factor to consider is the overall performance status of the patient and whether the patient has symptoms associated with the disease. In the absence of tumor-related symptoms, it is entirely reasonable to proceed with best supportive care and to wait to provide active treatment. If treatment must be initiated, one possibility would be to consider an anti-EGFR antibody therapy with either cetuximab or panitumumab, if not previously used and only in the setting of wild-type *RAS* and *BRAF*. Although regorafenib and the oral fluoropyrimidine TAS-102 have had equal clinical efficacy in this disease-refractory setting, regorafenib should be preferred because it has not been associated with myelosuppression, in contrast to TAS-102. To reduce the potential side effects observed with regorafenib, it would be important to consider alternative dosing schedules such as the ReDOS (regorafenib dose-escalation strategy in refractory advanced

colorectal cancer) strategy,[14] the 120 mg/d 3-week on and 1-week off schedule, or an intermittent dosing regimen of 160 mg once daily for 1 week on and 1 week off.

Conclusion

The COVID-19 pandemic has presented an unparalleled challenge to the delivery of clinical care to our patients with cancer. In just the past 3 to 4 months, medical oncologists and other healthcare professionals involved in the cancer care of patients with colorectal cancer have had to modify their approach to ensure patient safety while, at the same time, not compromising clinical efficacy. We have provided practical recommendations on how to approach patients with colorectal cancer during COVID-19. Although the hope is for the United States to be able to return to the normal, pre—COVID-19 practices, the ongoing concern is the increasing number of states in the United States that are experiencing a continued increase in COVID-19 cases. Thus, it is conceivable that we might need to continue with a modified approach for the foreseeable future until a significant reduction has occurred in the incidence of COVID-19 infections.

Disclosure

The authors declare that they have no competing interests.

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