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COMMENTARY

Impact of the COVID-19 outbreak on adjuvant chemotherapy for patients with stage II or III colon cancer: experiences from a multicentre clinical trial in China

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BACKGROUND

Since January 2020, the outbreak of the novel coronavirus disease designated COVID-19 by the World Health Organization, a human-to-human contagious viral pneumonia that began in 2019, has been extensively influencing daily life in China[1,2]. Up to 21 February 2020, more than 50,000 cases had been diagnosed in Mainland China. To prevent and control transmission of the virus, central and local governments established a first-level response to this major public health emergency with policies such as restriction of public transportation, cancellation of public activities, and suspension of school and some industries[3]. Although medical settings—including hospitals and clinics—are the chief frontiers in the fight against COVID-19, certain effects on the administration and operation of medical resources remain[4]. During this special period, treatments for patients with cancer could be affected to a certain extent, because most cancer treatments are periodic and time-dependent. Evidence is limited, however.

Adjuvant chemotherapy (aCTx), a radical cancer treatment after surgery, is one of the most time-dependent cancer treatments, especially for colon cancer[5]. Evidence recommends that completion of aCTx (usually a dual-drug regimen) within 6 months after radical surgery can lower the risks of recurrence and metastasis for patients with high-risk stage II or III colon cancer[6,7]. In 2018, we launched a multicentre randomized controlled trial of the efficacy of a Traditional Chinese Medicine herbal for improving the completion rate of aCTx (capecitabine–oxaliplatin regimen) and reducing chemotherapy-induced side effects in patients with stage II or III colon cancer (see NCT03716518 at https://ClinicalTrials.gov/). The study planned to enrol 400 participants from 12 hospitals located in the cities of Beijing, Shanghai, Tianjin, Chongqing, and the provinces of Henan, Jiangsu, and Guangdong. However, from the beginning of January 2020, we noticed that recruitment had slowed, and researchers from several clinical centres reported that participants might delay their next cycle of chemotherapy because of the COVID-19 outbreak. To add to the knowledge about the effects of the COVID-19 outbreak on cancer patients and any related coping strategies, we share in this article the data and experiences that we have collected and analyzed from our ongoing multicentre randomized controlled trial.

METHODS

On 21 February 2020, we collected the latest data from each centre about the numbers of patients who had been recruited and were still under observation, about the patients who had experienced treatment delay (longer than the guideline-recommended 3-week gap between cycles), and about modifications to the aCTx regimen (removal of oxaliplatin, and use of single-agent capecitabine). We also calculated the days of delay as the gap between the scheduled date and the actual date on which the next cycle of chemotherapy started. If the patient had not started treatment by the day of data collection, 21 February 2020 was used to calculate the delay. We also asked researchers from each centre to provide us with the reasons for regimen delays or modifications (because of chemotherapy-induced side effects or for other specific reasons). For this article, the period of the COVID-19 outbreak was defined as 1 January 2020 to the data collection date. To protect the privacy of all the hospitals in the study, we removed the hospital names and any identifying information such as specific location and care level of the hospitals in Table I.

RESULTS

By 21 February 2020, the 12 hospitals had recruited a combined total of 86 patients, including 62 patients who were still receiving aCTx during the COVID-19 outbreak period (Table I). No participant at any clinical centre in our study had been diagnosed with or was suspected of having COVID-19 infection.

Of the 62 patients who were still receiving aCTx during the COVID-19 outbreak period, 31 (50%) had a delay to the

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TABLE I Hospitals enrolling study patients and incidences of chemotherapy delay or regimen modification

Hospital ID	Patients recruited (*n*)	Hospital type	Department	Patients under observation (*n*)	Delays		Modification of regimen (*n*)
					(*n*)	Mean delay (days)	
1	20	Traditional Chinese medicine	Internal oncology	7	1	11±0	0
2	3	Western medicine	Surgery	2	2	NA	0
3	9	Western medicine	Internal oncology	9	0	NA	0
4	20	Western medicine	Surgery	18	13	14±5	3
5	1	Traditional Chinese medicine	Surgery	1	0	NA	0
6	0	Western medicine	Internal oncology	0	NA	NA	NA
7	0	Western medicine	Surgery	0	NA	NA	NA
8	2	Western medicine	Internal oncology	2	1	6±0	1
9	1	Traditional Chinese medicine	Internal oncology	1	0	NA	0
10	7	Traditional Chinese medicine	Surgery	3	3	20±7	0
11	3	Traditional Chinese medicine	Internal oncology	3	1	NA	0
12	20	Western medicine	Surgery	16	10	12±6	2
TOTAL[a]	86	—	—	62	31	13.6±6.1	6

[a] Number of drop-outs not shown.
NA = not applicable.

start of their next cycle of aCTx, and 6 (9.7%) had their regimen modified to single-agent capecitabine (Table I). For the 31 patients whose regimen was delayed, mean days of delay were 13.6 ± 6.1 (maximum: 26 days; minimum: 1 day). The main reason for delay or regimen modification, as provided by the researchers and physicians at the clinical centres, was "hospital policy" [some departments did not admit any patients, others did not admit patients from outside their city (24 of 37, 64.9%)], followed by "transportation blockage" [either the patients could not leave their own cities, or they could not enter the city where their hospital was located (3 of 37, 8.1%)]. Another 3 patients were not willing to come to the hospital for chemotherapy (8.1%, Figure 1). Chemotherapy-induced thrombocytopenia and hepatic dysfunction resulted in a regimen modification to single-agent capecitabine for 2 patients. Six patients travelled back to their hometown or to a local city to receive their chemotherapy, and four of them eventually had a therapy delay (11%). One patient had a delay for an unknown reason (3%). Excluding delays or modifications because of side effects or patient willingness, the total rate of delay or regimen modification because of the COVID-19 outbreak was about 43.6%.

Of the 12 hospitals involved in the study, 6 had recruited patients from their internal oncology department; the other 6 had recruited from the surgery department. Delay or modification of an aCTx regimen was more likely to occur in hospitals recruiting patients from the surgery department than from the internal oncology department (incidence: 82.5% vs. 18.5%; $p < 0.001$).

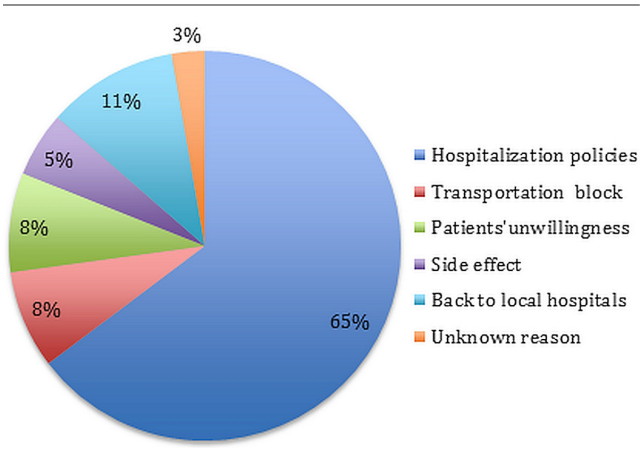

FIGURE 1 Reasons for delay or modification of chemotherapy regimens.

DISCUSSION

Even though participants in clinical trials receive more intensive follow-up and careful treatment management, based on our data, they still experienced a 50% chance of regimen delay or modification directly or indirectly attributable to the COVID-19 outbreak. Previous clinical trials of aCTx for patients with stage II or III colorectal cancer showed that, on average, patients eventually complete 6.6 cycles of capecitabine–oxaliplatin, with a rate of dose reduction of about 23–25%[8]. Another study showed that the total instances of delay lasting 3 days or more for all cycles of FOLFOX aCTx (leucovorin–fluorouracil–oxaliplatin) numbered 1.7[9]. The effect of the COVID-19 epidemic on the completion of aCTx in our study population might therefore far exceed real-world projections.

In a departure from the common reasons for delay or dose reduction of aCTx (side effects, morbidities, and patient willingness)[10–12], we found that "hospital policy" was the major reason, especially for patients recruited from surgery departments. Given the fact that most surgeries

are performed in operating rooms with clean laminar flow, which makes virus spread easy, many hospitals suspended non-emergency surgeries and inpatient hospitalizations. To reduce the risk of cross-transmission, other hospitals denied admission to patients from outside their city. Because it is common in China for many patients with cancer to receive their treatment outside their residential hometowns, in hospitals operating at higher care levels, policies at those hospitals and transportation blockages between cities had a significant influence. In addition, reallocation of medical resources in many hospitals also restricted their ability to admit patients during the study period[13].

A paper published in *Lancet Oncology,* based on an analysis of a Chinese national database, found that cancer patients who were infected with COVID-19, especially those who had undergone chemotherapy or surgery, were more likely to experience severe life-threatening clinical events[14]. Thus, it was quite necessary for cancer patients to avoid overexposure to a public environment with a risk of cross-transmission. We also noted from our data that 8% of patients were unwilling to come to the hospital for treatment during the epidemic, resulting in discontinuation of their aCTx. Nonetheless, the risk to patients coming to a hospital is controllable if patients protect themselves effectively and if the hospital restrictively screens for suspected infection and carefully sterilizes the environment.

SUMMARY

Currently, colorectal cancer is still the 4th most frequently diagnosed cancer and the 2nd leading cause of cancer-related death worldwide[15]. For most patients with localized or regional disease, colorectal cancer is currently curable after radical surgery and adjuvant chemotherapy. Whether the effect of COVID-19 on aCTx will jeopardize survival outcomes for our patients with colon cancer requires long-term follow-up and further evaluation. To cope with the current situation, we suggest that doctors refer patients with stage III colon cancer to their internal oncology department or to local hospitals where the patients can receive timely treatment[16]. For patients with high-risk stage II disease, some Chinese experts suggest that modification of the regimen to single-agent capecitabine is acceptable[17]. We also suggest that doctors follow their patients remotely, monitor their condition, and offer advice about health management during the epidemic period.

Given that COVID-19 is still spreading in Asia, Europe, and the Americas[18], we hope that our experience from this ongoing clinical trial in China might be helpful for other countries that are trying to balance the management of cancer patients and control of the pandemic. We also want to commend the self-sacrifice of every single person, even cancer patients, who are fighting the COVID-19 pandemic for China and the world.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

1. Xu XW, Wu XX, Jiang XG, *et al.* Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020;368:m606.
2. Ayittey FK, Ayittey MK, Chiwero NB, Kamasah JS, Dzuvor C. Economic impacts of Wuhan 2019-nCoV on China and the world. *J Med Virol* 2020;92:473–5.
3. Zhao S, Zhuang Z, Cao P, *et al*. Quantifying the association between domestic travel and the exportation of novel coronavirus (2019-nCoV) cases from Wuhan, China in 2020: a correlational analysis. *J Travel Med* 2020;27:taaa022.
4. Wang X, Zhang X, He J. Challenges to the system of reserve medical supplies for public health emergencies: reflections on the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic in China. *Biosci Trends* 2020;14:3–8.
5. Chan GHJ, Chee CE, Making sense of adjuvant chemotherapy in colorectal cancer. *J Gastrointest Oncol* 2019;10:1183–92.
6. Petrelli F, Labianca R, Zaniboni A, *et al.* Assessment of duration and effects of 3 vs 6 months of adjuvant chemotherapy in high-risk stage II colorectal cancer: a subgroup analysis of the TOSCA randomized clinical trial. *JAMA Oncol* 2020;6:547–51.
7. Iveson T, Boyd KA, Kerr RS, *et al*. 3-Month versus 6-month adjuvant chemotherapy for patients with high-risk stage II and III colorectal cancer: 3-year follow-up of the SCOT non-inferiority RCT. *Health Technol Assess* 2019;23:1–88.
8. Pectasides D, Karavasilis V, Papaxoiniset G, *et al*. Randomized phase III clinical trial comparing the combination of capecitabine and oxaliplatin (CAPOX) with the combination of 5-fluorouracil, leucovorin and oxaliplatin (modified FOLFOX6) as adjuvant therapy in patients with operated high-risk stage II or stage III colorectal cancer. *BMC Cancer* 2015;15:384.
9. Cespedes Feliciano EM, Lee VS, Prado CM, *et al.* Muscle mass at the time of diagnosis of nonmetastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: the C-SCANS study. *Cancer* 2017;123:4868–77.
10. Kaerlev L, Iachina M, Trosko O, *et al.* Colon cancer patients with a serious psychiatric disorder present with a more advanced cancer stage and receive less adjuvant chemotherapy—a nationwide Danish cohort study. *BMC Cancer* 2018;18:1050.
11. Boyne DJ, O'Sullivan DE, Heeret EV, *et al.* Prognostic factors of adjuvant chemotherapy discontinuation among stage III colon cancer patients: a survey of medical oncologists and a systematic review and meta-analysis. *Cancer Med* 2020; 9:1613–27.
12. Arhi CS, Burns EM, Bouras G, Aylin P, Ziprin P, Darzi A. Complications after discharge and delays in adjuvant chemotherapy following colonic resection: a cohort study of linked primary and secondary care data. *Colorectal Dis* 2019;21:307–14.
13. Wax RS, Christian MD. Practical recommendations for

critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. *Can J Anaesth* 2020;67:568–76.
14. Liang W, Guan W, Chen R, *et al.* Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21:335–7.
15. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
16. Gao P, Huang XZ, Song YX, *et al.* Impact of timing of adjuvant chemotherapy on survival in stage III colon cancer: a population-based study. *BMC Cancer* 2018;18:234.
17. Mizumoto Y, Yokoyama S, Matsuda K, *et al.* Modulation of capecitabine administration to improve continuity of adjuvant chemotherapy for patients with colorectal cancer: a phase II study. *Mol Clin Oncol* 2020;12:126–33.
18. Jernigan DB on behalf of the CDC COVID-19 Response Team. Update: public health response to the coronavirus disease 2019 outbreak—United States, February 24, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:216–19.