LETTER

Management of Cancer During the COVID-19 Pandemic: The Rewritten Rules

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Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel zoonotic RNA virus.¹ The first cases were reported in December 2019 in Wuhan, China, and within weeks, this infection reached the USA and Europe.^{2,3} Indeed, the fast-spreading COVID-19 pandemic has impacted upon every facet of human life. Throughout known history, processions of pandemics have shaped society, which has included the shaping of the fundamental principles of the health sciences.⁴ The oncology community has been no exception, and it has also faced unprecedented hurdles.⁵ COVID-19 can be extremely dangerous for patients with cancer; therefore, oncologists and hematologists must think about ways to: (a) balance a delay against the danger of COVID-19 exposure; (b) mitigate the risks of significant care disruptions; and (c) manage the appropriate allocation of the limited healthcare resources.

The European Society of Medical Oncology (ESMO) established guidance for clinicians to provide a framework for the medical community to treat several cancer types during the COVID-19 pandemic, including colorectal cancer (CRC).⁶ Three levels of priorities for medical interventions were defined: tier 1, high priority interventions; tier 2, medium priority interventions; and tier 3, low priority interventions. The prioritization is based on the Ontario Health, Cancer Care Ontario framework of resource-prioritization⁷ and the ESMO Magnitude of Clinical Benefit Scale (MCBS), a public health tool that is intended to support the uptake of medical interventions in oncology.⁸ The tiers are described as follows:

- **Tier 1, high priority:** The patient condition is immediately life-threatening, clinically unstable, and/or the magnitude of the benefit qualifies the intervention as high priority (e.g., significant patient overall survival [OS] gain and/or substantial improvement in quality of life [QoL]). Example: severe complications due to a primary tumor, treatment, or disease progression.
- **Tier 2, medium priority:** The patient situation is noncritical, but if delay beyond 6 weeks might have an impact upon the overall outcome and/or the magnitude of benefit qualifies for intermediate priority. Examples: adjuvant treatment in stage II-III disease; diagnostic imaging/endoscopy for clinically suspected CRC or for a high-risk population; neoadjuvant CRT first-line or second-line treatments.
- **Tier 3, low priority:** The patient condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is nonpriority based on the magnitude of benefit (e.g., no survival gain with no change in QoL). Examples: routine tests and radiological examinations; all treatments with modest benefit expected.

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In Europe in 2020, colorectal cancer accounted for 12.7% of all new cancer diagnoses and 12.4% of all deaths due to cancer; this made it the second most frequently occurring cancer (after breast cancer), and the second greatest cause of cancer deaths (after lung cancer).⁹ The overall colorectal cancer trends are increasing in terms of incidence, but decreasing in terms of mortality, although there are national and regional exceptions and large variability. These can be explained by the different levels of healthcare expenditure and the resulting quality of screening, diagnosis, and treatment. The economic burden of colorectal cancer in 2015 was € 19.1 billion (10% of the economic cancer burden in Europe), of which € 11.6 billion represented nonhealthcare costs (mainly loss of productivity due to disability, premature death, opportunity costs for informal careers) and € 7.5 billion represented direct healthcare costs (mainly hospital care, systemic anti-cancer therapies, outpatient care, primary care, emergency care).¹⁰

The COVID-19 pandemic and the associated lockdowns have led to unprecedented economic costs around the world. The European Union (EU) and its member states have taken action to support the economic recovery and to minimize the fallout of the economy. The overall EU recovery package amounts to € 2,364.3 billion for 2021–2027.¹¹

Although the pandemic has posed an unprecedented threat to humanity, it has also provided cancer professionals with a unique opportunity to learn new lessons in terms of novel treatment options and accelerated clinical research.

LESSON LEARNED 1: REMOTE HEALTHCARE SOLUTIONS AND INNOVATION

Cancer patients have been reported to have an increased risk of being infected with SARS-CoV-2, as well as to show increased morbidity and mortality from COVID-19. Therefore, additional safety measures need to be taken to ensure their safety. These can include reducing hospital visits through implementation of telemedicine services such as electronic patient-reported outcomes (ePRO), electronic follow-up applications, and telephone-based symptom reporting.¹² In addition, blood tests performed in patient's homes or at local health hubs can help to minimize the risks of infection. One of the most significant telemedicine advances in the next decade might be telesurgery.¹³ Telesurgery refers to a procedure in which the surgeon and patient are at separate locations, and the patient is operated on remotely, with the assistance of an operating robot. Telesurgical procedures will be made easier due to the faster data transmission speeds and lower signal latency of 5G. The need to reduce hospital visits during the pandemic significantly enforced innovation in this area, and the first examples of successful telesurgical procedures are being built on for the future.¹⁴

In addition, during the pandemic, open surgery under locoregional anesthesia might be a crucial option to deliver acute-care surgery when Intensive Care Unit beds are not available and when postponing the surgery is not acceptable. A clinical case was reported recently on the use of a 3D mobile theatre intraoperatively for pain distraction and for delivering postoperative psychological care during social distancing.¹⁵

LESSON LEARNED 2: CLINICAL RESEARCH

Randomized prospective trials have become more time consuming and expensive to carry out over the last two decades, due in part to the increased complexity of the approval procedures and other bureaucratic difficulties.¹⁶ According to the Global Coronavirus COVID-19 Clinical Trial Tracker, about 2,908 COVID-19 trials have been registered worldwide since April 2019.¹⁷ This is exceptional, as prior to the pandemic, the regulation and bureaucracy were key hurdles for clinical trial research. The cancer community must use the lessons learned to drive a significant shift in the way clinical cancer research is conducted in the future, and must address the issue that existing regulatory and trial approval processes are sometimes too long to meet patient demands.¹⁶

Although COVID-19 has revealed how high levels of bureaucracy in research regulations can create undue burdens for patients and clinicians, it is critical to emphasize that reducing bureaucracy does not imply laxity.¹⁸ Reducing bureaucracy could have serious consequences on the quality and consistency of clinical research, and a careful balance must be maintained between simplification of the procedure and reliability of the data.¹⁸

LESSON LEARNED 3: NEW THERAPEUTIC PERSPECTIVES - mRNA VACCINES AND IMMUNOTHERAPY

The COVID-19 pandemic significantly accelerated the development of synthetic mRNA vaccines for SARS-CoV-2. Within a year of the identification of SARS-CoV-2, Pfizer/BioNTech and Moderna (Cambridge, MA, USA) developed mRNA vaccines to SARS-CoV-2, known as BNT162b2 and mRNA-1273, respectively.^{19–22} BNT162b2 is a nucleoside-modified RNA vaccine that received Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA) in December 2020²¹, followed by approval by Swissmedic in January 2021²³. In early 2021, Moderna published the safety and efficacy data on the mRNA-1273 vaccine.²⁴ This vaccine received FDA EUA approval in December 2020²⁴, and was authorized by Swissmedic in January 2021²⁵.

Synthetic mRNA provides a template for the synthesis of any protein fragment or peptide, and it lends itself to a wide range of pharmaceuticals, including different modalities of cancer immunotherapy. In this context, a phase I, open-label,

multicenter study is ongoing to assess the safety and tolerability of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab in patients with *KRAS*-mutated advanced or metastatic non-small cell lung cancer (NSCLC), CRC, or pancreatic adenocarcinoma.²⁶

LESSON LEARNED 4: ACCELERATED PUBLISHING

Since January 2020, research on COVID-19 has been conducted at an unprecedented pace, and >150,000 articles have been published on LitCovid: an open database of COVID-19 literature.²⁷ Indeed, on average, there were 367 COVID-19 articles published per week, while the median time from submission to acceptance for COVID-19 articles was just 6 days.²⁸ Research carried out during the pandemic was quickly published, with many researchers publishing their findings on the medRxiv and bioRxiv preprint servers. However, standards must be maintained in the future while facilitating the speed

of circulation, which includes transparency in data sources and analytic processes, as well as reproducibility and robust peer review.¹⁶

CONCLUSIONS

The COVID-19 pandemic forced clinicians and health-care providers to change their practices. Therefore, the oncology community should make use of the lessons learned to create an environment for innovation to thrive, with the implementation of nontraditional care delivery strategies (e.g., telemedicine, telesurgery) and the development of new treatment strategies (e.g., mRNA vaccines for cancer immunotherapy). Sustaining a faster publication process and reducing the bureaucracy of clinical trials without compromising on quality will further support innovation in cancer treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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