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Commentary

How to Guarantee the Best of Care to Patients with Cancer During the COVID-19 Epidemic: The Italian Experience

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

Abstract

Italy and the rest of the world are experiencing an outbreak of a novel beta-coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this context, in Italy, we reorganized the National Health System and prioritized the clinical cancer care scenario, balancing risk of SARS-CoV-2 transmission versus the magnitude of clinical benefit deriving from a specific therapeutic approach. As initial actions, we recommended that routine screening be suspended and that patients with early and advanced cancer be treated as outpatients as much as possible and at the nearest medical center. Patients who need to be hospitalized for cancer treatment were protected from potential SARS-CoV-2 infection by creating a dedicated diagnostic and therapeutic internal pathway for cancer treatment. We implemented reorganization of the hospital networks, based on a hub-and-spoke design. Stronger personal protection was made available for patients with cancer. Because of the extreme burden created by COVID-19, antitumor treatment was initiated only after considering patient performance status, comorbidities, biology of disease, and the likely impact of treatment on outcome. Treatment strategies were discussed in the context of a multidisciplinary tumor board. Treatment decision making balanced risk and benefits of treatment in the context of the specific pandemic level, on a case-by-case basis. ***The Oncologist*** 2020;25:463–467

Introduction

Italy and the rest of the world are experiencing an outbreak of a novel beta-coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. By April 8, 2020, the rapid spread of the virus had caused 139,422 positive cases (of 807,125 screened subjects) and 17,669 deaths in Italy [2]. In the Lombardia region, where I live, 53,414 positive cases (of 167,557 screened cases) were detected. Of those, 10,022 (19%) have died, 11,179 (21%) are hospitalized with symptoms, and 1,257 (2%) are in intensive care for acute respiratory distress syndrome [2]. Since February 24, 2020, in the Lombardia region, the epicenter of the outbreak, 9,722 patients have died because of SARS-CoV-2 infection.

The case fatality rate in our country, as in others, increases in the elderly population and in patients with comorbidities. Most of the COVID-19–positive patients had no or mild illness, but in our experience, half of them needed hospital admission, suggesting that many cases were mild and went undiagnosed. Of patients hospitalized, approximately 10% needed care in an intensive care unit (ICU), leading to an unprecedented number of people admitted to ICU. In less than 3 weeks, the coronavirus had overloaded the health care system all over northern Italy. For mild and moderate cases in Milan, we created a mobile cabin hospital in Fiera Milano Exhibition Center (converted from a convention center into a temporary large-space treatment center with 250 beds). As we have learned, every country should be ready with extraordinary measures to restrict viral spread and to expand ICU capacities and workforce to take care of new patients.

Very limited data are available for patients with cancer during the COVID-19 epidemic. In a retrospective analysis including 1,572 cases of patients with COVID-19, the authors identified 18 patients (1%) with cancer [3]. Patients with cancer were observed to have a higher risk of severe events (a composite endpoint defined as the percentage of patients being admitted to the intensive care unit requiring invasive ventilation, or death) compared with patients without cancer (7 [39%] of 18 patients vs. 124 [8%] of 1,572 patients) [3, 4]. Moreover, patients with cancer who underwent chemotherapy or surgery in the past month had a higher risk (three [75%] of four patients) of clinically severe events than did those not receiving chemotherapy or surgery (6 [43%] of 14

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patients) [4]. A report by the Istituto Superiore di Sanità on March 30, 2020, described the characteristics of 10,026 patients with COVID-19 dying in Italy [5]. The mean age of patients dying from SARS-CoV-2 infection was 78 years (median, 79 years; range, 26–100 years; interquartile range, 73–85 years). Women accounted for only 30.8% of deaths and were of an older age than men dying of the disease (median age in women, 82 years; median age in men, 78 years) [5]. Data on comorbidities were based on chart review of patients dying in hospital. The mean number of comorbidities was 2.7 (median ± SD, 3 ± 1.6) [3]. Overall, only 2.1% of the sample presented with no comorbidities, 21.6% with a single comorbidity, 24.5% with two, and 51.7% with three or more. Before hospitalization, 28% of COVID-19 deaths occurred in patients being treated with angiotensin-converting enzyme inhibitor therapy, and 16% were being treated with angiotensin receptor blocker therapy [5]. This information likely underestimates comorbidities and medications, because preadmission histories were not always available or complete. In this series of fatal COVID-19 cases, 150 patients (16.5%) had active cancer [5].

The Lombardia region area contains 10,085,021 inhabitants and has a cancer incidence of 535 per 100,000 [6]. The largest comprehensive cancer centers in Italy are concentrated in this region.

How to Manage Patients with Cancer in the Face of the COVID-19 Epidemic

Management of patients with cancer was a major issue for medical oncologists working in the Milan area. First, it was mandatory to establish an adapted risk communication with periodic updates of statistics of infected cases and an adjusted level of alert of patients and health professionals, provision of adequate personal protective equipment (PPE) for health care workers, and rigorous application of infection prevention and control measures in health care facilities, all implemented to reduce the risk of the infectious transmission to a vulnerable population. Secondly, it was necessary to ensure adequate resource allocation in terms of hospitals and health care workforce to take care of patients with cancer in the face of the COVID-19 epidemic [7].

The cancer hospitals in the Lombardia region defined new clinical pathways for patients with cancer. Our legislative authorities temporarily incorporated all public and private health care activity into a coordinated plan, thus extending the health care workforce and facilities for patients with cancer. The Lombardia region identified three comprehensive cancer centers in Milan (Istituto Nazionale dei Tumori, European Institute of Oncology, and Humanitas Cancer Center), along with several specialized cancer departments in the general hospitals; these facilities were available for incorporation into a hub-and-spoke network [8]. The specialized hubs for oncology were connected with spokes within the general hospitals to establish three health networks for the-specific referral of patients with cancer, distinct from the COVID-19 pathway. These networks provide for the essential care for patients with cancer. Public and private institutions have been asked to synergize their capacities, including the workforce, thus assuring the deployment of the best national

Figure 1. Organization of Regione Lombadia in hub (blue dot) and spoke (black dot) for referral of patients with cancer. In the Milan area, three hub hospitals were defined.

expertise for cancer control [7]. On March 8, 2020, a Regional Council Resolution was adopted, reorganizing the hospital networks, based on a hub-and-spoke design [7, 8]. Figure 1 shows the hub-and-spoke organization for the three hub hospitals in Milan; it describes all hospitals referring priority patients to our hub hospital. The hubs for cancer care were designated on the basis of performance criteria (e.g., volumes of specialized cancer surgery), each connected to one or more spokes for selected services (e.g., administration of standard chemotherapies). The Regional Council Resolution aimed to assure the continuity of care for essential cancer treatments while allowing a scale-up of the capacity for the serious health care demand of COVID-19 outside the cancer network.

How to Prioritize Treatments for Patients with Cancer in the Face of the COVID-19 Epidemic

The National Health System defined "priorities" [9]. Two groups of patients were identified: the "patients off therapy" (group A) who completed treatment with curative intent and the "patients on treatment" with curative intent or in the metastatic setting (group B). Patients "on treatment" were defined as those requiring surgery, chemotherapy and/or radiotherapy, biological therapy, endocrine therapy, and/or immunotherapy (either in the adjuvant or in the metastatic setting). For all patients (groups A and B), health education was conducted, including a personal phone call and use of social media advertising regarding prevention of COVID-19 according to World Health Organization (WHO) guidelines: (a) avoid crowded places, (b) wear PPE when you enter the hospital for visits and treatments, (c) wash your hands, (d) do not have contact with friends and relatives with COVID-19 symptoms or with those living in endemic zones, and (e) guarantee social distancing.

For patients receiving active treatment (group B), living in epidemic zones or not, we identified specific pathways in

Table 1. National strategy to guarantee access to care of patients with cancer

Setting	Strategy	Measures
Patients "off treatment"	Prevention Symptom-oriented follow-up Implement telemedicine follow-up	Education on COVID-19 symptoms to increase patient awareness Phone contact with all patients in the epidemic areas to implement social isolation measures Suggestion for protection supplies in case of suspect contacts
Patients "on treatment" with curative intent	Prevention Implement cancer care within a hub-and-spoke network Guarantee a "COVID-19–free" clinical pathway in the hub hospital	All measures listed above Guarantee the best of care Reduce access to hospital for relatives and vendors Cancer team using PPE Establish checkpoint in the hub to avoid access of infected patients Intensify safety monitoring for patients receiving active treatment using telemedicine
Patients "on treatment" in the metastatic setting	Prevention Implement cancer care within a hub-and-spoke network Guarantee a COVID-19–free clinical pathway in the hub hospital	All measures listed above Prioritize treatment according to magnitude of clinical benefit that qualifies patient for a specific treatment (e.g., significant overall survival gain and/or substantial improvement in QoL) When chemotherapy is recommended, prefer oral treatments to reduce access to hospital All patients must be assured of the best home-based supportive care and enhanced symptoms control via telemedicine

Abbreviations: PPE, personal protection equipment; QoL, quality of life.

order to guarantee appropriate timing of treatment. Three "Hub Cancer Centers" have been designated in the Lombardia area, where patients with cancer can be transferred to receive all necessary treatments. Patients eligible for surgery had priority access. For all patients with cancer, the Hub Centers guarantee an appropriate diagnostic-therapeutic pathway, reducing the risk of SARS-CoV-2 infection [8]. As a Hub Center, the European Institute of Oncology received in 3 weeks at least 80 patients who were candidates for thoracic, head and neck, gastrointestinal, and breast surgery. Outpatient visits for patients with cancer were reduced to the safest and most feasible level consistent with adequate cancer care. For patients receiving oral treatment for which monitoring could be done remotely, we provided a drug supply for at least three courses to reduce access to the hospital. Blood monitoring for those patients would be done in local labs close to home. We implemented telemedicine services. We delayed all follow-up visits.

We used more intensive surveillance during treatment for patients with lung cancer or who had received previous lung surgery and for older patients or those patients with comorbidities. Intensive measures were undertaken to avoid nosocomial infection. Triaging procedures were established to assess any COVID-19 symptoms in patients with cancer and the urgency and necessity of hospitalization. In order to regulate access to the Hub Centers, we established "checkpoint areas" screening for early detection of potentially infectious persons. Clinical staff responsible for the checkpoint area received special training regarding COVID-19–related symptoms and wore PPE. Individuals who met criteria for SARS-CoV-2 infection were placed in a private examination room as soon as possible, as per the infectious control guidance of the WHO. Those with COVID-19 symptoms were tested and then transferred to COVID-19 hospitals.

Table 1 summarizes the general strategy adopted at national level. We also implemented, in our hospital, cancer treatment prioritization according to the recommendations adopted by the European Society for Medical Oncoogy (ESMO). We applied a tiered approach, namely, high-priority intervention, medium-priority intervention, and low-priority intervention, defined within the criteria of the Ontario Health Cancer Care, Huntsman Cancer Institute, and ESMO Magnitude of Clinical Benefit Scale [10, 11].

- High priority: patient condition is immediately life threatening or clinically unstable, and/or the magnitude of benefit from treatment qualifies the intervention as high priority (e.g., significant overall survival gain and/or substantial improvement of the quality of life [QoL]).
- Medium priority: patient situation is noncritical, but delay beyond 6–8 weeks could potentially affect overall outcome and/or the magnitude of benefit qualifies for intermediate priority.
- Low priority: patient's 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 or reduced QoL).

Table 1 summarizes the national Italian strategy to guarantee training and access to care for patients with cancer. Table 2 summarizes actions of the ESMO to prioritize clinical scenarios for early breast cancer treatment in the medical oncology setting.

Table 2. Examples of prioritizing cancer treatment: European Society for Medical Oncology model for early breast cancer medical treatment

High priority	Medium priority	Low priority
Neoadjuvant and adjuvant chemotherapy for patients with triple-negative breast cancer	Prefer endocrine therapy and delay surgery for postmenopausal women with stage I cancers, low-intermediate grade tumors, lobular breast cancers, low-risk genomic signatures	Follow-up imaging, restaging studies, echocardiograms, electrocardiograms, and bone density scans can be delayed if patient is clinically asymptomatic or there are clinical signs of response in the neoadjuvant setting
Neoadjuvant and adjuvant endocrine therapy ± chemotherapy for estrogen receptor+/HER2− breast cancer		
Completion of neoadjuvant chemotherapy (with or without anti-HER2 therapy) that has already been initiated		
Continuation of standard adjuvant endocrine therapy in pre- and postmenopausal setting Use telemedicine to manage potential toxicity reported by patients		
Continuation of treatment in the context of a clinical trial, provided patient benefits outweigh risks, with possible adaptation of procedures without affecting patient safety and study conduct		

How to Manage Clinical Trials for Patients with Cancer During the COVID-19 Epidemic

Although various degrees of flexibility can be acceptable for standard cancer treatments, it is far more difficult to reconcile the demands of clinical trial protocols within the context of an infectious epidemic and its rapidly evolving scenarios, when the priority is both to ensure patients' safety and to maintain high scientific rigor. Clinical trials represent the cornerstone of drug development and guarantee access to innovation for our patients. Such trials are intended to offer important therapeutic options; however, clinical trials are often demanding in terms of procedures and require multiple patient contacts with the health care institution. In this framework, in March 2020, the U.S. Food and Drug Administration released a guidance, which we have followed, on the conduct of clinical trials of medical products during the COVID-19 pandemic [12]. As we are committed to quality drug development, we have been asked to make difficult decisions regarding the demands of clinical care versus research during the pandemic. In my comprehensive cancer center, we immediately discussed trial strategy with sponsors, on a case-by-case basis, focusing on the potential impact on the safety of trial participants and modifying the study conduct. Study decisions included whether to continue trial recruitment (reducing patient accrual), continuing treatment for patients already enrolled (drug delivery at home), and changing the frequency of patient monitoring during the trial (limited access to hospital consistent with the general lockdown). In all cases, we guaranteed that trial participants would be kept informed of impactful changes to the study and to plans for monitoring toxicity and outcomes. Ensuring the safety of trial participants and health care staff was of paramount importance. We provided clinic staff with additional training on symptom recognition, screening procedures, and use of personal protective equipment. A phone contact the day before the visit was instituted to limit hospital access for patients with COVID-19 symptoms. We excluded access to the clinical care facilities for vendors, minimal ancillary services, all visitors, and medical monitors and auditors. We established a triage checkpoint outside the facility, clinic, or office, with social distancing of at least 6 feet to screen patients for COVID-19 symptoms, including fever, before patients enter. We converted any current open infusion suite to semiprivate space with at least 6 feet distance between patients and/or set up curtains as a barrier between patients. We moved all multidisciplinary discussions to a virtual platform.

When safety measures were fully implemented, we dealt with logistic issues. One of the most effective measures aiming to contain the pandemic spread is social restriction, including quarantine of entire areas and travel bans. These norms can pose significant challenges to patients residing far from the study center, demanding the implementation of flexibility in performing the experimental clinical procedures. Therefore, a set of solutions were discussed with the sponsors. Overall, optional trial procedures (e.g., biopsies) have been eliminated. Biochemical and radiological assessments, with the permission of the sponsors, have been performed in the accredited facility nearest to the patient's home. We centrally reviewed all scans performed locally in order to guarantee the high quality of data.

In our experience, scheduled visits at clinical sites have been significantly affected for patients outside our region. For certain investigational products, such as those distributed for self-administration, we agreed with the sponsors to establish alternative safe delivery methods. For other investigational products normally administered in a health care setting (intravenous or subcutaneous treatments), we maintained scheduled appointments for all local patients, and we delayed chemotherapy administration, within the window of treatment allotted by the protocol, for patients with difficulties in accessing the facility. We implemented telemedicine for more intense safety and active monitoring of patients [13]. As a result of facing the COVID-19 pandemic, we generated a significant number of protocol deviations, and many protocol amendments are still being submitted to ethical committee. Deviations from the protocol rules were discussed in advance with the sponsor, always maintaining the safety of patients as the first priority and minimizing the avoidable risk of COVID-19. The implementation of

alternative processes should be consistent with the protocol to the greatest possible extent, and sponsors and clinical investigators should document the reasons for any contingency measures. Sponsors and clinical investigators should document how restrictions related to COVID-19 led to the changes in study conduct, the duration of those changes, and which trial participants were affected. Developing a patient-centered set of safety recommendations to maintain the quality of research during the pandemic is thus a priority in oncology care, whenever possible in a framework of close cooperation between all stakeholders.

All measures in our country have been driven by a need to concentrate resources and to provide expertise in a manner that reduces the fatality rate of COVID-19 and, at the same time, provides necessary care for patients with cancer.

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