Cancer in COVID-19 Times

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Abstract

Coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first reported to produce atypical pneumonia in Wuhan, China, in December 2019. This outbreak escalated very quickly due to the high transmission rate, and therefore, on March 11, 2020, it was declared a pandemic by the World Health Organization. COVID-19 caused a massive hospital overload worldwide and instigated urgent adjustments in resource allocation. Compared to the general population, cancer patients are considered to be at high risk of developing severe infection due to their immunocompromised status. The purpose of this review was to highlight the impact of the COVID-19 pandemic on cancer care, available guidelines, and recommendations.

Keywords: COVID-19, cancer, healthcare, pandemic

1. Introduction

Coronavirus disease 2019 (COVID-19) represented the latest threat to global health [1]. This respiratory disease was first reported in the Hubei Province of the People's Republic of China. The outbreak was hereafter identified to be caused by the novel coronavirus- severe acuterespiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. On March 11, 2020, the COVID-19 outbreak was declared a pandemic [3].

Coronaviruses consist of four subfamilies of enveloped single-stranded RNA viruses that can infect both animals and humans. Alpha and beta-coronaviruses originate from bats. However, gamma and delta-coronaviruses are thought to come from birds and pigs [4]. This family of viruses was considered to infect only animals until the world witnessed an outbreak of acute respiratory syndrome (SARS) caused by SARS-CoV in
Guangdong, China, back in 2002 [5]. A decade after, Middle East respiratory syndrome coronavirus (MERS-CoV), another pathogenic coronavirus, was responsible for an endemic in the Middle East countries [6]. SARS-CoV, MERS-CoV, and also SARS-CoV-2 are members of the beta-coronaviruses subgroup [7]. One of the differences between them comes from the fact that SARS-CoV-2 is less deadly but with a higher transmission rate compared to SARS-CoV and MERS-CoV [8]. The median incubation period for SARS-CoV2 was reported to be 5.1 days, and it is expected that more than 97% of infected symptomatic patients develop their clinical manifestations within 12 days of infection [9].

The majority of patients with COVID-19 experience mild to moderate symptoms consisting of fever, cough, fatigue, ageusia, anosmia; other organ systems can also be affected. About 15% of them will develop severe pneumonia, and 5% will eventually develop ARDS (acute respiratory distress syndrome), multiple organ failure, or septic shock [10–12]. Worse outcomes of COVID-19 were connected to various comorbidities such as cardiovascular disease, hypertension, and also lung disease. Men were also suggested to suffer from a more severe disease than women. The infection with SARS-CoV-2 can activate both adaptive and innate immune responses. Hence, uncontrolled innate inflammatory response along with a weakened adaptive response can generate severe organ damage [13]. The treatment consists mostly of oxygen supplementation and symptomatic management. Different antiviral drugs have been tested with some clinical benefits [14].

By the time this paper was written, SARS-CoV-2 had infected more than 100 million individuals and killed more than 2 million worldwide [15]. The majority of the studies reported that most of the patients dying of COVID-19 had underlying comorbidities such as heart failure, type 2 diabetes, chronic kidney disease, COPD, obesity, and also cancer [16,17]. Cancer patients tend to have a dysregulated immune system generated by anti-tumor treatments, or cancer itself [18]. Consequently, further alterations of the immune response caused by SARS-CoV-2 may lead to poorer outcomes for this subcategory of patients [19].

COVID-19 pandemic changed all aspects of cancer care worldwide, including screening, diagnostic, and treatment options [20]. This review highlights the impact of the COVID-19 pandemic on cancer care, available guidelines, and recommendations.

2. Cancer patients and COVID-19

The significant number of patients infected with SARS-CoV-2 forced oncologists worldwide to re-organize all activities to protect oncological patients without endangering cancer outcomes [21]. Compared to the general population, cancer patients were repeatedly mentioned to be at a higher risk of infection due to the immunocompromised status caused by antineoplastic therapy, malignancy itself,
and also supportive medications like steroids. Furthermore, cancer patients usually have significant comorbidities, are often older (aged ≥60 years), and very frequently in contact with healthcare providers. Hence, this may result in severe complications, followed by unnecessary hospitalization, delay treatment, and worse outcomes [22].

As aforementioned, most of the cytotoxic drugs used in cancer treatment can lead to bone marrow suppression, which will result in neutropenia and thrombocytopenia, making patients more vulnerable. Early reports coming from retrospective studies in China stated that cancer patients were more susceptible to SARS-CoV2 infection, and they were also associated with a greater rate of complications. In their paper, Liang et al. reported for the first time that the risk of severe events (ICU admission, mechanical ventilation, or death) was about 3.5-fold higher in cancer patients with COVID-19 than non-cancer patients. Moreover, patients who had undergone surgery or chemotherapy in the past month also had a worse outcome with a higher risk of severe events [19]. First, the rate of cancer patients in the COVID-19 cohort highlighted above was higher than in the general population. Also, the small sample size (18 cancer patients) with variable disease course and treatment strategies is not sufficient to assume that cancer patients have a higher risk of COVID-19 [23]. Nonetheless, based on previous immunological studies, the cause of severe lung injury in COVID-19 was linked to cytokine storm and uncontrolled inflammatory reactions [24]. Cancer, on the contrary, was demonstrated to be associated with an impaired immune system correlated to immunosuppressive cytokines, malfunction of dendritic cells, increased population of immunosuppressive leucocytes [25]. A study from Wuhan, including 28 cancer patients diagnosed with COVID-19, reported a mortality rate of 28.6%. Patchy consolidations on CT (HR = 5.438, 95% CI 1.498-19.748, P = 0.010) and antitumor treatment administered within 14 days admission (HR = 4.079, 95% CI 1.086-15.322, P= 0.037) were correlated with a high risk of severe events. Interestingly, the study reported that 28.6% of the patients developed COVID-19 while hospitalized, which was considered nosocomial transmission (26). Another retrospective study, including 2051 COVID-19 patients (non-cancer, n=1959; cancer, n=93), compared the two groups' immunological features. The results showed that cancer patients had severely dysregulated immune responses, which are thought to account for their worse outcomes. The mortality rate was reported higher in the cancer cohort compared to non-cancer (24.7% vs. 10.8%) [27].

Conflicting data did not take long to arrive. A cohort study based on the COVID-19 and Cancer Consortium (CCC19) database claimed that cancer type, anticancer therapy, and recent surgery were not correlated with mortality. On the other hand, smoking status, age, male sex, underlying comorbidities, ECOG performance status ≥2, and taking azithromycin plus hy-
droxychloroquine were independent factors linked to increased 30-day mortality [28]. A cohort study from Gustave Roussy Cancer center consisting of 178 adult cancer patients diagnosed with COVID-19, identified a mortality rate of 17.4%, which was similar to the mortality rate of non-cancer patients admitted in the Paris area at the time [29]). Unlike the initial warnings regarding the possible synergy between COVID-19 pathogenesis and immunotherapy [30], this study did not report any detrimental effect with the use of immune checkpoint inhibitors, neither with hormone therapy and targeted therapy. Similarly, data from a cohort of lung cancer patients showed that PD-1 blockade was not correlated with worse outcome in COVID-19 [31]. However, the administration of systemic cytotoxic chemotherapy was associated with a worse outcome and a tendency to higher death risk. In patients with hematological malignancies, it was noticed a tendency towards severe COVID-19 (HR=1.80 (95% CI=0.91–3.55), also observed in other studies [32]. A German study showed a case fatality rate of 50% in patients suffering from hematological malignancies. However, the outcome might have been affected by the uncontrolled underlying disease. They also reported that after recovering from COVID-19, patients could safely restart anticancer therapies [33].

In response to the repeated question on whether chemotherapy could worsen COVID-19 outcome, the UKCCMP (UK Coronavirus Cancer Monitoring Project) showed that mortality from COVID-19 was not significantly influenced by chemotherapy or any other anticancer treatment but by male sex, age, and underlying comorbidities [34], results that were further confirmed by other publications [35,36]. It was, moreover, postulated that chemotherapy could decrease SARS-CoV-2 induced inflammation [37].

Most of the studies prior mentioned revealed that age is an independent predictor for both mortality and severe outcome in COVID-19 patients [28, 29, 34]. Likewise, the case fatality rate was reported to be higher in Italy compared to China because of the elderly population [38]. On the contrary, pediatric patients infected with SARS-CoV-2 are less affected by the disease than the adult population, mostly because of the differences between adaptive and innate immune responses in the two categories [39].

In cancer patients with COVID-19, the mortality rate was variable among studies from 11% [40] to 33%, the last one found in cancer patients with thoracic malignancies (TERAVOLT study) [41]. To date, one of the highest mortality rates, of 36%, was published in a retro-prospective French cohort study in patients with thoracic cancer [36]. Moreover, the study reported the risk factors associated with COVID-19 severity already mentioned in other datasets [28, 34, 42], such as age, male sex, ECOG PS, or comorbidities. The disparities regarding comorbidities, tumor types, performance
status, could explain the variations between the mortality rates postulated in literature.

As SARS-CoV-2 is a new human pathogen, there is insufficient knowledge regarding its possible tumorigenic capacity. Considering the similarities with SARS-CoV-1, which is known to interfere with the molecular pathways linked to carcinogenesis, future research could focus on the long-term implications of SARS-CoV-2 [43].

3. Recommendations and Vaccine development

Even if tremendous efforts have been made to provide appropriate healthcare for cancer patients, it is still a matter of debate whether to stop or to continue anticancer treatments. Countless guidelines and proper recommendations were published, hoping to help oncologists and patients in the battle against this virus. Healthcare professionals have the responsibility to guarantee that cancer patients are not exposed to SARS-CoV-2, knowing it is highly contagious.

In times of unprecedented medical crisis, oncology scientific societies promptly released guidelines to provide the best care possible for cancer patients. The Italian Association of Medical Oncology (AIOM) published a detailed guideline on March 13 [44], followed by the National Comprehensive Cancer Network (NCCN) on March 20 [45], and shortly after by the European Society of Medical Oncology (ESMO) [46]. The general policy of the European dedicated cancer centers (Institute Gustave Roussy, German Cancer Research Center, Istituto Nazionale dei Tumori di Milano, and Netherlands Cancer Institute) was to remain COVID-19 free. This strategy allows them to attend critical cancer patients, manage chemotherapy side effects, and also emergency surgeries. All non-urgent appointments, for routine follow-ups and surgeries, were postponed when possible. The consultation took place via telephone calls or web, whenever possible [47]. The ESMO multidisciplinary expert consensus published a series of statements available online that can be applied in many situations of uncertainties regarding cancer patients in COVID-19 times. It is generally accepted that cancer patients undergoing curative treatment should continue their therapeutic strategy despite the risk of SARS-CoV-2 infection. Delayed cancer treatment could be an option for early-stage diseases such as prostate, breast cancer, nonmelanoma skin cancer. Surgical treatment could be postponed in some cases, for example, in the case of early-stage breast cancer with ER-positive [46]. In cases with a high-risk of disease progression and patients with very aggressive malignancies, it is not recommended to delay cancer treatment, for example, colon cancer with obstruction, pancreatic cancer, small cell lung cancer, or ovarian cancer [46]. No matter what efforts are required, it is vital to ensure proper care for cancer patients. The most affected area in Italy, the Lombardy region, reported a diminished patient attendance for therapy in...
2020 compared to 2019. The radiological examinations were also significantly reduced compared to the past four years [48]. Delaying diagnosis and treatment in cancer patients may not be immediately estimated, but it could become a complex healthcare problem in the future.

In the past months, pharmaceutical companies, government agencies, and academics have worked tirelessly to develop a safe and effective vaccine [49]. Some studies have also focused on using vaccine adjuvants to improve the outcomes of vaccinations and therapeutic index [50]. It could be of great importance in immunocompromised patients, such as cancer patients, in which the COVID-19 vaccine may be less effective.

Nine months after COVID-19 was declared a pandemic, on December 21, 2020, following the EMA (European Medicines Agency) positive evaluation, the European Commission conceded CMA (conditional marketing authorization) for the BioNTech COVID-19 mRNA vaccine [51]. Its efficacy in the pivotal trial (NCT04368728) was at 95% (95% CI 90·3–97·6) with a good safety profile (52). On January 6, 2021, the Moderna COVID-19 mRNA vaccine was approved in the EU, showing a similar efficacy (94·1%, [89·3–96·8]) to the BNT162b2 vaccine [53]. Shortly after, the Vaccine AstraZeneca was also approved by the EMA on January 28, 2021 [54]. Given the unprecedented consequences of COVID-19 on healthcare systems worldwide, the approval of these first vaccines in the EU represents a key breakthrough in response to the COVID-19 pandemic. As the COVID-19 pandemic affected cancer patients' quality of life in many ways, ESMO started a Call to Action on January 08, 2021, to discern the importance of vaccinating all cancer patients, including those undergoing active anticancer treatments [55].

4. Conclusion

During these exceptional times, COVID-19 overwhelmed healthcare systems worldwide and caused important psychological consequences to the general population associated with social distancing, home restriction, stressful headline news. Cancer patients were exposed to the same, and, also, they had to face the news of a disease that could be terminal. Vaccination became a crucial element of the race towards normality in order to get their treatments back on schedule. The oncology communities had to predict changes in cancer assistance and the possible negative repercussions on cancer patients.

**Abbreviations:**
AIOM – Italian Association of Medical Oncology
ARDS – acute respiratory distress syndrome
Statements:

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