Treatment Decisions for Patients with Cancer during the COVID-19 Pandemic

Chris Labaki1, Solange Peters2, and Toni K. Choueiri1,3

Summary: Patients with cancer have been disproportionally affected by the COVID-19 pandemic, with high rates of severe outcomes and death. Similarly, treatment decisions in this vulnerable population have been altered to a major degree during the past year, with significant disruption of care reported. Although complex, therapeutic choices in patients with cancer in times of COVID-19 are critical, as they may save thousands of lives. A mounting body of evidence, in addition to clear recommendations by multiple international societies, can help oncologists decide appropriately the necessity to administer antineoplastic regimens, helping to avoid a surge in cancer-related deaths in the upcoming months.

As of March 2021, more than 127 million people have been affected worldwide by the COVID-19 outbreak, with more than 2.7 million resulting deaths. Many groups of patients at high risk of adverse outcomes have been identified, with patients with cancer representing one of the most vulnerable populations. This has been described in multiple large cohorts of oncologic patients who contracted COVID-19, with a mortality rate ranging between 12% and 28%, as compared with 2% in the general population (1–10). Among the different types of malignancies, patients with lung (7, 10) and hematologic (1, 2) cancers have experienced the highest death rates. This high propensity for adverse outcomes is potentially complicated by an increased risk of COVID-19 infection in patients with cancer, as outlined in some of the cohorts (11, 12). Demographic factors shared between COVID-19 and cancer are also predictive of worse outcomes and include male sex, smoking, medical comorbidities, poor performance status, and advanced age (refs. 1, 6, 7, 10, 13; Fig. 1). Additionally, laboratory variables indicative of an inflammatory state, such as D-dimers, C-reactive protein (CRP), a high absolute neutrophil count (ANC), and low platelets, have been linked to an increased mortality risk in patients with cancer and COVID-19 (14). From a biological perspective, oncologic patients present a higher risk of developing thrombosis (15) and display varying degrees of immunosuppression, due to either the intrinsic state of their disease and/or the type of systemic therapies employed (16). Similarly, severe COVID-19 has been associated with an increased risk of thrombotic events (17), termed COVID-19–associated coagulopathy, and immunosuppression has been well defined as a risk factor for adverse outcomes (18). Thus, the observed poor outcomes seen in patients with cancer during COVID-19 can be explained by a significant overlap between clinical and biological factors characterizing patients with cancer and risk factors for severe COVID-19 complications.

ANTINEOPLASTIC TREATMENTS AND OUTCOMES OF PATIENTS WITH CANCER AND COVID-19

Many therapeutic modalities currently used in patients with cancer exhibit cytotoxic and immunomodulatory properties, with an array of resulting adverse events. As shown in an international survey of more than 300 oncologists at the beginning of the pandemic, a significant proportion of participants considered that the use of certain regimens, including chemotherapy and immune-checkpoint inhibitors (ICI), may be unsafe during the pandemic (19).

Outcomes of patients with cancer and COVID-19 in relation to the receipt of various antineoplastic agents have been analyzed in a number of studies, providing evidence to help guide clinicians in their decision-making. In four large retrospective cohorts accounting for more than 2,500 oncology patients with COVID-19, the use of cytotoxic chemotherapy was associated with an increased risk of death (1, 5, 8, 10), though several studies did not corroborate these findings (Table 1). When evaluating targeted therapies as a potential risk factor, only one study out of five, comprising around 200 patients, showed worse outcomes (ref. 8; Table 1). Although these cumulative findings point to the safety of targeted therapies in patients with COVID-19, more substantiation is still warranted, as this category encompasses a wide variety of drugs, from B cell–depleting (e.g., rituximab) to other less immune-affecting (e.g., bevacizumab) agents. A recent exploratory analysis has shown that anti-CD20 therapy results in near-complete abolition of SARS-CoV-2–specific IgG and IgM responses, and that patients with cancer with defective humoral immunity are subject to worse outcomes (20). Additionally, another multicenter study identified a severe and prolonged course of COVID-19 in oncologic patients receiving B cell–depleting therapies, with a rapid clinical
benefit reported after the administration of convalescent plasma transfusion, further stressing the importance of a robust humoral immunity (21). From a biological standpoint, the use of ICIs during the pandemic raised serious concerns, and it has been hypothesized that ICIs could possibly shift the immune balance toward an increased inflammatory state (22), which is associated with poor outcomes in patients with COVID-19 (23). Only one study found an increased risk of severe disease in patients with cancer and COVID-19 receiving ICIs (ref. 24; Table 1). However, a subsequent study showed that confounding factors, including smoking status, must be taken into consideration, as they can influence to a great extent the interpretability of some positive associations (25). When considering endocrine therapies administered to patients with cancer, no study has thus far shown any increased risk of death or other adverse outcomes during COVID-19 infection. On the other side, it has been postulated that androgen deprivation therapy (ADT), used in the treatment of prostate cancer, could reduce the severity of COVID-19. This assumption is based on the observation that expression of TMPRSS2, a membrane-bound serine protease that plays a role in SARS-CoV-2 internalization and which is expressed in the lung tissue, is upregulated at the transcriptomic level by androgens (26). However, clinical studies evaluating this hypothesis have so far shown no effects of ADT on the outcomes of patients with prostate cancer and COVID-19 (27).

In addition to the above-stated findings, recently published data from the COVID-19 and Cancer Consortium (CCC19) provided a more in-depth analysis of the effects of different antineoplastic regimens on the outcomes of oncologic patients with COVID-19 (4). The analysis performed included more than 4,900 patients with cancer and COVID-19, and explored in a temporal trend the impact of different antineoplastic treatments.
Table 1. Cohorts of patients with cancer with COVID-19 infection and effect of antineoplastic regimens on patient outcomes

<table>
<thead>
<tr>
<th>Region</th>
<th>Region Int.</th>
<th>France</th>
<th>UK</th>
<th>Europe</th>
<th>Int.</th>
<th>Europe</th>
<th>France</th>
<th>USA</th>
<th>China</th>
<th>China</th>
<th>Italy</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>4,966</td>
<td>1,289</td>
<td>800</td>
<td>890</td>
<td>200</td>
<td>435</td>
<td>178</td>
<td>423</td>
<td>205</td>
<td>232</td>
<td>536</td>
</tr>
<tr>
<td>Types of cancer</td>
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<td>All</td>
<td>All</td>
<td>All</td>
<td>Lung</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Cytotoxic chemotherapy</td>
<td>Increased risk of deatha</td>
<td>Increased risk of death</td>
<td>Increased risk of death</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td>Increased risk of death</td>
<td>NS</td>
<td>Increased risk of death</td>
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<tr>
<td>Targeted therapies</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td>—</td>
<td>NS</td>
<td>—</td>
<td>Increased risk of death</td>
<td>—</td>
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<td>Immune-checkpoint inhibitors</td>
<td>NS</td>
<td>—</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
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<td>NS</td>
<td>NS</td>
<td>—</td>
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<td>NS</td>
<td>—</td>
<td>NS</td>
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</tr>
</tbody>
</table>

Abbreviations: Int., international; NS, nonsignificant.

aOnly recent therapy (<4 weeks) from COVID-19 infection.
systemic therapies on COVID-19 outcomes. It showed specifically that recent chemotherapy, administered within four weeks of symptomatic infection, may be associated with an increased mortality risk, though unmeasured confounding factors are always a possibility. Conversely, the receipt of cytotoxic chemotherapy more than four weeks and up to months before contracting viral infection did not affect patient outcomes. As for targeted therapies, no increased risk of mortality was identified in patients with cancer administered regimens in the time period extending from 0 to 3 months preceding symptomatic COVID-19 infection. Ideally, this should be further evaluated in a separate fashion for each type of targeted therapy, especially for B cell-depleting regimens. Similarly for patients receiving ICIs and endocrine therapies, no increased risk of severe COVID-19 outcomes was identified throughout all the time periods considered. Overall, these results show that the biological interactions between the different categories of antineoplastic drugs, SARS-CoV-2, and cancer are quite complex and remain elusive. More evidence is still needed to dissect clearly the corresponding clinical implications before modifying the current evidence-based standards of care.

Patients with hematologic malignancies can be subject to other more aggressive therapeutic strategies. These are represented most importantly by autologous and allogeneic hematopoietic stem cell transplant, leading to severe immunosuppression. One cohort reported the outcomes of transplant recipients infected by COVID-19 and showed a high mortality rate, exceeding 30% (2). In light of the current pandemic, the guidelines of the American Society of Transplantation and Cellular Therapy and the National Institute for Health and Care Excellence (NICE) have stressed the safety of recipients in both pre- and post-transplant periods, with the necessity of performing polymerase chain reaction tests at defined time points and the importance of strict isolation (28, 29). The rationale behind these rigorous measures derives from the limited evidence about SARS-CoV-2 infection in transplant recipients (2), and from previous studies showing high incidence and mortality rates of other respiratory viruses, such as respiratory syncytial virus and influenza A, in these patients (30, 31). Consequently, such approaches can help guarantee patients’ safety without having to compromise the administration of these potentially curative modalities.

**DISRUPTION TO ONCOLOGIC CARE DURING THE COVID-19 PANDEMIC AND POTENTIAL CONSEQUENCES**

During the current pandemic, another major issue facing patients with cancer is the disruption experienced in oncologic care. This has been reported in two large U.S. cancer centers, with a significant drop in in-person visits and challenges in telehealth adoption by specific vulnerable patients. In fact, Black and Hispanic patients were less likely to have an increase in telehealth utilization and were more likely to develop COVID-19 infection compared with white patients (32). Irrespective of demographic factors, a recent international survey in oncologists showed that the administration of antineoplastic regimens was delayed or canceled in substantial proportions of patients with cancer, due to pandemic-related matters (33). This was further confirmed in a large retrospective analysis of healthcare services administered by institutional and private providers, which showed a significant drop in the billing frequency of the most commonly prescribed oncology drugs (34). Not surprisingly, the pandemic also affected cancer screening, as recently reported in one healthcare system in the northeastern United States (35) and in a large-scale national study (34), with drop rates as high as 70% during the early stages of the pandemic. In a modeling study based on England’s national cancer registries, delays in cancer diagnosis and subsequent management due to COVID-19 have been shown to significantly affect patient survival (36). More specifically, delays in the care of gastrointestinal and oropharyngeal cancers appeared to result in the highest attributable lives lost, whereas prostate and thyroid cancers showed the lowest survival reduction (36). This clearly outlines the large impact of COVID-19 on treatment decisions in the oncologic field. In its guidelines on cancer patient management during the pandemic, ESMO stresses the importance of prioritizing therapy administration in patients who are expected to derive significant benefit from it in terms of survival outcomes or improvement of quality of life. A stratification of patients with cancer across three priority levels is proposed, based on the assessment of the importance or urgency of the planned interventions and the risk of contracting COVID-19. This approach is applied to multiple cancer types, with a detailed description based on disease stage and the type of intervention planned. Furthermore, an international multidisciplinary consortium was established and expert consensus statements were published concerning critical topics in management of patients with cancer (37). The main statements emphasized the need to continue potentially lifesaving antineoplastic regimens, such as those administered in the neoadjuvant or adjuvant setting. In its recommendations regarding cancer treatment and supportive care during the COVID-19 pandemic, the American Society of Medical Oncology similarly asserted that withholding critical anticancer or immunosuppressive therapy is not recommended. It also emphasized the importance of rigorously assessing the balance between interrupting antineoplastic treatment and the risk of adverse COVID-19 outcomes.

Among the therapeutic modalities delayed or canceled due to COVID-19, surgery appeared to be most affected according to a multinational survey of oncologic practices (33), with a relative decrease in prostatectomy, colectomy, and mastectomy rates of more than 50% described in the United States (34). In a simulation study evaluating the impact of oncologic surgery deferral based on national observational data, even modest delays in cancer surgery could result in significantly reduced survival, with the highest death rates reported in gastrointestinal, urothelial, and ovarian cancers in comparison with other malignancies (38). This finding was further confirmed in a large meta-analysis reporting that surgery delay by 12 weeks could result in substantial alterations in overall survival in breast, lung, and colon cancers (39). One global predictive modeling system estimated 37% of cancer operations to be canceled or postponed (40), stressing the importance of...
recovery plans and implementation of strategies to restore surgical activity safely and mitigate any potential lost lives. To help guide decision-making during the present pandemic, the Society of Surgical Oncology has created a list of disease-specific resources, regularly updated based on the latest available evidence. The necessity of timely surgical interventions in multiple cancer types is described across the different stages of disease, and alternative approaches are proposed in selected cases.

CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, adequate treatment decisions in oncologic practice during the COVID-19 pandemic are of utmost importance, as they offer lifesaving possibilities for many patients. Multiple factors must be taken into account, in a conservative perspective, in such complex scenarios, including the types of drugs or interventions available, the local prevalence of SARS-CoV-2 infection rate, the availability of adequate resources for the prevention and management of potential COVID-19 infection in this vulnerable population, the severity of the infection, and, most importantly, the expected benefits from cancer therapy. The choices to be made can affect to a major extent oncologic practice and cancer-related outcomes in the near future and must be tailored accordingly based on the available evidence and the specific considerations for each patient with cancer. The different challenges faced during the past year in relation to cancer care are a source of lessons for potential future pandemics. Importantly, these relate to the appropriate prioritization of therapeutic strategies in patients with cancer to ensure optimal oncologic outcomes, particularly in the curative setting, and the need to maintain adequate screening procedures, especially in high-risk patients, even during critical times.

Authors’ Disclosures

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