

REVIEW

Supportive care in patients with cancer during the COVID-19 pandemic

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Cancer care has been profoundly impacted by the global pandemic of severe acute respiratory syndrome coronavirus 2 disease (coronavirus disease 2019, COVID-19), resulting in unprecedented challenges. Supportive care is an essential component of cancer treatment, seeking to prevent and manage chemotherapy complications such as febrile neutropenia, anaemia, thrombocytopenia/bleeding, thromboembolic events and nausea/vomiting, all of which are common causes of hospitalisation. These adverse events are an essential consideration under routine patient management, but particularly so during a pandemic, a setting in which clinicians aim to minimise patients' risk of infection and need for hospital visits. Professional medical oncology societies have been providing updated guidelines to support health care professionals with the management, treatment and supportive care needs of their patients with cancer under the threat of COVID-19. This paper aims to review the recommendations made by the most prominent medical oncology societies for devising and modifying supportive care strategies during the pandemic.

Key words: COVID-19, symptom management, supportive care

INTRODUCTION

Cancer care has been profoundly impacted by the global pandemic of the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), resulting in unprecedented challenges. In an effort to understand the impact of COVID-19 and to provide guidance for clinicians in their efforts to overcome the challenges of the pandemic, the oncology community is committed to collecting data and sharing information at an exceptional rate. The number of scientific publications on PubMed about COVID-19 has increased exponentially,¹ and as of the middle of October 2020, almost 60 000 publications related to COVID-19 and cancer were listed.² The necessity to expedite data acquisition about COVID-19 and cancer has placed pressure on researchers and authors.

Therefore, interpretation of rapidly published data necessitates caution, with context provided.

Patients with cancer are more likely to develop COVID-19 than those without cancer and are also more likely to experience severe complications than patients without cancer who develop COVID-19.³⁻¹¹ Moreover, the need to modify effective cancer treatments in response to SARS-CoV-2 infection represents additional potential risk.¹² The impact of COVID-19 also appears to be greater for certain types of cancer; for example, patients with haematological malignancies represent a high-risk group, based on age, compromised immune function and risk of infections.¹³

Supportive care is an essential component of cancer treatment, seeking to prevent and manage chemotherapy complications such as febrile neutropenia (FN), anaemia, thrombocytopenia/bleeding, thromboembolic events and nausea/vomiting, all of which are common causes of hospitalisation. As such, these adverse events are an important consideration under routine patient management, but particularly so during a pandemic, a setting in which clinicians aim to minimise patients' risk of infection and need for hospital visits. Although studies regarding chemotherapy complications in patients with cancer and COVID-19 are limited, a study of 63 patients with cancer and COVID-19

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reported a significantly higher mortality rate in patients with neutropenia.¹⁴

International and national cancer consortia have been collecting data on cancer care and real-time outcomes during the pandemic.^{5,6,15-18} In addition, professional medical oncology societies have been providing updated guidelines to support health care professionals with the management, treatment and supportive care needs of their patients with cancer under the threat of COVID-19.¹⁹⁻²⁴ For example, the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) all suggest reducing the FN risk threshold for the use of prophylactic granulocyte colony-stimulating factor (G-CSF) to include lower-risk patients receiving chemotherapy regimens that have a low or intermediate risk of developing FN.^{20,24-26}

This paper provides an overview of the recommendations made by the most prominent medical oncology societies for devising and modifying supportive care strategies during the COVID-19 pandemic.

CANCER TREATMENT DURING THE COVID-19 PANDEMIC

Given that patients with cancer receiving chemotherapy and other treatments are susceptible to developing infections, medical oncology societies and organisations worldwide are providing invaluable guidance on the management of solid and haematological malignancies in response to the COVID-19 pandemic. The volume of literature relating to new guidance is too extensive to summarise in a single manuscript. Nevertheless, it is underpinned by a common need to achieve several key

goals. For patients who currently do not have COVID-19, there is a requirement to reduce the risk of exposure to SARS-CoV-2 and minimise the negative impact on cancer outcomes. For patients with COVID-19, the negative impact on cancer outcomes should be minimised while limiting the risk of COVID-19 complications and reducing the risk of spread within the health care facility. General considerations for managing cancer care in the presence or absence of COVID-19 are included in Table 1. Treatment decisions should be based on an analysis of risks and benefits, made in consultation with patients. Key factors include the presence or absence of SARS-CoV-2 infection, the type and stage of cancer, and treatment intent (palliative or curative).

CARING FOR PATIENTS WITH CANCER DURING THE PANDEMIC WHO DO NOT HAVE COVID-19

Since patients with cancer are at increased risk of contracting SARS-CoV-2 and developing COVID-19, there is a need to manage at-risk patients with cancer at the ‘pre-infection’ stage. This has been the subject of many published expert opinions since the start of the COVID-19 outbreak.²⁷⁻³⁵ These are not evidence-based, in the sense that they have not been developed following prospective studies. Nonetheless, they can help inform clinicians on the most appropriate strategies to reduce the risk of exposure to SARS-CoV-2. However, it should be noted that such publications include recommendations only and are not intended to replace either institutional policies and guidance or the judgment of clinicians making decisions on a case-by-case basis.

Table 1. Considerations for managing cancer care in patients with and without COVID-19

Patient group	Goal	Actions
Patients with cancer without COVID-19 infection; no prior infection	Reduce risk of exposure to SARS-CoV-2 Minimise negative impact on cancer outcomes	Discuss options and understand the patient’s perspectives. Use telemedicine for consultations and remote monitoring. Continuous monitoring for COVID-19 signs and symptoms to prevent infection spread within clinic/hospital. Switch to local laboratory for blood analyses instead of a high-volume hospital (confirm unexpected results in reference laboratory). Modify or postpone cancer treatment; switch from intravenous to oral formulation if available. Minimise the risk of hospitalisation due to complications, including neutropenia/infection, anaemia, thrombocytopenia/bleeding, thromboembolic events and CINV. Administer supportive care in outpatient setting, where possible, or use long-acting formulations.
Patients with cancer with COVID-19	Minimise negative impact on cancer outcomes Minimise complications of COVID-19 Reduce risk of spread of SARS-CoV-2 within health care facility	Discuss risks and benefits of continuing or modifying cancer therapy with the patient. Administer supportive care in outpatient setting, where possible, or use long-acting formulations. Solid tumour patients: adjuvant therapy with curative intent likely should proceed. For patients with metastatic disease, treatment delays may lead to worsening performance status and loss of the window to treat. Considerations should include how such delays may lead to admission for symptom palliation, which further stresses inpatient resources. Cancer surgery is not considered elective, but surgical intervention needs prioritisation; changes to usual practice are necessary. Patients with aggressive haematological malignancy: stem cell transplantation and cellular immunotherapies provide curative treatments for many with aggressive disease and in many cases cannot be delayed. Travel bans limit access to international donors for allogeneic stem cell transplantation; cryopreservation of donor products is recommended.

CINV, chemotherapy-induced nausea and vomiting; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Proposed strategies should involve prioritisation of patients according to the urgency of their need for treatment. For example, some patients may require immediate treatment; other patients may not require urgent therapy, but should start treatment before the pandemic is over; for others it may be appropriate to have treatment deferred indefinitely without adversely impacting clinical outcomes.^{35,36} For patients requiring treatment during the pandemic, cancer therapy modifications may be required. This may involve dose delay, home care, alternative treatment regimens, extended intervals between treatment cycles and the use of treatments that can be administered more rapidly. However, any modifications to treatment should be evidence-based. Regarding acceptable dose delay, this should be considered according to the type of tumour.³⁷ Many health systems separate patients with cancer into health care facilities isolated from suspected or diagnosed COVID-19 patients, to reduce the risk of nosocomial COVID-19 spread.³⁸ This may involve moving treatment clinics and staff from acute care hospitals into standalone facilities left unused due to the COVID-19 pandemic; for example, in Bristol, UK, infusion chemotherapy has been delivered in adapted dental treatment facilities.³⁹ Providing home infusion of chemotherapy may be an option in certain countries and could be supervised by telemedicine.^{37,40} The level of treatment complexity and the potential for complications should be considered before starting home infusions.

There is also a need for supportive care interventions to minimise hospitalisation risk due to complications, including neutropenia/infection, anaemia, thrombocytopenia/bleeding, thromboembolic events and chemotherapy-induced nausea/vomiting (CINV). Supportive care interventions play a crucial role in reducing the risk of complications associated with cancer therapy, which, in the COVID-19 era, is particularly important for reducing patient interactions with health care systems and keeping patients well. It is important to note that some of the recommendations for managing haematopoietic cancer therapy complications described in the following subsections would be considered 'off-label' based on the current prescribing information for some interventions. A summary of the recommendations is provided in [Table 2](#).

PATIENTS WITH CANCER WHO HAVE COVID-19

In patients with cancer who have confirmed or suspected COVID-19, it may be necessary to delay or change the sequence of immunosuppressive treatments based on evaluation of risks and benefits of a particular treatment given in a specific regimen, prevent neutropenic complications and reduce the risk of thrombotic and/or haemorrhagic complications.^{26,41}

There are also implications based on treatment intent. In the curative setting, the main goals of treatment are to maintain the dose density of treatment. In the palliative setting, the main aim is to avoid hospitalisation due to complications such as FN.

SPECIFIC RECOMMENDATIONS

Neutropenia

FN is a severe complication of cancer chemotherapy that typically requires emergency hospital treatment. Fatalities can arise due to infection/sepsis, as well as chemotherapy delays, dose reductions or discontinuations that impact cancer treatment outcomes.⁴² Patients with FN have a high risk of infection-related mortality and of requiring secondary care. Therefore, FN is an essential consideration under normal circumstances, but particularly during a pandemic where clinicians strive to keep patients infection-free and out of the hospital. Early in the European phase of COVID-19, the UK National Institute for Health and Care Excellence warned oncologists that 'symptoms of COVID-19, neutropenic sepsis and pneumonitis may be difficult to differentiate at initial presentation' and proposed increased attention be focused on avoiding neutropenia and its complications.⁴³

Prophylactic use of G-CSF reduces the incidence of FN and infection-related mortality and allows the relative dose intensity of chemotherapy to be maintained.⁴⁴ Established guidelines (before the emergence of the COVID-19 pandemic) recommend prophylactic use of G-CSF when the overall risk of FN from the prescribed chemotherapy regimen is $\geq 20\%$.⁴⁵⁻⁴⁸ Individual risk factors (such as age ≥ 65 years, presence of selected comorbidities and poor performance status) for FN are included in these international guidelines for the prophylactic use of G-CSF.⁴⁵⁻⁴⁸ They are validated using a claims database including data from 160 304 patients⁴⁹ and through a systematic review.⁵⁰ Among the five most common cancer types and regimen combinations, the absolute FN risk is close to or exceeds the 20% risk threshold for most patients with one or more risk factors, compared with those with no risk factors.^{49,50}

There are several ways in which the risk of neutropenic complications can be reduced, including neutropenia prevention. ESMO also recommends that in patients with solid tumours not treated for cure, regimens unlikely to induce FN should be considered and that there should be substantial evidence to support using regimens with a greater risk of neutropenia.²⁵ Neutropenia can also be prevented by reducing the FN risk threshold for the use of G-CSF to include lower-risk patients, thereby administering G-CSF to more patients receiving chemotherapy. Long-acting treatments (e.g. pegfilgrastim), particularly in solid tumours, may be used to provide the necessary coverage while reducing contact with health care professionals. Prophylactic antibiotics can also be used to reduce infections if patients do become neutropenic. However, this approach is controversial since it may lead to antibiotic resistance, which further complicates patient management.⁵¹ Hence most guidelines now recommend the use of prophylactic G-CSF over prophylactic antibiotics. ASCO, ESMO and NCCN updated recommendations suggest expanded use of prophylactic G-CSF to include patients receiving chemotherapy regimens with

Table 2. Summary of recommendations for the supportive care of patients with cancer during the COVID-19 pandemic

Complication	Recommendations
Neutropenia	<ul style="list-style-type: none"> • Prophylactic antibiotics may be used to reduce the risk of infections if patients become neutropenic. • Expand antibiotic prophylaxis to mitigate potential delays in emergency visits for patients who develop fever (ESMO). • Use of steroids to be reduced, if possible (ESMO). • Use long-acting treatments, e.g. pegfilgrastim. • Patients with solid tumours not treated for cure should ideally receive regimens unlikely to induce FN and only receive regimens with a greater risk of neutropenia if there is substantial supporting evidence (ESMO). • Expand use of prophylactic G-CSF to include patients receiving chemotherapy with an intermediate risk of FN (>10%). • Extend the use of G-CSF to all patients, not just those with risk factor complications, if patients not previously on G-CSF develop FN (NCCN). • Outpatient administration of G-CSF is recommended for lower-risk patients (ESMO). • Self-administration is recommended to reduce the frequency of outpatient visits, or alternatively, use long-acting agents in patients with solid tumours. • Assess potential for neutropenic status in febrile patients using telemedicine or telephone calls to determine whether an assessment in the clinical or ED is required (ASCO). • In patients with known neutropenic fever, follow standard guidelines for care of neutropenic patients, regardless of COVID-19 status. • Rapid COVID-19 testing is required to determine the suitable level of PPE and location for continued care. In the absence of rapid testing, the patient should be managed under the presumption of COVID-19 infection. • Consider expanding the indication for G-CSF after chemotherapy to reduce the risk of FN (ESMO) • The benefits of treatment with G-CSF outweigh the theoretical risk that G-CSF may cause further harm in patients with active COVID-19.
Anaemia and iron deficiency	<ul style="list-style-type: none"> • ESAs can be considered for prophylactic use if serious/symptomatic cancer or treatment-related anaemia is expected. • A revised haemoglobin threshold of <7 g/dl was suggested to trigger the need for a rapid haemoglobin increase (ESMO). • Use the lowest dose of ESA to avoid transfusion (NCCN). • Adopt a series of measures if blood supply is limited: use limited blood draws (reducing frequency and volume); utilisation of iron infusions in improving response to response to ESAs with transferrin saturation <50%, ferritin <800; assessment of baseline values for B12 and folate, and consideration of nutritional supplements B12 500-1000 µg daily and folate 1 mg daily (NCCN).
Thromboembolic events and thrombocytopenia-related complications	<ul style="list-style-type: none"> • Prophylaxis of thromboembolic events should be continued according to existing guidelines (ESMO). • If there is a shortage of blood supply or suitable human leukocyte antigen-matched units, prophylactic antifibrinolytics should be considered for patients with low platelet counts (<10 000/µl) (NCCN). • Thrombopoietin mimetics should be considered in patients with severe thrombocytopenia after chemotherapy. • Patients receiving chemotherapy through an implanted port should be considered for prophylaxis and outpatient management is preferable. • All patients hospitalised with COVID-19 should receive thromboprophylaxis with low molecular weight heparin or fondaparinux (patients with renal impairment should receive unfractionated heparin) (ESMO). • Drug interactions with oral anticoagulants and medications tested for use against COVID-19 should be considered.
Chemotherapy-induced nausea and vomiting	<ul style="list-style-type: none"> • A generous antiemetic prophylactic regimen should be prescribed for any patient at risk of emesis to lower the risk of additional clinical visits and suffering. Choice of regimen is dependent on emetogenic potential and individual risk factors (ESMO).

Guideline sources are indicated in parentheses.

ASCO, American Society of Clinical Oncology; COVID-19, coronavirus disease 2019; ED, emergency department; ESA, erythropoiesis-stimulating agent; ESMO, European Society for Medical Oncology; FN, febrile neutropenia; G-CSF, granulocyte colony stimulating factor; NCCN, National Comprehensive Cancer Network; PPE, personal protective equipment; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

an intermediate risk of FN (>10%).^{20,24-26,52} NCCN suggests that therapeutic use of G-CSF should be extended if patients not previously on G-CSF develop FN, to include all patients, not just those who have a risk factor for complications.²⁴ ESMO notes, however, that expanding G-CSF to lower-risk patients may require additional visits to the outpatient clinic,²⁵ while NCCN advice suggests self-administration to reduce the frequency of outpatient visits, or alternatively, use of long-acting agents, in those with solid tumours.²⁴

ASCO recommendations suggest that telemedicine or telephone calls be used to evaluate the potential for neutropenic status in the febrile patient, to determine whether a patient requires assessment in the clinic or emergency department.^{20,26} In patients with known neutropenic fever, standard guidelines for neutropenic patient care should be followed, regardless of COVID-19 status. Rapid COVID-19

testing should be used to determine the level of personal protective equipment necessary for caregivers and the appropriate location for continued care. In the absence of rapid testing, the patient should be managed following standard guidelines for patients with neutropenic fever under the presumption of COVID-19 infection.

Despite controversy, ESMO guidelines propose expanding antibiotic prophylaxis to mitigate potential delays in emergency visits for patients who develop fever.²⁵ ESMO also recommends that the use of steroids be critically reviewed and reduced if possible.²⁵

The crucial role of expanded access to G-CSF in cancer is to prevent neutropenia and maintain anticancer treatment dose intensity. Guidelines emphasise that primary prophylaxis with G-CSF is more effective than withholding use until secondary prophylaxis (prescribing G-CSF after a FN episode or dose delay through myelosuppression) because the

absolute risk of FN is most significant in the first cycle of chemotherapy.⁵³ There is little evidence to support prescribing G-CSF at the time of acute neutropenic sepsis.⁵⁴ Despite this, ASCO guidelines recommend that complicated FN cases should be treated with G-CSF.²⁰

Regarding neutropenia prophylaxis in patients with cancer with COVID-19, ESMO guidelines note that the theoretical concern that G-CSF may cause further harm in patients with active COVID-19, due to its potential to augment the production of inflammatory cytokines, does not outweigh the benefit of treatment.²⁵ It should be noted that prescribing information for G-CSFs and the existing NCCN guidelines include a warning on the use of G-CSF in patients with acute respiratory distress syndrome due to rare pulmonary adverse events, in particular, interstitial lung disease following G-CSF administration.^{24,47}

Anaemia and iron deficiency

Anaemia and iron deficiency are frequent complications in patients with cancer, particularly those receiving chemotherapy.^{55,56} Red blood cell transfusion is recommended for the treatment of severe [haemoglobin (Hb) <7-8 g/dl] anaemia⁵⁷; however, this requires hospitalisation, and transfusion itself is associated with an increased risk of infections. While it is unlikely that SARS-CoV-2 can be transmitted through allogeneic blood transfusion, this needs to be fully determined.⁵⁸ The COVID-19 pandemic has also limited blood donation availability, with donation centres in many areas of the world closing and donors quickly diminishing; this has created pressure to restrict transfusion further.^{33,58,59} Updated recommendations to manage anaemia during the pandemic are based on avoidance of transfusion and preservation of blood products during a time of limited donor access and reduced blood supply.^{20,24-26} ASCO suggests that erythropoiesis-stimulating agents (ESA) be considered for prophylactic use if serious/symptomatic cancer or treatment-related anaemia is anticipated.^{20,26} ESMO updated guidance suggests an Hb threshold of <7 g/dl to trigger the need for a rapid Hb increase (2018 guidelines⁵⁷ indicate 7-8 g/dl).²⁵

ESMO and NCCN reiterate the risk of thrombosis with ESA use^{24,25}; NCCN also includes a suggestion to use the lowest ESA dose to avoid transfusion, in line with currently approved labels for these medicines.²⁴

NCCN includes considerations for situations when blood supply is severely limited, recommending the adoption of guidelines usually reserved for patients who refuse blood transfusions, including limited blood draws (reducing both frequency and volume); utilisation of iron infusions in improving response to ESAs with transferrin saturation <50%, ferritin <800; assessment of baseline values for B12 and folate and consideration of nutritional supplements B12 500-1000 µg daily and folate 1 mg daily.²⁴

ASCO, ESMO and NCCN guidelines do not include any additional recommendations regarding anaemia and iron deficiency in patients with cancer who have COVID-19; recommendations made for patients with cancer, but without COVID-19, also apply to these patients.^{20,24-26}

Thromboembolic events and thrombocytopenia-related complications

The risk of thromboembolic events is substantially increased in patients with cancer, especially older patients and those with major medical comorbidities (including pulmonary disease).⁶⁰ The risk of venous thromboembolism (VTE) in patients with cancer and COVID-19 appears to be most significant in those on active systemic treatment, most notably in those with progressive malignancy.⁶¹ The risk of VTE in patients with cancer with COVID-19 is further increased in patients requiring hospitalisation, especially in those admitted to the intensive care unit. In the light of COVID-19, ESMO recommendations note that prophylaxis of thromboembolic events should be continued according to existing guidelines.²⁵ ASCO does not include guidance related to thromboembolic events and thrombocytopenia in the COVID-19 guidance.^{20,26}

NCCN recommendations focus on thrombocytopenia, with a reduced threshold for transfusion proposed.²⁴ Prophylactic antifibrinolytics should be considered for patients with low platelet counts of <10 000/µl when there is a shortage of blood supply or suitable human leukocyte antigen-matched units. Thrombopoietin mimetics should be considered in patients with severe thrombocytopenia after cancer chemotherapy.

Consideration should also be given to preventing thrombosis in patients receiving chemotherapy through an implanted port; outpatient management is preferable and thromboprophylaxis (e.g. with low molecular weight heparin or factor Xa inhibitors) may be prudent.

Patients with COVID-19 generally show changes in coagulation parameters and associated complications, including disseminated intravascular coagulation (associated with worse prognosis), thrombocytopenia (typically mild, but cases of severe manifestation have been described) and a potential higher risk of VTE.^{62,63} The updated ESMO guidelines recommend thromboprophylaxis with low molecular weight heparin or fondaparinux for all patients hospitalised with confirmed COVID-19, or unfractionated heparin in critically ill patients with substantial renal impairment.²⁵ When oral anticoagulants are used, possible drug interactions with medications that are tested for use against COVID-19 have to be considered.²⁵ This recommendation is consistent with other published opinions and recommendations.^{64,65} The role of full anticoagulation in severely ill patients with COVID-19 remains controversial at the time of this writing.

CINV

Poorly controlled CINV is associated with higher rates of unscheduled clinic visits, increased needs for intravenous hydration and emergency admissions.⁶⁶⁻⁶⁸ During the COVID-19 pandemic, every visit to health care facilities increases the potential for nosocomial spread and represents another opportunity for optimised supportive care to deliver essential benefits. Guidelines for preventing CINV from ASCO, ESMO and the Multinational Association of

Supportive Care in Cancer (MASCC) emphasise that optimal control is associated with the appropriate use of three classes of medicines; serotonin (5-HT₃) receptor antagonists (RAs), corticosteroids and neurokinin 1 RAs.⁶⁹⁻⁷¹ ESMO recommends that if there is any doubt of the risk of emesis, a generous antiemetic prophylactic regimen should be prescribed to lower the risk of additional clinical visits and suffering.²⁵ Such a regimen should be chosen according to the emetogenic potential and individual risk factors, and could include a 5-HT₃ RA plus a neurokinin 1 RA plus dexamethasone (single dose on the day of treatment) plus olanzapine.²⁵ Regarding the choice of 5-HT₃ RA, the long-acting agent palonosetron may be considered due to its apparent improved efficacy in the delayed phase of CINV, particularly when sparing the dexamethasone dose.²⁵

Other considerations in onco-haematology

Haematological malignancies. Patients with haematological malignancies represent a high-risk group, on account of age, compromised immune function and risk of infections. For example, patients with lymphoid malignancies such as follicular lymphoma (FL) and chronic lymphoid leukaemia (CLL) have an increased risk of infection due to hypogammaglobulinemia.^{72,73}

Approaches to managing patients with lymphoid malignancies who have an increased risk of infection due to hypogammaglobulinemia and corticosteroid use should include consideration of less intensive and less cytotoxic regimens, together with optimising clinic visits in outpatient centres, for example, monthly treatment.^{23,72,74} ESMO states that although current immunoglobulin replacement therapy does not contain specific antibodies against SARS-CoV-2, products containing specific antibodies are expected later in the pandemic.²⁵ The recommendations state that secondary immunodeficiency can represent an indication for immunoglobulin replacement therapy as a protection against infections. The indication should be viewed in the context of the existing guidelines, and benefits should be weighed for the individual patient against the risk of frequent clinic visits.^{23,25,74}

Immune therapies. There is a strong physiological basis for concerns regarding COVID-19 and immune cancer therapies. Patients with active SARS-CoV-2 infection can present with lymphopenia and T-cell exhaustion, while persistent SARS-CoV-2 infection inhibits the wider immune system.⁷⁵ While immune-based treatments can restore a patient's immunocompetence against cancer, such therapies may have a detrimental effect on protecting the patient from infection. In some patients, particularly children, COVID-19 has been associated with a hyperinflammatory systemic inflammatory response syndrome (SIRS).⁷⁶ Hyperinflammatory SIRS can accompany other severe infections such as bacterial septicaemia, but is usually reduced by a compensatory anti-inflammatory response syndrome.⁷⁷

Anti-CD20 antibodies such as rituximab, obinutuzumab and ofatumumab are essential components of anticancer regimens, which are highly effective in patients with various

haematological malignancies.⁷⁸ However, as anti-B-cell treatments, these agents cause cytotoxicity through direct, complement-mediated and antibody-dependent mechanisms, leading to severe immunodeficiency and, as such, have implications for risk of infection, including the development of hypogammaglobulinemia and lymphopenia.^{79,80} Although published evidence regarding anti-B-cell treatments in patients with cancer and COVID-19 is very limited, a recent case report described how two patients treated with rituximab for haematological malignancies died due to respiratory failure following SARS-CoV-2 infection.⁸⁰ Anti-CD20 antibodies are also used as disease-modifying treatments in multiple sclerosis. Early reports from regions in Italy and Spain with a high prevalence of COVID-19 suggest that anti-CD20 agents may have a potentially protective effect for suppressing symptoms and reducing severe complications of COVID-19.^{81,82} Reassuringly for patients on anti-B-cell treatments, people with genetic B-cell deficiencies can recover from COVID-19 infection, while some patients have recovered in the apparent absence of anti-COVID-19 antibody responses.⁸³⁻⁸⁵

The CD19-targeted chimeric antigen receptor T-cell (CAR-T) therapeutic agent, tisagenlecleucel, is an efficacious treatment in B-cell acute lymphoblastic leukaemia and diffuse large B-cell lymphoma (DLBCL). However, CAR-T therapy is associated with an inability to elicit antibody responses in certain infectious diseases, with recipients often treated as inpatients due to the potential for rapid development of a cytokine release syndrome.⁸⁶ To date, we are unaware of any published reports of patients with cancer with COVID-19 receiving CAR-T therapy.

Immunodeficiency associated with anti-B-cell treatment has implications for the use of rituximab, ofatumumab, obinutuzumab and tisagenlecleucel in patients with cancer during the COVID-19 pandemic. The American Society of Hematology (ASH) suggests avoiding the use of anti-B-cell treatment, especially in combination with other targeted treatments, in patients with CLL and small lymphocytic lymphoma.⁷⁴ ASH and ESMO both recommend delaying anti-B-cell maintenance treatment in patients with FL,^{25,87} while ASH recommends using anti-B-cell treatment in patients with DLBCL.⁸⁸ As such, it is necessary to consider the use and evaluate the benefits and risks of rituximab, ofatumumab, obinutuzumab and tisagenlecleucel in each patient while considering curative treatment goals.

The development and approval of immune checkpoint inhibitors (ICIs) have revolutionised the treatment of several types of cancer. While immune-related adverse events with ICIs are largely non-severe and manageable,⁸⁹ an estimated 7% require hospital admission.⁹⁰ Immune-related adverse events share features with COVID-19 including exacerbated immune activation and excessive pro-inflammatory cytokine production, indicating that ICIs could have a detrimental effect on the clinical course of COVID-19.^{91,92} Nonetheless, the evidence is limited regarding the use of ICIs in patients with cancer with COVID-19. A study of 423 cases of symptomatic COVID-19 in patients with cancer found that age >65 years and use of ICIs were predictors of hospitalisation

and severe disease.⁹³ A smaller study of 74 patients with cancer receiving ICIs found that of the four patients who developed COVID-19 symptoms and tested positive for SARS-CoV-2, all four were still alive 28-38 days after receiving a positive result.⁹⁴ Additionally, data from the TERA-VOLT registry suggest that immune-oncology treatments (including ICIs) do not increase the risk of death in patients with thoracic malignancies and COVID-19⁹⁵; the highest risk appears to be associated with the use of neutropenia-inducing chemotherapy.

Therapies associated with lung toxicity. Use of therapies with known lung toxicity risk (e.g. bleomycin, erlotinib, everolimus, irradiation of large areas of the lungs) should be considered carefully, considering the tumour type and intention of therapy. In patients who present with COVID-19 symptoms, early lung imaging (including computed tomography scans) may help the detection of SARS-CoV-2 infection. Due to the risk of severe complications of COVID-19 in patients with pre-existing lung damage, ESMO recommends that the potential of treatment-induced pulmonary toxicity be considered, and therapies such as ICIs be administered with caution.²⁵

Corticosteroids. Corticosteroids are used widely in cancer care and have been shown to have a direct anticancer effect in leukaemia or lymphoma, an anti-oedema effect in both primary and metastatic brain tumours and are essential medicines to prevent infusion reactions and nausea and vomiting associated with anticancer chemotherapy.⁹⁶ They are also crucial for managing immune-related adverse events in patients receiving ICIs, with prolonged courses often used in this setting.⁹⁷ ESMO guidelines state that the use of steroids should be critically reviewed and reduced if possible.²⁵ ESMO recommends that a reduced dose of dexamethasone on day 1 of chemotherapy without further use on the following days should be considered, even in highly emetogenic chemotherapy.²⁵ A completely steroid-free antiemetic regimen should only be considered in individual patients strongly felt to be at increased risk of COVID-19 complications with even a single dose of dexamethasone.²⁵

Currently, there is no evidence that corticosteroid therapy increases the risk of COVID-19 infection in patients with cancer or leads to worse clinical outcomes in confirmed cases.⁹⁸ However, available data are limited; therefore, the risk–benefit of corticosteroid use should be evaluated on a case-by-case basis, considering the severity of COVID-19 in the patient.⁹⁸

Stem cell transplantation. Patients undergoing stem cell transplantation are another group of immunocompromised patients for whom SARS-CoV-2 infection poses a significant risk.⁹⁹ This risk must be considered in patients receiving their own stem cells (autologous transplantation) and those receiving stem cells from a donor (allogeneic transplantation). Patients receiving allogeneic transplantation will require immunosuppressive therapy, often long term, to reduce the risk of graft versus host reactions. Allogeneic

recipients frequently require hospital admissions,¹⁰⁰ with evidence suggesting that outcomes are typically poor following intensive care unit admission in this group.¹⁰¹ A further concern in patients undergoing allogeneic transplantation is that SARS-CoV-2 can be detected in blood, although to date there have been no reports of transmission from donor to recipient either in the transfusion of blood products or cellular therapies.¹⁰²

Both autologous and allogeneic stem cell transplantations place patients at high risk of infection.³³ The American Society for Transplantation and Cellular Therapy (ASTCT) and the European Society for Blood and Marrow Transplantation (EBMT) have published recommendations to alleviate the challenge of managing patients undergoing stem cell transplantation during the COVID-19 epidemic.^{103,104} EBMT recommends that non-urgent transplants should be delayed.¹⁰⁴ In patients for whom urgent transplants are required, there are several considerations. Pretransplantation, community transmission of SARS-CoV-2 should be considered, with patients self-isolating to minimise infection risk before they undergo transplantation.³³ Patients should also be tested for SARS-CoV-2 and receive a negative result before treatment is started.^{103,104} Staff working in the transplant unit should be dedicated to a COVID-19-free unit and should not be allocated to the care of patients with COVID-19.¹⁰⁴ After transplantation, patients should also self-isolate to avoid SARS-CoV-2 transmission in the community.¹⁰⁴ The immunodeficiency scoring index may be used, although it is noteworthy that this has not been validated for SARS-CoV-2.³³ Regarding donors, a diagnosis of COVID-19 necessitates the exclusion of a donor and collection deferred for ≥ 28 days after recovery.^{103,104} However, if no alternative donor is available, the transplant need is urgent and the donor is well, an earlier collection may be permitted. This must be evaluated on a case-by-case basis.¹⁰⁴

In the case of a stem cell transplant candidate becoming infected with SARS-CoV-2, the decision of whether to proceed with the transplant must be taken, based on the risk associated with delaying the procedure versus the risk of receiving the transplant.¹⁰⁴ A deferral of 3 months is advisable, although this may not be possible due to the risk of disease progression. A 14-day delay is a minimum advised by ASTCT and EBMT.^{103,104} Further, ASTCT recommends that the candidate is asymptomatic with two consecutive negative PCR tests each 1 week apart before transplant,¹⁰³ while EBMT recommendations note that lung function and general performance should have improved (if not returned to pre-COVID-19 levels) before transplant.¹⁰⁴

EXPERT OPINION

COVID-19 presents an unprecedented challenge for oncologists and other health care professionals managing the care of patients with cancer. Within a short time, collaborative efforts and data sharing have led to updated recommendations for managing patients with cancer in this new era, including adjustments to supportive care interventions. Although appropriate supportive care reduces

the risk of complications associated with cancer therapy and contributes to curing, enhancing quality of life and survival, in the COVID-19 era, optimal supportive care is vital for reducing patient interactions with health care systems and reducing the spread of SARS-CoV-2. Several of the recommendations, such as use of G-CSF to prevent/treat neutropenia in lower FN risk groups, will lead to expanded use of some interventions. While these are not necessarily based on a depth of evidence, they are entirely justified in the context of a global pandemic, when reduced contact with health care facilities and professionals are key components of any strategy to contain the spread of infection. The situation is evolving rapidly, and oncologists are encouraged to make use of the resources provided by professional oncology societies, to ensure they keep pace with a fast-changing situation as well as rapidly emerging data.

Health systems are facing unprecedented pressures due to COVID-19-related care costs. Strategies to improve patient access and reduce the additional costs of broader access, such as the use of biosimilar and generic medicines when available, should be considered both now and in the COVID-19 recovery phase. For example, biosimilar G-CSF has been shown to be cost-effective/cost-minimal when expanding G-CSF administration to include larger patient numbers in the lower FN risk groups, due to lower drug acquisition costs combined with savings from preventing FN incidence.¹⁰⁵ Other approaches to controlling costs, such as abbreviated schedules for supportive care interventions, have been studied, but require further investigation. Hospital admissions should be minimised where possible to free resources to treat severe cases of COVID-19. It is of note that G-CSF is associated with reduced hospitalisation.¹⁰⁶

As the pandemic continues, there will be new challenges and hurdles to overcome. Prospective well-designed studies are required to improve the level of evidence and the quality of the recommendations available. However, with ongoing collaboration and international effort within the oncology community, we will better understand the impact of COVID-19 and enhance our ability to provide optimal care for patients with cancer.

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DATA SHARING

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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