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Original Research

Evidence-based management of COVID-19 in cancer patients: Guideline by the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO)

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Abstract Since its first detection in China in late 2019 the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated infectious disease COVID-19 continue to have a major impact on global healthcare and clinical practice. Cancer patients, in particular those with haematological malignancies, seem to be at an increased risk for a severe course of infection. Deliberations to avoid or defer potentially immunosuppressive therapies in these patients need to be balanced against the overarching goal of providing optimal antineoplastic treatment. This poses a unique challenge to treating physicians. This guideline provides evidence-based recommendations regarding prevention, diagnostics and treatment of SARS-CoV-2 infection and COVID-19 as well as strategies towards safe antineoplastic care during the COVID-19 pandemic. It was prepared by the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO) by critically reviewing the currently available data on SARS-CoV-2 and COVID-19 in cancer patients applying evidence-based medicine criteria.
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1. Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus first described in China in late 2019 as the causative agent of a coronavirus disease (COVID-19) [1,2]. Since then, SARS-CoV-2 has spread around the globe putting a major strain on healthcare worldwide. While many people infected by SARS-CoV-2 seem to remain asymptomatic or oligosymptomatic, SARS-CoV-2 can cause significant upper respiratory tract infectious disease (URTID) and lower respiratory tract infectious disease (LRTID). After an incubation period of about 3–5 days, typical symptoms of an influenza-like illness may occur and include fever, dry cough and myalgia. Olfactory or taste disorders occur frequently, which are rarely observed after infections with other community-acquired respiratory viruses [1,3]. In contrast to SARS-CoV or Middle East respiratory syndrome-related coronavirus (MERS-CoV) infection, gastrointestinal symptoms occur less frequently following SARS-CoV-2 infection [1,4]. In case of viral pneumonia, rapidly progressing impairment of oxygenation and life-threatening respiratory failure may occur [4]. This progressive hypoxaemia may be clinically silent, characterised by exceedingly low blood oxygen saturation levels without signs of dyspnoea [5]. Further complications include renal and cardiac impairment as well as hypercoagulopathy resulting in pulmonary embolisms or stroke [6,7].

Pathophysiologically, after infection, the increasing viral replication leads to local and systemic activation of the innate immune response. In severe courses, progressive viral cytopathic damage, fluid leakage and innate immune activation of resident and invading macrophages coincide with impaired gas exchange, respiratory failure as well as systemic involvement resulting from endothelial dysfunction, complement activation and hypercoagulopathy [8,9]. Abundant viral antigens, pro-inflammatory cytokines, and antigen-presenting cells activate the SARS-CoV-2–specific adaptive immunity consisting of SARS-CoV-2–specific T cells and neutralising antibodies permitting to eventually clear SARS-CoV-2 replication. Accordingly, treatment emphasis should shift from initially antiviral curtailing, to dampening anti-inflammatory responses and supporting specific lymphocyte effector function [10].

It is generally assumed that cancer patients may be at an increased risk of severe COVID-19 [11–14]. In addition to the underlying disease impairing virus-specific immunity, which is presumably more prominent in haematological malignancies, many antineoplastic therapies, but also the underlying malignancy itself, can lead to significant immunosuppression and

thus contribute to patient vulnerability towards severe infection [15]. Cancer patients on active therapy, e.g. those receiving intravenous chemotherapy, may require more frequent interactions with healthcare providers than the general population, potentially increasing the opportunity of exposure to SARS-CoV-2. Thorough hygiene measures and implementation of adequate organisational strategies are therefore important to minimise patients' risk. However, it should also be noted that in most publications cancer patients are older and have more comorbidities than patients of the non-cancer cohort [13]. To address this point, a recent publication compared age-matched groups of cancer and non-cancer patients detecting no difference in mortality [16]. Moreover, some publications even describe a below average mortality in cancer populations [17–19]. On the other hand, as uncontrolled malignancy seems to be an independent risk factor for severe COVID-19 [20], administration of state-of-the art cancer therapy to reach the best possible remission remains an essential goal. Treating physicians must balance all these aspects to safely provide optimal antineoplastic care for their patients. In any case, the risk of infection and the disease COVID-19 itself should not be taken lightly, especially not in cancer patients. However, unnecessary precautions must by no means jeopardise the administration of the required antineoplastic treatment. It has been shown to be possible to find the right balance during the COVID-19 pandemic [17,21].

This guideline aims to help clinicians make informed decisions with regard to prevention, diagnostics and treatment of SARS-CoV-2 infection and COVID-19 as well as devising strategies towards safe antineoplastic care during the current pandemic. These recommendations apply to adult patients with solid tumours or haematological malignancies. For specific considerations regarding stem cell transplantation, we kindly refer to the current guidelines by the European Society for Blood and Marrow Transplantation [22].

2. Methods

This guideline was developed by an expert panel from the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). The panel consisted of 18 specialists certified in haematology, medical oncology, infectious diseases, critical care, emergency medicine and virology.

2.1. Search strategies and selection criteria

After definition of topics and formation of subgroups, a systematic search of MEDLINE for publications in English language was performed using one of the following search terms: "coronavirus", "SARS-CoV-2", or "COVID-19". Given the current dynamic of research into COVID-19, publications on the preprint server www.medRxiv.org were also evaluated; however, the lack of formal peer review in these cases was taken into consideration with regard to grading of quality of evidence. Publications were evaluated that appeared online until August 19th 2020.

2.2. Guideline process

The relevant literature was thoroughly reviewed; the data were extracted and rated. Based on the results of data assessment, preliminary recommendations were first discussed within subgroups and then discussed and revised in a step-by-step process by the specialist panel. Strength of recommendation and quality of evidence were graded applying the scale proposed by the European Society of Clinical Microbiology and Infectious Diseases ESCMID(Table 1) [23]. In short, recommendations were graded as follows: A, AGIHO strongly supports a recommendation for use; B, AGIHO moderately supports a recommendation for use; C, AGIHO marginally supports a recommendation for use; and D, AGIHO supports a recommendation against use. The final recommendations presented in this guideline were discussed and agreed upon by the AGIHO general assembly in a web meeting on June 23rd 2020 and again on July 9th 2020.

Table 1
Grading system for strength of recommendation (SoR) and quality of evidence (QoE) as proposed by the European Society of Clinical Microbiology and Infectious Diseases [23].

Strength of recommendation	
A	AGIHO strongly supports a recommendation for use
B	AGIHO moderately supports a recommendation for use
C	AGIHO marginally support a recommendation for use
D	AGIHO supports a recommendation against use
Quality of evidence	
I	Evidence from at least one properly designed randomised, controlled trial
II*	Evidence from at least one well-designed clinical trial, without randomisation; from cohort– or case–control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinion of respected authorities, based on clinical experience, descriptive case studies, or report of expert committees
*added index for level II	
R	Meta-analysis or systematic review of randomised controlled trials
T	Transferred evidence, i.e. results from different patients' cohorts or similar immune status situation
H	The comparator group is a historical control
U	Uncontrolled trial
A	Abstract published at an international meeting or manuscript available on preprint server only

AGIHO, Infectious Diseases Working Party

3. Risk factors

Cancer patients are generally assumed to be at an increased risk of severe illness by respiratory virus infections when compared with healthy individuals, amongst others as they tend to be older and more frequently suffer from comorbidities than the general population [24]. However, in case of SARS-CoV-2, both healthy and immunocompromised individuals are immunologically naïve to this infection. Data on SARS-CoV-2 infection rates vary among patients with malignant diseases [1,13,26–28]. Overrepresentation of cancer patients among hospitalised patient populations may contribute to a higher reported prevalence of SARS-CoV-2 infections among cancer patients compared with the general population, which is supported by a study showing similar infection rates in hospitalised patients with haematological malignancies and a comparator group of healthcare workers (HCWs) [29].

In cancer patients, uncontrolled malignancy seems to confer a higher risk of severe or even fatal outcome of COVID-19 [20,30]. With regard to specific cancer types, both haematological malignancies and lung cancer were repeatedly identified as factors for poor prognosis compared with other (solid) cancers [12,29–35]. Interestingly, myeloid or lymphoid malignancies as underlying disease do not appear to differ in their impact on COVID-19 mortality [36]. Among cancer patients, advanced stage [11,12] and recent antineoplastic therapy within the last 2–4 weeks were reported as risk factors [37–39]. However, data on the impact of different cancer treatment modalities (immunotherapy, endocrine therapy, targeted therapy, radiotherapy, chemotherapy or surgery) on the outcome of COVID-19 are contradictory [11,20,39,40].

Of note, patients with lymphopenia [11,41–43] and granulocytosis [33,44] were reported to be at an increased risk for severe or fatal COVID-19. Further factors with possible impact on the COVID-19 course and outcome are listed in Table 2.

Table 2
Risk factors for severe COVID-19 in cancer patients.

Risk factors	Comments	References
Patient-related		
Age	Higher age associated with a higher risk for severe disease or death (OR = 1.04–1.84)	[11, 20, 31, 33]
Male sex	Male sex associated with a higher risk for death (OR 1.63–3.86, HR = 2.75)	[20,39,42]
ECOG	A higher ECOG score associated with a higher risk for death (OR 2.80–3.89, HR = 4.87)	[11, 20, 42]
Comorbidities	A higher number of comorbidities associated with a higher risk for death (OR = 4.50)	[20,31,33]
Smoking	Smoking associated with a higher risk for death (OR = 1.60–3.18)	[20,145]
Cancer-related		
Cancer history	Cancer history associated with a higher risk for death (OR = 2.98)	[146]
Cancer type	A higher death rate for haematological (31–62%, OR = 2.40) and lung cancers (55%, OR = 1.80) than for other (solid) cancers (25%)	[29–35, 147]
Active cancer	Active cancer associated with a higher risk for death (OR = 5.20, HR = 14.29)	[20,30]
Stage IV cancer	Metastatic cancer associated with a higher risk for severe disease or death (OR = 2.60)	[11,147]
Cancer treatment <2–4 weeks	Cancer treatment before disease associated with a higher risk for severe disease or death (OR = 3.51–3.99, HR = 4.10)	[37, 38, 41]
Blood counts		
Lymphopenia	A lower lymphocyte count associated with a higher risk for severe disease or death (OR = 2.99, HR = 3.05)	[11, 41–43]
Granulocytosis	A higher neutrophil count associated with a higher risk for death	[32,44]
Summary of risk factors		
Increased risk of death was reported for patients of higher age, male sex and with limitations in daily activity and comorbidities. Both history of cancer and active cancer, particularly haematological and lung cancer and advanced-stage cancer, as well as lymphopenia and granulocytosis were associated with a higher risk of death in COVID-19 patients.		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OR, odds ratio.

4. Prevention

4.1. Hygiene measures

Given the current lack of herd immunity, an effective vaccine, or antiviral prophylaxis, hygiene measures and contact precautions are the cornerstones in preventing SARS-CoV-2 infection and transmission (Table 3). Community-wide face masks and physical distancing measures were effective in several population-based studies and are thus strongly recommended (AII_u) [45–49]. A distance of at least 1.5 m (6 ft) is usually considered appropriate; however, depending on environmental conditions a wider distance may be considered [50].

Hand hygiene is crucial for infection control, and regular washing of hands with water and soap is strongly recommended for any population (AII_t) [51,52]. Alcohol-based hand rubs were shown to be virucidal to SARS-CoV-2 if applied for at least 30 s at a concentration of ethanol or 2-propanol $\geq$ 30% [53]. We strongly recommend hand disinfection for HCWs and cancer patients in healthcare settings (AII_u).

SARS-CoV-2 can remain viable on surfaces for up to 3 days [54,55]. We strongly recommend disinfection of frequently touched surfaces such as doorknobs, elevator buttons or hand rails for cancer patients in healthcare settings ($AII_{r,u}$) and moderately outside of healthcare settings ($BII_{r,u}$) [54–56].

Table 3
Recommendations regarding prevention of SARS-CoV-2 infection and COVID-19 in cancer patients during the COVID-19 pandemic.

Population/clinical situation	Intention	Intervention	SoR	QoE	References
Hygiene measures					
Any population	To prevent SARS-CoV-2 transmission and infection	Physical distancing measures	A	II_u	[45–48, 50]
Any population	To prevent SARS-CoV-2 transmission and infection	Community-wide face masks	A	II_u	[49]
Any population	To prevent SARS-CoV-2 transmission and infection	Hand washing with soap	A	II_t	[51,52]
Cancer patients, healthcare setting, and healthcare workers	To prevent SARS-CoV-2 infection	Hand disinfection with ethanol or 2-propanol at >30% concentration for 30s	A	II_u	[56]
Cancer patients, healthcare setting	To prevent SARS-CoV-2 infection	Disinfection of touched surfaces	A	$II_{r,u}$	[54–56]
Healthcare workers	To prevent SARS-CoV-2 infection	Surgical mask or FFP2/N95 respirator	A	$II_{r,t}$	[58–60]
Healthcare workers in contact with (confirmed/suspected) SARS-CoV-2-positive patients	To prevent SARS-CoV-2 infection	Personal protective equipment (PPE) incl. FFP2/N95 respirator	A	$II_{r,t}$	[22, 61–64]
Cancer patients with (confirmed/suspected) SARS-CoV-2 infection	To prevent SARS-CoV-2 transmission	Surgical mask or FFP2/N95 respirator (without exhalation valve)	A	II_t	[22, 57, 58]
Cancer patients with SARS-CoV-2 infection	To prevent SARS-CoV-2 transmission	Single room isolation, cohort isolation or self-quarantine	A	$II_{t,u}$	[65]
Cancer patients with SARS-CoV-2 infection	To prevent SARS-CoV-2 transmission	Requirement of negative SARS-CoV-2 test result prior to discontinuation of isolation	A	$II_{t,u}$	[66, 68, 69, 70, 71]
Cancer patients, outside of healthcare setting	To prevent SARS-CoV-2 infection	Disinfection of frequently touched surfaces	B	$II_{r,u}$	[54–56]
Cancer patients	To prevent SARS-CoV-2 infection	Regular ventilation of rooms	B	III	[54]
Cancer patients	To prevent SARS-CoV-2 infection	Surgical mask or FFP2/N95 respirator	B	$II_{r,t}$	[58–60]
Cancer patients, outside of healthcare setting	To prevent SARS-CoV-2 infection	Hand disinfection with ethanol or 2-propanol at >30% concentration for 30s	C	II_u	[53]
Supportive measures					
Cancer patients with severe COVID-19 and hypogammaglobulinaemia	To reduce mortality	Adjuvant IVIG treatment <48 h	B	$II_{t,u}$	[77, 148]
Cancer patients	To prevent SARS-CoV-2 infection	Vitamin D level (supply)	C	III	[75, 76, 149]
Cancer patients with RAAS inhibitors	To prevent SARS-CoV-2 infection	Discontinuation of RAAS inhibitors	D	II_u	[72, 73]
Cancer patients with RAAS inhibitors and COVID-19	To prevent hospitalisation and severe COVID-19	Discontinuation of RAAS inhibitors	D	II_u	[73, 74]

Abbreviations: FFP, filtering facepiece; IVIG, intravenous immunoglobulin; QoE, quality of evidence; RAAS, renin-angiotensin-aldosterone system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoR, strength of recommendation.

Surgical masks covering nose and mouths of an infected person reduce coronavirus RNA in expiration air [57,58]. Particulate-filtering facepieces (FFPs) such as the US-regulated N95 respirators and the functionally-equivalent EU-regulated FFP2 masks are characterised by a tighter fit and a finer mesh. Several randomised trials in HCWs provide evidence of the protective effect of surgical masks against respiratory virus infections with a potential additional benefit of FFP2/N95 respirators [59–61]. If worn to prevent infection, FFP2/N95 masks may be equipped with an exhalation valve for greater comfort, whereas to prevent transmission they must not have an exhalation valve [22].

We strongly recommend that cancer patients and HCWs wear a surgical mask to prevent SARS-CoV-2 transmission and infection (AII_t) [57–60]. If caring for COVID-19 patients, we strongly recommend that HCWs wear FFP2/N95 respirators (AII_t) and personal protective equipment including gloves, gowns and eye protection such as goggles or face shields (AII_r) [22,61–64]. Patients with COVID-19 are strongly recommended to wear a surgical mask or FFP2/N95 respirator without an exhalation valve (AII_t) taking into account the protective equipment of their surroundings [22,57,58].

Cancer patients diagnosed with SARS-CoV-2 infection should undergo either self-quarantine, single-room or cohort isolation ($AII_{t,u}$) [65]. While infectiousness of SARS-CoV-2 seems to decline significantly within 7–8 days after onset of symptoms [66,67], prolonged

Table 4
Recommendations regarding organisational aspects of outpatient and inpatient management of cancer patients during the COVID-19 pandemic.

Population/Clinical situation	Intention	Intervention	SoR	QoE	References
Healthcare providers	To prevent nosocomial SARS-CoV-2 transmission	Implement organisational strategies	A	III	[21, 83, 84, 150]
Healthcare providers	To prevent nosocomial SARS-CoV-2 transmission	Consider surveillance screening taking into account local epidemiology	A	$II_{t,u}$	[85, 151]
Healthcare providers	To provide best care for cancer patients with COVID-19	Implement dedicated teams	A	III	[19]
Healthcare providers	To keep risk for cancer patients as low as possible	Strict adherence to guidelines; consider restrictive transfusion strategies, if possible	A	III	[88–90, 152,153]
Healthcare providers	To prevent SARS-CoV-2 transmission and infection	Consider treatments with fewest and shortest visits to hospital/outpatient clinic	A	III	[21,29,86, 87, 155]
Healthcare providers	To provide best care for cancer patients with COVID-19	Increase ICU and ventilation capacity	B	III	[19,153]
Healthcare providers	To prevent SARS-CoV-2 transmission and infection	Consider erythropoietin as an alternative to red cell transfusion	B	III	[85,151,90]

Abbreviations: ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoR, strength of recommendation; QoE, quality of evidence.

shedding of viral RNA for many weeks was observed, especially in immunocompromised patients and in severe COVID-19 [68–70]. We strongly recommend requirement of a negative SARS-CoV-2 polymerase chain reaction (PCR) test result before discontinuation of isolation ($AII_{t,u}$), which should be considered no earlier than 14 days after onset of symptoms and 2 days after cessation of symptoms. The possibility of false-negative test results must be kept in mind. A positive test after one negative test was reported in up to 30% of COVID-19 patients, which declined to 5% after three consecutive negative tests [68,71]. Requirement of more than one consecutive negative test before discontinuation of isolation should therefore be considered, especially in patients with risk factors for prolonged viral shedding.

With regard to participation in activities of daily life of cancer patients not in quarantine/isolation because of suspected or confirmed SARS-CoV-2 infection, special consideration should be given to current local epidemiology and requirements of local and national health authorities. As a general recommendation, restriction of activities to places that have adequate hygiene concepts implemented seems to be reasonable and a preference of outdoor versus indoor activities, where possible.

4.2. Supportive measures

Several large trials could not establish an association between renin-angiotensin-aldosterone system (RAAS) blockers and risk of SARS-CoV-2 infection or severe COVID-19 disease [72–74]. Discontinuation of RAAS blockers is therefore not recommended (DII_u).

A correlation between vitamin D levels and risk of COVID-19 has not been established to date [75]. However, in other infectious diseases, supplementation has been shown to be beneficial [76]. Thus, we marginally support appropriate vitamin D supplementation (CIII). For other nutrients such as iron, selenium or vitamin C, no conclusive data support supplementation with regard to COVID-19.

Administration of intravenous immunoglobulin (IVIG) may be considered in cancer patients with hypogammaglobulinaemia and COVID-19 ($BII_{t,u}$) [77]. As specific antibodies against SARS-CoV-2 are most likely absent in current products because of low herd immunity at the moment, IVIG will primarily act against possible co-infections with other pathogens. However, with an increase of SARS-CoV-2 infections in populations over the course of the COVID-19 pandemic future IVIG preparations may contain specific antibodies against SARS-CoV-2 possibly allowing for a broader use of IVIG in COVID-19 patients than according to present recommendations.

Prophylaxis with granulocyte colony-stimulating factor (G-CSF) might help in reducing vulnerability to infections due to shortened neutropenia. However, G-CSF has also been associated with a risk of hyper-inflammation during neutrophil regeneration, and cases of severe COVID-19 have been reported after G-CSF administration [44]. We therefore do not recommend additional G-CSF prophylaxis on top of current recommendations (DIII) [78].

Several preclinical and early clinical trials on vaccine candidates against SARS-CoV-2 have shown promising results [79–81]. As cancer patients are usually not included in these trials, it is too early to make any specific deliberations on SARS-CoV-2 vaccine strategies in these patients. However, based on experiences from other vaccines, depending on the type of vaccine, efficacy and/or safety might be an issue in immunocompromised cancer patients, rendering vaccinations of HCWs, caregivers and relatives especially important [82].

Table 5
Recommendations regarding management of cancer care during the COVID-19 pandemic.

Population/Clinical situation	Intention	Intervention	SoR	QoE	References
General recommendations					
Cancer patients during COVID-19 pandemic	To reduce risk of severe COVID-19	Perform cancer therapy to reach best possible remission	A	II_u	[20,30]
Cancer patients with suspected SARS-CoV-2 infection (e.g. contact patients, hot spots)	To reduce risk of severe COVID-19	Quarantine and delay/discontinue anti-cancer therapy for up to 14 days, if not detrimental for cancer prognosis	A	III	No reference.
Cancer patients with suspected SARS-CoV-2 infection (e.g. contact patients, hot spots)	To reduce risk of severe COVID-19	Test for SARS-CoV-2	A	III	No reference.
Cancer patients with SARS-CoV-2 infection	To reduce risk of severe COVID-19	Delay/discontinue cytotoxic chemotherapy, if possible	A	II_u	[11]
Cancer patients with SARS-CoV-2 infection	To reduce mortality	Delay surgery, if possible	A	II_u	[95]
Cancer patients with SARS-CoV-2 infection	To reduce risk of severe COVID-19	Delay/discontinue radiotherapy, if possible	B	II_u	[11]
Cancer patients during COVID-19 pandemic with controlled disease	To reduce risk of severe COVID-19	Consider to delay/discontinue cytotoxic chemotherapy, if not detrimental for cancer prognosis, taking into account local epidemiology	B	II_u	[6, 11, 13, 37]
Cancer patients with SARS-CoV-2 infection	To reduce risk of severe COVID-19	Delay/discontinue targeted therapy, if possible	C	III	[11]
Cancer patients during COVID-19 pandemic	To reduce risk of SARS-CoV-2 infection and severe COVID-19	Routinely delay/discontinue anti-cancer therapy	D	II_u	[18, 20,31,33, 40, 92–94]
Cancer patients during COVID-19 pandemic	To reduce mortality	Delay/discontinue radiotherapy, endocrine therapy, targeted therapy or surgery	D	II_u	[18, 20,31,40, 94]
Cancer patients with SARS-CoV-2 infection	To reduce mortality	Delay/discontinue endocrine therapy	D	III	[18]
Specific recommendations					
Cancer patients during COVID-19 pandemic	To reduce risk of severe COVID-19	Consider to delay/reduce/ discontinue steroids, if not detrimental for cancer prognosis	C	$II_{t,u}$	[98]
Lung cancer patients during COVID-19 pandemic	To reduce risk of severe COVID-19	Delay/discontinue PD1 inhibitors	D	II_u	[99, 100]
Lung Cancer patients receiving TKI with SARS-CoV-2 infection	To reduce risk of severe COVID-19	Discontinue TKI	D	II_u	[100]
CML patients with SARS-CoV-2 infection	To reduce risk of severe COVID-19	Discontinue TKI	D	III	[104]
Cancer patients receiving BTKi with SARS-CoV-2 infection	To reduce risk of severe COVID-19	Discontinue BTKi	D	III	[101, 102]
Cancer patients receiving ruxolitinib with SARS-CoV-2 infection	To reduce risk of severe COVID-19	Discontinue ruxolitinib	D	II_t	[103]

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; CML, chronic myelogenous leukaemia; QoE, quality of evidence; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoR, strength of recommendation; TKI, tyrosine kinase inhibitor.

5. Organisational aspects

The prevention of nosocomial SARS-CoV-2 transmission is of major importance during treatment of cancer patients. This relates to both inpatient and outpatient management. Therefore, we strongly recommend the implementation of specific organisational pathways in hospitals and outpatient clinics (AIII, Table 4) [21,83,84]. This includes precise scheduling of in-person appointments to reduce waiting times, increasing telemedical approaches including phone or video consultations when clinically possible and special routing and zoning for cancer patients. Particularly with regard to patient care in outpatient clinics we recommend to reduce the seating capacity in waiting areas and treatment rooms to ensure a distancing of at least 1.5 m. To reduce the number of visitors, relatives and non-essential other attendants should be advised to stay outside the clinic during the patient visit. In high-volume contact areas such as front desks, installation of transparent shields may offer additional protection for HCWs.

To provide best care for cancer patients with COVID-19, intensive care unit (ICU) and respirator capacity should be increased (BIII). If possible, dedicated treatment teams should be implemented to ensure continued cancer care in case of infected medical personnel (AIII) [19]. Early detection of infected staff is crucial. Surveillance screening related to local epidemiology should be considered, especially in inpatients, to prevent presymptomatic transmission of SARS-Cov-2 ($AII_{t,u}$) [85].

The risk of transmission strongly correlates with the number of consultation and treatment appointments [21,29,86,87]. However, optimal control of the underlying malignancy is considered favourable as patients with active cancer appear to have an increased risk of severe COVID-19 [20]. To ensure high-quality cancer care, visits should by no means be avoided or unnecessarily delayed, but reduced if possible without interfering with treatment goals. We strongly recommend considering therapeutic strategies with the fewest and shortest clinic visits adapted to curative or palliative intent taking the patient's individual situation and risk into account (AIII). This might e.g. include substitution of intravenous by oral regimens (e.g. 5-fluorouracil/capecitabine) or hypofractionated radiotherapy. Transfusion strategies should be as restrictive as recommended per guidelines and iron, folic acid, vitamin B12 or erythropoietin should be supplemented rigorously as indicated (BIII) [88–90]. Clinic visits for surveillance might be postponed or be substituted by telephone or video calls [91].

6. Management of cancer care

6.1. General recommendations

Given the immunocompromising effect of many cancer therapies and the fact that most cancer patients belong to high-risk groups regarding adverse outcome of COVID-19 it seems reasonable to debate whether it may be the safer course of action to delay or discontinue certain antineoplastic therapies. However, uncontrolled malignancy was identified as an independent risk factor for severe COVID-19 [20]. We therefore strongly recommend performing antineoplastic therapy to reach the best possible remission (AII_u, Table 5).

Routine delay or discontinuation of antineoplastic therapy in patients without suspected/confirmed SARS-CoV-2 infection is not recommended even in times of pandemic (DII_u) [18,20,31,33,40,92–94]. In case of suspected SARS-CoV-2 infection, e.g. because of contact with a confirmed case or a high incidence in the area, we strongly recommend to quarantine the patient and delay antineoplastic therapy for up to 14 days, if not detrimental for cancer prognosis (AIII). Given the average incubation time of 3–5 days, a delay for a shorter time period and (re-)start of antineoplastic therapy under quarantine conditions may be considered especially in patients with significant prognostic impact of per-protocol administration of treatment. Obviously, these patients should be tested for SARS-CoV-2 (AIII) but the possibility of false-negative test results should be kept in mind.

Cytotoxic chemotherapy was reported as a risk factor for severe COVID-19 by some [11,13,37,39], although not consistently across all studies [20,40]. We therefore moderately recommend to consider to delay/discontinue chemotherapy in areas with high SARS-CoV-2 infection rates in patients with controlled malignancy if no significant detrimental impact on cancer prognosis is to be expected (BII_u). This might be especially relevant in the palliative setting, if the benefit of chemotherapy is marginal, and if other risk factors for severe COVID-19 are present. Furthermore, dose reductions might be a reasonable strategy in the palliative setting to reduce neutropenia. We do not recommend to delay/discontinue radiotherapy, targeted therapy, endocrine therapy or surgery in cancer patients without suspected/confirmed SARS-CoV-2 infection (DII_u) as no impact on mortality of such prior treatments was seen in several large cohort studies of COVID-19 patients [18,20,31,40,94].

In patients with COVID-19, it is strongly recommended to delay/discontinue chemotherapy, if possible, as chemotherapy within two weeks of admission was a major risk factor for severe COVID-19 in a large Chinese cohort study (AII_u) [11]. Similarly, we strongly recommend delaying surgery in COVID-19 patients (AII_u), as perioperative SARS-CoV-2 infection was associated with a high rate of pulmonary complications and increased mortality [95]. We recommend to delay/discontinue radiotherapy in patients with COVID-19 with moderate strength (BII_u) taking into account field size, location and dosage [11,12,31,40].

A small cohort study in breast cancer patients with COVID-19 reported very favourable outcomes in several patients who did not discontinue their endocrine therapy despite diagnosis of infection [18]. Given that endocrine therapy is usually not associated with significant immunosuppression, we do not recommend discontinuing endocrine therapy in patients with COVID-19 (DIII). It is important to note that this does not apply to CDK4/6 inhibitors jointly administered with endocrine therapy which can induce significant neutropenia [96].

Targeted therapy was reported as a risk factor for severe COVID-19 in one study, although patient numbers for this subgroup were small [11]. Given that many targeted agents adversely affect immune function we marginally support discontinuation of targeted therapy in COVID-19 patients (CIII). In support, a recent small German study on multiple myeloma (MM) patients with COVID-19 reported favourable outcomes

after discontinuation of various types of targeted anti-MM therapies until resolution of symptoms [17]. However, the heterogeneity of drugs summarised as targeted therapy has to be acknowledged, and depending on the available data, substance-specific recommendations should be applied.

6.2. Specific recommendations on some cancer treatments

In the following passages, we summarise current knowledge regarding specific cancer treatments. This summary is in no way complete and subject to change as knowledge accumulates.

While corticosteroid therapy can be beneficial to treat severe COVID-19,[97] long-term systemic steroids were identified as a risk factor to develop severe COVID-19 in a large registry study of patients with inflammatory bowel disease [98]. We marginally recommend considering to delay, discontinue or reduce treatment with systemic steroids in cancer patients during the COVID-19 pandemic ($CII_{t,u}$). Any potential impact of steroid reduction on treatment success needs to be carefully evaluated, most importantly in curative settings.

Immune checkpoint inhibitors were initially suspected to increase the risk of severe COVID-19 [12]. However, later studies did not find a significant association after adjustment for smoking [99,100]. We therefore do not recommend delaying/discontinuing immune checkpoint inhibitors (DII_u).

Prior treatment with tyrosine kinase inhibitors (TKIs) was not associated with adverse outcomes in a cohort study of lung cancer patients with COVID-19, although patient numbers in this subgroup were small and no further details on the type of TKIs were provided [100]. Routine delay/discontinuation of TKIs in patients with lung cancer is thus not recommended (DII_u).

Two small case series reported a favourable outcome of patients with chronic lymphocytic leukaemia (CLL) or Waldenström macroglobulinaemia diagnosed with COVID-19 and continuous administration of Bruton tyrosine kinase inhibitors (BTKis) [101,102]. We therefore recommend against discontinuation of BTKis in patients with COVID-19 (DIII).

The JAK inhibitor ruxolitinib was evaluated in a small randomised controlled trial (RCT) against placebo for the treatment of severe COVID-19 given its anti-inflammatory properties. While no statistically significant difference in the outcome was observed, time to clinical improvement of patients receiving ruxolitinib was numerically shorter [103]. Discontinuation of ruxolitinib in patients with COVID-19 is therefore not recommended (DII_t).

Further data on the risks of specific antineoplastic drugs with regard to COVID-19 are scarce at this time. In a small case series of five patients with chronic myelogenous leukaemia (CML) and COVID-19, TKI treatment could safely be continued [104]. Regarding the impact of rituximab on COVID-19, several cases are published reporting outcomes ranging from very mild to fatal [105,106]. B-cell depletion seems to be associated with prolonged shedding of SARS-CoV-2 [68,105]. Several case reports on lenalidomide-based therapies describe severe to fatal outcomes of COVID-19 [107,108]. However, it remains unclear whether this is mainly due to the drug or the underlying malignancy. As hypersensitivity pneumonitis has been reported as a rare side-effect of lenalidomide, an adverse impact on the course of COVID-19 is, however, conceivable [109]. In contrast, a recent German study on MM patients on active therapy at the time of COVID-19 diagnosis including lenalidomide- , proteasome inhibitor− , and daratumumab-based therapies reported favourable outcomes after therapy was discontinued in all patients until resolution of symptoms with no fatalities [17].

7. Diagnostics

For diagnosis of SARS-CoV-2 infection, the AGIHO guideline panel categorised the following clinical situations: a) asymptomatic cancer patients scheduled for antineoplastic treatment in whom delay is likely to increase risk of death, b) asymptomatic cancer patients scheduled for antineoplastic treatment in whom delay is unlikely to increase risk of death, and c) cancer patients presenting with respiratory symptoms compatible with COVID-19. With regard to diagnosing SARS-CoV-2 infection and COVID-19 there should be no differences between these groups. A comprehensive approach should be applied to all cancer patients (Table 6).

7.1. Molecular, blood antigen and antibody testing

Upper respiratory samples obtained by nasopharyngeal or posterior oropharyngeal swabs at the time of symptom onset are standard to diagnose acute SARS-CoV-2 infection [110,111]. Sampling bias may be decreased by combining a nasopharyngeal swab and an oropharyngeal swab in one universal transport medium [112]. If a nasopharyngeal swab is contraindicated, expectorated sputum can be used, in particular during thrombocytopenia or if nasopharynx tumours increase bleeding risks [111]. New evidence has become available indicating that morning saliva may be a viable alternative, but data are currently only available preprint [113]. In case of mechanically ventilated patients, lower respiratory samples by tracheal aspirate or bronchoalveolar lavage are standard in the ICU population [111]. Tracheal aspirate is often preferred to limit droplet and aerosol exposure of HCWs. Generally, it has to be emphasised that diagnostic material should be sampled from the focus of symptoms, that is, samples from the upper respiratory tract for those with symptoms of URTID

Table 6
Recommendations regarding diagnostics of SARS-CoV-2 infection and COVID-19.

Population	Intention	Intervention	SoR	QoE	References
Cancer patients	To diagnose infection	Upper respiratory sample (Swab PCR)	A	II_u	[110,111]
Cancer patients	To diagnose infection	Lower respiratory sample (BAL/TA PCR)	A	II_u	[111]
Cancer patients	To diagnose infection, if PCR inconclusive	Low-dose chest CT Scan	A	II_u	[117–119]
Cancer patients	To diagnose infection	Expectorated sputum (PCR)	B	II_u	[111]
Cancer patients	To diagnose infection	Saliva (PCR)	B	II_a	[113]
Cancer patients	To identify previous infection	Antibody assay	C	II_u	[114–116]
Cancer patients	To diagnose infection	Antigen assay	D	III	No reference.

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography; PCR, polymerase chain reaction; QoE, quality of evidence; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoR, strength of recommendation; TA, tracheal aspirate.

only and samples from the lower respiratory tract for those with LRTID.

Currently, antigen assays for diagnosing SARS-CoV-2 infection are being developed and should only be used in clinical studies. Antibody assays should not be used to diagnose active/ongoing SARS-CoV-2 infection, but depending on sensitivity and specificity may be helpful to identify patients with previous SARS-CoV-2 infection [114–116]. A major caveat is the uncertainty associated with undetectable or low antibody levels in individuals with asymptomatic/oligosymptomatic courses of SARS-CoV-2 infection, the level and duration of detectable antibodies in immunocompromised cancer patients, and the protection from re-infection or severe disease.

We strongly recommend that all cancer patients before antineoplastic therapy receive upper respiratory sampling to diagnose SARS-CoV-2 infection by PCR (AII_u), taking into account local epidemiology, individual patient risk and potential for nosocomial transmission. In intubated patients, we strongly recommend additional testing of tracheal aspirate (AII_u). If the aforementioned techniques are contraindicated in individual patients, testing of saliva or expectorated sputum is recommended with moderate strength ($BII_{a,u}$).

7.2. Thoracic imaging

Imaging studies show characteristic findings and are highly sensitive to identify patients with COVID-19 LRTID in a timely manner [117–119]. They complement molecular testing strategies. Chest computed tomography (CT) imaging abnormalities can evolve rapidly from focal unilateral to diffuse bilateral ground-glass opacities, even in asymptomatic patients. Ground-glass opacities may be accompanied by consolidations which evolve during the course of disease [119].

We strongly recommend low-dose chest CT in all cancer patients with suspected COVID-19 to diagnose LRTID due to SARS-CoV-2 (AII_u) [117–119].

8. Treatment

Because the treatment of COVID-19 is a rapidly changing field, it is strongly recommended to include patients into clinical trials if at all possible (AIII). To evaluate treatment indications and outcomes in COVID-19, the World Health Organization (WHO) Ordinal Scale for Clinical Improvement should be applied (Suppl. Table 1) [120]. It summarises disease severity during the course of COVID-19 from uninfected to ambulatory, hospitalised with mild disease or severe disease or dead and allocates scores from 0 to 8. The WHO Ordinal Scale is the foundation to most clinical trials on COVID-19 and allows to measure end-points and to facilitate interpretation of results across studies.

8.1. Prophylaxis

To date, there is no agent that has shown convincing efficacy as post-exposure prophylaxis. A double-blind RCT (N = 821) compared post-exposure prophylaxis with hydroxychloroquine or placebo. The incidence of either laboratory confirmed infection or illness compatible with COVID-19 within 14 days did not differ between the groups. Participants receiving hydroxychloroquine experienced a higher rate of adverse events, in particular gastrointestinal or neurological [121]. A retrospective study evaluated umifenovir, an antiviral agent targeting haemagglutinin, as prophylaxis and reported an effect in HCWs, albeit with a small sample size [122]. Other compounds have not been tested so far. Therefore, post-exposure prophylaxis with any drug with presumed antiviral activity outside of controlled clinical trials is not recommended (DIII, for hydroxychloroquine DI, Table 7).

8.2. Antiviral treatment

8.2.1. Remdesivir

A double-blind RCT (N = 1063) compared intravenous remdesivir with placebo in adults hospitalised with COVID-19 and evidence of LRTID. Preliminary results were published after the data and safety monitoring board recommended to unblind. Remdesivir was superior to placebo in shortening the time to recovery (11 days versus 15 days). This effect was most pronounced in patients requiring oxygen but not mechanical ventilation (corresponding to WHO Scale 5) at presentation.

Table 7
Treatment Recommendations for cancer patients with COVID-19 by WHO Ordinal Scale Patient State [156].

Population	Intention	Intervention	SoR	QoE	References
Antiviral or immunomodulatory treatment					
Any patient	To improve outcome	Treatment in clinical trials	A	III	No reference.
Uninfected cancer patients (WHO 0)	To prevent infection	PEP with hydroxychloroquine	D	I	[121]
		PEP with any other antiviral agent	D	III	No reference.
Ambulatory cancer patients with COVID-19 (WHO 1–2)	To shorten time to recovery or increase survival	Remdesivir	D	III	[123]
		Hydroxychloroquine (+/− azithromycin)	D	II_u	[20,125]
		Lopinavir/ritonavir	D	III	No reference.
		Dexamethasone	D	II_t	[97]
		Tocilizumab	D	III	[130]
		Anakinra	D	$II_{h,t}$	[136]
		Baricitinib	D	III	No reference.
		Convalescent plasma	D	III	No reference.
Hospitalised cancer patients with COVID-19, no oxygen therapy (WHO 3)	To shorten time to recovery	Remdesivir, d1 200 mg/d, d2-10 100 mg/d	A	II_t	[123]
		Convalescent plasma	C	$II_{t,u}$	[139,157]
	To increase survival	Remdesivir, d1 200 mg/d, d2-10 100 mg/d	C	II_t	[123]
		Convalescent plasma	D	$II_{t,u}$	[139,157]
	To shorten time to recovery or increase survival	Baricitinib d1-14 4 mg/d	C	II_t	[137]
		Hydroxychloroquine (+/− azithromycin)	D	II_u	[20,125]
		Lopinavir/ritonavir	D	II_t	[126]
		Dexamethasone	D	I	[97]
		Tocilizumab	D	III	[130]
		Anakinra	D	$II_{h,t}$	[136]
Hospitalised cancer patients with COVID-19, oxygen therapy (WHO 4–7)	To shorten time to recovery	Remdesivir, d1 200 mg/d, d2-10 100 mg/d	A	II_t	[123]
		Convalescent plasma	C	$II_{t,u}$	[139, 157]
	To increase survival	Remdesivir, d1 200 mg/d, d2-10 100 mg/d	C	II_t	[123]
		Convalescent plasma	D	$II_{t,u}$	[139, 157]
	To shorten time to recovery or increase survival	Dexamethasone d1-10 6 mg/d	A	I	[97]
		Tocilizumab	C	II_u	[130–135]
		Anakinra d1-3 200 mg/d, d4-7 100 mg/d	C	$II_{h,t}$	[136]
		Hydroxychloroquine (+/− azithromycin)	D	II_u	[20,125]
		Lopinavir/ritonavir	D	II_t	[126]
		Baricitinib	D	III	No reference.
Anticoagulation					
Ambulatory cancer patients with COVID-19 (WHO 1–2)	To prevent thromboembolic complications	Consider prophylactic dose of LMWH after individual risk assessment	C	II_t	[142, 158]
Hospitalised cancer patients with mild COVID-19 (WHO 3–4)	To prevent thromboembolic complications	Prophylactic dose of LMWH	A	II_t	[158]
		Intermediate dose of LMWH (prophylactic dosage of LMWH BID or semi-therapeutic dosage of LMWH daily)	C	III	No reference.
Hospitalised cancer patients with severe COVID-19 (WHO 5–6)	To prevent thromboembolic complications	Prophylactic dose of LMWH	A	II_t	[159]
		Intermediate dose of LMWH (see before)	B	$II_{h,t}$	[7, 143]
Cancer patients with COVID-19, intubated (WHO 6)	To reduce mortality	Therapeutic dose of LMWH or UFH	B	II_t	[144]
Cancer patients with COVID-19, on ECMO (WHO 7)	To prevent thromboembolic complications	Therapeutic dose of UFH	A	III	[160]

For anticoagulants, dose adjustments in case of renal failure, thrombocytopenia or other bleeding risks apply. Abbreviations: BID, twice a day; ECMO, extracorporeal membrane oxygenation; LMWH, low molecular weight heparin; PEP, post-exposure prophylaxis; QoE, quality of evidence; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoR, strength of recommendation; UFH, unfractionated heparin; WHO, World Health Organisation.

The Kaplan–Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo which was not statistically significant [123]. A second, open-label RCT compared remdesivir for 5 days with remdesivir for 10 days. In patients with WHO Scale 3–5 the trial did not show a difference between the short or longer course of remdesivir. However, as the study did not include placebo control the degree of benefit cannot be determined [124].

We strongly support a recommendation for use of remdesivir for 10 days in patients with COVID-19 LRTID (WHO Scale 3–7) to shorten time to recovery in COVID-19 (AII_t).

8.2.2. Hydroxychloroquine

An open-label RCT (N = 150) compared hydroxychloroquine with standard of care in mild to moderate disease. Conversion rates to SARS-CoV-2 negative did not differ between the groups, patients on active drug experienced a higher rate of gastrointestinal adverse events [125]. A cohort study (N = 928) found a 3-fold risk of death in cancer patients treated with hydroxychloroquine/azithromycin combination for COVID-19 [20].

We therefore recommend against hydroxychloroquine treatment of COVID-19 (DII_u).

8.2.3. Other antiviral agents

The HIV-drug lopinavir/ritonavir, a protease inhibitor combination, has been extensively evaluated in clinical trials. Recently, the lack of efficacy shown in a small open-label RCT [126] was confirmed by the respective arm of the RECOVERY trial. Thus, lopinavir/ritonavir cannot be recommended for treatment of COVID-19 (DII_t).

Several influenza antiviral agents, such as oseltamivir, umifenovir, or favipiravir, have been tested in COVID-19 cases. Favipiravir showed an increased radiographic improvement in a small retrospective cohort trial [127]. Interferons were shown to eliminate SARS-CoV-2 effectively *in vitro* [128], and early clinical data reported possible benefits of inhaled or systemic interferons of different types [129]. However, available evidence is too limited to give specific recommendations on influenza drugs or interferons for treatment of COVID-19.

8.3. Immunosuppressive agents

8.3.1. Dexamethasone

The effect of corticosteroids was studied in an open-label RCT with hospitalised COVID-19 patients receiving standard of care (N = 4321) compared with additional low-dose dexamethasone (N = 2104). In the entire cohort, application of dexamethasone showed a significant reduction in 28-day mortality (rate ratio 0.83) and a shorter time to hospital discharge (12 days versus 13 days). The impact was most pronounced in patients requiring mechanical ventilation with 28-day mortality reduced by one third compared with a reduction of one fifth in patients only requiring non-invasive oxygen supplementation. In contrast, patients who were not requiring oxygen had a numerically higher mortality when treated with dexamethasone, however, without reaching statistical significance [97].

We strongly recommend dexamethasone in COVID-19 patients requiring oxygen or mechanical ventilation (WHO Scale 4–7, AI). In contrast, all asymptomatic patients or those well enough to be on ambient air should not receive low-dose dexamethasone for treatment of COVID-19 (DI). Clinicians need to be aware of potential adverse effects of corticosteroid treatment.

8.3.2. Cytokine inhibition

Tocilizumab, a humanised monoclonal antibody against interleukin-6 showed mixed results in severe COVID-19 patients. While clinical trials are still ongoing, available evidence is mainly based on retrospective or case–control studies. Four observational studies with a cumulative of 295 patients treated with tocilizumab reported only a non-significant trend towards clinical improvement and lower mortality compared with standard treatment [130–133].

A recent retrospective study in 544 patients with severe COVID-19 demonstrated that, after multivariable adjustment, the tocilizumab group (N = 365) had a 39% lower risk for the primary composite outcome of death or need for mechanical ventilation than the standard treatment [134]. Tocilizumab, however, was repeatedly associated with an increased rate of superinfections [134,135].

We marginally recommend tocilizumab in patients with a severe course of COVID-19 likely due to hyperinflammation (WHO Scale $\geq$ 5, CII_u). Further randomised trials are needed to confirm whether tocilizumab is effective and, if so, identify subsets of patients most likely to benefit from the drug.

In a prospective cohort study (N = 52) COVID-19 WHO Scale $\geq$4 patients received the human interleukin-1 receptor antagonist anakinra and were compared with a historical control (N = 44). Rates of progression to mechanical ventilation or death were 25% versus 73% [136].

We therefore marginally recommend anakinra in COVID-19 patients with WHO Scale $\geq$4 ($CII_{h,t}$).

8.3.3. JAK-inhibition

Baricitinib, an inhibitor of the JAK/STAT pathway commonly used in rheumatology patients, was evaluated in a retrospective cohort study in patients with COVID-19 WHO Scale 3 (N = 113). Patients treated with baricitinib experienced a significantly lower case fatality rate and rate of ICU admission as well as a higher rate of hospital discharge after two weeks [137]. We therefore

marginally recommend baricitinib in COVID-19 patients with WHO Scale 3 (CII_t).

A small RCT evaluated the JAK inhibitor ruxolitinib in patients with severe COVID-19 (N = 43) and observed a non-significantly shorter time to clinical improvement [103]. A case series of 14 patients with severe COVID-19 treated with ruxolitinib reported improvement in 12/14 patients [138].

8.4. Supportive therapy

8.4.1. Convalescent plasma

The effect of convalescent plasma was studied by one RCT which randomised 103 patients to receive a transfusion or not with patients enrolled 14 days after disease onset [139]. Furthermore, one comparative study investigated ten patients treated with convalescent plasma to ten matched historical controls [140]. Taken together, convalescent plasma transfusion failed to show beneficial effects on mortality. Convalescent plasma appears safe with <1% severe adverse events reported within the first 4 h after administration in 5000 patients with severe COVID-19 enrolled in the US Food and Drug Administration Expanded Access Program for COVID-19 [141].

We generally do not recommend convalescent plasma as treatment outside of clinical trials (DII_t). It might be considered in hospitalised COVID-19 patients (WHO Scale 3–7) to shorten time to recovery ($CII_{t,u}$).

8.5. Anticoagulation

Several studies described an increased incidence of thromboembolic events in patients with COVID-19. A study from Italy reported a cumulative rate of thromboembolic events in 21% of hospitalised patients, half of whom were diagnosed within 24 h after admission [142]. As cancer patients are *per se* at increased risk of thromboembolic events, we marginally recommend considering thrombosis prophylaxis with low molecular weight heparins (LMWHs) in outpatients with COVID-19 (WHO Scale 1–2, CII_t).

In all hospitalised COVID-19 cancer patients (WHO Scale 3–6), we strongly recommend thrombosis prophylaxis with LMWH (AII_t) to prevent thromboembolic complications. Despite prophylactic anticoagulation, an increased incidence of thromboembolic disease associated with COVID-19 in ICU patients was reported [7,143]. In a single-center cohort study, the use of therapeutic anticoagulation in COVID-19 patients requiring ventilation (N = 234) significantly reduced hospital mortality (29.1% versus 62.7%) compared with ventilated patients without anticoagulation (N = 161) [144]. We therefore moderately recommend therapeutic anticoagulation in ventilated COVID-19 patients (WHO Scale 6–7) with cancer to reduce mortality while carefully weighing the risk–benefit ratio of bleeding (BII_t).

For hospitalised COVID-19 patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localised loss of peripheral perfusion. Those patients who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy. Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy per the standard institutional protocols for those without COVID-19 (AIII).

For cancer patients with severe COVID-19 (WHO Scale 5–7), we recommend daily monitoring of coagulation parameters associated with worse clinical outcomes (thrombocyte count, activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, D-dimer, anti-Xa). If anticoagulant or antiplatelet therapy is applied, consideration must be given to potential accumulation (renal function) or drug–drug interactions and individually balanced against bleeding risk.

9. Conclusion and outlook

Cancer patients are especially vulnerable to SARS-CoV-2 infection and severe COVID-19 disease. Providing state-of-the art cancer care in times of COVID-19 poses a unique challenge to clinicians, patients and families, which mandates comprehensive treatment and management strategies. While first studies hint at potential treatment options for COVID-19, further trial results on antiviral therapies and vaccine candidates are eagerly awaited.

Author contributions

All authors actively participated in the guideline panel. N.G. coordinated the guideline panel and wrote the final version of the manuscript. All authors agreed upon guideline topics, performed a systematic literature search, extracted and rated the data, discussed and agreed upon the final recommendations, helped in writing and critically revised the first draft of the manuscript, and approved the final version of the manuscript.

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