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Original Research

2021 update of the AGIHO guideline on evidence-based management of COVID-19 in patients with cancer regarding diagnostics, viral shedding, vaccination and therapy



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Abstract The worldwide spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated infectious coronavirus disease (COVID-19) has posed a unique challenge to medical staff, patients and their families. Patients with cancer, particularly those with haematologic malignancies, have been identified to be at high risk to develop severe COVID-19.

Since publication of our previous guideline on evidence-based management of COVID-19 in patients with cancer, research efforts have continued and new relevant data has come to light, maybe most importantly in the field of vaccination studies. Therefore, an update of our guideline on several clinically important topics is warranted. Here, we provide a concise update of evidence-based recommendations for rapid diagnostics, viral shedding, vaccination and therapy of COVID-19 in patients with cancer. This guideline update was prepared by the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology by critically reviewing the currently available data on these topics applying evidence-based medicine criteria.

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Evidence regarding SARS-CoV-2 infection and COVID-19 is rapidly accumulating. A few months after publication of our evidence-based guideline on management of COVID-19 in patients with cancer [1], an update seems warranted on several clinically relevant topics. We have therefore summarised an update of recommendations for rapid diagnostics, viral shedding, vaccination and therapy of COVID-19 (Table 1).

1. Rapid antigen tests

Rapid antigen tests are generally known to exhibit an inferior accuracy (in particular with regard to sensitivity) compared with nucleic acid amplification technique and are therefore not recommended for patients with cancer [2]. This applies to rapid antigen tests for SARS-CoV-2 as well because comparative studies showed a reduced sensitivity compared with the reverse transcription polymerase chain reaction (RT-PCR) [3–6]. Sensitivity is particularly low in cases with a high cycle-threshold (Ct) value of the PCR with a reported sensitivity of approximately 40% in cases with Ct

values >30 [7]. However, even low viral loads are clinically relevant in patients with cancer because infectious virus has been successfully isolated from samples with Ct values >30, viral loads may be low or undetectable in throat swabs of patients presenting with lower respiratory tract involvement (LRTI), and recurrent clinical infection after viral load decrease to Ct values >30 has been reported [8–10]. Therefore, we do not recommend tests that may fail to diagnose clinically relevant infections and rather emphasise our recommendation to use RT-PCR for the diagnosis of SARS-CoV-2 infection in patients with cancer (AII_u). In certain emergency scenarios, where prompt diagnosis of SARS-CoV-2 is required, point-of-care RT-PCR tests may offer a valuable additional option with sensitivity and specificity according to the respective manufacturer to be kept in mind.

2. Viral shedding

Prolonged viral shedding of >100 days has been observed in immunocompromised patients with SARS-CoV-2

Table 1
Summary of new or revised recommendations.

Population/clinical situation	Intention	Intervention	SoR	QoE	References
Cancer patients with suspected SARS-CoV-2 infection	To diagnose SARS-CoV-2	RT-PCR from respiratory samples	A	II _u	[4,40]
Cancer patients after SARS-CoV-2 infection	To diagnose prolonged shedding	Test subsequent samples from respiratory material	A	II _u	[8,9,11,12,15]
Cancer patients with prolonged viral shedding	To avoid transmission	Assume infectiousness and continue adequate hygiene measures	B	III	[8,9,12]
Patients with cancer in general	To prevent COVID-19	Vaccination with an mRNA-vaccine as per protocol	A	II _t	[21–23]
Cancer patients with an increased risk of severe COVID-19 (i.e. haematological malignancy, active solid tumour or history of solid tumour <5 years ago)	To prevent COVID-19	Prioritise for vaccination	A	III	[30–32]
Healthcare providers	To keep risk for cancer patients as low as possible	Prioritise for vaccination	A	II _t	[33]
Hospitalised cancer patients with COVID-19, no oxygen therapy (WHO 3)	To shorten time to recovery or increase survival	Remdesivir	D ^a	II _t	[36]
Hospitalised cancer patients with COVID-19, oxygen therapy, no mechanical ventilation (WHO 4–5)	To shorten time to recovery	Remdesivir, d1 200 mg/d, d2-10 100 mg/d	B ^a	II _t	[35,36,38]
Hospitalised cancer patients with COVID-19, oxygen therapy, no mechanical ventilation (WHO 4–5)	To increase survival	Remdesivir, d1 200 mg/d, d2-10 100 mg/d	C ^a	II _t	[35,36,38]
Hospitalised cancer patients with COVID-19, mechanical ventilation (WHO 6–7)	To shorten time to recovery or increase survival	Remdesivir	D ^a	II _t	[36]
Hospitalised cancer patients with COVID-19, oxygen therapy, no mechanical ventilation (WHO 4–5)	To shorten time to recovery	Add baricitinib to remdesivir	B	II _t	[35,36,38,39]

SoR, strength of recommendation; QoE, quality of evidence; both as proposed by ESCMID [41].

^a Revised from previous AGIHO guideline [1].

infection [8,9,11,12]. This phenomenon is well known for other community acquired respiratory viruses [13,14]. In case of SARS-CoV-2 infection, especially patients with impaired B cell function and after haematopoietic stem cell transplantation (HSCT) have been found at an increased risk of prolonged viral shedding [8,9,11,12,15]. Although detection of viral RNA does not necessarily indicate clinically relevant infectiousness, clear proof of infectiousness has been demonstrated in several cases of extremely prolonged SARS-CoV-2 shedding by viral culture or detection of subgenomic RNA [8,9,12]. A lower Ct-value and thus a higher viral load increases the probability of successful viral culture, however, currently available data do not allow for definition of a clear cut off Ct-value above which successful viral culture can be ruled out [16,17]. Therefore, we strongly recommend follow-up testing of respiratory samples in patients with cancer with SARS-CoV-2 infection to identify prolonged viral shedding (AII_u). The possibility of intermittent negative test results due to inadequate sampling has to be kept in mind [11]. In case of prolonged detection of SARS-CoV-2, we moderately recommend to generally assume infectiousness and continue adequate hygiene measures (BIII).

3. Vaccination

Many vaccine candidates against SARS-CoV-2 are currently being developed including mRNA, protein

subunit, viral vector or inactivated vaccines. The first licenced vaccine is based on mRNA (BNT162b2). In a large phase III randomised controlled trial (RCT), 43,448 participants received 2 doses of the vaccine or placebo 21 days apart [18]. The primary end-point was the efficacy of the vaccine in reducing the cases with laboratory-confirmed COVID-19 with onset at least 7 days after the second dose. After a median follow-up of 2 months, the number of COVID-19 was 8 versus 162 in the vaccine or placebo arm, corresponding to a vaccine efficacy of 95%, and 1 versus 9 severe COVID-19 cases. Adverse events are reported for >50% of participants (most frequently local reactions, fatigue or headache). Fever (temperature >38 °C) occurred in approximately 15% of participants who received the vaccine. Approximately 3% of participants had an underlying malignant disease, ongoing immunosuppressive therapy was excluded. A second recently licenced mRNA-vaccine (mRNA-1273) showed in a phase III RCT with >30,000 participants a very similar efficacy of 94.1% and a comparable safety profile [19]. An interim analysis of several phase I/II-III trials on a replication-deficient adenoviral vector vaccine (ChAdOx1 nCoV-19) (N = 11,636) reported an overall vaccine efficacy of 70.4% [20]. Here, < 10% of participants were older than 65 years, patients with current cancer diagnosis were excluded, and different dosing regimens were assessed, rendering clear interpretation of results difficult at this time.

Generally, vaccination can be successful in patients with cancer even when they undergo immunosuppressive therapy [21–23]. Therefore, it can be assumed that vaccination against COVID-19 in patients with cancer will be effective in most cases. However, extrapolating from data from other vaccines, the level of efficacy may be expected to be reduced in certain populations of patients with cancer with intense immunosuppression such as recipients of allogeneic HSCT [21–23]. Patients treated with B-cell-depleting agents such as monoclonal anti-CD20 antibodies or anti-CD19 CAR T cells within the past 6 months typically mount little to no immune response to vaccines [24–28].

Patients with cancer have been shown to be at a higher risk of severe COVID-19, possibly because of older age and more frequent comorbidities [29]. In particular, patients with haematological malignancies are at a persistently increased risk, whereas solid tumour patients appear to suffer an increased risk mostly in the first year after diagnosis which drops to baseline >5 years after diagnosis [30]. For any malignancy, active disease confers a significantly increased risk of severe COVID-19 [31,32].

In conclusion, patients with cancer should be offered vaccination against COVID-19 using an mRNA-vaccine (AII_t). Other types of vaccine (viral vector or inactivated virus) have not been tested sufficiently to give a recommendation for patients with cancer. In patients who recently received an allogeneic HSCT or B-cell-depleting agents, it may be sensible to respect an interval of 6 months after therapy to achieve a better vaccine response. Patients with haematological malignancies, active disease or those with a recent diagnosis of a solid tumour should be prioritised (AIII). In addition, healthcare workers caring for patients with cancer should be prioritised in receiving the vaccination because vaccinating healthcare staff against influenza has been shown to reduce nosocomial transmission of the infection in cancer care (AII_t) [33].

4. Update on therapy

Several antiviral and immunosuppressive agents are being evaluated in patients infected with COVID-19 with promising results for some therapeutics, most prominently dexamethasone in hospitalised patients requiring oxygen (WHO scale 4–7) [34]. For specific recommendations in patients with cancer, please refer to our original guideline [1]. With regard to two agents, new trial data have since been published requiring a revision of prior recommendations, which will therefore be discussed in this update. Remdesivir is currently the only antiviral agent licenced by both American and European regulatory authorities for treatment of COVID-19 based on results from the ACTT-1 trial. This double-blind, placebo-controlled RCT in hospitalised

patients with COVID-19 and evidence of LRTI (N = 1063) showed a significant reduction in time to recovery which was most pronounced in patients requiring low-flow oxygen [35]. In contrast, the recently published WHO Solidarity trial, a large open-label RCT (N = 11,330) in hospitalised adult patients with COVID-19 that compared four different antivirals, amongst them remdesivir, to no trial drug, did not find any significant benefit of any of the regimens with regard to mortality, initiation of ventilation or duration of hospitalisation [36]. Subgroup analyses show in both trials a non-significant trend towards reduced mortality for remdesivir in patients requiring oxygen but not mechanical ventilation (WHO scale 4–5), whereas a trend towards inferior outcome was seen in patients with mechanical ventilation (WHO scale 6–7).

However, the WHO Solidarity trial was not placebo-controlled. Primary end-points in both trials differed and time to recovery was only assessed indirectly in the WHO Solidarity trial as patients on any trial drug were expected to stay longer in hospital simply to continue trial treatment. Furthermore, although the ACTT-1 trial was conducted in highly industrialised countries, the WHO Solidarity trial was conducted worldwide in a variety of healthcare settings which might impact implications of results on resource-rich countries.

Benefit of remdesivir has been suggested especially early in the phase of active viral replication in COVID-19. Patients with cancer, however, in particular those with impaired humoral immune function, have been noted to be at risk of prolonged periods of active viral replication [8,9,11,12]. In COVID-19, a recent case report on a patient with complete absence of humoral immunity showed viral clearance following remdesivir administration [37]. A large retrospective cohort study of patients with cancer with COVID-19 (N = 2186) treated in the US also found a potential benefit for remdesivir with regard to mortality [38].

Although the WHO does no longer recommend remdesivir for treatment of COVID-19 in the general population, this guideline panel still sees a potential benefit for immunocompromised patients with cancer at risk of impaired viral clearance. However, we feel it necessary to downgrade the strength of recommendation, as well as narrow the population with potential benefit as follows: we moderately recommend remdesivir for up to 10 days in patients with non-invasive oxygen therapy (WHO scale 4–5) with the intent to shorten time to recovery (BII_t) and weakly with the intent to reduce mortality (CII_t). We recommend against remdesivir in patients without requirement of oxygen therapy (WHO scale 3) and with invasive ventilation (WHO scale 6–7) (DII_t).

Another class of agents with potential efficacy against COVID-19 are JAK inhibitors, such as ruxolitinib which were reviewed in our prior guideline [1]. A recently published double-blind, placebo-controlled

RCT analysed the effect of remdesivir plus the JAK inhibitor baricitinib or placebo in hospitalised patients (N = 1033) with COVID-19. The primary end-point of reduced time to recovery was met in the entire cohort (7 versus 8 days) and was most pronounced in those patients receiving high-flow oxygen or non-invasive ventilation (10 versus 18 days) [39]. Therefore, we moderately recommend the addition of baricitinib to remdesivir in patients WHO scale 4–5 (BII₁).

5. Conclusion and outlook

Intense efforts with regard to basic and translational research and clinical trial activities have allowed us to fast expand our preventive, diagnostic and therapeutic options for patients with cancer with regard to SARS-CoV-2 infection and COVID-19. Ongoing studies will further improve our understanding of this infectious disease and will further optimise our current management strategies.

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