Managing haematology and oncology patients during the COVID-19 pandemic: Interim consensus guidance

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Abstract

A pandemic coronavirus, termed SARS-CoV-2, causes a respiratory illness called COVID-19 disease, which is often severe or life-threatening. Patients with cancer may have compromised immunity due to their disease or its treatment, and early reports suggest cancer is a risk factor for severe COVID-19 disease. Community transmission of SARS-CoV-2 has the potential to overwhelm healthcare services, compromising the delivery of cancer investigations and care. Pending definitive evidence, this interim consensus guidance summarises the clinical presentation and diagnosis of COVID-19 disease, provides factors to consider when managing patients with cancer, and discusses risk factors for severe COVID-19 disease. Possible actions for clinicians managing patients with cancer are suggested, and are phased according to the presence or absence of community transmission and disruption to normal healthcare provision. Key communication points for patients are proposed, and the potential impacts of COVID-19 disease on transfusion practice, stem cell transplantation and cellular therapies, clinical trial participation and provision of palliative care are discussed.

Introduction

Following a cluster of viral pneumonia cases in late 2019, a novel coronavirus was isolated and reported in Wuhan, China in January 2020[1]. This virus, now termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a respiratory disease called COVID-19 in infected individuals. COVID-19 disease spread rapidly worldwide, with epidemics in multiple countries and continents meeting conventional definitions of a pandemic. Although 81% of patients with COVID-19 have a mild illness, 14% have severe illness requiring hospitalisation and supplemental oxygen, and the remaining 5% become critically ill with respiratory failure, septic shock and/or multi-organ dysfunction[1]. Recent estimates of COVID-19 case fatality rates are around 2%, rising to 15% in patients aged 80 years or over[1].

By early March 2020, the first instances of community spread of COVID-19 were documented in Australia, and the first COVID-19 cases were diagnosed in New Zealand. Given the spread of COVID-19 disease in other countries, including the dramatic rise in case numbers in Europe and the United States in March 2020, a further rise in cases across Australasia over the following month appears likely. At present, no vaccine or specific antiviral therapy is available. The only measures available to prevent or delay community spread of COVID-19 are containment and rigorous case finding. Once COVID-19 becomes widespread within a community, quarantine and social distancing measures may slow its further spread, and have been adopted in many jurisdictions.

Patients with cancers are frequently immunosuppressed by their disease and/or treatment, and are at increased risk of severe complications of respiratory viruses[2].

Moreover, many haematology and oncology patients will have additional risk factors for severe COVID-19 disease, such as advanced age and comorbidities[3].

Early review of a Chinese national data repository suggested a disproportionately higher prevalence of cancer (mainly lung cancer) in patients with confirmed COVID-19, when compared to the general population[4]; however no data are available on the incidence of COVID-19 in cancer patients compared to the general population[5]. Early COVID-19 outcome data suggested a case fatality rate of 5.6% among patients with cancer[1], and one study suggested patients with cancer had a 3.5 times higher risk of severe COVID-19 disease.[4] However, reported case numbers remain low, and the relative contribution of other risk factors, including age, to this risk is not clear.[6] Haematopoietic stem cell transplant (HSCT) recipients could be at particularly high risk: prior to the emergence of SARS-CoV-2, progression of the less pathogenic seasonal coronavirus infections from the upper to lower respiratory tract occurred in up to 30% of HSCT recipients[7].

Patients with cancer could be at elevated risk of severe COVID-19 disease, while delivery of cancer therapies could be disrupted by quarantines, social distancing measures, or disruption to routine healthcare delivery by the pandemic. Pending more definitive evidence, this article presents interim guidance, based on expert opinion, to aid decision-making for clinicians treating patients with cancers. The suggestions provided here may be relevant to both adult and paediatric patients.

1. Clinical presentation, diagnosis and treatment considerations

Clinically, COVID-19 disease is most frequently associated with fever (90 – 98%), cough (59 – 76%) and lethargy (38 – 70%) [3,8-10]. Abnormalities on CT chest have been reported in 80 – 100% of admitted patients, with bilateral ground glass opacities the most common finding[3,8,10-12]. Median time to development of dyspnoea has been reported as 5 – 8 days [3,9] with median hospital admission stay of 7 – 10 days[3]. In adults, intensive care admission has been reported in 26% of all admissions at a median time of 12 days after illness onset, coinciding with the onset of acute respiratory distress syndrome (ARDS).[10] Atypical clinical presentations of other infections are common among cancer patients receiving highly immunosuppressive therapies,[13] although whether this applies to COVID-19 disease is no yet known.

The clinical impact of COVID-19 disease in children with cancer or haematological malignancy is currently unknown. Although the mechanism is not clear, children appear less frequently affected by SARS-CoV-2, representing only 2% of COVID-19 presentations in a large Wuhan series, with no deaths reported in those under 9 years of age[1,14]. When symptomatic illness does occur in children, it is usually mild, with fever and cough most frequently reported. Diffuse pulmonary infiltrates in an asymptomatic child were recently described[15]. However, while asymptomatic or mild illness following SARS-CoV-2 infection is the norm in otherwise well children, the risk of severe illness may be higher in those with immune compromise. This is highlighted by a report of severe COVID-19 disease in a child receiving chemotherapy for acute lymphoblastic leukaemia[16].

Diagnosis can be made by specific RT-PCR of nasopharyngeal or oropharyngeal swabs and lower respiratory tract samples[3] with median viral shedding of 20 days (interquartile range 17-24 days)[10]. The SARS-CoV-2 virus may also be detected in stool samples. Although the impact of this on virus transmission remains uncertain, this should be considered in patients with therapy-associated diarrhoea or with stomas[17]. Clinicians must note that the coronavirus testing incorporated in routine respiratory virus PCR panels may not detect SARS-CoV-2, and should verify suitability of the assays in local use for COVID-19 disease testing. Following infection, SARS-CoV-2 viral shedding might be more prolonged in patients with cancer: viral shedding of seasonal coronaviruses lasts up to 4 weeks in patients with cancer,[7] and shedding of other respiratory viruses is prolonged in immunosuppressed patients.[18]

Interim guidance for the treatment of COVID-19 disease is available elsewhere[19]. Antiviral therapies such as lopinavir-ritonavir and remdesivir are undergoing evaluation in clinical trials, and the role of anti-cytokine therapies such as tocilizumab for severe infections is under exploration. Pending further information, we suggest that management of COVID-19 disease should be similar for patients with and without cancer. Immunocompromised patients with suspected or confirmed COVID-19 should be discussed with an infectious disease or clinical microbiology specialist. However, clinicians should be aware of the following considerations for patients with cancer who develop symptoms of COVID-19 disease:

i. Among immunocompromised patients, the differential diagnosis of fever and respiratory symptoms is broad, and clinicians should be alert to the possibility of alternative or secondary infections, including bacterial, fungal

or other viral infections. Early recognition and treatment of bacterial sepsis remains vital, particularly in severely neutropenic patients;

ii. Pneumonitis can occur following certain cytotoxic chemotherapies, immune checkpoint blockade or radiotherapy, and shares clinical and radiological features with COVID-19 disease. Corticosteroids should be considered if therapy-related pneumonitis is suspected, acknowledging that a detrimental impact of corticosteroids on the risk of severe COVID-19 disease has not been excluded;

iii. Temporary discontinuation of cancer therapies may be warranted for some patients with cancer who develop COVID-19 disease, to minimise treatment-related immunosuppression or to reduce the risk of drug interactions. This should be undertaken in discussion with an oncologist or haematologist familiar with management of the malignancy, who can advise on the benefits and risks of pausing therapy.

For each of the reasons above, community assessment and management procedures developed for healthy people with COVID-19 disease may be less well suited for some patients with cancer.

2. Possible risk factors for severe COVID-19 disease

Established risk factors for severe COVID-19 disease in adults include advanced age and medical comorbidities[3]. In-hospital death has been independently associated with higher age, higher Sequential Organ Failure Assessment (SOFA) score and elevated D-dimer[10]. Importantly, some laboratory findings associated with adverse COVID-19 disease outcomes, such as lymphopenia, neutrophilia, elevated D-dimer and elevated lactate dehydrogenase, are frequent in patients with cancer.

The applicability of these biomarkers of COVID-19 disease severity to patients with cancer has not been established, and they should be interpreted with caution.

In an early report of patients with COVID-19 disease in China, receipt of chemotherapy or cancer surgery was a risk factor for severe complications[4]. Patients with cancer were also reported to be at higher risk of severe complications including intensive care unit (ICU) admission, invasive ventilation or death[4] and deteriorated more rapidly (median of 13 days vs. 43 days). Receipt of cancer therapy or surgery within the preceding month was associated with an increased risk of severe events after adjusting for other factors (odds ratio 5.34, $p<0.01$)[4]. However, the number of COVID-19 cases with cancer were small and had a higher rate of smoking, which may also increase risk of severe disease[5].

Risk factors for severe COVID-19 disease in children are currently unknown, although a study of common circulating coronaviruses in children found that co-infection, younger age and immunocompromised were associated with an increased risk of severe lower respiratory tract infection[20].

Specific risk factors for severe respiratory viral infection in patients with solid tumours are poorly described in the literature. Although many treatments for solid tumours do not cause prolonged severe lymphopenia or neutropenia, severe infection risk may be elevated due to disruption of mucosal barriers by chemotherapy-induced mucositis, or due to altered anatomy and reduced physiological reserve due to the malignancy itself or as a consequence of surgery or radiotherapy[21]. This may be of

particular relevance to patients with lung cancer, who made up the majority of cancer patients affected by COVID-19 disease in an early report[4].

Among adult haematology and HSCT patients with seasonal coronavirus (not SARS-CoV-2) infections, the following risk factors for lower respiratory tract disease were identified [2,7,22]: Age 50 years and above; receipt of corticosteroids; graft versus host disease (GvHD); lymphopenia; neutropenia; hypogammaglobulinaemia < 4 g/L.

Until specific risk factors for severe COVID-19 disease among patients with cancer have been identified, we suggest clinicians use their clinical judgement, referencing established risk factors for severe manifestations of other respiratory viruses, to evaluate an individual patient's risk of severe COVID-19 disease.

3. **Actions for consideration by haematologists and oncologists**

The healthcare system and policy responses to COVID-19 are evolving rapidly. Haematologists and oncologists should regularly review and follow institutional, specialist college, state-level and federal government recommendations. We encourage haematology and oncology representatives to engage with, and participate in, pandemic planning within their health organisations.

As many patients with cancer may be at increased risk of severe COVID-19 disease, we suggest clinicians take a proactive approach. In Table 1, we propose actions to consider, phased according to the presence or absence of community spread of COVID-19 disease locally, and the capacity of healthcare services to deliver routine

care. The actions suggested in Table 1 will not be appropriate for all settings, and are not exhaustive, but are intended to prompt discussion among clinicians planning their own service's COVID-19 response. At each phase, clinicians should review actions they could take to prepare for the subsequent phase. These actions are cumulative – the measures in phases B and C are suggested in addition to the earlier phases. Institutional, local, state-wide or federal/national policies/recommendations (including for social distancing, isolation, quarantine or personal protective equipment use) are likely to cover some or all of these actions, and should take priority.

Social distancing measures, quarantine and visitor limitations will limit opportunities for family support and advocacy, impacting an important sense of connection and source of strength and wellbeing, particularly for Indigenous peoples. We recommend that the impact of these measures is recognised, and is counterbalanced with measures to ensure safe non-physical contact and support, such as facilitation of video and telephone contact. Clinicians should refer to guidance for the delivery of culturally safe care.[23,24]

Overseas experience is that COVID-19 spread can occur rapidly, and in some regions, primary care and acute care facilities have become overwhelmed[1,25]. This may be compounded by COVID-19 infection of medical personnel, quarantine requirements and school closures, all of which may reduce available staffing levels[3]. If acute care facilities are overwhelmed, institutions might make alternative provisions for the care of patients with non-communicable diseases such as cancers. Adaptive measures could include increased use of community care (including

'hospital in the home' services) or of private healthcare facilities. Clinicians may need to work flexibly to facilitate safe service provision in alternative settings.

In extreme situations, resource constraints may mandate the prioritisation or modification of patients' cancer therapies. While it is anticipated that institutions will develop their own management plans, which will take priority over suggestions made here, individual patient decisions should be the responsibility of clinicians who are familiar with the malignancy, its treatment, and with other therapeutic options. Clinicians may have to balance the relative risks of developing COVID-19 disease while severely immunosuppressed, or of developing a severe treatment complication, against the risks of tumour progression, while taking into account the prevailing state of the healthcare service. Decisions around treatment and resource allocation must be fair, just and grounded in the principles or equity and sustainability. Refer to relevant regulatory guidance, such as that provided in the Medical Council of New Zealand document, "Safe practice in an environment of resource limitation"[26], and to relevant ethical frameworks, such as that outlined in the 2020 "Australian Health Sector Emergency Response Plan for Novel Coronavirus (COVID-19)".[27]

If possible, we suggest discussing the risks and benefits of any treatment modifications among clinical peers within a multidisciplinary or team meeting. Clinicians should take account of ethical principles including equity, proportionality and transparency, and the need to protect vulnerable populations, including indigenous peoples, who experience a higher burden of cancer and infectious disease[26-30]. We recommend any treatment modifications, and the reasons for them,

are clearly documented in each patient's medical record, and are communicated to the patient and their GP. We recommend clinicians make follow-up arrangements, so once resource availability allows, any treatment modifications can be reviewed - in some circumstances it may be appropriate to resume a postponed treatment, or to complete an abbreviated treatment course.

Table 1: Actions to consider, according to community-level COVID-19 transmission and healthcare capacity

Phase	Aims	Issue	Actions to consider
A: No apparent community-level COVID-19 transmission*	Reduce risk of nosocomial acquisition of respiratory viruses Inform & educate patients and staff	Staff education	Education or re-education, including of receptionists and administrators, ward and day unit staff, junior & senior clinicians, allied health teams: • Hand hygiene practices • Use of PPE • Institutional policies for respiratory virus isolation • Policies to limit unwell ward visitors Importance of staying away from work if unwell with fever or respiratory symptoms
		Early identification of potential cases	Discuss patients hospitalised with febrile respiratory illnesses & no identified cause with infectious diseases or microbiology team regarding role of investigation for COVID-19
		Vaccination	Encourage staff & patient uptake of seasonal influenza vaccination
		Advice to patients	Advice for concerned patients (see Section 4) How to present if febrile with respiratory symptoms
B: Community-level COVID-19 transmission; healthcare service provision as normal	Reduce risk of nosocomial SARS-CoV-2 acquisition Reduce risk of staff acquisition of SARS-CoV-2	Clinics	Screen for COVID-19 disease symptoms before clinic attendance (e.g. via written information, telephone contact, or direct symptom enquiry) Conduct outpatient clinics away from acute care facilities Conduct selected consultations remotely (via telephone, video, written advice) Defer some non-urgent new & follow-up appointments Limit visitors attending with patients
		Routine investigations	Review frequency & location of routine tests (e.g. blood tests, scans), which may bring patients with cancer into contact with those with respiratory symptoms
		In-department	Establish COVID-19 isolation/assessment process for haematology/oncology patients,

	Support any recommended social distancing measures	isolation/assessment facility (e.g. fever clinic)	aiming to avoid exposure to SARS-CoV-2 and to separate from other haematology/oncology waiting and treatment areas
		Cancer therapy and supportive care	Optimise prophylactic measures (e.g. G-CSF, antimicrobial prophylaxis, immunoglobulin replacement) to reduce risk of infections requiring inpatient therapy Employ alternatives to transfusion (see Section 5) Reduce unnecessary immunosuppression if safe to do so Defer or delay selected non-time critical cancer therapies if will not compromise outcome
		Community or hospital-in-the-home services	Enhance capacity for community care as alternative to cancer centre or inpatient care
		Wards/inpatient care	Limit ward visitors Minimise non-essential hospital admissions Consider early discharge from hospital if safe to do so Reduce non-essential staff & student contact with inpatients
		Clinical meetings	Limiting meeting attendance to key attendees Use teleconferencing facilities when possible
		Education	Postpone non-essential face-to-face educational meetings Provide education via teleconferencing or other electronic formats
		Staff working arrangements and leave	Ask staff to work from home when not required in person Review upcoming annual and study leave to provide contingency for sickness/absence Define minimum staffing for provision of skeleton service
C: Community-	Reduce demand on acute services	Alternative treatment delivery settings	Implement any plans to deliver cancer investigation & treatment in alternate settings (e.g. in community or private healthcare facilities)

level COVID-19 transmission; healthcare service capacity exceeded			Maximise use of remote consultations (via telephone, video, written advice)
	Prioritise and deliver urgent and essential cancer therapies Reduce risk of treatment complications that cannot be adequately managed Ensure adequate staffing for essential services	Treatment prioritisation and demand limitation meetings	Prioritise urgent and potentially-curative treatments Ensure equity, proportionality and transparency; refer to ethical & regulatory guidance Document decisions and review regularly
		Treatment modifications	If necessary, clinician-led modification of cancer treatments on case-by-case basis. Risk/benefit will vary. Seek peer review & support. Examples could include: • Oral alternatives to parental therapy • Selection of less myelosuppressive regimens • Abbreviated or shorter-course treatments • Schedules requiring less frequent cancer centre attendance • Deferral of treatment where appropriate Document & communicate decisions clearly, including to patients Arrange review of decisions at appropriate interval
		Transfusion support	Adopt restrictive transfusion thresholds (see Section 5)
		Staff leave	Cancel annual and study leave Implement plans for skeleton service provision

The lists of actions to consider are cumulative; actions suggested during phase B are in addition to those during phase A, and actions from all phases should be considered during phase C. PPE, personal protective equipment

*At the time of writing, some jurisdictions had already progressed past this phase

4. Information for patients

Many patients with cancer, and their families, will be concerned or distressed about the risk of developing COVID-19 disease. A list of suggested messages for haematologists and oncologists to communicate to their patients is outlined in Box 1.

As COVID-19 recommendations are likely to change frequently, clinicians should direct patients towards the most up to date resources, from the Department of Health in Australia (https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert), and from the Ministry of Health in New Zealand (https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus).

Steps should be taken to avoid the risk of patients with symptoms suggesting COVID-19 disease, or with a known SARS-CoV-2 contact, presenting unannounced to cancer centers or clinics. We suggest cancer centers advise patients of the appropriate mode of presentation if they develop consistent respiratory symptoms, or have been in contact with someone with COVID-19 disease. This may include use of a triage line, assessment in an acute care setting with isolation facilities, or use of a dedicated community assessment facility. This advice should be consistent with institutional, state or federal guidance, and should be disseminated to receptionists, nursing and clinical staff, as well as to patients themselves. The advice should take account of the possibility that cancer patients presenting with fever may be at elevated risk of bacterial or fungal infection requiring prompt antimicrobial therapy,

and that the differential diagnosis of fever should not be limited to COVID-19 disease (see Section 1).

Regarding overseas travel, we suggest patients with cancer follow advice from the Australian Department of Foreign Affairs and Trade (https://www.smarttraveller.gov.au) or New Zealand Ministry of Foreign Affairs and Trade (https://safetravel.govt.nz), and consider avoiding travel to or via countries with community transmission of the SARS-CoV-2 virus. Patients should ensure they travel with a sufficient supply of their medicines, taking into account the potential risk of being quarantined during or after their journey. Patients must be aware that in addition to a higher risk of infection with SARS-CoV-2, that access to medical services may be difficult or impossible in countries or regions where COVID-19 disease has exceeded the medical and hospital capacity of their destination. The World Health Organisation (WHO) issues a daily situation report for all regions (https://www.who.int/docs/default-source/coronaviruse/situation-reports), which may help inform clinicians and their patients regarding decisions for essential travel.

Both domestically and for overseas travel, we suggest patients carry a copy of a recent clinic letter detailing their cancer diagnosis, its treatment, and contact details for their lead oncology or haematology clinician, and communicate this to any healthcare providers. Measures that might be widely implemented in a pandemic setting, and which may require modification for immunocompromised patients with cancer, include: community-based assessment; home treatment of COVID-19 disease; cohorting with other infected patients in a non-specialist ward; symptomatic

COVID-19 treatment without confirmatory investigations or without empiric antibiotics.

Patients with family members or other close contacts who have suspected or confirmed COVID-19 disease, should aim to remain isolated from these contacts, and should inform their cancer centre of any quarantine requirements. The recommendations of the relevant health department regarding quarantine and isolation should be followed.

BOX 1: Communication points regarding COVID-19 disease for patients with cancer

- Severe COVID-19 disease is possible in any individual, but patients with cancer may be at higher risk due to their disease and/or its treatment
- Patients with cancer should review, monitor, and closely adhere to recommendations from the Department of Health (Australia) or Ministry of Health (New Zealand) regarding hand hygiene, social distancing and other measures to avoid COVID-19 disease
- Preventive action to reduce the opportunity for transmission of infection should take high priority for patients and carers
- Shedding of the SARS-CoV-2 virus may be protracted in patients with a suppressed immune system
- Patients should not present unannounced to the cancer center or clinic if they have symptoms suggesting COVID-19 disease, or had recent contact with a person with COVID-19 disease; provide advice on how to present
- COVID-19 disease is not the only potential cause of fevers or respiratory symptoms; patients must continue to follow febrile neutropenia recommendations (if applicable), and be alert to other side effects of treatment (including pneumonitis, if applicable)
- Patients should communicate their cancer diagnosis and any current treatments to clinicians, or to telemedicine advice providers, if under assessment for possible or proven COVID-19 disease or exposure – it may be helpful to carry a copy of a recent clinic letter
- If planning overseas travel, patients should advise their clinician, check travel insurance coverage and exclusions, review travel advice from the Australian Department of Foreign Affairs and Trade (www.smarttraveller.gov.au) or the New Zealand Ministry of Foreign Affairs and Trade (https://safetravel.govt.nz), and ensure they have sufficient medication for their journey, taking the risk of quarantine into account
- No vaccine for COVID-19 is available, but vaccination against influenza (and against other infections if appropriate), and adherence to other measures to reduce infection risk (e.g. prophylactic antimicrobials, limiting dusts & soil exposure if prolonged severe neutropenia) may reduce the risk of other infections

5. Transfusion considerations

Transfusion support for patients with cancer and blood disorders accounts for the majority of outpatient red cell and platelet utilisation, and for a large fraction of inpatient transfusions[31].

Transfusion requires close patient monitoring, placing demands upon in- and outpatient cancer services, which could fall under strain if COVID-19 disease spreads within the community. Visits to acute care facilities for transfusions could expose immunocompromised patients to other patients, or to staff, who are shedding SARS-CoV-2. Community spread of COVID-19 may reduce the blood donor pool, and threaten blood supplies, both through deferral of donors, and through blood service staff shortages, or shortages of consumables and reagents. Finally, although there have been no cases of transfusion-transmitted infections (TTI) documented and there is no precedent for transfusion transmission of respiratory viruses, SARS-CoV-2 viral RNA can be detected in the plasma of people with COVID-19 disease, and donor deferral is the only current mechanism in place for preventing transmission via blood components[32]. Pathogen reduction technologies (PRT) that can be applied to platelets or clinical plasma have been shown to be effective for other coronaviruses but are not in routine use in Australia or New Zealand, and no licensed PRT is available for whole blood or red cells.

Updated information on risk of transfusion-transmission and donor deferrals in place to prevent TTI can be found from the Australian Red Cross Lifeblood (www.donateblood.com.au) and AABB.[33] Information about the National Blood Authority's response to COVID-19 and the National Blood Supply Contingency Plan

is available from the National Blood Authority.[34] The World Health Organization also provides guidance for national blood services on managing national blood supplies.[35]

Community spread of COVID-19 disease, therefore, has the potential to diminish the donor pool, to threaten the capacity of cancer services to provide routine transfusion support, and to increase the risks that transfusion-dependent patients come into contact with other individuals with SARS-CoV-2. Each of these factors may favour the adoption of more restrictive transfusion practices once community spread of COVID-19 is established, and especially if cancer and blood services experience capacity constraints.

Restrictive red cell transfusion strategies have been assessed in a variety of settings, although optimal red cell transfusion thresholds in patients with haematological malignancies have not yet been established,[36] and practice varies widely[37]. Preliminary data in outpatient transfusion support for myelodysplastic syndromes suggests that more restrictive red cell transfusion thresholds require fewer red cells, although could be associated with inferior quality of life[38]. Red cell transfusion thresholds have been reviewed elsewhere[39], and it should be noted that highly restrictive thresholds may be inappropriate in patients with cardiovascular disease[40]. For some patients, iron, folic acid, vitamin B12 or erythropoietin may present alternatives to red cell transfusion, or could be used to limit transfusion requirement.

Due to their short shelf-life, platelets are most likely to be impacted by blood supply shortages. While prophylactic platelet transfusion reduces the risk of bleeding among

patients with haematological cancers receiving intensive chemotherapy, an impact on survival has not been demonstrated[41]. International guidelines recommend a 'no prophylactic platelet transfusion' strategy for asymptomatic patients with chronic bone marrow failure (including patients taking low dose oral chemotherapy or azactidine) and to consider not giving prophylactic platelet transfusions to well patients without evidence of bleeding after an autologous stem cell transplant[42]. A trial to assess efficacy and safety of prophylactic tranexamic acid during severe thrombocytopenia from intensive therapy in haematology and oncology patients is ongoing[43]. Research into alternatives, such as frozen platelets, is ongoing, but these products are not yet available for routine use[44,45]. In the event of healthcare capacity restraint or a threat to the supply of platelets for transfusion, clinicians should consider transfusing only those patients at highest risk of bleeding, and consider alternatives to platelet transfusion (such as tranexamic acid), adoption of restrictive platelet transfusion criteria and deferral of non-urgent therapies that may require platelet transfusion support.

6. Special situations

Bone marrow transplantation and cellular therapies

Both autologous and allogeneic stem cell transplantation, and cellular cancer therapies, such as chimeric antigen receptor (CAR) T-cell therapies, present specific challenges, as they may place recipients at high risk of infection, often for an extended period. Moreover, if healthcare services are overwhelmed by demand, there is a risk that prompt intensive care therapy for transplant and cellular therapy recipients cannot be delivered.

The regulatory and ethical considerations for modifying or deferring bone marrow transplants and/or cellular therapies mirror those for non-cellular therapies. Team-based discussion, application of the principles of equity, transparency and proportionality, and clear documentation of decisions and their reasons, with subsequent review once capacity allows, are recommended.

Recipients of autologous and allogeneic transplantation

Infection with respiratory viruses can present an increased mortality risk for HSCT recipients,[46] and transplantation of recipients with active respiratory infections is often delayed, where possible. Inclusion of SARS-CoV-2 in pre-transplant infectious disease screening of symptomatic recipients should be considered if community transmission is present, a positive result prompts consideration of delay or deferment. Widespread community transmission of SARS-CoV-2 should be taken into account when considering the risks and benefits of proceeding to transplantation, which are likely to differ on a case-by-case basis. If community SARS-CoV-2 transmission is occurring, transplant recipients should be advised to self-isolate prior to the procedure.

Post-transplant care should be guided by the principles outlined in previous sections, with particular attention to the period of greatest risk prior to immune recovery. Among adult HSCT recipients, the immunodeficiency scoring index (ISI), initially developed for respiratory syncytial virus (RSV), might assist with evaluation of the risk of progression to lower respiratory tract disease and of mortality[47]. This index has been applied to HSCT recipients with influenza virus infection[48], but it has not

yet been validated for SARS-CoV-2 infection. Consideration should be given to early vaccination for respiratory pathogens (seasonal influenza and *S. pneumoniae*).

Donor considerations

For allogeneic stem cell transplantation, travel restrictions may limit availability of overseas donors, and as a consequence position statements have been provided by a number of transplant organisations including the World Marrow Donor Association.[49] Donor registries and bone marrow transplant and cellular therapy societies have produced guidelines and position statements,[49-52] which are frequently updated.

Australasian HSCT recipients receive a large proportion of unrelated donor stem cell products from international donors (72% in 2018)[53]. The complex logistics of cross-national allogeneic stem cell product donation is vulnerable to disruption from donor availability, donor site staffing, international travel disruption, courier availability, and specialist laboratory staffing. The presence of community SARS-CoV-2 transmission in donor regions, as well as travel restrictions may limit availability of donors. Donor cancellation may occur at short notice and between donor assessment and stem cell collection, placing recipients at risk of having no stem cell product following myelosuppressive conditioning. Contingency planning could include securing back-up donors if possible, or collection, transportation, cryopreservation, and storage of the stem cell product at the receiving transplant unit before commencing recipient conditioning.

It is currently unclear whether SARS-CoV-2 is transmissible in cellular therapy products. As noted above, viral RNA can be detected in plasma of COVID-19 patients, but the presence or absence of infectious virus has not been reported.[33] At the current time no recommendation can be made for testing of donors due to variable availability of PCR testing at donor collection centres and the lack of a serologic assay, but SARS-CoV-2 testing of donors may be adopted in future. Donors in all regions should be assessed for risk based on current knowledge of local COVID-19 prevalence, travel history, exposures and symptoms.

The impact of COVID-19 on international transport may affect the supply chain for autologous chimeric antigen receptor T-cells. For example, tisagenlecleucel (Kymriah©) is currently manufactured at a US facility. As for stem cell donors, patients undergoing apheresis and awaiting infusion of CAR T-cells should consider self-isolation to minimise the risk of SARS-CoV-2 exposure during the period of greatest vulnerability.

Clinical trial participants

In accordance with principles of ICH GCP (paragraph 2.3), the “rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.”[54] At phases B and C (see Section 3), it may be necessary to reduce routine follow-up appointments, institute remote or telehealth reviews or modify treatment plans and strategies for treatment delivery in the interest of the study participant. If this will lead to protocol deviations or violations, clinicians should contact the medical monitor or sponsor of their study, and contact the relevant human ethics committee. International travel restrictions

could affect trial monitoring, start-up and investigator meetings, and distribution of investigational products and laboratory samples. When enrolling new participants, Principal Investigators should take reasonable steps to ensure a trial is proceeding as usual, and consider the potential impact of COVID-19 disease on the capacity of their own centre to conduct study procedures according to the trial protocol.

Palliative Care

Palliative care services will play a critical role during a COVID-19 pandemic to ensure quality end-of-life care. This will include managing symptoms of both cancers and COVID-19 disease, rapid reassessment of an individual patients' goals if treatment plans are changed, helping patients and families navigate decisions regarding end-of-life care during a period of potential social and economic disruption, and delivering culturally safe and responsive care.[23,24] Visitor restrictions on wards, quarantine or isolation requirements, and any imposition of travel restrictions or social distancing measures, are likely to complicate the planning and delivery of palliative care. Goals of care, enduring powers of attorney or advance care directives should be clearly documented.

At the same time as raising demand, COVID-19 disease presents a threat to palliative care staffing and capacity. Many of the suggestions in Table 1 will be relevant to palliative care services, and we encourage cancer services to involve palliative care representatives during COVID-19 contingency planning.

Summary

The COVID-19 pandemic presents a challenge of global reach and significance, which is unprecedented in the era of modern haematology and oncology. We present interim COVID-19 guidance for clinicians caring for patients with cancer, who may be particularly vulnerable both to severe COVID-19 disease, and to the potential impact of the pandemic on the provision of cancer investigations and treatment.

This is a rapidly-evolving situation, and we emphasise again that clinicians must regularly review and implement institutional, local, state-wide and federal/national policies, modifying or adapting the suggestions provided here as needed. Finally, given the potential severe impact of COVID-19 disease on people with cancer, we propose that oncologists and haematologists advocate for the timely application of public health measures that might contain, delay or mitigate the spread of COVID-19 disease, and for rigorous adherence to these measures.

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