INTERNAL MEDICINE JOURNAL

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doi:10.1111/imj.14859

POSITION PAPER

Australian and New Zealand consensus statement on the management of lymphoma, chronic lymphocytic leukaemia and myeloma during the COVID-19 pandemic

Pietro Di Ciaccio,[1,2] Georgia McCaughan,[1,2,3] Judith Trotman,[3,4] Phoebe Joy Ho,[3,5] Chan Y. Cheah,[6,7,8] Shane Gangatharan,[8,9] Joel Wight,[10,11] Matthew Ku,[11,12] Hang Quach,[11,12] Robin Gasiorowski,[3,4] Mark N. Polizzotto,[1,2,13] Henry Miles Prince,[11,14,15] Stephen Mulligan,[3,16] Constantine S. Tam,[11,12,14] Gareth Gregory,[17] Greg Hapgood,[18] Andrew Spencer,[11,19] Michael Dickinson,[11,14] Maya Latimer,[20] Anna Johnston,[21,22] Tasman Armytage,[23] Cindy Lee,[24] Tara Cochrane,[25,26] Leanne Berkhahn,[27,28] Robert Weinkove,[29,30] Richard Doocey,[27] Simon J. Harrison,[11,14] Nicholas Webber,[31] Hui-Peng Lee,[32] Scott Chapman,[33] Belinda A. Campbell,[11,34] Simon D. J. Gibbs[35,36] and Nada Hamad[1,2,3]

Departments of [1]Haematology, and [33]Infectious Diseases, St Vincent's Hospital, [2]University of New South Wales, [3]University of Sydney, [4]Department of Haematology, Concord Repatriation General Hospital, [5]Department of Haematology, Royal Prince Alfred Hospital, [13]The Kirby Institute, University of New South Wales, and [16]Department of Haematology, Royal North Shore Hospital, Sydney, [23]Department of Haematology, Gosford Hospital, Gosford, New South Wales, [6]Department of Haematology, Sir Charles Gairdner Hospital, [7]Department of Haematology, Pathwest Laboratory Medicine, [8]University of Western Australia, and [9]Department of Haematology, Fiona Stanley Hospital, Perth, Western Australia, [10]Townsville University Hospital, Townsville, [18]Department of Haematology, Princess Alexandra Hospital, [26]Griffith University, and [31]Royal Brisbane and Women's Hospital, Brisbane, [25]Department of Haematology, Gold Coast University Hospital, Southport, Queensland, [11]University of Melbourne, [12]Department of Haematology, St Vincent's Hospital, [14]Department of Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, [15]Department of Haematology, Epworth Healthcare, [17]Department of Haematology, Monash Health, [19]Department of Haematology, The Alfred Hospital, [34]Department of Radiation Oncology, Peter MacCallum Cancer Centre, [35]Department of Haematology, Eastern Health, and [36]Monash University, Melbourne, Victoria, [20]Department of Haematology, Canberra Hospital, Canberra, Australian Capital Territory, [21]Department of Haematology, The Royal Hobart Hospital, and [22]University of Tasmania, Hobart, Tasmania, [24]Department of Haematology, Queen Elizabeth Hospital, and [32]Department of Haematology, Flinders Medical Centre, Southern Adelaide Local Health Network, Adelaide, South Australia, Australia, and [27]Department of Haematology, The Auckland City Hospital, and [28]University of Auckland, Auckland, and [29]Department of Haematology, Wellington Blood and Cancer Centre, Capital and Coast District Health Board, and [30]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, Wellington, New Zealand

Key words
COVID-19, lymphoma, myeloma, chronic lymphocytic leukaemia.

Correspondence
Nada Hamad, St. Vincent's Hospital – The Kinghorn Cancer Centre, Level 5, Haematology, 370 Victoria St, Darlinghurst, NSW 2010, Australia.
Email: nada.hamad@svha.org.au
Twitter: @prp_diciaccio; @nadahamad; @gjmccaughan
Di Ciaccio and McCaughan are joint first authors.

Received 8 April 2020; accepted 15 April 2020.

Abstract

The COVID-19 pandemic poses a unique challenge to the care of patients with haematological malignancies. Viral pneumonia is known to cause disproportionately severe disease in patients with cancer, and patients with lymphoma, myeloma and chronic lymphocytic leukaemia are likely to be at particular risk of severe disease related to COVID-19. This statement has been developed by consensus among authors from Australia and New Zealand. We aim to provide supportive guidance to clinicians making individual patient decisions during the COVID-19 pandemic, in particular during periods that access to healthcare resources may be limited. General recommendations include those to minimise patient exposure to COVID-19, including the use of telehealth, avoidance of non-essential visits and minimisation of time spent by patients in infusion suites and other clinical areas. This statement also provides recommendations where appropriate in assessing indications for therapy, reducing therapy-associated immunosuppression and reducing healthcare utilisation in patients with specific haematological malignancies during the COVID-19 pandemic. Specific decisions regarding therapy of haematological malignancies will need to be individualised, based on disease risk, risks of immunosuppression, rates of community transmission of COVID-19 and available local healthcare resources.

Introduction

Since the emergence of the COVID-19 pandemic, multiple epidemiologic studies have described the clinical presentation and biological features in the general population.[1,2] The

Funding: None.
Conflict of interest: None.

Table 1 NHMRC levels of evidence (Adapted from Merlin *et al.*[87])

Level of evidence	Study design
I	Systematic reviews of relevant randomised controlled trials
II	At least one randomised controlled trial
III	Comparative studies, including non-randomised studies, cohort studies, case–control studies and two or more single-arm studies
IV	Case series, single single-arm studies

estimated overall case fatality rate has varied, however, is likely at least 1%,[3] and the intensive care unit admission rate for infected patients may be as high as 12%.[4] Although we acknowledge that the potential impact of COVID-19 infection in immunocompromised haematology patients is largely unknown, it is potentially severe. Viral pneumonia is known to cause disproportionately severe disease in cancer patients, such as the H1N1 pandemic, which saw high rates of hospitalisation (50%), pneumonia (23%) and death (9.5%).[5,6] Bacterial co-infection occurs in up to 25% of the cancer patients with viral pneumonia and is an independent predictor of mortality.[7,8]

The COVID-19 pandemic is likely to impact significantly healthcare resources, including clinical staff and acute care services, and as a consequence the routine delivery of care to patients with haematological malignancies. There will be geographic and temporal variation in community transmission and individual institutions will need to consider the local resource limitations and patient risk as the pandemic evolves. This consensus statement was developed among experts in the field and may not reflect practice within their individual institutions. This statement is intended to support clinical decision-making in this evolving COVID-19 pandemic with supportive evidence, including National Health and Medical Research Council (NHMRC) levels, wherever possible (table 1).

General principles

Building upon recently published Australian and New Zealand guidelines,[9] we aim to provide consensus-based potential strategies to consider when attempting to mitigate risk in patients with lymphoma, chronic lymphocytic leukaemia (CLL) and myeloma in a continuously developing situation with potential limitations on clinical resources. In general, we suggest:

- Patients should be informed of their vulnerability to COVID-19 infection due to their impaired immune system.
- The importance of adherence to current state and federal government recommendations to reduce COVID-19 transmission should be stressed to patients. This includes recommendations relating to good hygiene (frequent hand washing, coughing and sneezing into tissues or elbow and cleaning frequently used surfaces and objects), social distancing, limits for public gatherings, avoiding unnecessary travel and self-isolation.
- Not deferring or omitting treatment options with a clear established benefit in terms of survival outcomes. In the setting of low-grade lymphomas, CLL, low-risk myeloma and palliative treatment, the strategies to mitigate risk and rationalise clinical resources may include treatment omission or deferral, curtailment of treatment, alternative regimen choice and/or delivering standard therapies in different environments.
- Mitigating risk of COVID-19 exposure by reducing patient time spent in clinical settings, such as outpatient departments/consulting rooms, hospital stay and infusion suites. Measures include the use of telemedicine, use of non-hospital pathology services, changing i.v. preparations to subcutaneous and direct-to-home delivery of oral medications. Outpatient management of neutropenic fever as per established guidelines may be considered.[10]
- Taking all available measures to optimise the patient's immune status and minimise the risk of infection and hospitalisation. This should include advice about smoking cessation.
- Variation in practice based on an altered patient risk–benefit analysis should be clearly documented in a virtual multidisciplinary team environment or by other means.
- The informed consent process for chemotherapy should include documenting a discussion about the risks of COVID-19 and strategies to avoid infection, as well as the potential risks of reduced hospital capacity to deliver on-time chemotherapy and routine supportive care.
- In the event of infection with COVID-19 during chemotherapy, the decision to continue or re-initiate chemotherapy needs to made on a case-by-case basis, weighing up the urgency of treatment which can often be deferred until the convalescent period.
- Patients should be referred to the most up-to-date government patient information regarding the evolving COVID19 pandemic.
- Enrolment in clinical trials should remain a consideration for all appropriate patients. It is acknowledged, however, that the availability of clinical trials may also be curtailed during the pandemic.

Testing for COVID-19

Screening and diagnostic testing

Current indications for testing are rapidly evolving in response to the COVID-19 pandemic and should proceed

as per institutional and jurisdictional guidelines. With increasing community transmission, the threshold for testing in an immunosuppressed patient may change. We suggest developing contemporaneous local protocols, based on public health advice and in consultation with infectious disease specialists, specific to the malignant haematology patient.

Additional testing in patients with COVID-19 at time of diagnosis

We recommend full blood count with differential white cell count, C-reactive protein, ferritin, immunoglobulin levels, lymphocyte subsets, routine coagulation profile, fibrinogen, D-dimer, troponin, routine respiratory virus, upper respiratory tract swab for co-infection, baseline electrocardiogram (ECG) and chest imaging (X-ray or CT).[11]

Progress testing

Recent data indicate the median duration of viral shedding in surviving patients is 20 days, with shedding observed as late as 37 days post diagnosis.[12] In consultation with infectious diseases, COVID-19 testing may take place periodically (every 2–3 weeks) to ensure clearance may be considered depending on the availability of testing kits. Immune profile surveillance testing, including ferritin, every 3–4 days until clinical stabilisation may be clinically useful as the cytokine profile of COVID-19 infection is reminiscent of that seen in macrophage activation syndrome/haemophagocytic syndrome.[11]

Non-Hodgkin lymphoma

Diffuse large B-cell lymphoma and high-grade B non-HL

Newly diagnosed diffuse large B-cell lymphoma and high-grade B-cell non-HL

We do not recommend delay of therapy in circumstances where the delay itself is likely to be deleterious to patient outcome as dose intensity and timeliness are important.

R-CHOP 14 versus R-CHOP 21

R-CHOP21 and R-CHOP14 have similar efficacy. We suggest growth factor support with both regimens.[13]

Stage I/II diffuse large B-cell lymphoma, non-bulky disease

We suggest considering four cycles of R-CHOP if the end of treatment PET is negative, as a number of studies has demonstrated, this is likely comparable with six cycles of R-CHOP (II). This is most applicable in patients with an age-adjusted IPI = 0 and age < 60, although the S1001 study suggests that this approach may be applicable more broadly (III).[14–16]

High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements ('double-hit' or 'triple-hit')

We suggest weighing up the resources needed and the immunosuppression risks associated with intensified regimens, such as dose-adjusted R-EPOCH, particularly in those with low IPI and older patients who may experience increased toxicity. It may be reasonable to treat such patients with R-CHOP (II,III).[17–19]

Consolidation radiotherapy to bulky disease

It is reasonable to consider hypofractionation or omitting consolidation radiotherapy in those who are in complete metabolic response after induction therapy, as reflected in the upcoming International Lymphoma Radiation Oncology Group (ILROG) Emergency Guidelines.[20]

Relapsed high-grade B-cell non-HL

Salvage regimen choice

We suggest the use of R-GDP as opposed to R-DHAP or R-ICE, given lower rates of infection and haematological toxicity, with similar efficacy, as well as deliverability in the outpatient setting (II).[21,22]

Autologous stem-cell transplantation delays

Prolonged delays of more than 2 months post last dose of salvage chemotherapy should be avoided where possible (II).[23] Given the poorer outcomes with autologous stem-cell transplant (ASCT) in patients who fail primary therapy with a rituximab-based regimen, we suggest proceeding to ASCT where chemosensitivity is demonstrated, at a minimum with partial response (PR) by computed tomography (CT) scan (II).[21,22] If there is residual positron emission tomography (PET) positivity post salvage, the decision to proceed with ASCT should be individualised given poorer outcome, particularly in primary refractory disease (III).[24]

Relapse after autologous stem-cell transplantation

Relapse following ASCT will prove challenging to treat in the COVID-19 environment. Chimeric antigen receptor (CAR) T-cell therapy and allogeneic stem-cell transplantation are resource intensive and highly immunosuppressive and are likely to be less accessible. We suggest

consideration of other treatment options, such as polatuzumab vedotin (if available) (II),[25] or enrolment in clinical trials if possible. Referral to palliative care and appropriate end of life planning should be discussed.

Primary mediastinal B-cell lymphoma

Six cycles of R-CHOP with consolidation radiotherapy are comparable to dose-adjusted R-EPOCH, however, R-CHOP is associated with less haematological toxicity (III).[26] Consider hypofractionation of radiotherapy in line with upcoming ILROG Emergency Guidelines or omission in older patients if the end of treatment PET is negative.[20,27] Ultimately, the choice between these two regimens will be based on clinical and resource factors.

Burkitt lymphoma

R-CODOX-M/R-IVAC remains a reasonable choice, provided resources are available, however, considering it is usually given in the inpatient setting. GMALL 2002 is a reasonable alternative in terms of efficacy and is deliverable in an outpatient setting (II).[28] Dose-adjusted R-EPOCH with intrathecal CNS prophylaxis can be considered on an individualised basis in low-risk patients with no CNS involvement (IV).[29] Given the relative rarity of Burkitt lymphoma, institutional resources and familiarity with regimen choice are a relevant consideration.

Peripheral T-cell lymphoma

Regimen choice

For most patients, and those over 60 years of age in particular, consider six cycles of CHOP rather than CHOEP, as the latter is associated with higher treatment-related toxicity without a proven overall survival benefit (III).[30,31]

Autologous stem-cell transplantation

Consider deferral or omission of consolidation ASCT in first complete remission depending on resource availability as the role of ASCT is not well established in this setting (III).[32]

Low-grade non-HL

For low-grade lymphomas, consideration should be given to the delay of planned initiation of therapy where possible. Ultimately, the initiation of treatment will be based on a risk–benefit discussion between patient and physician, taking into account disease characteristics, in particular the tempo of disease progression, individualised infectious risk and patient preference. We suggest:

- Where there is clinical equipoise between the use of a higher- and lower-intensity regimen, or if the use of a higher-intensity regimen is based on relatively low-quality evidence, lower-intensity regimens are preferred.
- The traditional Groupe d'Etude des Lymphomes Folliculaires (GELF)/British National Lymphoma Investigation (BNLI) thresholds for the initiation of therapy can be relaxed in patients who tolerate them.[33,34]
- Consider a higher treatment threshold when based on constitutional symptoms.
- For patients with symptomatic sites of disease, low-dose radiotherapy (4 Gy in one to two fractions) can provide effective palliation and may be an effective temporising measure.[35]
- In patients who are already receiving treatment and have had a good response, consideration should be given to abbreviating the number of treatment cycles.

Follicular lymphoma

First-line therapy

This should be highly individualised based on local resources, pandemic evolution and patient characteristics. R-CVP (or obinutuzumab-CVP) or R-CHOP (or obinutuzumab-CHOP) may be considered over bendamustine-based regimens considering the concerns around risks of delyed infection with the latter. Consideration should be made to continue with chemotherapy on a cycle-by-cycle basis and it may be reasonable to reduce bendamustine cycles from six to four cycles in patients with a good response (III).[36–40]

Maintenance immunotherapy

If there is significant community transmission of COVID-19, maintenance immunotherapy should be avoided if possible due to increased rates of neutropenia and infection, without proven overall survival benefit (II).[41]

Mantle cell lymphoma

Younger, fit, patients should continue with current institutional practices, such as regimens containing high-dose cytarabine, but consolidation ASCT may need to be deferred in the setting of limited acute care services. For older or unfit patients, consider R-CHOP or R-CVP therapy with growth factor support, based on patient characteristics and the concerns around risks of infection with bendamustine-based regimens (III).[42]

Lymphoplasmacytic lymphoma

Immunochemotherapy regimen choice

If chemotherapy is being considered, while R-bendamustine is associated with superior progression-free survival, rituximab with cyclophosphamide and dexamethasone is less immunosuppressive. Regimen choice needs to consider individual patient's characteristics and pandemic evolution.

Patients on Bruton kinase inhibitors

If these patients develop COVID-19, careful deliberation should be made before stopping due to the risk of exacerbating any potential cytokine-release syndrome and rapid symptomatic disease progression on cessation. Conversely, the possibility of blunted immune response and cardiac toxicity are also considerations.

Hodgkin lymphoma

Classical HL

In general, local treatment practices for classical Hodgkin lymphoma (HL) should continue to apply, however, we advise consideration of resource limitations and the following treatment strategies that involve reduced toxicity with comparable outcomes.

Of note, symptoms of pulmonary toxicity of bleomycin, checkpoint inhibitors and radiotherapy toxicities may mimic those of COVID-19 disease.

Early stage favourable HL

While radiotherapy services can be provided, two cycles of ABVD followed by 20 Gy involved-site radiotherapy (ISRT) will likely remain standard of care in many centres. While radiotherapy services are limited or an alternative strategy is more desirable, an approach based on the RAPID trial is to treat with three cycles of ABVD without radiotherapy, provided an interim PET after two cycles is negative (II).[43]

Early stage unfavourable HL

Consider four cycles of ABVD followed by ISRT, in an effort to reduce toxicity and resource allocation, as the approach of two cycles of ABVD after two initial cycles of escalated BEACOPP in the HD14 trial was not associated with an overall survival benefit (II).[44] Patients commencing on ABVD who have a positive interim PET after two cycles could be considered for intensification to escalated BEACOPP provided patient fitness permits (II).[45]

Advanced-stage HL

- Expert opinion regarding first-line therapy is mixed.[46–48] However, when using escalated BEACOPP, we suggest abbreviating to four cycles rather than delivering six in patients with a negative PET after two cycles (II).[49]
- For patients experiencing significant toxicity or infection during the first two cycles of escalated BEACOPP, we suggest considering descalation to ABVD if an interim PET after cycle 2 is negative as described in the AHL2011 trial (II).[50]
- For patients treated with six cycles of ABVD, we recommend the omission of bleomycin after cycle 2 in patients with advanced-stage disease treated with ABVD having a negative interim PET, in line with the RATHL study (II).[51]
- Radiotherapy to initial bulky disease may be omitted while interim PET after cycle 2 is negative.

Relapsed HL

- Salvage chemotherapy and ASCT should not be delayed as this is potentially curative therapy.
- Alternatively in patients at higher risk of treatment-related toxicity, brentuximab vedotin as a single agent may be considered as salvage (depending upon accessibility) prior to ASCT (IV).[52]
- ASCT in patients with residual PET-positive disease should not be prioritised in the setting of limited acute care services, due to poor outcomes (III).[53] Consider using second-line salvage with a novel agent instead, to improve response.
- Options for second salvage, or transplant-ineligible patients, include both brentuximab vedotin and pembrolizumab.The risk of respiratory complications with PD-L1 inhibitors in the context of the COVID-19 pandemic is unknown (III).[36,54,55]

Chronic lymphocytic leukaemia

CLL patients are likely to be at increased risk of severe disease and mortality with COVID-19. Many patients with CLL are immunocompromised, even with early stage disease, and have additional risk factors, such as age and comorbidities. Consideration should be given to the delay of planned initiation of therapy where possible.

Front-line immunochemotherapy

In the event that front-line therapy is essential, consider the use of oral therapies if accessible. If immunochemotherapy with FCR is considered

appropriate, in immunoglobulin heavy chain variable region (IgHV)-mutated CLL, i.v. administration for six cycles remains standard of care, however, in IgHV-unmutated CLL, dose reduction and oral administration of both fludarabine and cyclophosphamide based on the CLL5 protocol could be considered (II).[56] Early cessation of therapy could be considered if clinically significant treatment-related cytopenias occur, or once disease control is achieved. Growth factor support should be given to avoid neutropenia. For older patients with comorbidities, chlorambucil plus obinutuzumab or rituximab may also be appropriate, with early cessation of therapy once disease control is achieved.

Relapsed or refractory CLL

If therapy is required, the Bruton kinase (Btk) inhibitor ibrutinib or bcl-2 inhibitor venetoclax should be standard of care (II). Ibrutinib is generally well tolerated and allows outpatient administration with minimal hospital visits. When considering venetoclax in combination with rituximab, consider deferring rituximab and administering venetoclax as monotherapy, both to limit the need for day unit attendance, and potentially to reduce the degree of immune compromise. The need for tumour lysis syndrome prophylaxis during venetoclax ramp-up and the desire to avoid associated hospital visits should also be considered.

Mitigating potential risks of novel agents

The risk of severe COVID-19 disease among patients receiving Btk inhibitors and venetoclax is unknown, but could plausibly be increased. Pulmonary infections are among the severe adverse events observed during clinical trials of Btk inhibitors and venetoclax.

Cardiac toxicity associated with ibrutinib may become a factor for those who acquire COVID-19, as hypertension and cardiac disease are risk factors for severe COVID-19, and are recognised adverse events of ibrutinib. To limit the potential for treatment-related immunosuppression and drug interactions, temporary cessation of ibrutinib or venetoclax should be considered for CLL patients who develop COVID-19, for the period of time that they are unwell.

Myeloma

The treatment of patients with multiple myeloma (MM) during the COVID-19 pandemic may ultimately be dictated by the available healthcare resources. Nonetheless, the overarching principle that should guide management within clinical resource constraints rests on the balance between the need for optimal disease control in high-risk patients and avoiding unnecessary treatment-related immune suppression in low-risk patients. Therapeutic decisions must be individualised, taking into consideration: disease factors, including newly diagnosed versus relapsed disease; stage and cytogenetics/fluorescence in situ hybridisation; disease burden and rate of progression; patient factors, including age, frailty, comorbidities and social circumstances and the capacity of the healthcare system.

For otherwise fit patients, particularly those with high-risk or rapidly progressive MM, prompt treatment is warranted to avoid further end-organ damage, deterioration in performance status and ultimately a loss of a window for treatment. Treatment delay in this group may result in complications which may necessitate hospitalisations that place further stress on the existing inpatient capacity. In contrast, for patients with disease stability, particularly in the elderly and frail patients, considerations must be given to mitigate further immune suppression by ceasing immunosuppressive agents that may not be essential for immediate disease control, such as ongoing dexamethasone.

The more difficult decision is whether to delay treatment for otherwise well patients with slow biochemical progression of MM but without end-organ damage, as the duration of this pandemic and its consequent impact on healthcare capacity remain unknown. Such a decision may ultimately be dictated by the stage of the pandemic faced at the time. In general, for MM, we suggest:

- Preferential utilisation of oral agents lenalidomide, pomalidomide and thalidomide as immunomodulatory drugs and if available, ixazomib as an oral proteasome inhibitor. If feasible, home or self-administration of subcutaneous bortezomib could be considered.
- The use of dexamethasone should be minimised, if not ceased, once maximal disease response is achieved and tumoricidal effects become less important.
- Cyclophosphamide, if needed, should be given orally rather than intravenously.
- For bortezomib and carfilzomib, weekly schedules are preferred over twice weekly schedules (III, II).[57,58]
- For patients on daratumumab, a shorter infusion time of 90 min can be considered from the third infusion onwards (IV).[59]
- Amino-bisphosphonates (zoledronic acid or pamidronate) remain an important aspect of MM treatment in preventing skeletal-related events and have been shown to improve overall survival (OS) based on the Medical Research Council (MRC) Myeloma IX study (II).[60] If the peak of the pandemic necessitates minimisation of hospital visits, consider reducing bisphosphonate infusions to every 3 monthly (IV).[61]

Asymptomatic patients (monoclonal gammopathy of uncertain significance and smouldering MM)

Establish telemedicine follow-up or general practitioner (GP) management for all patients at the frequency dictated as standard of care by the Myeloma Australia Medical and Scientific Advisory Group (MSAG) Guidelines.[62]

Newly diagnosed MM

In patients with MM as defined by the presence of positive biomarkers as opposed to overt end-organ damage, namely hypercalcaemia, renal failure, anaemia or bone disease (CRAB),[63] the need for immediate treatment must take into consideration the available healthcare capacity to avoid placing patients at risk of hospitalisation at the height of the pandemic. Treatment delay in these patients is not unreasonable, but as risk of developing overt end-organ damage in these patients is in the order of 70% within 2 years, closer monitoring is warranted. We suggest monthly monitoring of paraproteins and serum-free light chain in addition to routine standard of care investigations. If overt end-organ damage occurs, immediate treatment is recommended.

Transplant-eligible patients

Standard-risk patients who achieve a partial response to induction

Consideration should be given to deferring ASCT if healthcare capacity is limited.

Patents who do not achieve a partial response after four cycles or who progress during induction therapy

In this setting, the risk of MM outweighs the risk of COVID-19 and we advise proceeding with salvage therapy as per the MSAG Guidelines.[62]

High-risk MM (as per Revised International Staging System (R-ISS) or other factors e.g. extramedullary disease)

We recommend proceeding to ASCT without delay if possible.

Stem-cell collection

Stem-cell collection should depend on local resources and, if feasible, outpatient mobilisation should be considered. A granulocyte colony-stimulating factor (GCSF)-only (+/− plerixafor) mobilisation technique should be considered (III).[64]

Transplant deferral

If ASCT is delayed, consideration should be given to continuing CyBorD beyond an initial four cycles of induction as per the transplant-ineligible approach. Additional cycles beyond four cycles have recently been approved by the Pharmaceutical Benefits Advisory Committee in Australia.

Based on the StaMINA study, delay in ASCT during the COVID-19 pandemic for up to 12 months after induction therapy could be acceptable (although the majority of these patients received bortezomib, lenalidomide and dexamethasone (VRd) induction) (II).[65] Beyond 12 months, the value of proceeding to ASCT is controversial.

Transplant-ineligible patients

Oral combinations, such as lenalidomide and dexamethasone, are preferred to minimise hospital/outpatient service visits. For responding patients who are beyond the ninth cycle of lenalidomide and dexamethasone, it is safe to cease dexamethasone and continue with lenalidomide monotherapy (II).[66]

Bortezomib-based treatments remain preferable in patients with impaired renal function or high-risk cytogenetics.[62] Consideration for doublet rather than triplet therapy ought to be given to elderly or frail patients in whom the risk of neutropenia is higher. Reduced dexamethasone of 20 mg weekly rather than 40 mg should be used.

Relapsed disease

The timing and type of salvage therapy for patients with relapsed MM should take into consideration available clinical resources and the safety of treatment delay.

Many, but not all, patients will require immediate treatment at first detection of myeloma relapse. For patients with worsening or new end-organ damage, immediate treatment is indicated as the risk of myeloma outweighs the risk of COVID19. In the absence of worsening or new CRAB features, immediate treatment may also be warranted in patients with rapidly progressive paraprotein or serum-free light chain levels to prevent the onset of irreversible end-organ damage as per MSAG Guidelines.[62] Otherwise, in patients with slow biochemical relapse, close monitoring monthly until significant progression occurs is acceptable.

The optimal salvage therapy for myeloma should be based on the patient's prior treatment exposure and associated response or toxicity.[62] If all else is equal with respect to the efficacy and toxicity profile between two

or more salvage therapies, then the option with less immune suppression and hospital visits is preferred. We recommend considering using oral treatment combinations. If patients are receiving carfilzomib at a stage when minimisation of hospital visits is necessary, consider weekly dosing (70 mg/m^2) rather than twice weekly dosing as per the ARROW study,[57] recognising that this schedule has only been compared favourably with carfilzomib 20/27 mg/m^2 rather than the pharmaceutical benefits scheme (PBS) (Australia) reimbursed schedule of 20/56 mg/m^2 as per the ENDEAVOR study (II).[67] In addition, this schedule may not be possible for patients with body surface area (BSA) > 1.7 m^2 given that the maximum carfilzomib dose reimbursed on the Australian Pharmaceutical Benefits Scheme is capped at 120 mg. If weekly dosing of carfilzomib is used, it is not unreasonable to consider adding cyclophosphamide (KCd) as this weekly schedule has been shown to be effective and safe in the upfront treatment setting (IV).[68]

Systemic AL amyloidosis

Treating patients with AL amyloidosis during the COVID-19 pandemic should be considered on a case-by-case basis. Rapid initiation of therapy is likely to remain the standard of care in line with MSAG Guidelines, in particular in patients with cardiac or extensive renal involvement.[69]

Patients with early stage disease could potentially have treatment postponed several months.[70] In patients who have achieved at least a very good partial response, or partial response with an organ response, a reduced number of treatment cycles or intensity could be considered.

Supportive care

The general principles of social distancing apply to the delivery of care of haematology patients during the COVID-19 pandemic. As outlined by others,[71] face-to-face contact with patients, patient presentation to infusion suites, radiotherapy and, for pathology, radiology testing should be minimised as much as possible for the safety of patients and healthcare workers. While appropriate, oral therapy should be chosen over parenteral. Chemotherapy treatment in the patient's home can also be considered if available. Rearrangement of chemotherapy suites to increase spatial distancing is recommended.

Subcutaneous rituximab

In patients with low-grade lymphoma, subcutaneous rituximab should be delivered in lieu of i.v. rituximab where possible to reduce time spent in infusion suites.[72,73]

Growth factor support

In the context of the COVID-19 pandemic, we generally recommend adding growth factor support to all chemotherapy regimens with an anticipated neutropenic nadir of $<1.0 \times 10^9$/L, in an effort to decrease infection risk and consequent hospital presentation.

Primary prophylactic GCSF is in most cases not required for ABVD, however, it could be considered in older patients or in patients not receiving bleomycin.

In the context of neutropenic fever, we suggest considering growth factor support use as it has been shown to reduce the duration of neutropenia and the duration of hospitalisation, both desirable.[74]

Antibacterial prophylaxis

Bacterial co-infection occurs in up to 25% of cancer patients with viral pneumonia and is an independent predictor of mortality. This has been shown in data generalisable to COVID-19 infection in patients being treated for haematological malignancy.[7,8]

We suggest considering the use of antimicrobial prophylaxis in high-risk patients, defined as a patient expected to be neutropenic ($<0.5 \times 10^9$/L) for at least 7 days or prior neutropenic fever episodes.[75–77] Primary prophylaxis should take into account local infectious diseases advice and local resistance profiles.

Herpes Simplex Virus (HSV)/Varicella Simplex Virus (VZV) prophylaxis

We suggest the use of antiviral primary prophylaxis with aciclovir or valaciclovir as per institutional practice.

Pneumocystis jerovicii prophylaxis

We recommend the use of prophylaxis as per institutional practice. Specific consideration should be given to patients with lymphoma treated with higher-intensity regimens, patients with a CD4+ count of <200/μL, or those on sustained use of prednisone at a dose >20 mg daily (or dose-equivalent corticosteroids) in line with a meta-analysis and published guidelines.[76,78–80]

Antifungal prophylaxis

For primary prophylaxis, in patients with lymphoma and myeloma, we recommend the use of antifungal prophylaxis as per local protocols.

Acute, severe COVID-19 infection is associated with the development of immune dysregulation and lymphopenia and is likely a risk of secondary fungal

infection.[36] Fungal prophylaxis may be considered in this context.[2]

Immunoglobulin supplementation

There is currently no strong evidence to support the practice of routine supplementation with immunoglobulin therapy for primary prophylaxis, however, it is reasonable in patients with recurrent infection (I,II).[81–83] Subcutaneous immunoglobulin should be considered in appropriate patients if this results in reduced time spent in the hospital setting.

Supplemental immunoglobulin is unlikely to provide meaningful protection against COVID-19 itself due to the presumed absence widespread immunity among donors in the early months of the pandemic. In patients with COVID-19 infection, supplementation for hypogammaglobulinaemic patients is reasonable in an effort to minimise the risk of co-infection.

Vaccinations

Immune-compromised patients are at a higher risk of influenza infection and invasive pneumococcal disease. We recommend all lymphoma and MM patients receive routine influenza and pneumococcal vaccination[84–86] (Table 1).

Conclusion

The COVID-19 pandemic is providing an unprecedented risk to patients with haematological malignancies. It is critical that health professionals work quickly to reduce the risk of transmission through creative and technological means to limit hospital contact while still providing the relatively intensive care required to mitigate the well-known side effects of treatment and disease complications. It may also be important to reduce the degree of immunosuppression in order to reduce mortality for those infected, provided this does not compromise efficacy and safety from the perspective of the underlying malignancy. Careful consideration, informed consent and a multidisciplinary approach are now more important than ever to tailor therapy to at-risk individuals, and thus, hopefully, reducing the impact of COVID-19 in our vulnerable patients.

Acknowledgements

The authors wish to acknowledge clinicians who reviewed and commented on the manuscript: Christina Brown (Department of Haematology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia), Ilona Cunningham (Department of Haematology, Concord Repatriation General Hospital, Sydney, New South Wales, Australia), Eliza Hawkes (Department of Clinical Haematology, Austin Health, Melbourne, Victoria, Australia), Mark Hertzberg (Department of Haematology, Prince of Wales Hospital, Sydney, New South Wales, Australia), Steven Lane (Department of Haematology and Bone Marrow Transplant, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia), William Stevenson (Department of Haematology, Royal North Shore Hospital, Sydney, New South Wales, Australia), William Renwick (Department of Haematology, Royal Melbourne Hospital, Melbourne, Victoria, Australia), Benedict Carnley (Department of Haematology, Royal Perth Hospital, Perth, Western Australia, Australia) and Nick Murphy (Department of Haematology, Calvary St John's Hospital, Hobart, Tasmania, Australia).

Endorsements

The Haematology Society of Australia and New Zealand (HSANZ) supports this document with recognition of the need for individual patient decision-making based on data available at that time.

Myeloma Australia Medical and Scientific Advisory Group.

Australasian Lymphoma Alliance.

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