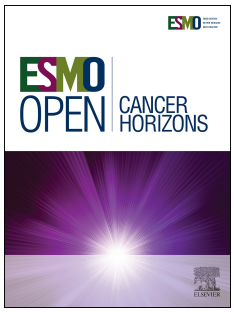

Managing hematological cancer patients during the COVID-19 pandemic: An ESMO-EHA Interdisciplinary Expert Consensus

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Managing hematological cancer patients during the COVID-19 pandemic: An ESMO-EHA Interdisciplinary Expert Consensus

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ABSTRACT:

Background

The COVID-19 pandemic has created enormous challenges for the clinical management of patients with hematological malignancies, raising questions about the optimal care of this patient group.

Methods

This consensus manuscript aims at discussing clinical evidence and providing expert advice on statements related to the management of hematological malignancies in the Covid-19 pandemic. For this purpose, an international consortium was established including a steering committee, which prepared six working packages addressing significant clinical questions from the Covid-19 diagnosis, treatment, and mitigation strategies to specific-HM management in the pandemic. During a virtual consensus meeting, including global experts and lead by the European Society for Medical Oncology and the European Hematology Association, statements were discussed and voted upon. When a consensus could not be reached, the panel revised statements to develop consensual clinical guidance.

Results and Conclusion

The expert panel agreed on 33 statements, reflecting a consensus, which will guide clinical decision making for patients with hematological neoplasms during the COVID-19 pandemic.

Keywords: COVID-19, hematological malignancies, consensus manuscript

Highlights:

- An expert consensus manuscript is provided on the optimal care of patients with hematological neoplasms in the COVID-19 pandemic
- Expert Advice is given on COVID-19 diagnosis, treatment and mitigation strategies in patients with hematological cancers
- This manuscript will guide clinical decision for patients with hematological neoplasms in the COVID-19 pandemic

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INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to a worldwide pandemic in 2020 and has become a major global health concern affecting over 220 million people and causing over 4.5 million deaths worldwide until September 2021 (https://coronavirus.jhu.edu/map.html). Covid-19 is a systemic disease with most of the patients presenting with mild or moderate symptoms. However, up to 5–10% will present severe or life-threatening disease course and dysfunctions, and complications can persist for at least 6 months after diagnosis.[1],[2]

Because of immunosuppression the potential threat of Covid-19 to cancer patients is significant and a higher mortality rate has been documented for multiple cancers worldwide.[3] Immunosuppression is particularly evident in hematological malignancies (HMs) such as leukemias, myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), lymphomas, and multiple myeloma (MM). This is based on the fact that malignant transformation in HM affects immunocompetent cells themselves and/or that anticancer treatments targeting the transformed immune cells regularly compromise their normal healthy counterparts. Based on large cohorts,[4, 5] international registries [6] and meta-analysis[7], the mortality of Covid-19 in HM is high with about 35% of patients dying with documented SARS-Cov-2 infection. Mortality was also assessed in distinct HM as MM,[8] chronic lymphocytic leukemia (CLL),[9] non-Hodgkin lymphomas (NHL),[10] and in patients who received hematopoietic stem-cell transplantation (HSCT)[11], disclosing a fatality rate of 33%, 33%, 34%, and 33%, respectively. In most of these studies, risk factors for worse outcome comprised of advanced age, more severe HM type, progressive disease status, and Covid-19 severity. Of note, treatment-mediated immune dysfunction, caused by e.g. chemoimmunotherapy or BTK inhibition is the main driver of the low rate of seroconversion post Covid-19, estimated at 69% in the whole HM population.[12].

The dismal outcome of Covid-19 in HM and the emergence of new virus variants with higher infectivity rate [13] emphasizes the need for early introduction of vaccination program in these patients. However, it has been convincingly shown that anti-COVID-19 vaccines elicit an impaired antibody response in patients with HM.[14-17] Lower rate of seroconversion (40-89%) has been reported in lymphoproliferative disorders due to disease and/or drug-induced B-cell or plasma cell depletion and/or disruption of the B-cell receptor signaling pathway.[18-

23] Longer time from their exposure can favor immune response in these conditions.[23].[21, 24-28] Myeloid neoplasms has been studied less: the rate of post vaccine seroconversion seems higher (85-90%) in MPNs and CML,[26, 29-32] except in patients receiving JAK inhibitors (near 60%).[30]

Based on the known frailty of HM, the rapidly changing situation during the pandemic with its multiple infectious waves and the spread of distinct virus variants worldwide, and the highly divergent situation of the health system in different countries, management of HM patients has focused on avoiding hospital stays and reducing immunocompromising treatments, up to delaying initiation of anti-cancer treatment if thought feasible. Most of this decision making was based on little evidence, raising many open questions with regard to the optimal care for HM during the pandemic. Thus, there is an urgent need for consensus statements on how to clinically manage HM patients in this unprecedented situation of the COVID-19 pandemic. To provide guidance for the clinical care in HM, a large interdisciplinary and international committee on behalf of the European Society for Medical Oncology (ESMO) and European Hematology Association (EHA) established an international and multidisciplinary group of experts to discuss clinical evidence (consensus) and to provide expert advice on areas of controversy in the management of HM patients in the pandemic. By this, a consensus was developed offering a comprehensive set of recommendations including a consensus on Covid-19 diagnosis, treatment, and mitigation strategies for the heterogenous group of HM. This concise consensus statement will help to optimise clinical management in HM and support multidisciplinary teams caring for HM patients in clinical decision making.

METHODS

A steering committee (SC) appointed by the ESMO and EHA boards prepared a series of questions to be voted upon at the consensus meeting. The multidisciplinary expert panel was compiled based on nominations from the European Society for Medical Oncology (ESMO) and from the European Hematology Association (EHA) . The SC consisted of 35 members with expertise across HMs, coordinated by two members, Christian Buske and Francesco Passamonti, each representing the ESMO and EHA, respectively. In order to develop the clinical questions to be addressed at the consensus meeting, the SC reviewed relevant clinical

evidence and basic research in HM patient management. Insights from the literature review were supplemented with expert clinical opinion to develop 6 working packages (WPs), each coordinated by one member of the SC (outlined in Table 1) with draft consensus statements included in the toolbox. The final Member Panel (including the SC members) consisted of 35 experts (including 2 individuals who did not participate in the voting of consensus recommendations). The following modified Delphi process was used for preparation, consensus and reporting between 21 May 2021 and 30 June 2021:. Background information including the WPs along with the Statements were sent to panelists for their structured feedback (Agree, Disagree, Abstain, with Comments) . The SC incorporated all comments and suggestions, with discussion of all disagreements, resulting in a revised set of WP Statements that were then sent for a second anonymous vote to all panelists. Consensus was considered to be reached if agreement was recorded by more than 75% of panelists. Lack of agreement on a Statement would elicit revision and a third voting round, resulting in either consensus or final rejection of the Statement.

RESULTS: CLINICAL QUESTIONS AND STATEMENTS

WP1: Covid-19 diagnosis, treatment, and mitigation strategies

What are efficient strategies to prevent SARS-CoV-2 infection?

STATEMENT 1: Patients, persons in their close relationship, and caregivers must apply common preventive strategies such as: hygiene measures, physical distancing, wearing facial masks and staying, if possible, in single bedrooms. Efforts in the reorganization of Hematology Units with telehealth to reduce clinic visits, regular SARS-CoV-2 swab testing and vaccination of Health Care Personnel, of persons in the close relationship to patients and caregivers are to be favored.

There are several studies indicating efficacy of preventing strategies such as keeping distance, using face masks, and implementing quarantine and isolation in the control of SARS-CoV-2 transmission and thereby disease burden.[33-39] Reorganization of clinic visits and management of Hematology Units to reduce the risk of transmission have been reported by many to be feasible.[40-42] Measures may include but are not limited to implementing tele-health, defining dedicated areas and teams for care of HM patients and screening of the staff. However, this needs to be adapted to local strategies and policies. There is evidence to support

the efficacy of vaccinating household members and care givers derived from studies on vaccination of staff in nursing homes.[43]

Final voting: agree 100%, disagree 0% (0/33)

Are anti Covid-19 vaccines indicated in HM patients to prevent SARS-CoV-2 infection?

STATEMENT 2: Vaccination is strongly recommended. Whenever possible, vaccination should be proposed before initiation of treatment. If this is not possible, vaccines can be administered anytime during disease course or any therapy in principle. In the case an urgent treatment is required, withholding the planned therapy for receiving vaccines is not justified. To note, immune response might be severely reduced in those receiving B-cell depleting agents.

Currently, there are efficient vaccines for immunocompetent individuals, licensed against Covid-19.[44-46] Generally, vaccines work in patients with HM with immune[47] and clinical responses[48-50] and are currently generally recommended.[51-53] By consequence, one can assume that vaccination against SARS-CoV-2 might be effective in HMs,[54] however, these immunocompromised patients have not been included in the registration clinical trials. Reports on anti-SARS-CoV-2 vaccine efficacy in HM disclosed a lower humoral immune response compared that obtained in the heathy population.[14-32] Special considerations need HM patients receiving B cell depleting therapy, anti-CD38 monoclonal antibodies, and JAK inhibitors for the higher risk of failing seroconversion after SARS-CoV-2 vaccines. [14-32] Concerning HSCT, many patients will lose their immunity following transplantation, but can generally begin to be vaccinated around three months after the procedure. In consideration of the potential ineffectiveness of immune system, HM patients should be tested for seroconversion after SARS-Cov-2 vaccines and should maintain all the protective measures. There is no rationale to stop ongoing therapy pre-vaccination since side effects are not influenced by concurrent HM treatment. [55]

Final voting: agree 96.97%, disagree 3.03% (1/33)

Are current available vaccines safe in HMs?

STATEMENT 3: The benefits of vaccination far outweigh the risks of vaccine-related adverse events and given the greater severity of the disease and higher risk of death, HM patients are considered a high-priority subgroup for SARS-CoV-2 vaccination.

Recent preliminary evidence in HMs showed that anti SARS-CoV-2 vaccines are safe.[14-32, 55, 56] Rare cases of cerebral sinus vein thrombosis or splanchnic vein thrombosis after ChAdOx1 nCoV-19 and Ad26.COV2.S vaccination have been reported in individuals between the ages of 20 and 55 years. [57-59] [60] More recently, some cases of myocarditis after Covid-19 mRNA vaccination have been described in younger cases.[61]. However, the benefits of vaccination far outweigh vaccine related risks and vaccination is strongly recommended for patients with hematological malignancies.

Final voting: agree 96.97%, abstain 3.03%, disagree 0% (0/33)

Who should be tested for SARS-CoV-2 at what time?

STATEMENT 4: Diagnostic testing is mandatory at presentation of any Covid-19 symptoms and after Covid-19 diagnosis until receiving two negative results, even after receiving vaccination against SARS-CoV-2. We recommend screening all asymptomatic patients for SARS-CoV-2 at admission for in-hospital stay, 2-3 days later, and then following local policy. Concerning out-patient clinic visits, we encourage developing local policies according to local risk and recommend testing in the case of high SARS-CoV-2 incidence in the community.

As there is clear evidence that patients with asymptomatic Covid-19 may spread the virus in any facility, screening of patients admitted for an in-hospital stay is the first and foremost step to keep care facilities Covid-free areas.[62] Testing at presentation of symptoms should be performed in all HM patients regardless of their current disease status and therapy. Following several reports on prolonged viral shedding especially in patients with severe course of the disease and those with low numbers of B cells,[63-65] it should be considered to perform follow-up tests until negative results are confirmed before the admission to the Care Units. Viability of SARS-CoV-2 can only be proven by viral culture, but this is not routinely recommended. Therefore, the interpretation of a positive detection should be carefully examined. Some Institutions perform screening in the outpatient clinic during phases of high incidence in their community. This is a feasible strategy to avoid spread amongst those patients whose treatment cannot be deferred. In the setting of acute leukemias, PCR testing before every chemotherapy cycle is strongly recommended.

Final voting: agree 93.94%, disagree 6.06% (2/33)

What type of test should be used with which material?

STATEMENT 5: NAT (Nucleic Acid Amplification Technique) testing is preferred, usually using RT-PCR as the most sensitive method. Material from respiratory tract should be used, swabs are preferred but spit-tests, throat gargles, sputum and naso-pharyngeal aspirates are also under investigation. The evaluation of serum neutralizing antibodies for detecting immune response after exposure to SARS-CoV-2 is encouraged, when feasible.

The current gold standard and most widely used assays for the diagnosis of SARS-CoV-2 infection are based on RT-PCR and reported on the web at https://www.360dx.com/coronavirus-test-tracker-launched-covid-19-tests. Target genes tested include RNA-dependent RNA polymerase (RdRp), open reading frame (ORF1), envelope (E), and nucleocapsid (N) genes of the SARS-CoV-2 genome. False-negative results may be due to improper sampling, degradation of the viral RNA during shipping/storage, low viral loads, incorrect nucleic acid extraction, presence of amplification inhibitors, and mutations in the RT-PCR target region. A false positive is mostly due to sample cross contamination. To note, in long lasting positive tests,[66] viability of SARS-CoV-2 can only be proven by viral culture, however, this is not recommended routinely. NAT is preferred over antigen testing to diagnose SARS-CoV-2 infection, because of higher sensitivity. In fact, the sensitivity of antigen tests may drop down to 50% in asymptomatic cases, which does not make them a reliable tool for the diagnosis of infection especially in HMs.[67-72] Most centres use swabs for detecting SARS-CoV-2 RNA, but alternative clinical samples like saliva or sputum may also provide reliable results and reduce contact between HCPs and infected individuals. However, it seems that the best results can be expected from nasopharyngeal swabs or saliva.[73-77] The evaluation of serum neutralizing antibodies for detecting immune response after exposure to SARS-CoV-2 is encouraged, and in HM, a lower rate of seroconversion is expected as estimated at 69%.[12]

Final voting: agree 90.91%, abstain 9.09%, disagree 0% (0/33)

WP2: HM treatment in the Covid-19 pandemic

With the aim to reduce hospital visits and stay during the pandemic, how is it possible to apply imaging techniques to efficiently stage and restage HM patients?

STATEMENT 6: A cancer care prioritization and treatment intensity approach has been adapted for HM patients during the pandemic. HM patients, deemed appropriate for treatment because

of their high-risk disease, should be imaged as needed and as closely as possible to pre-pandemic levels. Imaging in HM patients with low-risk disease should be restricted to that level which is necessary to assess their clinical risk status.

For HM in the curative setting, the risk-benefit balance during the SARS-COV-2 pandemic clearly favors maintaining established treatment guidelines and multidisciplinary discussions should recommend standard imaging. In HM patients with low-risk disease, imaging should be restricted to that necessary to assess clinical risk status. To note, imaging resources may be limited during the pandemic for monitoring Covid-19 patients. Finally, a careful scheduling of imaging may avoid unnecessary hospital visits.

Final voting: agree 100%, disagree 0% (0/33)

Should fertility preservation facilities be guaranteed during SARS-CoV-2 pandemic?

STATEMENT 7: Fertility preservation facilities should be offered wherever possible, particularly in young patients before undergoing intensive chemotherapy. The decision must consider the availability and accessibility of the local facilities.

While hematologists should continue to discuss fertility issue with patients to maximize the likelihood of a successful pregnancy after chemo regimens, the possibility to offer fertility preservation during the pandemic may be compromised by limited facility availability. Depending on patients' preferences, less intensive regimens (e.g., ABVD instead of eBEACOPP for patients with Hodgkin lymphoma) may be an option when semen or oocyte/ovarian tissue cryopreservation is not feasible.

Final voting: agree 90.91%, disagree 9.09% (3/33)

Are there different indications/thresholds for growth factor support (granulocyte-colony stimulating factors or erythropoietin stimulating agents) or immunoglobulin replacement during the SARS-CoV-2 pandemic?

STATEMENT 8: To lower the risk of febrile neutropenia, consider extending the indication of granulocyte colony- stimulating factor (G-CSF) for patients with intermediate (10%-20%) and high risk for febrile neutropenia (>20%), and specifically for elderly patients with comorbidities. Immunoglobulin replacement whose administration should be carefully weighed against the risk of additional hospital visits can be used, favorably by SC application.

Most systemic therapies used in high-risk HM are associated with a significant risk of immunosuppression. Therefore, relevant supportive measures should be implemented such as prophylactic use of hematopoietic growth factors in all regimens with a medium/ high risk of immunosuppression.[78] Moreover, to lower the risk of febrile neutropenia, the indication for G-CSF can be extended. The theoretical concern raised of acute respiratory failure due to G-CSF induced leukocyte recovery in patients with a pulmonary infection due to SARS-COV-2 does not outweigh the benefit, but G-CSF should be applied with caution. [79]The use of erythropoietin, within guidelines indication, can be considered to prevent patient's visits for blood transfusion. After careful review and confirmation of the indication, immunoglobulin replacement should be maintained where possible to avoid further infectious complications. If available, subcutaneous formulations can be a useful alternative and avoid prolonged hospital stays and unnecessary visits.

Final voting: agree 96.97%, disagree 3.03% (1/33)

Should the prevention and the management of thromboembolic events be different in HM patient with SARS-CoV-2?

STATEMENT 9: In HM patients with SARS-CoV-2 infection, there is an increased risk of thromboembolic events and associated complications such as lung vessel obstructive thrombo-inflammatory syndrome. For hospitalized patients prophylaxis using low molecular weight heparin (LMWH) is recommended for SARS-CoV-2 infected patients.

There are a number of hemostatic alterations associated with SAR-CoV-2.[80, 81] In HM patients' prophylaxis of thromboembolic events should be continued according to existing guidelines. Patients should receive careful monitoring as routinely as possible to prevent possible bleeding complications. Patients hospitalized with a confirmed diagnosis of Covid-19 should receive prophylaxis of thromboembolic events using LMWH or fondaparinux or even unfractionated heparin, if critically ill with a significantly reduced kidney function. When direct oral anticoagulants are used as prophylaxis, possible drug interactions with medications that are tested for use against SARS-CoV-2 must be considered and reviewed by pharmacists. The role of full therapeutic anticoagulation in severely ill patients with SARS-COV-2 remains controversial.

Final voting: agree 93.94%, disagree 6.06% (2/33)

When can a SARS-CoV-2 infected HM patient be considered cured and be rechallenged with anti-cancer treatments?

STATEMENT 10: There is no clear definition of the time point when HM patients can be considered healed from COVID-19. The decision to rechallenge anti-cancer treatment in the absence of symptoms of active viral infection should be individualized. Doctors may consider the time elapsed since the beginning of SARS CoV2 infection, sequential negative PCR tests, the presence of neutralizing antibodies, the type and risk of HM, and the treatment to be administered.

Initially, two negative PCR tests more than 24h apart were required to confirm cure of SARS-CoV-2 infection. To note, many HM patients have positive PCR tests for prolonged periods without active infection.[66] However, studies on the associations between swab test result, number of cycle thresholds, viral loads, viral cultures and disease status and infectivity did not include significant numbers of severely immunosuppressed patients or patients with HM[82, 83] and therefore this data cannot be considered final. Viral persistence, reactivation, or reinfection with novel variants of SARS CoV2 is a potential risk for the patients resuming therapy, and for other HM patients in the same wards and outpatient clinics. There are a number of reports of prolonged infections in immunosuppressed patients, especially if receiving corticosteroids, intensive treatments and anti CD20 monoclonal antibodies.[84, 85] The decision to rechallenge with anti-cancer therapy should consider the type of treatment being proposed, since there is a suggestion that some targeted therapies are relatively safe even during SARS-Cov-2 infection (20-23), whereas immunochemotherapy poses bigger risks.

Final voting: agree 93.94%, abstain 6.06%, disagree 0% (0/33)

During the SARS-CoV-2 pandemic, has the risk/benefit balance for including an individual patient in a clinical trial changed?

STATEMENT 11: Even in the SARS-CoV-2 pandemic, participation in appropriate clinical trials should be pursued for HM patients. However, the risk/benefit balance for including an individual patient in a clinical trial is determined by multiple factors such as the R0 index and case load of the pandemic, health care organization characteristics and resources as well as the nature of the interventional study. Telemedicine or local testing should be encouraged in this setting.

In many instances, clinical trials represent the best possible chance of a successful outcome for HM patients. Trials with a high probability to need in-patient care, intensive care facilities, and

in areas with high incidence of SARS-CoV-2 infection can be temporarily considered of lower priority and deferred during the pandemic. Therefore, depending on the level of resources available for clinical trial activities, doctors should prioritize interventional studies with the following characteristics: (i) trials with drugs with expected high likelihood of benefit (e.g. very promising activity in early phase or molecularly-selected therapy), (ii) trials with experimental drugs supposed to be safer than the standard of care (iii) trials with low intensity treatment and (iv) trials in diseases or conditions without an effective standard of care. During the SARS-CoV-2 pandemic, deviations from clinical trial protocols have very often been unavoidable. However, treating physicians should remain as close as possible within the provisions of clinical trial protocols so that the risk/benefit balance of the clinical trial remains acceptable.

Final voting: agree 93.94%, abstain 6.06%, disagree 0% (0/33)

WP3: HM management in the Covid-19 pandemic: Lymphoma including CLL

When should we initiate lymphoma treatment in the COVID-19 pandemic? Indolent vs aggressive lymphoma

STATEMENT 12: In indolent lymphomas, including CLL and Waldenstrom's macroglobulinemia (WM) "watch and wait" is the recommended strategy for asymptomatic patients with low tumor burden. When treatment is indicated according to consensus guidelines, treatment should be administered. However, in unvaccinated patients, treatment deferral after anti-SARS-Cov2 vaccination should be considered in the absence of an urgent treatment indication.

In newly diagnosed or relapsing aggressive lymphoma, patients should be treated according to guidelines and a general delay of treatment initiation is not recommended. However, in unvaccinated patients, in the absence of urgent treatment indication, an individual treatment deferral after anti-SARS-Cov2 vaccination (at least one injection) may be considered. Whenever possible, patients with lymphoma should be vaccinated against SARS-Cov2 before the initiation of therapy. In the absence of an urgent treatment indication, a congruous interval (up to four weeks) before an anti-CD20 antibody-containing regimen should be respected.

Patients with lymphoma should be treated in highly specialized hematology centers in which general principles have been implemented to minimize the risk of COVID-19 spreading, such as repeat testing. For indolent lymphoma/CLL/WM requiring therapy, more flexibility in the initiation of therapy may be frequently explored. However, if indolent lymphoma requires therapy according to national consensus guidelines, then treatment should not be delayed. For

aggressive lymphoma delays in treatment initiation can result in significant worsening of the outcome.

Final voting: agree 87.88%, abstain 12.12%, disagree 0% (0/33)

Should we modify lymphoma treatment in the COVID-19 pandemic? In indolent lymphoma/CLL/WM, first line, maintenance, relapse

STATEMENT 13: If treatment is necessary in indolent lymphoma, less immunosuppressive therapies (e.g. therapies avoiding anti-CD20 antibodies in CLL and anti-CD20 maintenance in follicular lymphoma) and treatments with less need for hospital stays, without compromising efficacy are recommended. Vaccination prior to start of treatment is recommended.

In indolent lymphoma with limited disease, if treatment is indicated, radiotherapy approach is encouraged according to established guidelines. When treatment is necessary, the type of therapy should be decided based on the most effective treatment and, only if with comparable efficacy, one should consider the less immunosuppressive alternative. Accordingly, if feasible, outpatient management with oral drugs may be preferred, limiting the access and length of stay in hospital. For patients with advanced follicular lymphoma (FL), monotherapy with rituximab, rituximab + lenalidomide (if available) or less intensive immunochemotherapy, or R/O-CVP (rituximab/binutuzumab, cyclophosphamide, vincristine, prednisone) should be considered. In first line, immunosuppressive approaches (i. e. bendamustine) should be avoided if possible and R/O-CVP or R/O-CHOP are preferred over B-R/O because of their lower immunosuppressive potential. Fludarabine-based regimens (FCR) should be avoided.

Risk of immunosuppression related to maintenance has to be considered and discussed with the individual patient. Decision to start or continue maintenance treatment with anti-CD20 may be considered according to the local epidemiological situation and vaccination status.

In the relapsed/refractory setting, if feasible, outpatient management with oral drugs should be considered with limited access to the hospital and drugs including lenalidomide in FL patients should be considered.

In CLL, targeted oral therapies, especially BTK inhibitors or venetoclax should be a preferred option over immunochemotherapy, if available, in both first line and refractory/relapse (R/R) setting, according to the approval of each drug. The use of anti-CD20 antibodies in association with novel inhibitors should be carefully evaluated and postponed if possible.

Final voting: agree 84.85%, abstain 9.09%, disagree 6.06% (2/33)

Should we modify lymphoma treatment in the COVID-19 pandemic? In first line aggressive lymphoma (DLBCL, MCL, PTCL) and HL?

STATEMENT 14: For aggressive lymphoma in the curative setting patients should be treated according to consensus guidelines without compromising efficacy of treatment. If treatment options are equivalent, less immunosuppressive therapies and treatment with less need for hospital stays are recommended.

Referral to COVID-free centers should be particularly considered for patients with aggressive lymphomas. R-CHOP is a standard of care also during the COVID-19 pandemic, due to its curative potential in DLBCL. R-mini CHOP with G-CSF support can be considered for the elderly, regimens different from R-CHOP (for instance DA-EPOCH-R) may be individually considered in specific situations (e.g. PBMCL, double hit lymphoma). Addition of high dose methotrexate and high dose cytarabine and/or intrathecal methotrexate should have a clinical justification.

In patients with MCL, HDT/ASCT as first line consolidation may be delayed depending on the local epidemiological situation. Differently from FL, rituximab maintenance should be considered due to the demonstrated improved survival. Subcutaneous rituximab is recommended to reduce the time spent in the clinic.

It is not recommended to delay therapy initiation for patients with PTCL and HL. Regarding PTCL, CHOP +/- etoposide is indicated for most patients with PTCL, even in the COVID-19 pandemic. However, etoposide may be omitted in patients over 60 years of age due to increased risk of myelotoxicity and no advantage in PFS in comparison with CHOP alone in this age group.

For patients with previously untreated high-grade double hit' or 'triple hit' B-cell lymphoma and primary mediastinal B-cell lymphoma immunochemotherapy with DA-EPOCH -R remains a frontline option during the Covid-19 pandemic, as R-CHOP may be suboptimal in this patient group.

Final voting: agree 96.97%, disagree 3.03% (1/33)

Should we modify lymphoma treatment in the COVID-19 pandemic? In relapsed aggressive lymphoma (DLBCL, MCL, PTCL) and HL? Should autologous, allogeneic SCT or CAR-T cell therapy be postponed in the pandemic?

STATEMENT 15: In the curative setting patients with relapsed aggressive lymphoma should be treated according to consensus guidelines without compromising efficacy of treatment. If treatment options are equivalent or patients are in a non-curative situation, less immunosuppressive treatments with less need for hospital stays are recommended. Patients with refractory and/or relapsed DLBCL, PTCL and HL who are eligible to autologous, allogeneic SCT or CAR T should first receive salvage regimens. HDT/ASCT or CAR-T should be considered in eligible patients with DLBCL and MCL. Delaying (or omitting) consolidative autologous SCT in PTCL patients in CR following induction therapy may be considered, as its role is still controversial.

A high risk of death in patients undergoing intensive chemotherapy treatment which causes profound cytopenia is expected. This includes treatments such as high-dose methotrexate, DHAP (cisplatin, cytarabine, dexamethasone), escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), intensive autologous, and allogeneic hematopoietic stem-cell transplantation. Despite this, in DLBCL, ASCT should be performed without delay if the procedure is considered.

Final voting: agree 93.94%, abstain 6.06%, disagree 0% (0/33)

How to treat lymphoma in the case of SARS-CoV-2 positive asymptomatic or oligosymptomatic patients? All histological types, at diagnosis, or during therapy

STATEMENT 16: All positive cases should be investigated with lung CT-scan. In indolent lymphomas, if possible, defer commencement of treatment until nasopharyngeal swab negativity and resolution of clinical symptoms. If already on treatment the decision to continue or stop treatment should be based on the nature of the treatment and the severity of Covid-19.

In all positive cases a characterization of Covid-19 patient with lung CT-scan, SARS-Cov2 PCR tests and serology is indicated. In indolent lymphomas, including CLL and WM, if possible, defer commencement of treatment until nasopharyngeal swab negativity and resolution of clinical symptoms. If already on treatment and with mild symptoms, BTK inhibitors therapy in WM might be continued, given the risk of IgM rebound and constitutional symptoms upon withdrawal.[86, 87] Therapy with other novel inhibitors might be continued in the presence of a mild form of the disease not requiring hospitalization. Targeted therapies should be withheld, in case of hospitalization and/or need of oxygen-therapy, until recovery. They could be resumed if patients are asymptomatic for at least 48 hours and at least 14 days after symptoms

have started[88] and, if possible, after two consecutive negative RT-PCR tests collected each approximately one week apart. Monoclonal antibodies and/or chemotherapy should be withheld until full characterization of the Covid-19 infection is performed and until the patient is asymptomatic for 48 hours, at least 14 days after symptoms start and, if possible, until nasopharyngeal swab negativity.[88] If there is no immediate threat from lymphoma, consider delaying chemotherapy until nasopharyngeal swab negativity.

In aggressive lymphoma, when feasible, it is better to delay the start of treatment without compromising treatment in a curative setting.

Final voting: agree 93.94%, abstain 6.06%, disagree 0% (0/33)

WP4: HM management in the Covid-19 pandemic: Multiple Myeloma

When is it mandatory to initiate myeloma treatment during the COVID-19 pandemic?

STATEMENT 17: Treatment should not be delayed for newly diagnosed MM (NDMM) patients with active disease, as well as in cases of myeloma medical emergencies. Although patients with established CRAB criteria should start treatment as soon as possible, MM patients presenting with one lesion or SLiM-only criteria may delay treatment only for a limited time period in cases of extreme Covid-19 dissemination in the community. Depending on the local incidence of Covid-19, patients with a solitary plasmacytoma as the sole indication for treatment may only receive local radiotherapy initially. Patients with a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (SMM) are typically in long-term monitoring of their disease status.

Patients with NDMM with active disease should initiate treatment.[89] In the presence of SLiM criteria, treatment initiation might be delayed only for a limited time period in cases of high Covid-19 dissemination in the community. Treatment cannot be postponed in cases of myeloma emergencies.[90] Severe anemia, hypercalcemia and renal failure may necessitate hospitalization and immediate initiation of anti-myeloma treatment along with supportive care.[91] Spinal cord compression may necessitate immediate initiation of radiotherapy and/or orthopedic decompensation.[92-94] Orthopedic treatment of impeding fractures and radiotherapy for palliation of pain unresponsive to analgesics should not be postponed.[92, 94] Patients with a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (SMM) do not require immediate treatment. Scheduled visits of patients with stable disease can be safely delayed. Alternatively, blood examination in local laboratories and

consultation via telemedicine is encouraged. It should be stressed that patients with high-risk disease should be carefully monitored for development of symptomatic disease requiring treatment.[95]

Final voting: agree 96.97%, abstain 3.03%, disagree 0% (0/33)

How to treat myeloma in the case of SARS-CoV-2 positive asymptomatic or oligosymptomatic patients?

STATEMENT 18: In cases of MM patients with a positive PCR test for SARS-CoV-2, but with no symptoms of Covid-19, a 14-day quarantine should be considered if myeloma related events allow the delay of treatment. Otherwise, treatment should be given with very close monitoring of symptoms for early detection of Covid-19 progression. If the patient has symptomatic Covid-19, anti-myeloma treatment should be delayed until total clinical recovery from COVID-19.

Patients with MM and Covid-19 should be treated as per standard guidelines starting from isolation measures. The immune deregulation due to both myeloma- and treatment-related factors may result in a prolonged viral shedding and, subsequently, positive PCR for SARS-CoV-2 for a prolonged time period.[84, 90, 96, 97] The management of MM in the era of Covid-19 is challenging.[8, 98] Asymptomatic patients for Covid-19 should stay quarantined at home for at least 14 days, under close surveillance for detecting Covid-19-associated signs and symptoms, in cases where anti-myeloma therapy can be delayed. In patients with acute renal failure or any myeloma related condition that requires medical attention, treatment should be administered.[90] If anti-myeloma treatment has been initiated, this might continue for patients with an asymptomatic Covid-19 and active myeloma (MM-related symptoms, new diagnosis, recent relapse, suboptimal response to treatment, e.g. less than VGPR) with close monitoring of Covid-19 related symptoms. Steroids and drugs inducing lymphopenia could be de-intensified. Prophylactic G-CSF for the prevention of neutropenia should be considered.

Upon the emergence of symptomatic infection, treatment should be interrupted and the dose of steroids should be adjusted according to the treatment algorithm for Covid-19.[99] Although symptomatic patients with mild Covid-19 may stay at home, close surveillance for aggravating symptoms is necessary.[90] Upon such clinical suspicion, patient referral to a reference center for Covid-19 should not be delayed, because the clinical presentation may deteriorate rapidly and early intervention may be life-saving. For patients enrolled in a clinical trial, investigational

agents should be interrupted until Covid-19 resolution and the reporting should abide with the corresponding guidelines.

Final voting: agree 90.91%, abstain 9.09%, disagree 0% (0/33)

Should first line myeloma treatment be adapted in the Covid-19 pandemic for transplant eligible/ineligible patients?

STATEMENT 19: The combination of bortezomib with lenalidomide or thalidomide and dexamethasone (VRd or VTD), as well as the combination of daratumumab with VTD (DaraVTD) is the most preferred induction therapy for transplant eligible patients with possible modifications for patients with sufficient response. Patients with high-risk disease features may receive ASCT, that could be postponed in patients with standard-risk disease, depending on the epidemiology of Covid-19 in the community, but not more than 3 months, if possible.

For transplant ineligible patients the indicated regimens include VRd or daratumumab-based therapies (DaraRd or DaraVMP). In cases of high incidence of Covid-19 in the community, an all-oral regimen such as Rd could be implemented and the addition of bortezomib or daratumumab could be made later or upon insufficient response.

In general patient visits to the hospital should be minimized, by e.g. de-intensification of treatment in responding patients, if treatment outcome is not compromised.

For transplant-eligible NDMM patients, induction treatment can be administered for an extended period for up to 6-8 cycles.[90] The combination of bortezomib with lenalidomide or thalidomide and dexamethasone (VRd or VTD), as well as the combination of daratumumab with VTD (DaraVTD) represent the preferred induction therapy.[100-103] The treatment schedule can be modified, for patients with sufficient response. Patients with high-risk disease features may receive ASCT after 6-8 induction cycles due to otherwise increased probability of progression. In view of the novel triplet (or quadruplet) upfront combinations for NDMM patients the necessity of upfront ASCT has been challenged.[104] In this context and due to the anticipated immunosuppression following ASCT, it is recommended to postpone mobilization, stem cell harvest, conditioning, and ASCT, mainly in patients with standard risk disease. Physicians may completely avoid ASCT in patients with marginal fitness due to age or comorbidities. Stem cell harvest without mobilization chemotherapy should be considered for patients receiving daratumumab and or lenalidomide-based induction in order to achieve a

sufficient stem cell yield.[105, 106] In this case, G-CSF-only mobilization with the potential addition of plerifaxor should be considered in order to avoid the immunosuppressive effect of high-dose cyclophosphamide. However, in case of close contact with a person diagnosed with COVID-19, stem cell harvests and any transplant procedures should not be performed within at least 14, and preferably 21, days from the last contact.

In transplant ineligible NDMM patients, treatment should be based on all-oral regimens, eg lenalidomide with dexamethasone (Rd), especially for unfit patients, whereas the addition of bortezomib or daratumumab can be considered for patients with high-risk disease, or for those without sufficient response to Rd.[90, 103] For fit or intermediate-fit myeloma patients Rd can be considered as a bridge for 2-3 cycles, in case the Covid-19 pandemic is at a peak in the hospital; otherwise, the approved VRd or daratumumab-based therapies (DaraRd or DaraVMP) should be considered. Dexamethasone should be reduced to 20 mg weekly, whereas de-escalation (or even interruption) should be considered for responding patients, especially after the completion of 9 cycles of treatment.

Final voting: agree 90.91%, abstain 9.09%, disagree 0% (0/33)

Should recommendations for maintenance therapy be changed in the Covid-19 pandemic?

STATEMENT 20: Patients with MM, who are in the maintenance phase of their treatment should continue with their oral therapy and reduce visits to the clinic. Subcutaneous bortezomib administration for high-risk patients might be self-administered at home, if feasible, to avoid omission or delay of treatment and to minimize visits to the hospital.

All oral regimens used for the maintenance phase of treatment can be safely administered in myeloma patients, whereas the disease monitoring and the safety assessment can be easily performed with tele-medicine. Bortezomib injections for high-risk patients can be administered in extended time periods, such as monthly instead of every two weeks, or delayed until the decrease in COVID-19 burden in the community.

Final voting: agree 93.94%, abstain 6.06%, disagree 0% (0/33)

Should treatment of relapsed myeloma be changed in the Covid-19 pandemic? Transplant eligible/non-eligible

STATEMENT 21: Patients with symptomatic relapse should not delay treatment. All oral regimens with equivalent efficacy should be preferred over regimens necessitating frequent hospital visits.

Alternatively, less intensive dosing schedules of intravenous and subcutaneous drugs should be implemented, such as weekly administration of proteasome inhibitors and rapid infusions of monoclonal antibodies. Salvage transplant can be avoided during the Covid-19 pandemic.

Depending on the Covid-19 circumstances in the community, watchful waiting may be considered for biochemical relapses, especially for patients with a slow and gradual increase in the paraprotein level. However, patients with refractory disease, new onset of CRAB features, or those with a biochemical relapse and a history of aggressive relapse with rapid deterioration of the clinical presentation should receive next-line treatment without delay.[90] Regarding the selection of treatment regimen, orally administered agents (ixazomib, lenalidomide, pomalidomide, panobinostat) should be considered based on logistics. Neutropenia due to lenalidomide or pomalidomide must be managed according to published recommendations.[107] Alternative therapeutic approaches are recommended instead of a salvage HSCT or an allogeneic transplant. Should a patient with relapsed/refractory MM (RRMM) achieve sufficient response [eg. very good partial response (VGPR) or better], modifications in the treatment schedule are advisable (once weekly instead of twice weekly bortezomib/carfilzomib, monthly daratumumab infusions). Substitution of bortezomib or carfilzomib with ixazomib, in cases of VGPR or better, is not recommended, as it is not supported by clinical studies. There is no data for isatuximab once monthly and thus in cases of combination with pomalidomide and dexamethasone, in Countries where the combination has been approved, the schedule of isatuximab administration has to remain unchanged (i.e. every two weeks).[108] Similarly, elotuzumab in combination with pomalidomide and dexamethasone should be given according to protocol.[109] Selinexor or belantamab mafodotin can be used in triple-class refractory patients.[103, 110, 111]

Final voting: agree 84.85%, abstain 15.15%, disagree 0% (0/33)

Are cellular therapies as ASCT or CAR T cells to be postponed in the pandemic?

STATEMENT 22: Patients with standard-risk MM may delay upfront ASCT in communities with high incidence of Covid-19, while those with high-risk MM may proceed. Patients eligible for a clinical trial with CAR T- cells without alternative treatment options can proceed as well. In this situation and in cases where ASCT or the CAR T-cell procedure cannot be postponed according

to physician's discretion, exclusion of COVID-19 by PCR for SARS-CoV-2 is deemed necessary, along with strict precautions to prevent SARS-CoV-2 transmission in the transplant department.

Both SCT and CAR T-cell should be offered to all MM patients with anticipated survival benefit. Strict precautions to prevent SARS-CoV-2 transmission in transplant centers should be taken along with exclusion of COVID-19 infection by PCR in patients undergoing ASCT or CAR-T cell therapy.

Final voting: agree 87.88%, abstain 12.12%, disagree 0% (0/33)

WP5: HM management in the Covid-19 pandemic: AML/MDS/ALL

Should any modification to standard of care treatment of myelodysplastic syndromes (MDS) during the COVID-19 pandemic be implemented?

STATEMENT 23: A risk-adapted treatment strategy based on patient's condition, therapeutic goals, and individual risk by IPSS-R should be adopted also in the pandemic.

Patients with lower-risk MDS (IPPS-R score <3.5) are usually RBC-transfusion dependent and the primary aim should be to minimize transfusions, decrease hospital visits, and avoid potential shortage of blood products. The transfusion threshold should be based on patient's clinical condition and reduced to a hemoglobin <7 g/dL whenever possible. Therapies driven to improve anemia (erythropoietic-stimulating agents, lenalidomide, and luspatercept) or thrombocytopenia (thrombopoietin agonists) should be started or continued as planned. Transfusions and those therapies should be ideally delivered and given at home, whenever possible. The start of immunosuppressive therapies should be delayed but continued in those already responding to treatment. For higher-risk MDS (IPSS-R score≥ 3.5), doctors should distinguish three different situations: 1) high priority (patients whose condition is life-threatening or clinically unstable and/or a planned treatment resulting in a significant clinical benefit): treatment with hypomethylating agents (HMA) should be started without delay. In those responding, HMAs should be continued as planned, but a short delay between cycles could be considered after at least 6 cycles of treatment. Targeted therapies and clinical trials should be taken into account; 2) intermediate priority (patients whose condition is not life-threatening, with moderate cytopenias, and fit): a short delay starting treatment could be considered depending on the local hospital and intensive care unit availability; and 3) low priority (patients with stable clinical conditions, for whom treatment is unlikely to provide a

significant benefit, relapsed/refractory without eligibility for salvage therapies, and/or with multiple comorbidities): best supportive care is indicated.

Final voting: agree 84.85%, abstain 12.12%, disagree 3.03% (1/33)

Should any modification to standard of care treatment of acute myeloid leukemia (AML) be implemented during COVID-19 pandemic?

STATEMENT 24: Intensive chemotherapy should be offered without delay for eligible patients both at diagnosis and relapse. Low intensity therapies (i.e. hypomethylating agent +/- venetoclax) might be preferable for older (>65 years of age) and/or unfit patients. For consolidation, the use of intermediate dose cytarabine and/or reducing the number of cycles could be considered. Treatment of acute promyelocytic leukemia (APL) should not be modified.

AML is an emergency medical condition in most cases and treatment cannot be postponed. Intensive chemotherapy is and should be the standard of care for fit patients with AML even during the Covid-19 pandemic. Decreasing the number of cycles during post-remission therapy (intermediate dose cytarabine, 1.0-1.5 g/m^2), especially in some prognostically favorable instances (i.e. *CBF* AML or *NPM1*^{mut}/*FLT3 ITD*^{neg} AML), can be considered to reduce the duration of neutropenia and hospitalization without affecting efficacy in selected cases. Potentially curable refractory/relapsed patients in whom in intensive chemotherapy could serve as a bridge to HSCT should also be treated without delay. Only in SARS-CoV-2 infected patients without proliferative disease or low transfusion requirements treatment may be postponed until the infection is resolved. Treatment for older or unfit patients, e.g. with hypomethylating agents (HMAs) or low-dose cytarabine coupled with venetoclax, should be started in most instances as it has been shown to induce high remission rates, can minimize transfusion requirements, and reduce hospital stay. Low-risk APL should be treated with ATRA and ATO whereas in high-risk patients idarubicin should be added to ATRA +/- ATO.

Final voting: agree 84.85%, abstain 15.15%, disagree 0% (0/33)

Should any modification to standard of care treatment of acute lymphoblastic leukemia (ALL) during COVID-19 pandemic be implemented?

STATEMENT 25: During the Covid-19 pandemic initial induction, intensive post-remission therapy, and maintenance therapy of ALL should be given with as few modifications as possible in children, adolescents, and young adults (AYA) as well as, in adult patients. All phases of therapy

and second line treatments for refractory/relapsed patients should be started without delay. For Ph+ALL a chemo-free approach should be considered.

In ALL modifications of the treatment plan are likely to be associated with poorer outcomes. Adults with additional risk factors for fatal Covid-19 (i.e. diabetes, asthma or chronic obstructive pulmonary disorders, and obesity) should be closely followed. Steroids are considered safe for Covid-19 management and crucial for ALL, hence, they should be used without dose modification in all instances. In Ph-negative ALL the general recommendation is to deliver ALL therapy without modifications. For adult patients with Ph-positive ALL, especially if a high Covid-19 incidence and hospital occupancy are present, a tyrosine-kinase inhibitor (TKI) with steroids is favored over an intensive multi-drug induction chemotherapy for initial treatment. In sharp contrast, intensive multidrug induction chemotherapy is recommended for children and AYA ALL patients. Aggressive post-remission therapy should be administered as scheduled but the use of rituximab for consolidation is controversial due to the frequent need of hospital visits that could put patients at risk. Patients with relapsed or resistant ALL should be treated on a case-by-case basis and considering the availability of clinical trials.

Final voting: agree 93.94%, abstain 6.06%, disagree 0% (0/33)

Should be standard of care treatment modified or stopped in a SARS-CoV-2 positive MDS, AML, blast phase of MPN/CML, ALL patient with asymptomatic or mild Covid-19 disease?

STATEMENT 26: Decisions about administering AML-, ALL-, and MDS-directed therapy in patients with asymptomatic or mild Covid-19 should consider the indication for treatment, goals of care, treatment intensity, and patient's history of tolerance to treatment. Delaying treatment until at least two weeks post resolution of symptoms and SARS.CoV-2 PCR negativity is recommended whenever possible.

Delaying treatment until Covid-19 symptoms have resolved is recommended whenever possible and should be made on a case-by-case basis, also considering treatment intensity. Lower-risk MDS patients responding to erythropoiesis-stimulating agents, luspatercept or lenalidomide as well as higher-risk MDS patients responding to hypomethylating agents (HMAs) beyond the third cycle without haematological toxicity should continue their therapy as planned, especially if treatment can be delivered at home. Treatment of the remaining MDS patients should be postponed. Intensive chemotherapy in AML or ALL should be delayed. In newly diagnosed patients with AML or ALL low-intensity therapies to avoid progression could

be used (i.e. prednisone plus central nervous system prophylaxis in ALL and hydroxyurea and/or HMAs or *FLT3* inhibitors in AML). AML, ALL or APL consolidation and maintenance therapies could be delayed. Thrombosis prophylaxis is recommended if asparaginase is to be used and asparaginase should be omitted if thrombotic events are present. A low intensity therapy as a bridge to HSCT in patients with a high risk of progression could be considered. Patients already under active treatment, especially if prolonged myelosuppression is expected (i.e. chemotherapy, conditioning regimen, first 3 HMAs cycles), must be admitted to a Covid-19 unit and closely monitored. Re-starting treatment should be based on resolution of COVID-19 disease, especially if COVID-19 IgG antibodies are present.

Final voting: agree 87.88%, abstain 12.12%, disagree 0% (0/33)

Should the standard of care treatment be modified or stopped in a SARS-Cov-2 positive patient with AML, blast phase of MPN/CML, ALL or MDS and severe COVID-19 disease?

STATEMENT 27: All AML, ALL, and MDS patients should interrupt any active treatment for his/her hematological malignancy and receive the best available therapy for Covid-19 along with the best supportive care for HM.

The risk of death due to Covid-19 in these patients is very high. Any treatment driven to cure/avoid progression of their HM could substantially increase this risk and should be avoided until resolution of Covid-19. Patients must be treated in a Covid-19 unit according to Institutional policy. As with other patients with severe Covid-19 disease, admission to ICU should be favored and based on their individual prognosis and expectancy of life.

Final voting: agree 87.88%, abstain 12.12%, disagree 0% (0/33)

Should allogeneic hematopoietic cell transplantation for patients with AML, blast phase of MPN/CML, ALL, or MDS be postponed, or conditioning regimen modified during the pandemic?

STATEMENT 28: Allogeneic HSCT is a curative treatment approach for patients with MDS, AML, and ALL. If indicated, a deferral of the HSCT or modification of the planned conditioning regimen is not justified but can be considered on a case-by-case basis. In case of Covid-19 hot spot regions and/or lack of ICU beds , transferring the patient to other centers should be considered.

Patients with Covid-19 after HSCT have a severe course and a higher risk of mortality. In contrast, any delay in postponing HSCT exposes patients to a high probability of relapse. A

perceived higher risk due to the COVID-19 pandemic does not justify a reduction of the conditioning intensity.

Final voting: agree 90.91%, abstain 9.09%, disagree 0% (0/33)

WP6: HM management in the Covid-19 pandemic: MPN/CML

How to treat MPN or CML in case of asymptomatic or mild/ moderate symptomatic Covid-19?

STATEMENT 29: In case of asymptomatic or mild/moderate Covid-19, newly diagnosed CML patients should initiate CML treatment without modifications, moreover there is no indication to interrupt or modify TKI therapy in previously diagnosed CML patients on continuous drug treatment. Likewise, therapy for MPN should not be adjusted in this situation.

Therapies used to treat MPN/ CML are not expected to increase the risk of evolution to severe/very severe Covid-19 and treatment interruption may expose patients to loss of response or in the case of ruxolitinib worsening of inflammatory symptoms.[112]

Final voting: agree 93.94%, abstain 6.06%, disagree 0% (0/33)

How to treat MPN or CML in the case of COVID-19 requiring hospitalization (severe or very severe)?

STATEMENT 30: Treatment initiation in newly diagnosed CML with severe/critical Covid-19 disease should be evaluated on a case-by-case basis, considering the urgency of remission induction. In case of previously diagnosed CML patients, there is no indication to systematically interrupt or modify TKI therapy. Attention should be paid on the impact of potential TKI/anti-Covid-19 drug-drug interactions. In MPNs, particular attention should be paid to patients receiving ruxolitinib. Otherwise, therapies such as anticoagulants or cytoreductive therapy may need to be adjusted depending upon the patient's individual clinical scenario.

In CML, the decision to interrupt TKI treatment in case of admission due to COVID-19 needs to be made on a case-to-case basis considering time on TKI, response to TKI, type of TKI, and risk of CML relapse. To note, TKIs are not considered immunosuppressive, and it is expected that almost all patients still respond after a TKI discontinuation. In patients with concomitant TKI-related organ damage such as cardiovascular or pulmonary toxicity, the TKI should be stopped

until both Covid-19 and adverse events are resolved. For MPN patients with Covid-19, ruxolitinib discontinuation could be harmful.[112]

Final voting: agree 90.91%, abstain 9.09%, disagree 0% (0/33)

Is there any indication to change the current approach to SARS-CoV-2 negative CML patients during the Covid-19 pandemic?

STATEMENT 31: The general approach to CML patients does not require major modifications in the pandemic, while monitoring and supportive care need careful planning to guarantee safe outpatient treatment of CML patients. Home delivery and telemedicine should be encouraged.

Treatment in newly diagnosed CML should not be postponed as remission induction is considered beneficial, even in the pandemic. However, caution is advised during the first 3 months of TKI treatment as severe cytopenia may occur, thus possibly increasing the severity of Covid 19. The pandemic should not affect the choice of TKI. A recent study found an increased mortality risk in CML patients with Covid-19 when treated with imatinib, but this may be confounded by older age, access to and quality of health services.[113] Patients already in treatment with TKIs should continue their treatment. In case of pulmonary side effects of TKIs, SARS-CoV-2 infection should be ruled out, and side effects aggressively managed. A switch to another TKI may be considered. In patients with long-lasting MR4 or better, TKI may be stopped according to current guidelines and patients may be molecularly monitored monthly for the first 6 months. During the pandemic, monitoring frequency and in person visits should not be modified. In patients progressing to blast crisis the indication for treatment should not be modified or postponed. Finally, in woman with CML who plan to become pregnant and in pregnant women with CML interferon treatment does not require adaptation due to the Covid-19 pandemic.

Final voting: agree 96.97%, abstain 3.03%, disagree 0% (0/33)

Is there any indication to change the current approach to MPN patients during the Covid-19 pandemic?

STATEMENT 32: The general approach to MPN patients does not require modifications due to the Covid-19 pandemic, while monitoring and supportive care need careful planning to guarantee safe treatment of MPN patients outside the hospital setting. Home delivery and telemedicine should be encouraged.

Many patients with MPN under on-going treatment have stable disease and can be supported with remote monitoring, in some countries this care is already provided under guidelines by specialist nurses, pharmacists, or family doctors. Some patients e.g. those with advanced phase or aggressive myelofibrosis and, transfusion dependence require closer monitoring mostly in a hospital setting. For selected MPN patients with stable disease intensity of monitoring could likely be reduced for a limited time provided the patient has good links to their routine team. For patients initiating or changing therapy the individual decision should be based on the advantage of initiating an effective treatment, the frequency of monitoring during the first months of therapy and the risk of Covid-19. In PV and ET, delaying treatment initiation can increase the risk of thrombosis. In MF, initiation of ruxolitinib requires specific considerations. For those patients already taking ruxolitinib, stopping the drug whilst having Covid-19 seems to be harmful. Overall, there is no indication to modify current MPN guidelines even in the pandemic.

Final voting: agree 96.97%, abstain 3.03%, disagree 0% (0/33)

Is SCT to be postponed for MPN/CML patients during the pandemic?

STATEMENT 33: HSCT should not be postponed for MPN/CML patients with strong indication for HSCT, while measures should be taken to guarantee post-HSCT treatment, monitoring and care for patients who acquire SARS-CoV-2 after HSCT.

SARS-CoV-2 negative patients with MPN/CML can receive HSCT as indicated. In the case of SARS-CoV-2 positive patients with high risk MPN/CML, HSCT should be deferred until the patient is asymptomatic and has two negative PCR swabs taken at least 24 hours apart. In patients with low-risk disease, who were asymptomatic or only mildly symptomatic with upper respiratory tract symptoms, a deferral of at least 14 days after first negative PCR is indicated with a new PCR test recommended before conditioning; for those with moderate to severe Covid-19, it is recommended to defer HSCT for at least three months.

Final voting: agree 96.97%, abstain 3.03%, disagree 0% (0/33)

CONCLUSIONS

Using a structured method and relying on a panel of experts, we have developed a detailed set of clinical statements to guide healthcare professionals and assist them in overcoming many of the clinical issues in the HM management during the Covid-19 pandemic. The % rate of

"abstain" seen in some Statements is due to the fact that several subspecialized working groups produced statements that were subsequently voted upon in a plenary session by all co-authors, among whom some felt outside their 'core expertise area'.

This set of recommendations reflects the knowledge at the time point of writing. This implies that based on the high dynamics of the COVID-19 pandemic, the rapid increase in our understanding of the COVID-19 biology and the fast changes in the vaccination status of the general population this expert consensus should be considered as a dynamic repository of clinical recommendations.

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Table 1. Overview of working packages and main statements

Working package (WP)	Questions	Statements
Covid-19 diagnosis, treatment, and mitigation strategies (Coordinator: M. von Liliefeld-Toal)	What are efficient strategies to prevent SARS-CoV-2 infection?	**STATEMENT 1: Patients, persons in their close relationship, and caregivers must apply common preventive strategies such as: hygiene measures, physical distancing, wearing facial masks and staying, if possible, in single bedrooms. Efforts in the reorganization of Hematology Units with telehealth to reduce clinic visits, regular SARS-CoV-2 swab testing and vaccination of Health Care Personnel, of persons in the close relationship to patients and caregivers are to be favored.**
	Are anti Covid-19 vaccines indicated in HM patients to prevent SARS-CoV-2 infection?	**STATEMENT 2: Vaccination is strongly recommended. Whenever possible, vaccination should be proposed before initiation of treatment. If this is not possible, vaccines can be administered anytime during disease course or any therapy in principle. In the case an urgent treatment is required, withholding the planned therapy for receiving vaccines is not justified. To note, immune response might be severely reduced in those receiving B-cell depleting agents.**
	Are current available vaccines safe in HMs?	**STATEMENT 3: The benefits of vaccination far outweigh the risks of vaccine-related adverse events and given the greater severity of the disease and higher risk of death, HM patients are considered a high-priority subgroup for SARS-CoV-2 vaccination.**
	Who should be tested for SARS-CoV-2 at what time?	**STATEMENT 4: Diagnostic testing is mandatory at presentation of any Covid-19 symptoms and after Covid-19 diagnosis until receiving two negative results, even after receiving vaccination against SARS-CoV-2. We recommend screening all asymptomatic patients for SARS-CoV-2 at admission for in-hospital stay, 2-3 days later, and then following local policy. Concerning out-patient clinic visits, we encourage developing local policies according to local**

		risk and recommend testing in the case of high SARS-CoV-2 incidence in the community.
	What type of test should be used with which material?	**STATEMENT 5: NAT (Nucleic Acid Amplification Technique) testing is preferred, usually using RT-PCR as the most sensitive method. Material from respiratory tract should be used, swabs are preferred but spit-tests, throat gargles, sputum and naso-pharyngeal aspirates are also under investigation. The evaluation of serum neutralizing antibodies for detecting immune response after exposure to SARS-CoV-2 is encouraged, when feasible.**
HM treatment in the Covid-19 pandemic (Coordinator: J. Gribben)	**With the aim to reduce hospital visits and stay during the pandemic, how is it possible to apply imaging techniques to efficiently stage and restage HM patients?**	**STATEMENT 6: A cancer care prioritization and treatment intensity approach has been adapted for HM patients during the pandemic. HM patients, deemed appropriate for treatment because of their high-risk disease, should be imaged as needed and as closely as possible to pre-pandemic levels. Imaging in HM patients with low-risk disease should be restricted to that level which is necessary to assess their clinical risk status.**
	Should fertility preservation facilities be guaranteed during SARS-CoV-2 pandemic?	**STATEMENT 7: Fertility preservation facilities should be offered wherever possible, particularly in young patients before undergoing intensive chemotherapy. The decision must consider the availability and accessibility of the local facilities.**

	Are there different indications/thresholds for growth factor support (granulocyte-colony stimulating factors or erythropoietin stimulating agents) or immunoglobulin replacement during the SARS-CoV-2 pandemic?	STATEMENT 8: To lower the risk of febrile neutropenia, consider extending the indication of granulocyte colony- stimulating factor (G-CSF) for patients with intermediate (10%-20%) and high risk for febrile neutropenia (>20%), and specifically for elderly patients with comorbidities. Immunoglobulin replacement whose administration should be carefully weighed against the risk of additional hospital visits can be used, favorably by SC application.
	Should the prevention and the management of thromboembolic events be different in HM patient with SARS-CoV-2?	**STATEMENT 9: In HM patients with SARS-CoV-2 infection, there is an increased risk of thromboembolic events and associated complications such as lung vessel obstructive thrombo-inflammatory syndrome. Prophylaxis using low molecular weight heparin (LMWH) is recommended for inpatients**
	When can a SARS-CoV-2 infected HM patient be considered cured and be rechallenged with anti-cancer treatments?	**STATEMENT 10: There is no clear definition of the time point when HM patients can be considered healed from COVID-19. The decision to rechallenge anti-cancer treatment in the absence of symptoms of active viral infection should be individualized. Doctors may consider the time elapsed since the beginning of SARS CoV2 infection, sequential negative PCR tests, the presence of neutralizing antibodies, the type and risk of HM, and the treatment to be administered.**
	During the SARS-CoV-2 pandemic, has the risk/benefit balance for including an individual patient in a clinical trial changed?	**STATEMENT 11: Even in the SARS-CoV-2 pandemic, participation in appropriate clinical trials should be pursued for HM patients. However, the risk/benefit balance for including an individual patient in a clinical trial is determined by multiple factors such as the R0 index and case load of the pandemic, health care organization characteristics and resources as well as the nature of the interventional study. Telemedicine or local testing should be encouraged in this setting.**

HM management in the Covid-19 pandemic: Lymphoma including CLL (Coordinator: L. Arcaini)	**When should we initiate lymphoma treatment in the COVID-19 pandemic? Indolent vs aggressive lymphoma**	**STATEMENT 12: In indolent lymphomas, including CLL and Waldenstrom's macroglobulinemia (WM) "watch and wait" is the recommended strategy for asymptomatic patients with low tumor burden. When treatment is indicated according to consensus guidelines, treatment should be administered. However, in unvaccinated patients, treatment deferral after anti-SARS-Cov2 vaccination should be considered in the absence of an urgent treatment indication.** **In newly diagnosed or relapsing aggressive lymphoma, patients should be treated according to guidelines and a general delay of treatment initiation is not recommended. However, in unvaccinated patients, in the absence of urgent treatment indication, an individual treatment deferral after anti-SARS-Cov2 vaccination (at least one injection) may be considered. Whenever possible, patients with lymphoma should be vaccinated against SARS-Cov2 before the initiation of therapy. In the absence of an urgent treatment indication, a congruous interval (up to four weeks) before an anti-CD20 antibody-containing regimen should be respected.**
	Should we modify lymphoma treatment in the COVID-19 pandemic? In indolent lymphoma/CLL/WM, first line, maintenance, relapse	**STATEMENT 13: If treatment is necessary in indolent lymphoma, less immunosuppressive therapies (e.g. therapies avoiding anti-CD20 antibodies in CLL and anti-CD20 maintenance in follicular lymphoma) and treatments with less need for hospital stays, without compromising efficacy are recommended. Vaccination prior to start of treatment is recommended.**

	Should we modify lymphoma treatment in the COVID-19 pandemic? In first line aggressive lymphoma (DLBCL, MCL, PTCL) and HL?	**STATEMENT 14: For aggressive lymphoma in the curative setting patients should be treated according to consensus guidelines without compromising efficacy of treatment. If treatment options are equivalent, less immunosuppressive therapies and treatment with less need for hospital stays are recommended.**
	Should we modify lymphoma treatment in the COVID-19 pandemic? In relapsed aggressive lymphoma (DLBCL, MCL, PTCL) and HL? Should autologous, allogeneic SCT or CAR-T cell therapy be postponed in the pandemic?	**STATEMENT 15: In the curative setting patients with relapsed aggressive lymphoma should be treated according to consensus guidelines without compromising efficacy of treatment. If treatment options are equivalent or patients are in a non-curative situation, less immunosuppressive treatments with less need for hospital stays are recommended. Patients with refractory and/or relapsed DLBCL, PTCL and HL who are eligible to autologous, allogeneic SCT or CAR T should first receive salvage regimens. HDT/ASCT or CAR-T should be considered in eligible patients with DLBCL and MCL. Delaying (or omitting) consolidative autologous SCT in PTCL patients in CR following induction therapy may be considered, as its role is still controversial.**
	How to treat lymphoma in the case of SARS-CoV-2 positive asymptomatic or oligosymptomatic patients? All histological types, at diagnosis, or during therapy	**STATEMENT 16: All positive cases should be investigated with lung CT-scan. In indolent lymphomas, if possible, defer commencement of treatment until nasopharyngeal swab negativity and resolution of clinical symptoms. If already on treatment the decision to continue or stop treatment should be based on the nature of the treatment and the severity of Covid-19.**
HM management in the Covid-19 pandemic: Multiple Myeloma	**When is it mandatory to initiate myeloma treatment during the COVID-19 pandemic?**	**STATEMENT 17: Treatment should not be delayed for newly diagnosed MM (NDMM) patients with active disease, as well as in cases of myeloma medical emergencies. Although patients with established CRAB criteria should start treatment as soon as possible, MM patients presenting with one lesion or SLiM-only criteria may delay treatment only for a limited time period in cases**

(Coordinator: M. Dimopoulos)		**of extreme Covid-19 dissemination in the community. Depending on the local incidence of Covid-19, patients with a solitary plasmacytoma as the sole indication for treatment may only receive local radiotherapy initially. Patients with a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (SMM) are typically in long-term monitoring of their disease status.**
	How to treat myeloma in the case of SARS-CoV-2 positive asymptomatic or oligosymptomatic patients?	**STATEMENT 18: In cases of MM patients with a positive PCR test for SARS-CoV-2, but with no symptoms of Covid-19, a 14-day quarantine should be considered if myeloma related events allow the delay of treatment. Otherwise, treatment should be given with very close monitoring of symptoms for early detection of Covid-19 progression. If the patient has symptomatic Covid-19, anti-myeloma treatment should be delayed until total clinical recovery from COVID-19.**
	Should first line myeloma treatment be adapted in the Covid-19 pandemic for transplant eligible/ineligible patients?	**STATEMENT 19: The combination of bortezomib with lenalidomide or thalidomide and dexamethasone (VRd or VTD), as well as the combination of daratumumab with VTD (DaraVTD) is the most preferred induction therapy for transplant eligible patients with possible modifications for patients with sufficient response. Patients with high-risk disease features may receive ASCT, that could be postponed in patients with standard-risk disease, depending on the epidemiology of Covid-19 in the community, but not more than 3 months, if possible.** **For transplant ineligible patients the indicated regimens include VRd or daratumumab-based therapies (DaraRd or DaraVMP). In cases of high incidence of Covid-19 in the community, an all-oral regimen such as Rd could be implemented and the addition of bortezomib or daratumumab could be made later or upon insufficient response.**

		In general patient visits to the hospital should be minimized, by e.g. de-intensification of treatment in responding patients, if treatment outcome is not compromised.
	Should recommendations for maintenance therapy be changed in the Covid-19 pandemic?	**STATEMENT 20: Patients with MM, who are in the maintenance phase of their treatment should continue with their oral therapy and reduce visits to the clinic. Subcutaneous bortezomib administration for high-risk patients might be self-administered at home, if feasible, to avoid omission or delay of treatment and to minimize visits to the hospital.**
	Should treatment of relapsed myeloma be changed in the Covid-19 pandemic? Transplant eligible/non-eligible	**STATEMENT 21: Patients with symptomatic relapse should not delay treatment. All oral regimens with equivalent efficacy should be preferred over regimens necessitating frequent hospital visits. Alternatively, less intensive dosing schedules of intravenous and subcutaneous drugs should be implemented, such as weekly administration of proteasome inhibitors and rapid infusions of monoclonal antibodies. Salvage transplant can be avoided during the Covid-19 pandemic.**
	Are cellular therapies as ASCT or CAR T cells to be postponed in the pandemic?	**STATEMENT 22: Patients with standard-risk MM may delay upfront ASCT in communities with high incidence of Covid-19, while those with high-risk MM may proceed. Patients eligible for a clinical trial with CAR T- cells without alternative treatment options can proceed as well. In this situation and in cases where ASCT or the CAR T-cell procedure cannot be postponed according to physician's discretion, exclusion of COVID-19 by PCR for SARS-CoV-2 is deemed necessary, along with strict precautions to prevent SARS-CoV-2 transmission in the transplant department.**

HM management in the Covid-19 pandemic: AML/MDS/ALL (Coordinator: G. Sanz)	**Should any modification to standard of care treatment of myelodysplastic syndromes (MDS) during the COVID-19 pandemic be implemented?**	**STATEMENT 23: A risk-adapted treatment strategy based on patient's condition, therapeutic goals, and individual risk by IPSS-R should be adopted also in the pandemic.**
	Should any modification to standard of care treatment of acute myeloid leukemia (AML) be implemented during COVID-19 pandemic?	**STATEMENT 24: Intensive chemotherapy should be offered without delay for eligible patients both at diagnosis and relapse. Low intensity therapies (i.e. hypomethylating agent +/- Venetoclax) might be preferable for older (>65 years of age) and/or unfit patients. For consolidation, the use of intermediate dose cytarabine and/or reducing the number of cycles could be considered. Treatment of acute promyelocytic leukemia (APL) should not be modified.**
	Should any modification to standard of care treatment of acute lymphoblastic leukemia (ALL) during COVID-19 pandemic be implemented?	**STATEMENT 25: During the Covid-19 pandemic initial induction, intensive post-remission therapy, and maintenance therapy of ALL should be given with as few modifications as possible in children, adolescents, and young adults (AYA) as well as, in adult patients. All phases of therapy and second line treatments for refractory/relapsed patients should be started without delay. For Ph+ALL a chemo-free approach should be considered.**
	Should be standard of care treatment modified or stopped in a SARS-CoV-2 positive MDS, AML, blast phase of MPN/CML, ALL patient with asymptomatic or mild Covid-19 disease?	**STATEMENT 26: Decisions about administering AML-, ALL-, and MDS-directed therapy in patients with asymptomatic or mild Covid-19 should consider the indication for treatment, goals of care, treatment intensity, and patient's history of tolerance to treatment. Delaying treatment until at least two weeks post resolution of symptoms and SARS.CoV-2 PCR negativity is recommended whenever possible.**

	Should the standard of care treatment be modified or stopped in a SARS-Cov-2 positive patient with AML, blast phase of MPN/CML, ALL or MDS and severe COVID-19 disease?	**STATEMENT 27: All AML, ALL, and MDS patients should interrupt any active treatment for his/her hematological malignancy and receive the best available therapy for Covid-19 along with the best supportive care for HM.**
	Should allogeneic hematopoietic cell transplantation for patients with AML, blast phase of MPN/CML, ALL, or MDS be postponed, or conditioning regimen modified during the pandemic?	**STATEMENT 28: Allogeneic HSCT is a curative treatment approach for patients with MDS, AML, and ALL. If indicated, a deferral of the HSCT or modification of the planned conditioning regimen is not justified but can be considered on a case-by-case basis. In case of Covid-19 hot spot regions and/or lack of ICU beds , transferring the patient to other centers should be considered.**
HM management in the Covid-19 pandemic: MPN/CML (Coordinator: D. Rea)	**How to treat MPN or CML in case of asymptomatic or mild/ moderate symptomatic Covid-19?**	**STATEMENT 29: In case of asymptomatic or mild/moderate Covid-19, newly diagnosed CML patients should initiate CML treatment without modifications, moreover there is no indication to interrupt or modify TKI therapy in previously diagnosed CML patients on continuous drug treatment. Likewise, therapy for MPN should not be adjusted in this situation.**
	How to treat MPN or CML in the case of COVID-19 requiring hospitalization (severe or very severe)?	**STATEMENT 30: Treatment initiation in newly diagnosed CML with severe/critical Covid-19 disease should be evaluated on a case-by-case basis, considering the urgency of remission induction. In case of previously diagnosed CML patients, there is no indication to systematically interrupt or modify TKI therapy. Attention should be paid on the impact of potential TKI/anti-Covid-19 drug-drug interactions. In MPNs, particular attention should be paid to patients receiving Ruxolitinib. Otherwise, therapies such as anticoagulants or cytoreductive therapy may need to be adjusted depending upon the patient's individual clinical scenario.**

	Is there any indication to change the current approach to SARS-CoV-2 negative CML patients during the Covid-19 pandemic?	**STATEMENT 31: The general approach to CML patients does not require major modifications in the pandemic, while monitoring and supportive care need careful planning to guarantee safe outpatient treatment of CML patients. Home delivery and telemedicine should be encouraged.**
	Is there any indication to change the current approach to MPN patients during the Covid-19 pandemic?	**STATEMENT 32: The general approach to MPN patients does not require modifications due to the Covid-19 pandemic, while monitoring and supportive care need careful planning to guarantee safe treatment of MPN patients outside the hospital setting. Home delivery and telemedicine should be encouraged.**
	Is SCT to be postponed for MPN/CML patients during the pandemic?	**STATEMENT 33: HSCT should not be postponed for MPN/CML patients with strong indication for HSCT, while measures should be taken to guarantee post-HSCT treatment, monitoring and care for patients who acquire SARS-CoV-2 after HSCT.**

AUTHOR'S COI STATEMENTS

1. Christian Buske reports honoraria from Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead Sciences, Celltrion, MorphoSys, Regeneron; he reports consulting or advisory Role: Gilead Sciences, Janssen, Roche, Pfizer, BeiGene, Celltrion, AbbVie, Incyte, Regeneron, MorphoSys, Novartis; he reports speaker's engagement: Roche, Janssen, BeiGene, Celltrion, AbbVie, Pfizer, Gilead Sciences; he reports research funding: Roche/Genentech, Janssen, Celltrion, MSD, Pfizer, Amgen,
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