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EHA/ESMO Clinical Practice Guidelines for the Management of Malignant Lymphoma: Recommendations for the Second Phase of the COVID-19 Pandemic

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Previously, the European Society of Medical Oncology (ESMO) had established cancer patient management during the coronavirus disease 2019 (COVID-19) pandemic.[1] These recommendations should be used as guidance for prioritizing the various aspects of cancer care in order to mitigate the negative effects of the COVID-19 pandemic on the management of cancer patients.

The tiered approach of ESMO in delivering a guidance during COVID-19 for cancer patients is designed across 3 levels of priorities, namely: tier 1 (high priority intervention), 2 (medium priority), and 3 (low priority)—defined with the criteria of the Ontario Health Cancer Care Ontario, Huntsman Cancer Institute and magnitude of clinical benefit scale, incorporating the information on the value-based prioritization and clinical cogency of the interventions.

- High priority: Patient condition is immediately life threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (eg, significant overall survival gain and/or substantial improvement of the quality of life [QoL]);
- Medium priority: Patient situation is noncritical but delay beyond 6-8 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority;
- Low priority: Patient condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is nonpriority based on the magnitude of benefit (eg, no survival gain with no change to or reduced QoL).

As the COVID-19 pandemic has meanwhile evolved and the situation has meanwhile improved in many countries, the European Hematology Association (EHA) has decided to establish clinical practice guidelines for the management of malignant lymphoma for the (chronic) second phase of the COVID-19 pandemic.

Essentially, the board of the EHA scientific working group lymphoma (EHA LyG)[2] was asked to establish and adapt recommendations for the current situation in most countries worldwide. In detail, statements have been formulated by individual members of the EHA LyG board, and these recommendations were evaluated in 2 separate voting rounds according to the published Delphi procedure.[3,4]

The here presented version of recommendations was unambiguously supported by all members and represents our current knowledge. However, as the future situation may evolve, these recommendations should be pragmatically adapted to deal with the local challenges of treatment in the best interest of our lymphoma patients.

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Hodgkin lymphoma

In general, the high efficacy favors curative standard-of-care approaches despite the infectious risk of COVID-19.

Limited stage disease

High priority

- Curative systemic treatment:
  - The potentially higher efficacy of myelosuppressive treatment has to be balanced against the infectious risk of COVID-19, which may differ locally
  - Use phone calls/telemedicine visits to reduce clinic visits on days when treatment is not scheduled
  - Consider broader use of G-CSF to reduce risk of neutropenia
- Curative radiotherapy
- Continuation of treatment in clinical routine as well as clinical trials

Medium priority

- In the case of COVID-19 infection, treatment should be delayed until viral clearance whenever possible. Patients on treatment who develop COVID-19 infection but without symptoms should be carefully watched and pausing of treatment should be considered depending on the individual patient situation. When patients develop COVID-19 symptoms, treatment should be stopped

Low priority

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Advanced stage disease

High priority

- Curative systemic treatment:
  - The higher efficacy of myelosuppressive treatment has to be balanced against the infectious risk of COVID-19, which may differ locally
  - Use phone calls/telemedicine visits to reduce clinic visits on days when treatment is not scheduled
  - Consider broader use of G-CSF to reduce risk of neutropenia
- If ABVD is used, consider PET-guided strategy as per the RATHL trial,[5] as omission of bleomycin may reduce the risk of pulmonary complications
- Continuation of treatment in clinical routine as well as clinical trials

Medium priority

- In the case of COVID-19 infection, treatment should be delayed until viral clearance whenever possible. Patients on treatment who develop COVID-19 infection but without symptoms should be carefully watched and pausing of treatment should be considered depending on the individual patient situation. When patients develop COVID-19 symptoms, treatment should be stopped

Low priority

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Relapsed disease

High priority

- High-dose chemotherapy with autologous stem cell support
- The high efficacy of palliative systemic treatment has to be balanced against the infectious risk of COVID-19, which may differ locally
- Palliative radiotherapy

Medium priority

- Maintenance brentuximab vedotin post Tx
- In the case of COVID-19 infection, treatment should be delayed until viral clearance whenever possible. Patients on treatment who develop COVID-19 infection but without symptoms should be carefully watched and pausing of treatment should be considered depending on the individual patient situation. When patients develop COVID-19 symptoms, treatment should be stopped

Low priority

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ABVD = doxorubicin/bleomycin/vinblastine/dacarbazine; G-CSF = granulocyte colony-stimulating factor; PET = positron-emission tomography; Tx = treatment.

Aggressive lymphoma (diffuse large B-cell, mantle cell, and T-cell lymphomas)

Diffuse large B-cell lymphoma

In general, the high efficacy favors curative standard of care approaches despite the infectious risk of COVID-19.

High priority

- Curative treatment for aggressive lymphomas:
  - Chemotherapy schedules may be modified so as to reduce clinical visits without compromising the curative potential of the treatment
  - Patients should receive G-CSF growth factor support so as to minimize neutropenia
  - The potentially higher efficacy of intensified treatment has to be balanced against the infectious risk of COVID-19, which may differ locally
  - The addition of high-dose methotrexate, high-dose cytarabine, and/or intrathecal methotrexate because of the risk of CNS involvement has to be balanced against the infectious risk of COVID-19, which may differ locally
- High-dose chemotherapy with autologous stem cell support in relapse of DLBCL
- Continuation of treatment in clinical routine as well as clinical trials
- CAR-T cell therapy in refractory DLBCL

Medium priority

- Noncurative treatment (eg, systemic therapy for relapsed aggressive lymphoma, not eligible for autologous stem cell transplant) may be modified to reduce clinical visits
  - Patients should receive G-CSF growth factor support so as to minimize neutropenia
- Consolidation radiotherapy (eg, due to initial bulk or extranodal disease) may be delayed
- In the case of COVID-19 infection, treatment should be delayed until viral clearance whenever possible. Patients on treatment who develop COVID-19 infection but without symptoms should be carefully watched and pausing of treatment should be considered depending on the individual patient situation. When patients develop COVID-19 symptoms, treatment should be stopped

Low priority

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Mantle cell lymphoma

In general, the high efficacy favors standard-of-care approaches despite the infectious risk of COVID-19.

High priority

- First-line treatment for MCL:
  - Chemotherapy schedules may be modified so as to reduce clinical visits
  - Patients should receive G-CSF growth factor support so as to minimize neutropenia
- Continuation of treatment in clinical routine as well as clinical trials

Medium priority

- Systemic therapy for relapsed MCL may be modified so as to reduce clinical visits
  - Patients should receive G-CSF growth factor support so as to minimize neutropenia
- The potential long-term benefit of high-dose chemotherapy with autologous stem cell support has to be balanced against the infectious risk of COVID-19, which may differ locally
- The overall survival benefit of maintenance therapy with rituximab has to be balanced against the infectious risk of COVID-19, which may differ locally
- Palliative radiotherapy may be delayed

• In the case of COVID-19 infection, treatment should be delayed until viral clearance whenever possible. Patients on treatment who develop COVID-19 infection but without symptoms should be carefully watched and pausing of treatment should be considered depending on the individual patient situation. When patients develop COVID-19 symptoms, treatment should be stopped
Low priority
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(Aggressive) T-cell lymphoma

In general, the high response rates favors standard-of-care approaches despite the infectious risk of COVID-19.

High priority
• First-line treatment: ◦ Chemotherapy schedules may be modified so as to reduce clinical visits ◦ Patients should receive G-CSF growth factor support so as to minimize neutropenia • Continuation of treatment in the context of a clinical trial
Medium priority
• Systemic therapy for relapsed disease may be modified so as to reduce clinical visits ◦ Patients should receive G-CSF growth factor support so as to minimize neutropenia • The potential long-term benefit of high-dose chemotherapy with autologous stem cell support has to be balanced against the infectious risk of COVID-19, which may differ locally • Palliative radiotherapy may be delayed • In the case of COVID-19 infection, treatment should be delayed until viral clearance whenever possible. Patients on treatment who develop COVID-19 infection but without symptoms should be carefully watched and pausing of treatment should be considered depending on the individual patient situation. When patients develop COVID-19 symptoms, treatment should be stopped
Low priority
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CAR-T cell = chimeric antigen receptor T cell; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; G-CSF = granulocyte colony-stimulating factor; MCL = mantle cell lymphoma.

Indolent B-NHL (follicular and marginal zone lymphoma, Waldenström's macroglobulinemia)

In general, the high efficacy favors curative standard-of-care approaches despite the infectious risk of COVID-19.

High priority
• In indolent B-NHL, life threatening situations are rare but might occur (eg, compression of a vital organ, hyperviscosity, or CNS involvement in Waldenström's macroglobulinemia [Bing-Neel syndrome]). Under these circumstances, the pros and cons of an immediate versus delayed treatment should be evaluated thoroughly and decisions have to take into account the individual patient situation ◦ Chemotherapy schedules may be modified to reduce immunosuppression or to minimize the necessity of clinical visits ◦ Consider G-CSF support to minimize risk of neutropenia • Radiotherapy with curative intent
Medium priority
• In advanced stage, indolent B-NHL patients should follow a watch & wait strategy whenever possible ◦ Patients in need of treatment should generally receive treatment following standard guidelines ◦ Less immunosuppressive treatments should be preferred as treatments requiring less clinical visits ◦ The improved long-term outcome of anti-CD20 antibody-based maintenance has to be balanced against the infectious risk of COVID-19, which may differ locally ◦ In the case of COVID-19 infection, treatment should be delayed until viral clearance whenever possible. Patients on treatment who develop COVID-19 infection but without symptoms should be carefully watched and pausing of treatment should be considered depending on the individual patient situation. When patients develop COVID-19 symptoms, treatment should be stopped, with the exception of BTK-inhibitors, given the risk of IgM rebound and constitutional symptoms upon withdrawal[6]
Low priority
• Watch & wait strategies should be followed strictly in all patients not clearly in need of treatment

BTK = Bruton's tyrosine kinase; CNS = central nervous system; G-CSF = granulocyte colony-stimulating factor; IgM = immunoglobulin M; NHL = non-Hodgkin lymphoma.

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