Saudi Lymphoma Group's Clinical Practice Guidelines for Diagnosis, Management and Follow-up of Patients with Various Types of Lymphoma during the Coronavirus Disease 2019 Pandemic

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Abstract

The Saudi Lymphoma Group had previously published recommendations on the management of the major subtypes of lymphoma. However, the effect the currently ongoing coronavirus disease 2019 (COVID-19) pandemic has on the management of patients with lymphoma has been paramount. Therefore, the Saudi Lymphoma Group has decided to provide clinical practice guidelines for the diagnosis, management and follow-up of patients with various types of lymphoma during the COVID-19 pandemic.

Keywords: COVID-19, guidelines, lymphoma

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INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 is a novel coronavirus that was identified in the late 2019 and rapidly caused a pandemic. The disease caused by this novel virus is designated as coronavirus disease 2019 (COVID-19). The Saudi Lymphoma Group has previously published its clinical practice guidelines for the diagnosis, management and follow-up of all major types of lymphoma.[1-8]

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However, during the COVID-19 pandemic, management should be modified to reduce the infection risk and its complications, maintaining reasonable waiting time without compromising the clinical outcomes.[9-11]

Studies have shown that patients with solid cancers and hematological malignancies, including lymphomas, are at

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higher risk of developing the COVID-19 infection.[12,13] For asymptomatic or minimally symptomatic patients, the therapy can be deferred until the COVID-19 threat has resolved. With the current limited and evolving knowledge about this novel virus, balancing individual versus societal benefits and estimating the risk versus benefit of administering myelosuppressive and/or immunosuppressive therapy to lymphoma patients with COVID-19 is the new global reality that poses ethical dilemmas to the medical community. Prioritization and case-by-case discussion is essential to maximize the benefit of any proposed intervention during the COVID-19 pandemic.[14-17] Currently, guidelines for the management of patients during the pandemic are mainly comprised of recommendations based on expert opinion given the lack of available evidence. Physicians treating patients with lymphoma must make critical decisions in the management of their patients regarding the type of chemotherapy regimen as well as the timing and use of hematopoietic stem cell transplant (SCT). Consensus guidelines are currently needed, especially at a national level, to streamline the management of lymphoma patients and support physicians in making the most appropriate decision.

METHODOLOGY

The Saudi Lymphoma Group assigned experts in the field of lymphoma to write clinical practice recommendations, to serve as national lymphoma management guidelines during the COVID-19 pandemic. This guideline is based on the experts' opinions and review of the evolving knowledge about cancer management during the pandemic. In Phase I, an agreement on the subtypes of lymphoma to be covered and the general layout of the recommendation were achieved through a short survey conducted between the authors of this guideline. Strengths of the general recommendations were considered either as higher or lower priority; however, evidence within these are not categorized by levels given that these are experts' based recommendations. In Phase II, each member wrote the assigned section of recommendations supported by the available evidence and literature review. In Phase III, each section was independently reviewed by two different members and the changes were incorporated after a collective discussion between the three members. Lastly, after compiling the sections, all members reviewed and approved the final manuscript of the recommendations.

HODGKIN LYMPHOMA

Recommendations

Higher priority

1. Doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is the preferred frontline therapy for the curative-intent treatment of patients with Hodgkin lymphoma (HL)
2. Reduction of the potential bleomycin-induced lung toxicity should be considered for all patients by considering the results of interim positron emission tomography (PET)-guided strategy, as per the RATHL trial[18]
3. Outpatient regimen is preferred for salvage therapy
4. High-dose chemotherapy with autologous SCT should be considered for chemosensitive relapsed HL.

Lower priority

1. Implementation of hypofractionation or delay radiation therapy during the pandemic
2. The systemic treatment for patients with palliative-intent therapy should be modified.

Initial therapy

Limited stage

ABVD alone (total of four cycles) is an effective approach if complete remission has been documented after two cycles according to the interim PET/computed tomography (CT).[2,19,20] This could help eliminate the need for daily radiation treatment visits and avoid the long-term risk of radiotherapy. However, if interim PET/CT is positive, it is recommended to complete the planned two cycles of ABVD plus involved-site radiotherapy (ISRT).[21-24] If end-of-induction (EOI) PET/CT is still positive for residual disease, it is recommended to re-biopsy, and, if positive, proceed to salvage therapy.[25] Bleomycin could be replaced with brentuximab vedotin, especially in patients with a history or at risk for lung disease.[26]

Advanced stage

ABVD (total of six cycles) is the preferred first-line therapy or alternatively replacing bleomycin with brentuximab vedotin.[26] Patients with a negative interim PET/CT after two cycles should continue four additional cycles of AVD.[18] If PET/CT is not available, then a CT scan and gallium scan, if available, can be utilized to assess response after three to four cycles. In clinically responding patients, a total of six cycles should be completed. However, if there is evidence of disease progression, it should be managed as a refractory disease.[25]

Relapsed refractory disease

A new biopsy must confirm any suspected relapse. Multiple salvage regimens are available, but most of them are highly myelosuppressive and require hospital admission.[25] Brentuximab vedotin plus bendamustine (BvB) is an outpatient salvage regimen that has been shown

to reduce the disease burden and mobilize stem cells before autologous SCT.[27]

As a general rule, SCT is limited to urgent indications. Because HL is a curable disease, autologous SCT should not be delayed, if possible, for transplant-eligible patients. If a decision is made to proceed with autologous SCT, high-dose melphalan (Mel200) as conditioning can preferably be used because it is safe, effective and feasible as an outpatient autologous SCT.[28,29] The use of brentuximab vedotin as maintenance therapy for 1 year after autologous SCT is highly recommended for high-risk patients; however, it might be reasonable to delay starting the maintenance therapy for a few months.[30] Patients who have confirmed relapse after autologous SCT could be offered other salvage options including immune checkpoint inhibitors (ICIs) such as nivolumab or pembrolizumab, especially as there is no evidence that ICIs are immunosuppressive and avoiding their use in such patients to reduce COVID-19 infections could deprive patients of a highly active class of drugs.[31]

DIFFUSE LARGE B-CELL LYMPHOMA

Recommendations

High priority

1. Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP 21) every 3 weeks is the standard of care for curative-intent treatment of patients with diffuse large B-cell lymphoma (DLBCL)
2. Central nervous system (CNS) prophylaxis with high-dose methotrexate (MTX) is restricted to selected high-risk groups for CNS involvement (e.g., with testicular, adrenal and renal involvement)
3. Subcutaneous rituximab can be considered for patients who tolerated their first intravenous rituximab dose
4. Encourage outpatient salvage chemotherapy with rituximab, gemcitabine, dexamethasone and cisplatin (R-GDP)
5. Autologous SCT can be considered for transplant-eligible patients with chemosensitive-relapsed DLBCL.

Low priority

1. The omission of consolidation radiotherapy to bulky sites of disease at presentation should be considered unless there is a positive PET/CT scan for residual disease at the end of therapy
2. The systemic treatment with palliative intent for patients who are not eligible for autologous SCT can be modified
3. Clinical visits for patients in complete remission can be postponed and virtual consultation should be encouraged.

Limited-stage diffuse large B-cell lymphoma

It is defined as Ann Arbor Stage I and II and nonbulky disease (<7.5 cm). Patients are stratified according to age-adjusted international prognostic index risk factors to either limited stage without adverse features (normal lactate dehydrogenase [LDH], Eastern Cooperative Oncology Group Performance Status [ECOG PS 0–1]) or limited stage with adverse features (elevated LDH and/or ECOG PS ≥2).[32,33]

For patients without adverse features, the recommended therapy is four cycles of R-CHOP 21 without radiotherapy. This recommendation is based on the Phase III FLAYER study, in which four cycles of R-CHOP 21 was not inferior to six cycles of R-CHOP 21, with a relevant reduction in toxicity.[34]

For patients with adverse features, the preferred option is a PET-adapted treatment strategy, where PET is performed after the third cycle of R-CHOP 21. Patients with a negative PET/CT receive one additional cycle of R-CHOP 21 (a total of four cycles).[35] However, patients with a positive PET/CT receive involved-site radiation therapy (ISRT) of 30-35 Gy. Patients who do not undergo an interim PET/CT receive either six cycles of R-CHOP 21 or three cycles of R-CHOP 21 followed by ISRT.[36,37]

Advanced-stage diffuse large B-cell lymphoma

It is defined as Ann Arbor Stage III/IV or bulky disease (≥7.5 cm), regardless of the stage. Based on multiple randomized clinical trials, six cycles of R-CHOP 21 remains the preferred regimen for advanced-stage DLBCL.[38-43] Subcutaneous rituximab is an acceptable alternative for patients who tolerated the first dose of intravenous rituximab.[44,45] We do not recommend consolidative radiotherapy to sites of initial bulky disease; however, the end-of-therapy PET/CT is recommended to guide further management. For patients with a positive PET/CT, ISRT is recommended if a biopsy is not feasible.[46]

The average risk of CNS relapse in DLBCL is approximately 2%–5% and expected to accumulate up to 10% for patients with four to six risk factors, based on the CNS-IPI score.[47,48] In general, there is no consensus on the number and type of risk factors or the timing of CNS prophylaxis. We suggest administering high-dose intravenous MTX for selected high-risk groups for CNS involvement (e.g., testicular, adrenal or renal involvement).[49,50]

Relapsed or refractory (R/R) diffuse large B-cell lymphoma

The preferred therapy for first-relapse or primary refractory DLBCL is salvage chemotherapy followed by

the autologous SCT.[51] We suggest outpatient salvage regimen with rituximab, gemcitabine, dexamethasone and cisplatin (R-GDP).[52,53] For transplant-eligible patients, autologous SCT should not be delayed, if possible.

In general, the treatment is palliative for transplant-ineligible patients.[54] However, for selected patients who are transplant ineligible, have relapsed after autologous SCT or have chemoresistant disease and have access to other therapeutic modalities, polatuzumab vedotin plus bendamustine with rituximab is a feasible option, if available. Chimeric antigen receptor T (CAR-T) cell therapy might be considered for selected patients based on a recent recommendation by the collective experience of the CAR T-cell consortium.[55-57]

INDOLENT LYMPHOMA

Recommendations

Higher priority

1. Potential curative radiation can be offered for eligible patients with early-stage disease
2. Rituximab plus CHOP/CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy should be used rather than rituximab plus bendamustine
3. Subcutaneous rituximab should be used instead of the intravenous formulation for eligible patients
4. The use of rituximab maintenance can be delayed during the COVID-19 pandemic.

Lower priority

1. Patients with nonbulky early-stage disease and noneligible for potential curative radiotherapy might only be observed
2. Frail patients with significant comorbidities and stable disease might only be observed
3. If treatment is required in frail patients, consider using single-agent rituximab.

Limited stage

Grade 1, 2 and 3A: The standard of care for contiguous Stage I and II is potentially curative ISRT, which results in 5-year failure-free progression rates of 74% and 48%, respectively.[58] With these figures, the committee recommends following this approach during the COVID-19 pandemic. Adding rituximab or chemotherapy to radiation lacks an overall survival benefit, and thus it is not recommended.[59] In affected body regions with nonbulky disease where radiation is expected to cause significant morbidity (i.e., abdomen), observation is a reasonable option. Patients with bulky disease may be treated with chemotherapy regimens, as in advanced stages of disease.

Advanced stage

Not all patients with newly diagnosed advanced stage disease require initiation of treatment. If the Groupe d'Etude des Lymphomes Folliculaires criteria are fulfilled, treatment shall be discussed.[60] Frail patients with significant comorbidities and stable disease might be observed. If required, they might be started on single-agent rituximab. Eligible patients in whom treatment cannot be deferred due to disease-related complications (i.e., organ compression and effusions), using CHOP or CVP-based chemoimmunotherapy is preferred over bendamustine because it is known to cause long-lasting significant immunosuppression and lymphopenia. Rituximab as an associate might be preferred over other anti-CD20 monoclonal antibodies because it can be given as a subcutaneous formulation and reduces the duration of stay at the hospital. In the RELEVANCE trial, the novel combination of rituximab and lenalidomide (R2) showed lesser Grade 3–4 neutropenia than other chemoimmunotherapy regimens, and thus it is a reasonable alternative as first-line therapy.[61]

Maintenance

In the PRIMA trial, rituximab maintenance after R-CHOP or R-CVP induction showed a 17% improvement of progression-free survival compared with the placebo. However, there was an increase of Grade 2–4 infections by 15% in the rituximab arm. There was no difference in the overall survival between both arms.[62] Therefore, maintenance with anti-CD20-directed therapy may be deferred during the COVID-19 pandemic.

Relapse

The criteria for initiation of treatment in first line are also applied in the relapsed setting. In addition to the above-listed regimens (RCHOP, RCVP and R2), the oral agent ibrutinib and duvelisib also showed clinical activity.

The indication for autologous or allogeneic stem SCT shall be highly restricted and deferred, if possible.

MANTLE CELL LYMPHOMA

Recommendations

Higher priority

1. Watchful waiting is indicated in indolent subtypes of mantle cell lymphoma (MCL)
2. Intensive regimens are justified during the pandemic for high-risk, transplant-eligible MCL patients
3. Less intensive regimens such as R-CHOP or R-CVP (preferred) or less preferred bendamustine–rituximab (B-R) are reasonable options as outpatient regimens

4. Switching to chemotherapy free (off-label use) with Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib is a reasonable alternative in some patients with very high risk for COVID-19.

Lower priority

1. Unlike other types of non-HLs, maintenance rituximab can reduce mortality in MCL and is justified to continue during the pandemic[63]
2. Autologous SCT can be delayed for patients in complete remission
3. Palliative radiotherapy can be offered to patients with compromised vital organ or for pain relief.

Initial therapy

In patients with the non-nodal leukemic form, smoldering or asymptomatic conventional nodal MCL, initial treatment can be deferred with no adverse impact on outcome.[64-67] However, in patients with symptomatic disease, off-label use of the BTK inhibitors ibrutinib, acalabrutinib or zanubrutinib or the immunomodulatory agent lenalidomide with rituximab could be considered an upfront therapy, if provisional access is approved locally, to avoid hospital visits for intravenous chemotherapy and thus the potential risk of COVID-19.[68-71] The Phase 3 randomized STiL and Bright studies have clearly demonstrated that B-R is superior to R-CHOP in terms of progression-free survival, but not in the overall survival.[72,73] Bendamustine is associated with a reduced risk of myelotoxicity and neutropenic fever but increased risk of lymphopenia. Some experts have raised concerns with its use in the COVID-19 pandemic; therefore, treatment decision should be made on an individual basis.

Although maintenance rituximab (M-R) is associated with improved overall survival in patients treated with R-CHOP, delaying its initiation or temporarily discontinuing M-R is advisable, depending on the local risk of COVID-19 epidemiology.[63] The subcutaneous form of rituximab is preferred, avoiding prolonged hospital visits. M-R after induction with B-R is not indicated, due to lack of evidence of any benefit. Aggressive regimens such as fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose MTX and cytarabine (hyper-CVAD/MA), although effective, could be avoided during the pandemic because they are associated with prolonged neutropenia and hospitalization.[74,75] Delaying or omitting autologous SCT can be considered during the COVID-19 pandemic because of the current risks associated with treatment.[76,77]

For blastoid and pleomorphic MCL, young and fit patients should be offered intensified high-dose cytarabine-containing regimens (e.g., hyper-CVAD/MTX).[78] The novel agents have modest and short-term activity in this setting, and it is recommended only for patients unfit for chemotherapy.[79]

Relapsed/refractory disease

Novel chemotherapy-free BTK inhibitors such as ibrutinib, acalabrutinib or zanubrutinib or the immunomodulatory agent lenalidomide plus rituximab (R^2) are recommended, minimizing or avoiding visits to the hospital for treatment.[68-71,79,80] Young, physically fit patients with a Mantle Cell Lymphoma International Prognostic Index high-risk score with or without TP53 mutations or blastoid/pleomorphic variants can be considered for allogeneic SCT.[81,82] Finally, for patients unfit for treatment, oral corticosteroids and alkylating agents can be offered for symptom relief. Palliative radiotherapy can be offered to patients with compromised vital organs or for pain relief.[83]

PRIMARY MEDIASTINAL B-CELL LYMPHOMA

Recommendations

Higher priority

1. Outpatient regimen such as R-CHOP-21 should be used as the preferred first-line therapy
2. Radiation can be omitted in patients with an end-of-therapy negative (Deauville score of 1–3) PET scan.

Lower priority

1. Patients who are in remission should be monitored by virtual visits to limit the hospital physical visits
2. If consolidative radiotherapy is considered, it is advisable to delay it in communities with high-risk COVID-19 epidemiology.

Initial therapy

For the treatment of PMBCL, as there is no single standard of care, the Group recommends R-CHOP 21 chemotherapy for six cycles as the first-line therapy. This regimen can be given as an outpatient regimen to minimize the need for admission to the health-care facility.[84] The use of protocols that cause more neutropenia and usually require admission to the hospital such as dose-adjusted (DA) etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (EPOCH-R) is discouraged during this period. DA-EPOCH-R without radiation has shown good event-free survival and overall survival outcomes in a single arm, Phase 2 prospective study.[85] There is no clear evidence for the superiority of DA-EPOCH-R over R-CHOP, which makes R-CHOP a reasonable and safer option.

Regarding radiation postchemoimmunotherapy, several retrospective studies have shown conflicting results

regarding its benefit.[86-88] However, other retrospective studies have shown that patients who achieve negative end-of-therapy PET scan (Deauville score 1–3) tend to have excellent outcomes without radiation.[89-91] There is also an ongoing clinical trial by the International Extranodal Lymphoma Study Group looking into this question (IELSG-37). Based on the available evidence, it is reasonable to omit radiation in patients who have negative end-of-therapy PET scan. If radiation is considered, it may be delayed in communities with high-risk COVID-19 epidemiology.

Relapsed refractory disease

Similar to DLBCL, second-line therapy for relapsed/refractory PMBCL is salvage chemotherapy followed by autologous SCT. We recommend using outpatient salvage chemotherapy regimen such as R-GDP.[53] ICIs such as pembrolizumab, administered at an outpatient basis, may be considered in patients who relapse after two lines of therapy.[92] The off-label outpatient combination of a ICI with brentuximab vedotin can be offered to patients unfit for salvage chemotherapy or refractory disease, if approved at the local institutional level.[93] Careful monitoring of patients is required, as these patients are at a higher risk of developing immune-related adverse events such as lung toxicity and fever, which may mimic COVID-19 symptoms.

AGGRESSIVE B-CELL LYMPHOMAS

Burkitt lymphoma

Recommendations

Higher priority

1. High-risk disease (Stage III and IV; LDH > upper limit of normal; ECOG PS ≥2) could be treated with intensified R-CODox-M/IVAC (cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine) or R-Hyper-C-VAD/MA
2. Six cycles of DA-R-EPOCH plus intrathecal (IT) MTX is an option for patients without CNS involvement
3. Low-risk disease (Stages I and II; normal LDH; ECOG PS ≤1) could be treated with three cycles of DA-R-EPOCH. Cycles 2 and 3 can be administered in the outpatient setting if resources are available
4. Patients not eligible for intensified chemotherapy can be given mini-R-CHOP (six cycles) plus IT MTX
5. Relapse disease should be treated with salvage chemotherapy followed by autologous SCT without delay for patients with chemosensitive disease.

Lower priority

1. For patients not eligible for intensive chemotherapy or those with refractory disease, palliative oral corticosteroids and cyclophosphamide can be offered
2. Palliative radiotherapy can be considered for comfort care if vital organs are compromised or for pain relief.

Management

Burkitt lymphoma is a highly aggressive lymphoma that is usually curable with intensified treatment.[94] Therefore, for patients fit for therapy, treatment is offered with intent to cure; hence, no modifications in the dosing or timing of standard protocols can be recommended during the COVID-19 pandemic.

High-risk patients could be treated with intensified R-CODox-M/IVAC or R-Hyper-C-VAD/MA, as these regimens are indicated for patients with CNS involvement and associated with a significantly reduced risk of CNS relapse in comparison to DA-R-EPOCH in patients with no CNS involvement at diagnosis.[95-97] For patients treated with DA-R-EPOCH, the second cycle and beyond can be administered in an outpatient ambulatory setting, if hospital resources are available.[98] On the other hand, for patients with low-risk disease, three cycles of DA-R-EPOCH is adequate treatment and associated with excellent outcome.[99] Chemosensitive relapses after salvage chemotherapy should proceed with autologous SCT. Increased use of granulocyte colony-stimulating factor, as well as antibiotic, pneumocystis pneumonia, antifungal and anti-viral prophylaxis is recommended to reduce the risk of hospital admissions.

High-grade B-cell lymphoma, not otherwise specified and high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements ("double-hit" or "triple-hit" lymphomas)

Recommendations

Higher priority

9. Intensified protocols such as R-CODox-M/IVAC (cyclophosphamide, doxorubicin, vincristine, MTX/ifosfamide, etoposide, high-dose cytarabine) or R-Hyper-C-VAD/MA are used in high-risk patients with CNS disease
10. For double- and/or triple-hit lymphomas, DA-R-EPOCH is a good option especially at centers with capacity to deliver it in the outpatient setting
11. For high-grade B-cell lymphoma (HGBL), not otherwise specified (NOS), the use of R-CHOP is the preferred option
12. R-CHOP or mini-R-CHOP is used for patients unfit for intensified regimens
13. Relapse disease should be treated with salvage chemotherapy followed by autologous SCT without delay for patients with chemosensitive disease.

Lower priority

1. Consolidation radiotherapy can be delayed or omitted in patients who achieve an EOI PET metabolic complete remission after six cycles of treatment
2. CNS prophylaxis with IT MTX or IV high-dose MTX can be omitted in patients with a low/intermediate CNS IPI score
3. Off-label ibrutinib or lenalidomide may also be considered
4. Palliative radiotherapy for patients with disease confined to a single radiation field or for comfort care if vital organ compromised or pain relief
5. Polatuzumab vedotin plus rituximab with bendamustine is an option for patients who fail salvage therapy or relapse after auto-SCT
6. CAR-T cell therapy can be offered to patients with relapsed/refractory disease, when indicated, if patients have access, and preferably tisagenlecleucel, which can potentially be given at an outpatient basis, which has less toxicity.

Management

Patients with HGBL, NOS and HGBL with MYC and BCL2 and/or BCL6 rearrangement ("double-hit" or "triple-hit"), referred to herein as DHL, are considered to have inferior outcome compared to DLBCL, NOS.[100] For DHL, studies have consistently shown that patients treated with R-CHOP have inferior outcome compared to those who receive intensive frontline therapy.[101,102] Despite limitations of data, DA-R-EPOCH is considered an acceptable treatment option, although IT MTX lacks adequate CNS prophylaxis.[103,104]

For patients with limited-stage DHL, a multicenter retrospective study showed excellent and noninferior overall survival and progression-free survival outcomes compared with DLBCL when treated with R-CHOP or R-CHOP-like therapy with or without radiation.[105] Therefore, the Group recommends using this approach during the COVID-19 pandemic to limit the hospitalization and prolong neutropenia associated with other intensified regimens.

For patients with MYC-rearranged (MYC-R) limited-stage HGBL, recent data suggest that there is no benefit of intensified therapy over R-CHOP, which should be accounted for when deciding treatment in the COVID-19 pandemic.[106] Moreover, the prognostic impact of MYC-R in DLBCL/HGBL is largely observed in patients with "double-hit" and "triple-hit" disease, in which MYC is translocated to an immunoglobulin (IGH) partner.[107] Therefore, patients with a newly diagnosed DLBCL/HGBL by morphology and with a non-MYC-IGH rearrangement, determined by fluorescence *in situ* hybridization, are considered as molecular standard risk, and R-CHOP should be considered for these patients, sparing them from the risk of inpatient intensified regimens and mitigate the risks of COVID-19 infection.[108] CAR-T cell therapy, when accessible, is a lifesaving treatment for patients with r/r DLBCL/HGBL, and should not be deferred in the COVID-19 pandemic, after weighing the potential risks and benefits for the patient and accounting for the CAR-T cell recourses and potential disruptions during the pandemic.[55,109,110] Finally, for patients considered for radiotherapy, the International Lymphoma Radiation Oncology Group (ILROG) emergency guidelines for therapy of hematological malignancies during the COVID-19 pandemic should be referred for useful guidance to alternative radiation treatment schemes.[83]

RADIATION THERAPY CONSIDERATIONS

Recommendations

Higher priority

1. Radiotherapy should be omitted when the risk of severe outcomes from COVID-19 infection clearly outweigh the benefit of radiotherapy
2. Radiotherapy can be delayed when there is no or little expected adverse effect on outcome from the delay.

Lower priority

a. The radiotherapy course can be shortened with the use of alternative hypofractionation regimens when radiotherapy could not be omitted or delayed
b. Radiotherapy can be potentially used as a bridging measure to delay the need to initiate systemic therapy.

Omitting radiotherapy

When the risk of severe outcomes from COVID-19 infection (aged ≥60 years and/or presence of serious underlying health conditions) outweighs the benefit of radiotherapy, the omission of radiotherapy can be considered. Examples of such situations include palliative indications when medical alternatives can be offered, completely excised localized low-grade lymphomas, completely excised localized nodular lymphocyte-predominant HL and consolidation radiotherapy in patients who achieved a complete remission after chemotherapy for DLBCL or aggressive non-HL.[22,23,35,88-91]

Delaying radiotherapy

Delaying radiotherapy can be considered in situations where there is little or no expected adverse effect on outcome from the delay. This can include asymptomatic localized low-grade lymphomas, localized nodular

lymphocyte-predominant HL or patients who develop COVID-19 infection prior to starting radiotherapy.

Shortening the course of radiotherapy

Shortening the radiotherapy course can be considered when radiotherapy cannot be omitted or delayed, and this is generally achieved using hypofractionation regimens with the aim of maintaining a similar cure or palliation rate without an increase in toxicity. The risks of acute and late toxicity to normal tissues associated with large dose per fraction are currently mitigated by the use of modern conformal radiotherapy techniques. The ILROG applied radiobiological considerations and clinical experience to generate a few suggested altered dose and fractionation schedules.[83] Examples of such hypofractionated courses include 36 Gy in 12 fractions for chemorefractory HL, 30 Gy in six fractions for aggressive chemorefractory non-HL or solitary plasmacytoma and single-fraction radiotherapy for palliative indications. It is important to note that the proposed shortened courses should always be used with careful consideration and clinical judgment in each individual patient.

HEMATOPOIETIC STEM CELL TRANSPLANT AND CELLULAR THERAPY

Recommendations

High priority

1. Patients with relapsed curable lymphoma who have completed at least two cycles of salvage regimen and deemed to be eligible for high-dose chemotherapy followed by autologous SCT
2. Allogeneic SCT can be carried out when considered curative in patients who achieved CR after relapse postautologous SCT
3. CAR-T cell therapy in relapse-refractory large B-cell lymphoma that is refractory to at least two lines of chemoimmunotherapy
4. All patients should follow the following precautions:
    - Screening of COVID-19, preferably by nasal swab polymerase chain reaction test, during their workup for transplant and 2 days prior to starting the conditioning regimen or the lymphodepleting regimen in CAR-T cell therapy for recipients and before stem cell collection for donors
    - Deferral of patients and donors for at least 3 months if tested positive for COVID-19
    - All patients should be admitted to the hospital in isolation rooms
    - Utilizing virtual clinic in the posttransplant follow-up, whenever possible
    - Limiting visitors and sitters to none, if possible, during the admission period
    - Use of growth factors to reduce the neutropenic period.

Low priority

a. Consolidation autologous SCT for noncurable intent
b. Allogeneic SCT in indolent cases.

Stem cell transplant and cellular therapy considerations

In the current situation of the COVID-19 pandemic, transplant programs face many challenges and transplant physicians are striving to protect patients, donors and staff from complications related to this highly contagious viral infection and at the same time trying to avoid delays in treatment that may harm patients from their underlying primary disease. Both the European Society for Blood and Marrow Transplantation and the American Society for Transplantation and Cellular Therapy have published recommendations in this context to minimize risks on recipients and donors.[111,112] Hematopoietic SCT is indicated in the treatment of lymphoma at different stages.

Taking into consideration the necessity of transplant as a potentially curative option for relapsed DLBCL and HL and the aggressiveness of the disease, it is recommended to proceed with the transplant without delay. In patients where autologous SCT is used as consolidation, a delay of 1–2 months is possible. Delay of allogeneic SCT or CAR-T cell therapy in the indications mentioned above is detrimental, and thus transplant should be performed as scheduled. Given the risk of acquiring the COVID-19 infection throughout the transplantation process, patients who are considered for transplant should be tested during the workup and 2 days before starting the conditioning regimen. Similarly, patients considered for CAR-T cell therapy should be tested prior to starting the lymphodepleting regimen. In the setting of allogeneic SCT, donors must be tested during their workup and 2 days before stem cell collection. For patients and donors who test positive for the virus, cellular therapies should be deferred for at least 3 months.[109-111]

SUPPORTIVE CARE

All efforts should be focused on enhancing communication, which helps in supporting patients to be cared for at home and minimize their need to visit emergency room or clinics and minimize patients' waiting time in all clinical/treatment areas.[15,16] Home delivery of oral prescriptions and virtual clinics are effective ways to support patients medically and psychologically during this pandemic. There is no known role for prophylactic antiviral therapy for COVID-19 in any patient, including immunosuppressed patients.

Growth factors and prophylactic antibiotics should be considered in all patients, especially in elderly patients and those with chronic medical illnesses to reduce the risk of emergency room visits and admission.[9,13,57]

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Conflicts of interest

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