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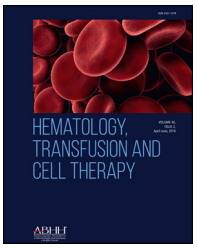

Special article

How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation

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ABSTRACT

The novel Coronavirus (CoVid-19) outbreak is now consider a world pandemic, affecting more than 300,000 people worldwide. Cancer patients are in risk for severe disease, including a higher risk of intensive care unit (ICU) admission, need for invasive ventilation or death. Management of patients with lymphoid malignancies can be challenging during the outbreak, due to need of multiple hospital visits and admissions, immunosuppression and need for chemotherapy, radiotherapy and stem cell transplantation. In this article, we will focus on the practical management of patients with lymphoid malignancies during the COVID-19 pandemic, focusing on minimizing the risk for patients.

The novel 2019 coronavirus disease (CoVid-19) has affected more than 1,340,000 people and has been responsible for more than 74,000 deaths worldwide as of March 23.[1] Cancer patients might be particularly at risk for severe cases of infection and dismal endpoints, such as intensive care unit (ICU) admission, need for invasive ventilation and/or death.[2] Moreover, cancer patients might be more exposed due to constant medical appointments, infusion clinic visits and exams. Also, multiple hospital visits may hinder the recommendation for less exposure in this high-risk population.

There is also concern about resource utilization during the CoVid-19 pandemic.[3] Multiple reports of a shortage of medical equipment, hospital and intensive care unit (ICU) beds have been published and impose difficult ethical choices on the medical community.[4] Cancer patients might be impacted by the overuse of medical resources and it may affect their treatment, as well as their follow-up. Multiple medical societies have published general guidelines regarding cancer care during times of medical overuse, including guidelines for the management of hematological patients[5] and bone marrow transplantation.[6]

For now, there are no definite guidelines regarding the management of lymphoid malignancies during the current pandemic. In this article, we will focus on the practical management of patients with lymphoid malignancies during the CoVid-19 pandemic, focusing on minimizing the risk for patients (Figure 1).

Aggressive B-cell Lymphomas

The diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma and most patients with DLBCL need immediate treatment.[7] The combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) remains the standard therapy for patients and can easily be outpatient-administered.[8] However, other high-grade B-cell lymphomas (double-hit or triple-hit lymphomas) may benefit from more intensive regimens, such as the combination of rituximab with dose-adjusted etoposide, prednisone, vincristine, doxorubicin and cyclophosphamide (R-DA-EPOCH),[9] although these regimens are usually inpatient-administered due to the lack of outpatient portable infusion pumps at most centers. Moreover, some patients with DLBCL also benefit from receiving central nervous system (CNS) prophylaxis as intravenous high-dose methotrexate (MTX), which is considered superior to intrathecal MTX.[10] Unfortunately, there is also a higher resource utilization with intravenous MTX, including hospitalization or multiple blood collection for MTX levels.

The primary mediastinal lymphoma (PML) is a subgroup of aggressive lymphoma that has shown excellent results when treated with R-DA-EPOCH.[11] However, there is no phase 3 randomized trial comparing R-CHOP and R-DA-EPOCH. Therefore, R-CHOP followed by radiotherapy is still an accepted therapy.[12] Other aggressive lymphomas in which the practice should not be changed include: Burkitt's lymphoma, plasmablastic lymphoma and lymphoblastic lymphoma. These are highly aggressive lymphomas that require immediate treatment due to the risk of life-threatening complications.

In the relapsed setting, patients also usually need immediate salvage. Outpatient regimens such as gemcitabine-based regimens, with rituximab, gemcitabine, cisplatin and dexamethasone (R-GDP),[13] or oxaliplatin-based, with rituximab, dexamethasone, cytarabine and oxaliplatin (R-DHAOX),[14] should be considered. The autologous stem-cell transplant (ASCT) should not be delayed, except in critical cases, due to the risk of progression and the need for more treatment. Recommendations for the care of patients submitted do ASCT during the CoViD-19 pandemic have been published elsewhere.[6]

Practical points:

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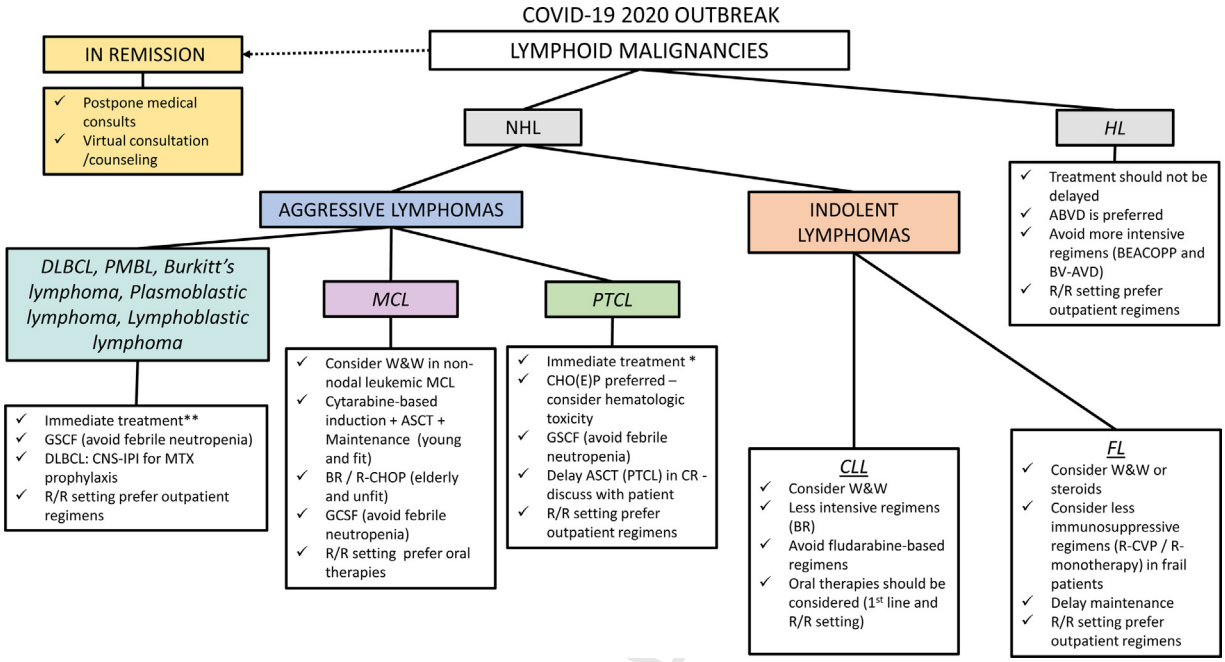

Figure 1 – Algorithm of how to manage lymphoid malignancies during the 2019 novel CoVid-19 Outbreak.
Legend: * Due to the high risk of life-threatening complications; DLBCL: diffuse large B-cell lymphoma; PMBL: primary mediastinal B-cell lymphoma; GCSF: granulocyte-colony-stimulating factor; CNS-IPI: Central Nervous System – International Prognostic Index; R/R: relapsed/refractory patient; MCL: mantle cell lymphoma; W&W: watch and wait; ASCT: autologous steam cell transplant; BR: bendamustine and rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; PTCL: peripheral T-cell lymphoma; CHO(E)P: cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; CLL: chronic lymphocytic lymphoma; HL: Hodgkin lymphoma; ABVD: doxorubicin, bleomycin, vinblastin and dacarbazine; BEACOPP: doxorubicin, cyclophosphamide, etoposide, procarbazine, prednisone, bleomycin and vincristine; BV-AVD: brentuximab, doxorubicin, vinblastin and dacarbazine; FL: follicular lymphoma; R-CVP: rituximab, cyclophosphamide, vincristine and prednisone; R-monotherapy: rituximab monotherapy.

1. Consider immediate treatment of patients with DLBCL with curative intent with R-CHOP. Granulocyte stimulating agents (G-CSF) may be considered to mitigate neutropenia and reduce the incidence of febrile neutropenia (independent of blood counts or age).
2. Subcutaneous rituximab should be considered to minimize patient time in health care facilities.
3. The R-DA-EPOCH should be the treatment of choice for some aggressive lymphomas, such as the primary mediastinal B-cell lymphoma (PMBL) and double/triple-hit lymphomas. However, in the case of unavailability of medical beds or portable infusion pumps for outpatient treatment, the R-CHOP followed either by the ASCT (double/triple hit) or radiotherapy (PMBL) could be considered.
4. The indication for CNS prophylaxis with intravenous MTX should consider the risk/benefit of exposing patients to risk in order to avoid an uncommon complication. Consider delaying the MTX to the end of the R-CHOP therapy. The CNS-IPI[15] can help in determining high-risk patients and mandatory prophylaxis during this period.
5. Do not delay the treatment for other aggressive lymphomas, such as Burkitt lymphoma, plasmablastic lymphoma, etc.
6. Outpatient salvage regimens should be preferred and if possible, ASCT should not be delayed.
7. Postpone medical appointments for patients in complete remission or for patients in which no immediate change in therapy is expected. Virtual consultation/counseling is encouraged.

Mantle cell lymphoma

A relatively small but significant number of patients with mantle cell lymphoma (MCL) do not need immediate therapy[16] and a watch-and-wait strategy may be used in these patients, especially for non-nodal leukemic MCL and asymptomatic patients. For patients in need of immediate treatment, chemotherapy regimens, albeit not curative, may lead to a long progression-free survival (PFS) and overall survival (OS). This is particularly true for young patients treated with cytarabine-based induction regimens followed by ASCT and rituximab maintenance.[17] For unfit patients, bendamustine-rituximab (BR)[18] or R-CHOP[19] are the current standard of care, although the benefit of rituximab maintenance after BR remains controversial.[20] Lenalidomide-based oral regimens for initial treatment of unfit patients with MCL can also be considered, if available.[21]

In the relapsed setting, oral medications should be preferred, including ibrutinib[22] and lenalidomide,[23] if not

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previously used. Allogeneic stem cell transplantation should be delayed in stable patients.

Practical points:

1. Consider the watch-and-wait approach for non-nodal leukemic MCL and for asymptomatic patients.
2. Due to the outstanding PFS and OS benefit of intensive regimens in fit patients, we recommend cytarabine-based induction followed by ASCT. If ASCT should be delayed, cell mobilization and collection should be performed after 3–4 cycles of therapy.
3. No consensus was achieved on rituximab maintenance during the CoVid-19 outbreak. There is an OS benefit in patients receiving maintenance after R-CHOP and after ASCT. Cases should be discussed individually.
4. There is unclear benefit of rituximab maintenance after BR and we do not recommend rituximab maintenance after BR in the current pandemic.
5. In the relapsed setting, we recommend oral therapies, including ibrutinib or lenalidomide, if possible.
6. Allogeneic stem cell transplantation should be postponed, if possible.

Indolent B-cell lymphomas

Patients with indolent lymphomas do not require immediate treatment unless they have symptomatic nodal disease, compromised end-organ function B symptoms, symptomatic extranodal disease, or cytopenias.[24] However, some patients may present with mild symptoms, and cytopenias are usually not life-threatening. Therefore, a watch-and-wait period might also be considered for oligosymptomatic patients, in order to avoid immunosuppressive therapy.

For patients who need immediate treatment, there is no consensus regarding the best chemotherapy backbone. In a phase 3 trial, patients with advanced-stage follicular lymphoma (FL) treated with rituximab, fludarabine and mitoxantrone (R-FM) and R-CHOP had a superior 3-year PFS, but no OS was observed.[25] The combination of BR has been proven non-inferior to R-CHOP and rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CVP) in the BRIGHT study.[26] In another phase 3 trial, BR was superior to R-CHOP in patients with FL and showed less toxicity, including less grade 3 and 4 leukopenia and neutropenia.[27] However, there was no OS benefit for any particular regimen, and some patients treated with bendamustine may have profound immunosuppression.

While maintenance rituximab improves PFS rates, there is an increase in toxicities and there is no OS benefit in a longer follow-up of the PRIMA trial.[28] Moreover, rituximab maintenance has been tested in different schedules, including every 2 or 3 months. Although it is assumed that rituximab infusions every 2 months may maintain better rituximab serum concentration,[29] there is no direct comparison in phase 3 trials. Therefore, it is reasonable to delay rituximab infusions during the CoVID-19 outbreak. Strategies to decrease the patient stay in healthcare facilities, including the use of subcutaneous rituximab, should also be considered.[30]

If oral regimens are available, such as the lenalidomide-based in the first line[31] or relapsed disease[32] or ibrutinib in relapsed marginal zone lymphoma (MZL),[33] they should be considered.

Practical points:

1. Consider short watch-and-wait periods for patients with mild symptoms and/or mild cytopenias. Short-course steroids for patients with B symptoms may mitigate the need for immediate therapy.
2. There is no consensus on using less immunosuppressive regimens (R-CVP) in patients initiating therapy. Rituximab monotherapy may also be considered in some frail patients.
3. Consider delaying anti-CD20 maintenance in patients with indolent lymphomas.
4. Consider using subcutaneous rituximab to minimize the time spent in the clinic.
5. Consider using oral regimens to minimize hospital visits.
6. Postpone medical appointments for patients in complete remission or for patients in which no immediate change in therapy is expected. Virtual consultation/counseling is encouraged.

Chronic lymphocytic leukemia

Patients diagnosed with chronic lymphocytic leukemia (CLL) usually do not need immediate therapy. The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) indications for treatment include significant disease-related symptoms (e.g., fatigue and night sweats), threatened end-organ function, progressive bulky disease, progressive anemia and progressive thrombocytopenia. A cutoff of hemoglobin <10 g/dL and platelets <100,000/L are usually regarded as indications for therapy. Other indications for treatment include lymphocyte doubling-time <6 months, massive/progressive splenomegaly and autoimmune complications unresponsive to steroids.[34]

Fludarabine-based regimens (FCR) can be considered the standard chemotherapy regimen in fit patients with CLL.[35] However, significant immunosuppression may occur during FCR therapy, including grade 3/4 cytopenia and febrile neutropenia.[36] If there is concern on the risk of FCR in a particular patient, less intensive regimens could be an option, such as BR. In the phase 3 CLL10 trial, no overall benefit was observed, comparing FCR and BR.[37] Exceptionally, patients currently receiving FCR could be considered for therapy interruption after three cycles, if they achieve peripheral blood minimal residual disease (MRD) negativity.[38] This decision should be shared with patients, balancing risk and benefits.

Elderly patients, who comprise the majority of CLL patients, are at great risk for CoVID-19 infections. The standard regimen for unfit CLL patients usually includes an anti-CD20 monoclonal antibody and chlorambucil. In the phase 3 trial comparing obinutuzumab and rituximab with chlorambucil in treatment-naïve patients, obinutuzumab showed superior PFS and OS.[39] However, the number of hospital visits and in-clinic time is usually superior with obinutuzumab, especially in cycle 1. If hospital utilization is very high, considering rituximab with chlorambucil or

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chlorambucil monotherapy should be appropriate to control the disease until a more efficient therapy could be started.

Finally, novel oral therapies have been changing the treatment of CLL, both in the first-line and relapsed settings. If available, ibrutinib could be considered for first-line therapy, since it has been proven superior to FCR[40] and BR[41] in phase 3 trials. Venetoclax combined with obinutuzumab has also been proven superior to obinutuzumab combined with chlorambucil in treatment-naïve unfit patients.[42] However, it should be noted that the time spent in the clinic and resource utilization with venetoclax in the ramp-up phase are greater than with ibrutinib. In the relapsed setting, both drugs have shown excellent results[43,44] and are currently considered the standard of care. If venetoclax is being considered in the relapsed setting, venetoclax monotherapy for the first 2–3 months could be appropriate.[45]

Practical points:

1. Consider delaying therapy in oligosymptomatic patients, as well as patients with non-life-threatening cytopenias.
2. Do not indicate therapy based on lymphocyte doubling time or splenomegaly, if patients are asymptomatic.
3. Consider less intensive chemotherapy regimens, such as BR, to avoid fludarabine-based regimens.
4. If the patient is already being treated with FCR, consider stopping therapy after 3–4 cycles, if MRD negativity is achieved.
5. For elderly patients, chlorambucil monotherapy could be considered to control symptoms for 2–3 months before the initiation of anti-CD20 therapy.
6. If possible, novel oral therapies should be considered, both in the first-line and relapsed settings, especially in patients with high-risk cytogenetics (del17p and TP53 disruption).
7. There has not been a direct comparison between ibrutinib and venetoclax, but resource utilization with venetoclax may be higher in patients who need aggressive tumor lysis syndrome (TLS) prophylaxis. Nevertheless, if venetoclax is the therapy of choice, consider monotherapy for 2–3 cycles before initiating anti-CD20 therapy to avoid unnecessary hospital visits. Consider Ibrutinib for patients at a high risk for TLS to avoid hospitalization.
8. Postpone medical appointments for patients in complete remission or for patients in which no immediate change in therapy is expected. Virtual consultation/counseling is encouraged.

Peripheral T-cell lymphomas

Peripheral T-cell lymphomas (PTCL) are aggressive lymphomas that almost always need immediate therapy. Postponing therapy in PTCLs should only be considered after extensive discussion with the patient. The optimal regimen for PTCL has yet to be determined, but most centers consider anthracycline-based regimens, mostly CHOP, for nodal PTCLs.[46] There are some questions if the addition of etoposide to CHOP could improve the outcome of patients with nodal PTCL, albeit at a higher hematological toxicity.[47] More intensive regimens have failed in improving responses in PTCL.[48] For fit patients achieving complete response (CR) or partial response (PR), ASCT should be considered as consolidation therapy.[49] Recently, the addition of brentuximab vedotin (BV) to CHP (CHOP minus vincristine) has been shown superior to CHOP. However, most of patients treated in this trial were anaplastic large cell lymphoma (ALCL), and the benefit for non-ALCL subtypes remains controversial.[50] Moreover, there is a substantially higher resource utilization with BV-CHP due to the need for G-CSF support.

Practical points:

1. Avoid delaying therapy in PTCL due to disease aggressiveness.
2. The CHOP +/− etoposide can be considered the standard of care for most nodal PTCLs. If there is concern about hematological toxicity, omitting the etoposide could be considered.
3. Taking into account the greater need for hospital resources, the BV-CHP should be avoided when possible.
4. Consider delaying the ASCT in PTCL patients in CR after explaining the risks and benefits for ASCT in this setting to them.
5. Postpone medical appointments for patients in complete remission or for patients in which no immediate change in therapy is expected. Virtual consultation/counseling is encouraged.

Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is highly curable with current treatment strategies.[51] The ABVD (doxorubicin, bleomycin, vinblastin and dacarbazine), a tolerable and effective therapy, is the most widely used regimen worldwide.[52] There is a low chance of febrile neutropenia with ABVD, and patients usually have a low utilization of medical resources.[53] Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) has shown superiority for disease control, compared to ABVD, albeit higher toxicity, and hematological toxicity has been observed.[54] In a phase 3 trial, BV-AVD (brentuximab-vedotin, doxorubicin, bleomycin, vinblastin and dacarbazine) was superior to ABVD, regarding a modified PFS endpoint, although no OS benefit was observed. A higher incidence of febrile neutropenia was observed with BV-AVD and G-CSF support was necessary.[55] Balancing the risks and benefits of a more intensive regimen during times of medical resource exhaustion is difficult. However, since there is no clear consensus on the role of more intensive regimens that consume more resources, ABVD seems a good choice as initial treatment. Radiotherapy for early stage disease is usually applied, but can be omitted if not available with a 5–8% impact on PFS.[56] A PET (Positron Emission Tomography – Computed Tomography) guided therapy may help identify patients in whom radiotherapy can be omitted.[57]

Regarding relapsed disease, outpatient salvage should be preferred, including gemcitabine-based regimens.[58,59] The transplant should not be delayed unless there is a critical lack of available beds, due to the chance of cure. The BV consolidation should be used if indicated.[60] If checkpoint inhibitors

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(CPI) are indicated, 4- and 6-week dosing for nivolumab[61] and pembrolizumab[62] should be preferred when possible.

Practical points:

1. Do not delay treatment of Hodgkin's lymphoma unless extremely necessary.
2. The ABVD is currently the most widely used regimen. More intensive regimens (BEACOPP and BV-AVD) should be discussed case by case.
3. Avoid unnecessary hospital visits for exams.
4. Radiotherapy could be omitted if not available, at the cost of 6–8% disease control. Patients might benefit from 6 cycles of ABVD if radiotherapy is not used. Consider using a PET-guided strategy and discuss the risks and benefits with patients.
5. Outpatient salvage should be preferred and ASCT should be delayed only in extreme cases.
6. There is no current recommendation for BV consolidation changes due to the CoVid-19 pandemic. However, it should be clear there is no OS benefit with BV consolidation and there is no data on the impact of delays on PFS.
7. The 4- and 6-week dosing for CPI should be attempted whenever possible.
8. Postpone medical appointments for patients in complete remission or for patients in which no immediate change in therapy is expected. Virtual consultation/counseling is encouraged.

Role of G-CSF

In order to minimize the risk of febrile neutropenia and, consequently, emergency rooms (ERs) visits and hospital admissions, we recommend considering G-CSF prophylaxis during chemotherapy if neutropenia is expected. Not only patients at high risk for febrile neutropenia (>20% risk of febrile neutropenia), but also patients with intermediate risk for febrile neutropenia (10–20% risk of febrile neutropenia).[63] If possible, pegylated G-CSF (pegfilgrastim) 1–3 days after chemotherapy should be preferred. If not possible, self-administration of G-CSF at home should be encouraged, and pharmacists and nurses should be available to train patients and caretakers.[64]

There is concern for the risk of G-CSF administration in patients with suspected or confirmed CoVid-19 infection. In an unpublished report from China, aberrant pathogenic GM-CSF$^+$ T-cells and inflammatory CD14$^+$CD16$^+$ monocytes were related to severe pulmonary syndrome in patients with CoVid-19 infection.[65] Therefore, physicians should avoid the use of, or discontinue, G-CSF in the case of respiratory infection in patients with suspected or confirmed CoVid-19 infection.[64]

Role of vaccination during CoVid-19 pandemic

We strongly recommend maintaining the vaccination schedule of patients, if indicated. In particular, the influenza vaccination should be offered to all patients, as per national guidelines.[66] Although there is concern about the lack of efficacy of the influenza vaccination in patients receiving rituximab,[67] it seems reasonable to recommend vaccination for all patients.

Conclusions

In a rapidly changing scenario of a pandemic, it is difficult to assess the optimal management of patients with lymphoid malignancies. Moreover, we are aware of the extreme variability of medical resources in different regions. In this review, we focused on recommendations for a more pessimistic scenario, hoping to help physicians to choose evidence-based information in the case of total medical resource utilization. We do recommend maintaining therapy as usual in less impacted facilities. However, we are aware of the multiple impacts of the CoVid-19 on medical resources, including hospital beds, ICU beds, blood products and medical staff. Careful utilization of medical resources in the next months is warranted and we hope our review helps physicians decide, case by case, the optimal management of lymphoma patients.

Finally, we strongly recommend postponing therapy in patients suspected of having active CoVID-19 disease. Testing before infusions is unclear and a testing strategy should be discussed case by case. Maintaining anti-bacterial and viral prophylaxis and optimizing antiemetics and pain control in order to minimize hospital visits is encouraged. Moreover, every center should work on a personalized flow for its patients.

Conflicts of interest

The authors declare no conflicts of interest. Q5

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