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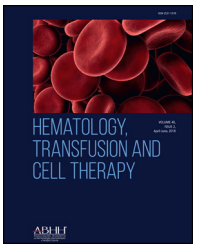


Special article

# 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 1,300,000 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.[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). It is important to note that in the light of dizzyingly rapid learning about the Covid-19 pandemic, these recommendations can be reformulated at any time. These reformulations will be informed on the ABHH website (http://abhh.org.br).

## 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]

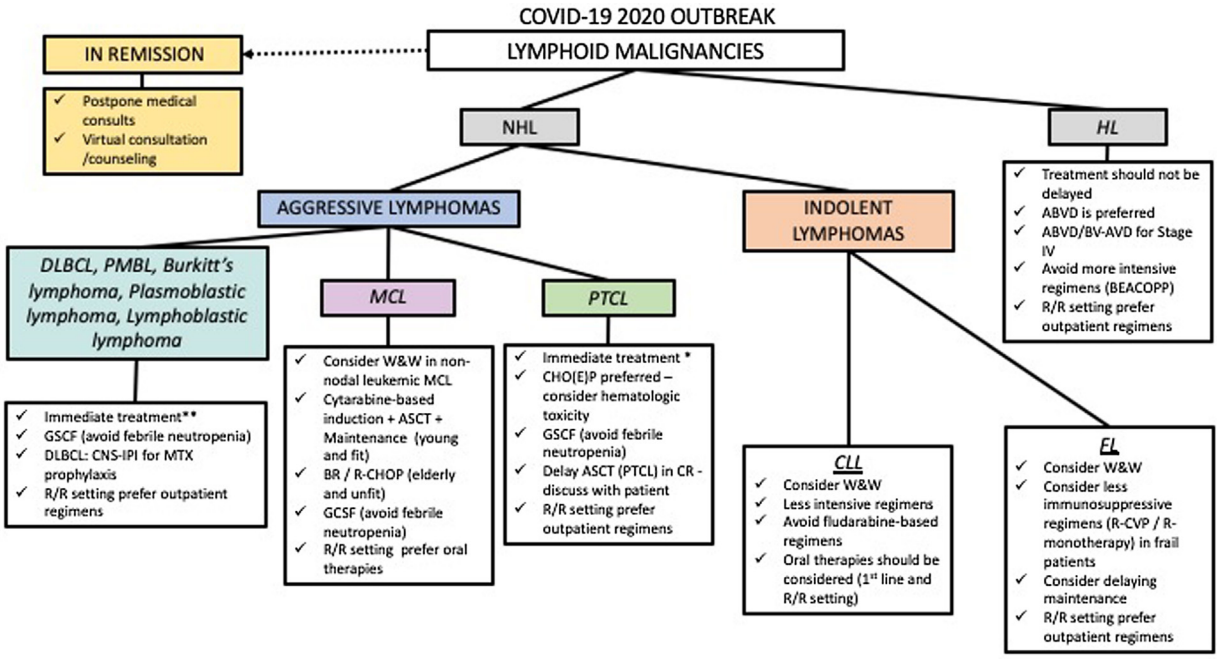


**Figure 1 – Algorithm of how to manage lymphoid malignancies during the 2019 novel CoVid-19 Outbreak.**
**Legend: * Due to the high risk of life-threatening complications; DLBCL: diffuse large B-cell lymphoma; PMBL: primary mediastinal B-cell lymphoma; GCSF: granulocyte-colony-stimulating factor; CNS-IPI: 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.**

Practical points:

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 is considered 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. CNS-IPI[15] can help decide patients with high risk 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 highly 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 Bruton's tyrosine kinase (BTK) inhibitors[22] and lenalidomide,[23] if not 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 done 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 BTK inhibitors 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.
2. There was no consensus on using less immunosuppressive regimens (R-CVP) in patients initiating therapy.
3. Rituximab monotherapy may also be considered in some frail patients.
4. Consider delaying anti-CD20 maintenance in patients with indolent lymphomas.
5. Consider using subcutaneous rituximab to minimize the time spent in the clinic.
6. Consider using oral regimens to minimize hospital visits.
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 highly 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 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 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 BTK inhibitors 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 BTK inhibitors 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 highly 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. 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. Although proven superior in a phase II trial, BV-CHP requires higher resource utilization. Cases should be discusses individually.
4. Consider delaying the ASCT in PTCL patients in CR after explaining the patient about the risks and benefits for ASCT in this setting.
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 highly 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

(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. ABVD is currently the most used regimen. No consensus on the choice of ABVD and BV-AVD in stage IV was achieved.
3. More intensive regimens (BEACOPP) should be avoided.
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. Interruption or delay of BV maintenance should be discussed individually.
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 highly 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.

## REFERENCES

1. WHO. Coronavirus disease (COVID-19) pandemic; 2020 [Internet] Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 [cited 27.03.20].
2. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. Lancet Oncol. 2020. S1470-2045(20)30149-2.
3. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of Covid-19. N Engl J Med. 2020. Epub ahead of print.
4. Willan J, King AJ, Jeffery K, Bienz N. Challenges for NHS hospitals during covid-19 epidemic. BMJ. 2020;20(368):m1117.
5. Willan J, King AJ, Hayes S, Collins GP, Peniket A. Care of haematology patients in a COVID-19 epidemic. Br J Haematol. 2020. Epub a of print.
6. American Society for Transplantation and Cellular Therapy. ASTCT response to Covid-19. Available from: https://www.astct.org/connect/astct-response-to-covid-19 [cited 27.03.20].
7. Grimm KE, O'Malley DP. Aggressive B cell lymphomas in the 2017 revised WHO classification of tumors of hematopoietic and lymphoid tissues. Ann Diagn Pathol. 2019;38:6–10.
8. Di Rocco A, De Angelis F, Ansuinelli M, Foà R, Martelli M. Is now the time for molecular driven therapy for diffuse large B-cell lymphoma? Expert Rev Hematol. 2017;10(9):761–74.
9. Chiappella A, Crombie J, Guidetti A, Vitolo U, Armand P, Corradini P. Are we ready to treat diffuse large b-cell and high-grade lymphoma according to major genetic subtypes? Hemasphere. 2019;3(5):e284.
10. Hall KH, Panjic EH, Valla K, Flowers CR, Cohen JB. How to decide which DLBCL patients should receive CNS prophylaxis. Oncology. 2018;32(6):303–9.

11. Wilson WH, Jung SH, Porcu P, Hurd D, Johnson J, Martin SE, et al. A cancer and leukemia group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. Haematologica. 2012;97(5):758–65.
12. Lees C, Keane C, Gandhi MK, Gunawardana J. Biology and therapy of primary mediastinal B-cell lymphoma: current status and future directions. Br J Haematol. 2019;185(1):25–41.
13. Hou Y, Wang HQ, Ba Y. Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma. Med Oncol. 2012;29(4):2409–16.
14. Manconi L, Coviello E, Canale F, Giannoni L, Minetto P, Guolo F, et al. Dexamethasone, oxaliplatin and cytarabine (R-DHAOx) as salvage and stem cells mobilizing therapy in relapsed/refractory diffuse large B cell lymphomas. Leuk Lymphoma. 2020;61(1):84–90.
15. Schmitz N, Zeynalova S, Nickelsen M, Kansara R, Villa D, Sehn LH, et al. CNS international prognostic index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol. 2016;34(26):3150–6.
16. Martin P, Leonard J. Is there a role for "watch and wait" in patients with mantle cell lymphoma? Semin Hematol. 2011;48(3):189–93.
17. Le Gouill S, Thieblemont C, Oberic L, Moreau A, Bouabdallah K, Dartigeas C, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. N Engl J Med. 2017;377(13):1250–60.
18. Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol. 2005;23(15):3383–9.
19. Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Trneny M, Geisler CH, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012;367(6):520–31.
20. Rummel MJ, Knauf W, Goerner M, Soeling U, Lange E, Hertenstein B, et al. Two years rituximab maintenance vs. observation after first-line treatment with bendamustine plus rituximab (B-R) in patients with mantle cell lymphoma: first results of a prospective, randomized, multicenter phase II study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial). Journal Clin Oncol. 2016;15 Suppl.:7503.
21. Ruan J, Martin P, Christos P, Cerchietti L, Tam W, Shah B, et al. Five-year follow-up of lenalidomide plus rituximab as initial treatment of mantle cell lymphoma. Blood. 2018;132(19):2016–25.
22. Dreyling M, Jurczak W, Jerkeman M, Silva RS, Rusconi C, Trneny M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet. 2016;387(10020):770–8.
23. Trněný M, Lamy T, Walewski J, Belada D, Mayer J, Radford J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. Lancet Oncol. 2016;17(3):319–31.
24. Cheah CY, Seymour JF. When to treat patients with relapsed follicular lymphoma. Expert Rev Hematol. 2017;10(3):187–91.
25. Federico M, Luminari S, Dondi A, Tucci A, Vitolo U, Rigacci L, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol. 2013;31(12):1506–13.
26. Flinn IW, van der Jagt R, Kahl BS, Wood P, Hawkins TE, Macdonald D, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944–52.
27. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203–10.
28. Bachy E, Seymour JF, Feugier P, Offner F, López-Guillermo A, Belada D, et al. Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: long-term results of the PRIMA study. J Clin Oncol. 2019;37(31):2815–24.
29. Tran L, Baars JW, Aarden L, Beijnen JH, Huitema AD. Pharmacokinetics of rituximab in patients with CD20 positive B-cell malignancies. Hum Antibodies. 2010;19(1):7–13.
30. Davies A, Merli F, Mihaljević B, Mercadal S, Siritanaratkul N, Solal-Céligny P, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. Lancet Haematol. 2017;4(6): e272–82.
31. Morschhauser F, Fowler NH, Feugier P, Bouabdallah R, Tilly H, Palomba ML, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med. 2018;379(10):934–47.
32. Leonard JP, Jung SH, Johnson J, Pitcher BN, Bartlett NL, Blum KA, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (alliance). J Clin Oncol. 2015;33(31):3635–40.
33. Noy A, de Vos S, Thieblemont C, Martin P, Flowers CR, Morschhauser F, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017;129(16):2224–32.
34. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446–56.
35. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukaemia. Lancet. 2018;391(10129):1524–37.
36. Fischer K, Bahlo J, Fink AM, Goede V, Herling CD, Cramer P, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016;127(2):208–15.
37. Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016;17(7): 928–42.
38. Strati P, Keating MJ, O'Brien SM, Burger J, Ferrajoli A, Jain N, et al. Eradication of bone marrow minimal residual disease may prompt early treatment discontinuation in CLL. Blood. 2014;123(24):3727–32.
39. Goede V, Fischer K, Engelke A, Schlag R, Lepretre S, Montero LF, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia. 2015;29(7):1602–4.
40. Shanafelt TD, Wang XV, Kay NE, Hanson CA, O'Brien S, Barrientos J, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019;381(5):432–43.
41. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018;379(26):2517–28.

42. Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019;380(23):2225–36.
43. O'Brien S, Furman RR, Coutre S, Flinn IW, Burger JA, Blum K, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood. 2018;131(17):1910–9.
44. Kater AP, Seymour JF, Hillmen P, Eichhorst B, Langerak AW, Owen C, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. J Clin Oncol. 2019;37(4):269–77.
45. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4):311–22.
46. Gleeson M, Peckitt C, To YM, Edwards L, Oates J, Wotherspoon A, et al. CHOP versus GEM-P in previously untreated patients with peripheral T-cell lymphoma (CHEMO-T): a phase 2, multicentre, randomised, open-label trial. Lancet Haematol. 2018;5(5):e190–200.
47. Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418–25.
48. Chihara D, Pro B, Loghavi S, Miranda RN, Medeiros LJ, Fanale MA, et al. Phase II study of HCVIDD/MA in patients with newly diagnosed peripheral T-cell lymphoma. Br J Haematol. 2015;171(4):509–16.
49. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093–9.
50. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3. Lancet. 2019;393(10168):229–40.
51. Townsend W, Linch D. Hodgkin's lymphoma in adults. Lancet. 2012;380(9844):836–47.
52. Longley J, Johnson PW. Options for first line therapy of Hodgkin lymphoma. Hematol Oncol. 2019;37 Suppl. 1:82–6.
53. Boleti E, Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. Ann Oncol. 2007;18(2):376–80.
54. Skoetz N, Will A, Monsef I, Brillant C, Engert A, von Tresckow B. Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma. Cochrane Database Syst Rev. 2017;5(5):CD007941.
55. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med. 2018;378(4):331–44.
56. Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Wells WA, Winter JN, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med. 2012;366(5):399–408.
57. Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015;372(17):1598–607.
58. Ganesan P, Mehra N, Joel A, Radhakrishnan V, Dhanushkodi M, Perumal Kalayarasi J, et al. Gemcitabine, vinorelbine and dexamethasone: a safe and effective regimen for treatment of relapsed/refractory hodgkin's lymphoma. Leuk Res. 2019;84:106188.
59. Ramzi M, Rezvani A, Dehghani M. GDP versus ESHAP regimen in relapsed and/or refractory Hodgkin lymphoma: a comparison study. Int J Hematol Oncol Stem Cell Res. 2015;9(1):10–4.
60. Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;385(9980):1853–62.
61. Bi Y, Liu J, Furmanski B, Zhao H, Yu J, Osgood C, et al. Model-informed drug development approach supporting approval of the 4-week (Q4W) dosing schedule for nivolumab (Opdivo) across multiple indications: a regulatory perspective. Ann Oncol. 2019;30(4):644–51.
62. Lala M, Li M, Sinha V. A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation. J Clinic Oncol. 2018;15 Suppl.:3062.
63. Crawford J, Becker PS, Armitage JO, Blayney DW, Chavez J, Curtin P, et al. Myeloid growth factors, version 2.2017. NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2017;15(12):1520–41.
64. NCCN hematopoietic growth factors. Short-term recommendations specific to issues with COVID-19 (SARS-CoV-2). https://www.nccn.org/covid-19/
65. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Yingjie Q, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus; 2020, pre-print [Internet]. Available from: https://doi.org/10.1101/2020.02.12.945576 [cited 27.03.20].
66. Ministério da Saúde. Informe Técnico da 22a Campanha Nacional de Vacinação contra a Influenza; 2020 [Internet]. Available from: https://www.saude.gov.br/images/pdf/2020/marco/30/GRIPE-Informe-Tecnico-Influenza–final-2.pdf [cited 27.03.20].
67. Eisenberg RA, Jawad AF, Boyer J, Maurer K, McDonald K, Prak ET, et al. Rituximab-treated patients have a poor response to influenza vaccination. J Clin Immunol. 2013;33(2):388–96.