PHILIPPINE SOCIETY OF MEDICAL ONCOLOGY (PSMO) CONSENSUS RECOMMENDATIONS IN THE MANAGEMENT OF NON-HODGKIN'S LYMPHOMA DURING COVID-19 PANDEMIC IN THE CORONAVIRUS DISEASE 2019 (COVID-19) ERA

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Background and Context

The COVID-19 pandemic is a serious health threat. Multiple global health organizations are committing to finding a cure however it is still not within our grasp. As so, it is our task to devise strategies and adapt to the new system in order to safeguard our patients' health as well as ours.

Underlying health conditions increases the risk for severe COVID-19 infections especially active cancers due to their innate immunosuppression. Patients with hematologic malignancies such as lymphoma are considered to be at a higher risk for COVID-19 infection by virtue of their cancer. Conventional coronaviruses have been shown to be associated with higher rates of oxygen requirement and mortality in patients with hematologic malignancies. With these in mind, the objective of this consensus is to provide local guidelines applicable in our setting for the management of Non-Hodgkin's Lymphoma in the COVID-19 era.

These guidelines are recommendations, and are not intended to supersede individual physician judgment, nor institutional policy or guidelines. Physicians should decide on the appropriate medical advice, diagnosis, and treatment for patients depending on their clinical judgment, institutional preferences, and the individual needs of their patients.

Goal and Objectives

To provide local guidance on the management of Non-Hodgkin's Lymphoma in the COVID-19 era.

Target Users

These Clinical Practice Guidelines were developed for health professionals working in the field of oncology, with an emphasis on Medical Oncology.

Methodology

A systematic review of available evidence regarding medical practice in time of the COVID-19 pandemic and other related literature was done by the fellows. The summary of recommendations was presented to each consultant for inputs and comments. Individual voting by the consultants for the grades of recommendation was done using the system shown in Table 1 which was adapted from the ESMO Clinical Practice Guidelines Methodology..

Clinical Issues

Are patients with hematologic malignancies considered to have a higher risk for COVID infection?

People who have hematologic malignancies are at a higher risk, especially when:

- Receiving chemotherapy, or who have received chemotherapy in the last 3-12 months
- Receiving immunotherapy or other continuing antibody treatments for cancer
- Receiving other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors (eg. ibrutinib)
- Those who have had a bone marrow or stem cell transplant in the last 6-12 months, or who are still taking immunosuppression drugs
- People with lymphoma or chronic lymphocytic leukemia which can damage the immune system, even if they have not needed treatment or are in remission with a compromised immune system
- People who are over 65 years or have co-morbidities (eg. Cardiovascular disease, lung disease or diabetes)

REFERENCE: Lymphoma Australia - news - coronavirus - covid-19 & lymphoma [Internet]. [cited 2020 May 20]. Available from: https://www.lymphoma.org.au/news/129/coronavirus-covid-19

A. AGRESSIVE LYMPHOMAS:

1. Should treatment be delayed?
    - Consider immediate treatment for aggressive lymphomas as indicated with curative intent [V,A]
    - Consider GCSF support to avoid neutropenia. [V,A]

        - Reference: Perini GF, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LLC, et al. How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. Hematol Transfus Cell Ther [Internet]. 2020 Apr 17 [cited 2020 May 20]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164906/

2. Should treatment regimens be changed?
    - For those who tolerate the first dose of rituximab given intravenously, subcutaneous administration is an option going forward that reduces time spent in the clinic. [I,A]

        - Davies A., Merli F., Mihaljević B., Mercadal S., Siritanaratkul N., Solal-Céligny P. 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–e282.

    - 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) should be considered. [II,C]

- Covid-19 and aggressive lymphoma - hematology. Org [Internet]. [cited 2020 May 20]. Available from: https://www.hematology.org:443/covid-19/covid-19-and-aggressive-lymphoma
- Reference: Perini GF, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LLC, et al. How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. Hematol Transfus Cell Ther [Internet]. 2020 Apr 17 [cited 2020 May 20]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164906/

- 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), or oxaliplatin-based, with rituximab, dexamethasone, cytarabine and oxaliplatin (R-DHAOX), should be considered. [IV,C]

- Reference: Perini GF, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LLC, et al. How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. Hematol Transfus Cell Ther [Internet]. 2020 Apr 17 [cited 2020 May 20]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164906/
- Lorenzo Manconi, Elisa Coviello, Filippo Canale, Livia Giannoni, Paola Minetto, Fabio Guolo, Marino Clavio, Riccardo Marcolin, Michele Cea, Antonia Cagnetta, Marco Gobbi, Maurizio Miglino, Filippo Ballerini & Roberto Massimo Lemoli (2020) Dexamethasone, oxaliplatin and cytarabine (R-DHAOx) as salvage and stem cells mobilizing therapy in relapsed/refractory diffuse large B cell lymphomas, Leukemia & Lymphoma, 61:1, 84-90, DOI: 10.1080/10428194.2019.1658102

3. Should treatment regimens be shortened?
    - Patients with the lowest risk or those with a negative positron emission tomography (PET) scan after 3 cycles require only 4 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) without RT. [III,B]

    - Persky DO, Li H, Stephens DM, et al: PET-directed therapy for patients with limited-stage diffuse large B-cell lymphoma - Results of Intergroup NCTN Study S1001. Blood 134(Suppl 1):349, 2019. https://ashpublications.org/blood/article/134/Supplement_1/349/426082/PET-Directed-Therapy-for-Patients-with-Limited?searchresult=1

- Percival M-EM, Lynch RC, Halpern AB, Shadman M, Cassaday RD, Ujjani C, et al. Considerations for managing patients with hematologic malignancy during the covid-19 pandemic: the seattle strategy. JCO Oncology Practice. 2020 May 5;OP.20.00241.

- For patients in complete response (CR) after four cycles of R-CHOP 21, consider giving it only for a total of six cycles. [II,A]

  - Gielmini et al, ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)

- For limited stage disease, R-CHOP X 4 may be considered rather than combined modality therapy. [V,A]

  - Covid-19 and aggressive lymphoma - hematology. Org [Internet]. [cited 2020 May 20]. Available from: https://www.hematology.org:443/covid-19/covid-19-and-aggressive-lymphoma

4. Should CAR T cell therapy be delayed?
   - Patients with relapse or recurrent aggressive B-NHL with preserved performance status (ECOG ≤2), limited comorbidities (cardiac, renal, hepatic, and bone marrow reserve), and tumor kinetics that afford the necessary time to undergo leukopheresis and CAR T cell manufacturing should be considered for cellular therapy at this time. [V,C]

     - Bachanova V, Bishop MR, Dahi P, Dholaria B, Grupp SA, Hayes-Lattin B, et al. Chimeric antigen receptor t cell therapy during the covid-19 pandemic. Biol Blood Marrow Transplant [Internet]. 2020 Apr 14 [cited 2020 May 20]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194685/

5. Should treatment with immune checkpoint inhibitors be delayed or interrupted? Are any special precautions or actions needed with respect to their use?
   - There is preclinical evidence of cytokine storm and/or potentially increase inflammatory reactions and complications such as pneumonitis for some novel immunotherapy agents and T-cell therapy agents. Given the long half-life of these drugs, safely spacing out infusion schedules should be considered for those who are deriving. [V,C]

   - Consider less frequent drug administration as an option for patients who are already receiving the drug. One modeling study suggested that Pembrolizumab 400 mg every six weeks leads to similar exposures as every three week administration of a single dose of either 200 mg or 2 mg/kg. [V,C]

- Both the US Food and Drug Administration and the European Medicines Agency have approved a new dosing regimen of 400 mg every six weeks for pembrolizumab across all currently approved adult indications, in addition to the current 200 mg every three week dosing regimen.

    - Uptodate [Internet]. [cited 2020 May 20]. Available from: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-cancer-care-during-the-pandemic#H2192480230
    - Short-Term Recommendations for the Management of T-Cell and Primary Cutaneous Lymphomas During COVID-19. Available from://www.nccn.org/

- For those with a known coronavirus exposure, it is recommended to hold immune checkpoint inhibitors until it is clear that the patient will not develop COVID-19. [V,A]

6. Should allogeneic stem cell transplantation be delayed?
    - In some cases of patients at high-risk for COVID-19, delaying a planned allogeneic SCT may be considered, particularly if the patient's malignancy is controlled with conventional treatment. [V,A]

        - Uptodate [Internet]. [cited 2020 May 20]. Available from: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-cancer-care-during-the-pandemic#H2192480230

7. Should maintenance therapy be delayed?
    - For patients in deep remission who are receiving maintenance therapy, stopping chemotherapy or spacing out cycles may be considered. [V,B]

    - 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. 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, there is no direct comparison in phase 3 trials. Therefore, it may be considered to delay rituximab infusions during the CoVID-19 outbreak. [IV,B]

    - Consider oral chemotherapy should be used where possible to avoid unnecessary hospital visits. [V,C]

        - Covid-19 patient care information [Internet]. ASCO. 2020 [cited 2020 May 20]. Available from: https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19

8. Should radiation therapy be delayed or omitted?
    - Consider delaying or omitting radiation in the palliative setting, where alternatives can be offered e.g. optimizing pain control. [V,C]

- Consider delaying or omitting consolidation RT for DLBCL / aggressive NHL in patients who completed full chemotherapy course and achieved a complete remission. [V,C]

    - Yahalom J, Dabaja BS, Ricardi U, Ng A, Mikhaeel NG, Vogelius IR, et al. Ilrog emergency guidelines for radiation therapy of hematological malignancies during the covid-19 pandemic. Blood [Internet]. [cited 2020 May 20]; Available from: https://ashpublications.org/blood/article/doi/10.1182/blood.2020006028/454357/ILROG-Emergency-Guidelines-for-Radiation-Therapy

9. Should follow-up visits be rescheduled?
    - Consider postponing routine follow-up visits of patients not on active cancer treatment or to conduct those appointments via telemedicine.[V,A]

B. INDOLENT LYMPHOMAS

1. Should treatment be delayed?

    - 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. [V,A]

    - 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. Short-course steroids for patients with B symptoms may mitigate the need for immediate therapy. [V,A]

        - Reference: Perini GF, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LLC, et al. How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. Hematol Transfus Cell Ther [Internet]. 2020 Apr 17 [cited 2020 May 20]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164906/

2. Should treatment regimens be changed?

    - For patients with limited-stage disease who are seeking localized symptom control, high response rates are seen with 1 or 2 fractions of palliative RT with minimal toxicity and may be considered. [V,A]

    - For asymptomatic patients with limited-stage disease who are seeking definitive RT, we recommend deferring treatment by 3-6 months. [V,A]

        - Percival M-EM, Lynch RC, Halpern AB, Shadman M, Cassaday RD, Ujjani C, et al. Considerations for managing patients with hematologic malignancy during the covid-19 pandemic: the

seattle strategy. JCO Oncology Practice. 2020 May 5;OP.20.00241.

- For patients with more extensive disease 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. 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. 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. However, there was no OS benefit for any particular regimen, and some patients treated with bendamustine may have profound immunosuppression.[II,C]

    - Reference: Perini GF, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LLC, et al. How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. Hematol Transfus Cell Ther [Internet]. 2020 Apr 17 [cited 2020 May 20]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164906/

- Given the lack of overall survival benefit in follicular lymphoma, we recommend against maintenance therapy with an anti-CD20 monoclonal antibody to allow for faster B-cell recovery. [I,B]

    - Percival M-EM, Lynch RC, Halpern AB, Shadman M, Cassaday RD, Ujjani C, et al. Considerations for managing patients with hematologic malignancy during the covid-19 pandemic: the seattle strategy. JCO Oncology Practice. 2020 May 5;OP.20.00241.

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

    - Reference: Perini GF, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LLC, et al. How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. Hematol Transfus Cell Ther [Internet]. 2020 Apr 17 [cited 2020 May 20]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164906/

3. Should radiation therapy be delayed or omitted?

    - Consider omitting radiation in the palliative setting, where alternatives can be offered e.g. optimizing pain control. [V,B]

    - Consider delaying or omitting radiation in localized low-grade lymphomas if completely excised (e.g., follicular lymphoma, marginal zone lymphoma, cutaneous B-cell lymphoma) . [V,B]
        - Yahalom J, Dabaja BS, Ricardi U, Ng A, Mikhaeel NG, Vogelius IR, et al. Ilrog emergency guidelines for radiation therapy of hematological malignancies during the covid-19 pandemic. Blood [Internet]. [cited 2020 May 20]; Available from: https://ashpublications.org/blood/article/135/21/1829/454357/ILROG-emergency-guidelines-for-radiation-therapy

APPENDIX

TABLE 1

Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading Systema)

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well- conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of Recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended