

Should etoposide be used in the treatment of cytokine storm of COVID-19?

Authors: Namnama P. Villarta-De Dios, MD, MSc, DPPS. npvdedios@gmail.com

Date of Review: [10-APRIL-2020 (version #1)] Last Updated: [16-APRIL-2020 (version #3)]

KEY FINDINGS

- There is no direct evidence in the effect of etoposide on possible symptoms of cytokine storm in COVID-19.
- Etoposide is a DNA topoisomerase used as a chemotherapy drug that is believed to exhibit potent deletion of activated pathologic T cells as well as efficient suppression of inflammatory cytokine production. [1, 2, 3, 4]
- Etoposide is part of the current treatment for infection-induced hemophagocytic lymphohistiocytosis (HLH). Symptoms are similar to the cytokine storm reported in some COVID-19 cases.
- There were no clinical studies found that directly assesses the effect of etoposide on cytokine storm or hyper-inflammation caused by COVID-19.
- Indirect evidence in one cohort study among patients with Epstein-Barr virus (EBV)—associated hemophagocytic lymphohistiocytosis [5] showed significant difference in overall survival rate with early treatment with Etoposide.
- The Histiocyte Society [6] stated that current data are insufficient to allow specific treatment recommendations on COVID-19.

Disclaimer: The aim of these rapid reviews is to retrieve, appraise, summarize and update the available evidence on COVID-related health technology. The reviews have not been externally peer-reviewed; they should not replace individual clinical judgement and the sources cited should be checked. The views expressed represent the views of the authors and not necessarily those of their host institutions. The views are not a substitute for professional medical advice.

Copyright Claims: This review is an intellectual property of the authors and of the Insititute of Clinical Epidemiology, National Insititutes of Health-UP Manila and Asia-Pacific Center for Evidence Based Healthcare Inc.

RESULTS

There were no clinical studies that directly assessed the effect of etoposide on cytokine storm or hyperinflammation caused by COVID-19.

The indirect evidence on etoposide in the management of cytokine storm was in a cohort study which enrolled 47 pediatric and young adult patients with Epstein-Barr virus (EBV)—associated hemophagocytic lymphohistiocytosis. [5] The long-term survival with those in the etoposide-based regimen was significantly higher compared to non-etoposide conventional treatment

However, as this is indirect evidence, applicability issues will arise when considering patients with COVID-19. The cohort is comprised of children and young adults, with 75% exhibiting moderate to severe Epstein-Barr virus (EBV)—associated hemophagocytic lymphohistiocytosis.

The Histiocyte Society [6] stated that current data are insufficient to allow specific treatment recommendations on COVID-19.

CONCLUSION

At present, there is no direct evidence in the effect of etoposide on possible symptoms of cytokine storm in COVID-19.

REFERENCES

- 1. Imashuku S, Tabata Y, Teramura T and Hibi S. (2000) Treatment Strategies for Epstein-Barr Virus-Associated Hemophagocytic Lymphohisticcytosis (EBV-HLH). *Leukemia and Lymphoma*. Vol 39 (1-2), pp.37-49.
- La Roseé P. (2015) Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology 2015. DOI link: https://doi.org/10.1182/ASHEDUCATION-2015.1.190
- 3. Dumancas CY, Reyes HAG, Cosico J, Savadkar A, Lah S (2018) Streptococcus Pneumoniae-Related Hemophagocytic Lymphohisticocytosis Treated with Intravenous Immunoglobulin (IVIG) and Steroids. American *Journal of Case Reports.* 19: 25-28
- 4. Johnson TS, Terrell CE, Millen SH, Katz JD, Hildeman DA, and Jordan MB (2014). Etoposide selectively ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymphohistiocytosis. *Journal of Immunology*. January 1; 192(1): 84–91. doi:10.4049/jimmunol.1302282.NIH-
- Imashuku S, Kuriyama K, Teramura T, Ishii E, Kinugawa N, Kato M, Sako M, and Hibi S. (2001) Requirement for Etoposide in the Treatment of Epstein-Barr Virus–Associated Hemophagocytic Lymphohistiocytosis. *Journal of Clinical Oncology.* Vol 19, No 10 (May 15), 2001: pp 2665-2673
- 6. Histiocyte Society. (2020) Recommendations and Considerations from the Histiocyte Society During the Evaluation of Hospitalized COVID-19 Patients for Hyperinflammation. [Position Paper]

Last Updated: 16/April/2020