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Are Patients on Cyclophosphamide at Higher Risk of Covid-19 Complications?

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Opinion Article

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ABSTRACT

Coronaviruses are closely related virus causing several types of respiratory tract infections ranging from common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). There are many other ways in which Covid-19 will impact the existing public health issues. With the rising number of covid19 cases, it has been reported that people with the weaker immune system are at higher risk. We identified the mechanism of action of cyclophosphamide and its impact on the lung. Pulmonary side effects associated with cyclophosphamide are rare and dose-related. They manifest as early-onset pneumonitis, in patients with symptoms especially like cough and dyspnea. Acrolein in cyclophosphamide is the main component linked with the toxic effect. We hypothesize that use of cyclophosphamide, an antineoplastic agent and immunosuppressive agent used in treating many cancers and autoimmune disorders (like rheumatoid arthritis and ANCA vasculitis), induces severe lung toxicity which can be one of the contributing factors for the increased risk of COVID 19 complication. These factors are to be recognized to improve prevention and control of the disease.

Keywords: Coronavirus; cyclophosphamide; cancer; autoimmune disorders; lung toxicity.

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1. INTRODUCTION

Cyclophosphamide an orally active alkylating agent, is widely used to treat a variety of malignant and nonmalignant disorders. It is mainly used for treating cancers and other autoimmune diseases. It works by stopping the growth of cancer cells and in other autoimmune diseases; it suppresses the body's immune system. [1,2] It is metabolized to form an active alkylating metabolite and acrolein. The activated form- Phosphoramide mustard binds to DNA. Its cytotoxic effect is mainly due to cross-linking of strands of DNA and RNA, and inhibition of protein synthesis. These effects also result in the immunosuppression. [1,3].

Consequently, both phosphoramide and acrolein are responsible for the pulmonary toxicity. But only acrolein induced pulmonary damage has been established [4,5]. They initiate peroxidative injury, which results in alteration in the physical state of the membrane lipids that further results in pulmonary toxicity [6,7]. Patients under Cyclophosphamide are already subjective to respiratory complications, since COVID-19 directly affects the lungs during the first contamination stage, patients under Cyclophosphamide may have a higher risk of COVID 19 infection and severe respiratory complications when compared with general COVID-19 patients. [Fig.1]. This article thus highlights the risk associated with the use of cyclophosphamide due to its capability to cause lung toxicity which is a contributing factor for increased risk of COVID-19 complication.

2. CYCLOPHOSPHAMIDE DRUG PROFILE

2.1 Indication

Cyclophosphamide is essential for the treatment of:

- Malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Multiple myeloma, Leukemias, Mycosis fungoides (advanced disease), Neuroblastoma (disseminated disease), Adenocarcinoma of the ovary, Retinoblastoma, Carcinoma of the breast.[2]

Pharmacokinetics

Absorption: Peak Concentrations occur at one hour after oral administration.

Half-life: 3-12 hours

Volume of Distribution: 30-50 L.

Protein binding: 20% of the drug is protein bound with no dose dependent changes. Some metabolites are bound to protein to an extent greater than 60%.

Metabolism: Metabolism and activation occurs at the liver. 75% of the drug is activated by cytochrome P450.

Clearance: Total body clearance: 63 ± 7.6 L/kg.

Elimination: Cyclophosphamide is eliminated primarily in the form of metabolites. 10-20% is excreted unchanged in the urine and 4% is excreted in the bile following IV administration. [8,9].

2.2 Adverse Effects

Pulmonary Toxicity, Myelosuppression, Immunosuppression, Bone Marrow Failure and Infections, Urinary Tract and Renal Toxicity, Cardiotoxicity, Secondary Malignancies, Veno-occlusive Liver Disease, Embryo-Fetal Toxicity, Infertility, Impairment of Wound Healing, Hyponatremia. [2,8,9,10]

2.3 Impact of Covid 19 on Lung

SARS-CoV-2 gains entry into the lungs through droplets or aerosol with the help of ACE 2 receptors. A protease called TMPRSS2 chemically splits off the spike protein and helps in the viral entry. In the lungs ACE 2 receptors are present on cells called pneumocytes, which plays an important role in producing surfactant that helps in the gas exchange in the alveolar sacs. [11,7] As soon as the body recognizes a foreign protein, it mounts its first immune response by producing first defense IgM antibodies and then IgG. And thus, patients show mild symptoms including fever, cough, etc.

With a further increase in viral load, there is reduction in the surfactant due to viral destruction of pneumocytes which will ultimately lead to reduced gas exchange. As a part of immune response neutrophils and macrophages rush into alveoli. [12,3] Blood vessels surrounding the air sacs become leaky due to inflammatory mediators released by white blood cells. The reduction in surfactant and increasing fluid pressure on alveoli leads to collapse. This results in breathlessness. [7]

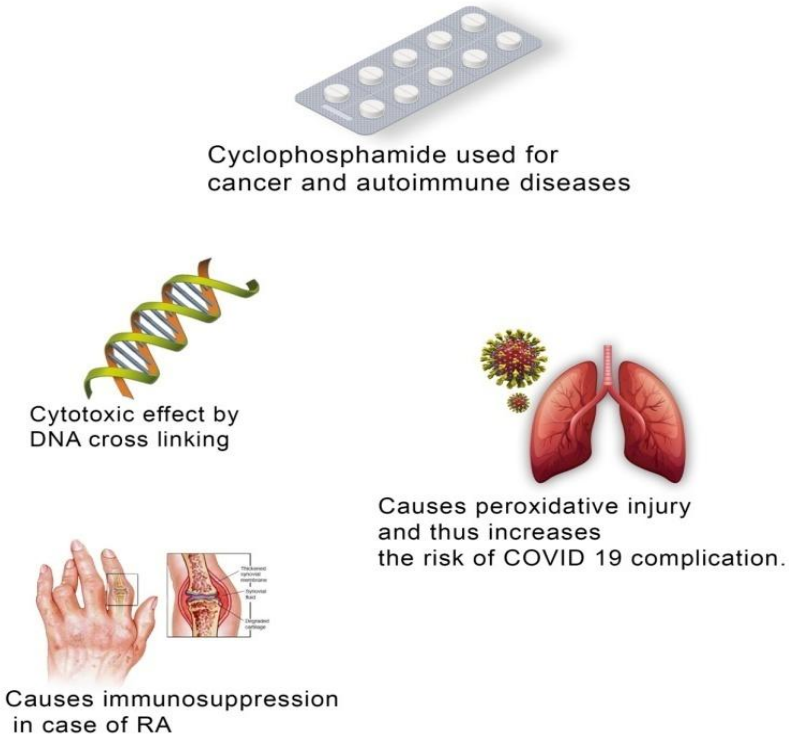

Fig. 1. Cyclophosphamide & COVID-19 impact in lung
***RA: Rheumatoid Arthritis**

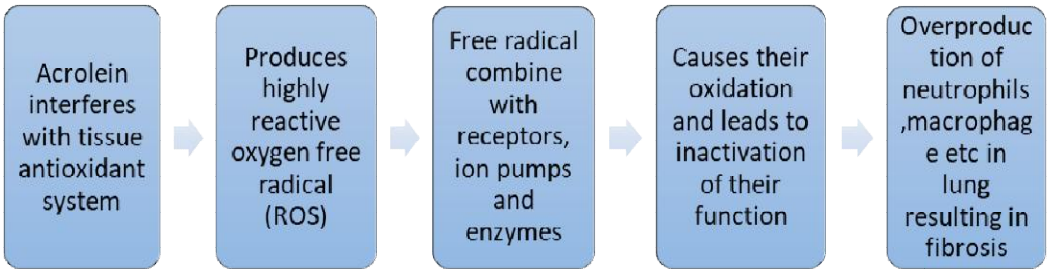

Fig. 1. Effect of Cyclophosphamide in lungs

3. CYCLOPHOSPHAMIDE INDUCED LUNG TOXICITY

Pulmonary side effects associated with cyclophosphamide are rare and dose related. They manifest either as early onset pneumonitis, with patients presenting with cough, dyspnea or as late onset pneumonitis with progressive pulmonary fibrosis and non-productive cough. Mechanism of pulmonary damage by cyclophosphamide is through its metabolism. [3] Acrolein is the main component linked with the toxic effect. [Fig.2]

4. CONCLUSION

Due to high prevalence of cyclophosphamide in the treatment of cancer and autoimmune disorders, it shows a negative impact on patients who are receiving it, To improve quality of life, as it directly affects lungs and immune system, such patients must be under proper care. Alternate

antineoplastic agents can be prescribed to avoid any complications.

And its negative influence on COVID 19 recovery should also be established. According to this hypothesis patients receiving cyclophosphamide might be vulnerable to COVID 19 infection with poorer prognosis. Though there is no established study or proof that use of cyclophosphamide can make a person more vulnerable to COVID-19 or severity of infection might increase. But it is clear from this article that both COVID-19 and cyclophosphamide tend to damage and thus put extra burden on lungs. So, there is need of optimizing the treatment protocol for such patients**.**

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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