

Review Article

The Impact of Covid-19 Outbreak among Lymphoma Patients: What Did We Learn?

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Abstract

A very high number of articles have been published regarding SARSCOVID-19 infection among oncohematology patients. However, outside epidemiologic data and guidelines regarding the management of SARSCOVID-19 disease, no shared recommendations or expert opinions are available to decide whether it is

advisable to initiate antineoplastic therapy during a phase of pandemic and, if so, how to modulate the treatment schedule. The need to administer antineoplastic or biological drugs and available monoclonal antibodies licensed for lymphoproliferative diseases makes it particularly complex in this perspective to define reasoned,

evidence-based choices. We reviewed published studies with the largest cohort of patients, intending to recognize the most relevant risk factors. We have highlighted some unresolved questions about immunologic perturbation during SARSCOV-19 infection that hinder a defined and biologically oriented approach, especially in the case of immunosuppression, both primary and acquired. It is interesting, in this context, that preliminary evidence shows a characteristic clinical course of SARSCOV-19 infection that suggests specific management. We also summarized the role of immunoglobulin replacement treatment or monoclonal antibody administration.

Keywords: Lymphoma patients; SARSCOV-19 infection

1. Introduction

The recent outbreak of SARSCOV-19 has heavily impacted the organization of healthcare systems in terms of morbidity, mortality, costs, utilization, and redistribution of resources across the countries, mainly because of the lack of scientific knowledge of this pathogen. Pagano et al. [1], in a very numerous cohort of hematological patients, reported a rate of severe/critical clinical presentation of COVID-19 of about 60%, a need for ICU admission of about 18%, and a mortality rate of 22%. Wood et al. [2] also provided similar data.

In this context, the status of immunosuppression of oncohematological patients (both for the pathology and the toxicities of treatments), has been the main obstacle in the decision-making process concerning the choice and delivery of the treatment plan.

2. Epidemiology and Analysis of the Risk Factors

Several studies have been published in this area, focusing almost exclusively on epidemiology data and risk factors of mortality. Passamonti et al. [3] and Garcia-Suarez et al. [4] demonstrated an increased risk of fatal or severe infection among advanced age patients; acute myeloid leukemia, multiple myeloma, and non-Hodgkin lymphoma patients were also at increased risk. Giesen et al. [5] for AIGHO, recently published the Guideline by the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO) for the evidence-based management of SARSCOV-19 infection. However, there are still no robust data to produce shared recommendations by scientific societies concerning the safety of administration of anticancer treatment during the outbreak [6,7].

Recently Visco et al. [8] published the paper entitled: "A prognostic model for patients with Lymphoma and COVID-19: a multicenter cohort study". This study included the largest described cohort of infected lymphoma patients, providing original insights. The authors found that male sex, age, lymphocyte, and platelet count were the variables associated with the higher risk of death; conversely, in their prognostic model, performance status (according to Charlson Index; CI), progressive disease, and lymphoma treatment were not relevant determinants. Notably, older age, male sex, lympho and thrombocytopenia had been already suggested as unfavorable prognostic determinants in the general population [9,10]. However, from Charlson Index (CI) we only know the number of existing comorbidities, but not the severity: this index has been used in the report of Passamonti et al. [3], and the paper of Prof.

Visco [8] is, at least, partially derived from this database. Nevertheless, the treatment choice for this cohort, mainly for patients older than 65 years hopefully, should have been made using the Comorbidity Index Risk Score (CIRS), according to what was suggested by Fondazione Italiana Linfomi [11]. CIRS, a geriatric assessment that stratifies patients according to comorbidities and their severity, provides a more precise evaluation of the relative risk.

From this point of view, we cannot exclude a potential bias in this and other similar studies concerning the severity rather than only the presence of comorbidities. This might have modulated the intended intensity of each therapeutic program before the SARSCoVID-19 pandemic, during it, and later on. Consequently, we could not exclude any role of severity of comorbidities, degree of disease, and treatment-related immunodeficiency in the risk of severe infection, ICU admission, and risk of death. Moreover, considering that the impact of the viral infection has not been geographically and temporarily homogeneous across the different countries, clinical decisions, therapeutic programs, and their actual delivery might have also been influenced by locally perceived risk, availability of ICU, and redistribution of healthcare personnel and resources. For these reasons, it is particularly hampering to achieve precise knowledge among the different reports on this problem worldwide.

3. Immunological Perturbances

Some authors hypothesized that the detrimental role of lymphopenia might be related to an impaired humoral and cell-mediated response [3,4]. However, we do not know whether the lymphopenia might have been pre-existing or

related just to the COVID-19 infection. Interestingly, the rate of viral infection during the treatment with bendamustine or rituximab in the trials has been reported as not significantly increased [12,13]. The well-known risk of viral infections in patients exposed to ruxolitinib or purine analogs did not translate to an increased risk of COVID infection instead [3]. Furthermore, the potential prognostic role of hypogammaglobulinemia has not been investigated definitively in the published reports. The COVID-19 impact on the immune system regulation combined with the hematological treatment and/or disease-related immune response impairment raises further considerations.

In this perspective, Bucciol et al. [14] recently reviewed the published case series and single cases describing the outcome of COVID-19 among patients with inborn errors of immunity. The evidence from this paper suggests the antibody deficiency itself (e.g. in Common variable immune deficiency (CVID) or agammaglobulinemia) did not translate into a worse prognosis; conversely, in the case of SCID and T cell subset immunodeficiency, the incidence of severe COVID-19 was substantially increased. That suggests that T cells might play a key role in defining COVID-19 prognosis, predicting an adverse outcome, and ICU admission [15,16]. Regardless, monoclonal antibodies (MoAbs) are helpful when promptly administered to at-risk patients [14,17]. Innate immune deficiencies have also been associated with the severity and poor prognosis of COVID-19 [18]. Innate immune responses may thus play a rapid and active role against viral replication while priming the adaptive immunity that takes time to generate sufficient cells to control a viral infection [14]. Innate immunity, CD4+, and CD8+ T cells and B cells may, as a result, have an active role against COVID-19. Immunodeficiency in

lymphoma patients might be less selective than in primary antibody immunodeficiencies, or might be characteristically influenced by different treatments, as also suggested by Scarfò et al. [19] among the patients affected by Chronic Lymphocytic Leukemia (CLL). In this setting, specific antineoplastic therapy (particularly BTK inhibitors) might even exert a protective effect in the COVID-19 course. So, the impact of a distinct mechanism of action of such drugs, including in the “biologicals” group, could be another intriguing goal for future research.

Because of this heterogeneous immune defect, lymphoma patients may be more prone to contract other viral, bacterial, or fungal infections, either because of histotype-related immunologic deficiencies or treatment-related immunologic impairment.

Furthermore, in all available reports, the rate and characteristics of superinfections have been not fully detailed, between the complications or the causes of death. In further studies, it would be interesting to investigate the lymphocyte function (e.g. T cell or antibody specific response against COVID-19) and the incidence of the superinfections (including opportunistic), to explore the impact of immunodeficiency on the disease course. Of note, no single study [1-4] performed an in-depth analysis to clarify if any specific schedule of lymphoma treatment had a distinct impact on COVID-19 prognosis. Recently, Andersen et al. [20] found an increased risk of mechanical ventilation or in-hospital death in the case of SARSCoVID-19 infection only in the case of the administration of rituximab for cancer and rheumatological diseases. That was not the case for other biological, antineoplastic, or antimetabolite therapies.

4. Clinical Course of SARSCoVID-19 among Patients Treated with Anti CD20 Monoclonal Antibody

Furlan et al. [21] also reviewed clinical data provided by six small series, showing that patients treated with anti-CD20 had a prolonged clinical course characterized by transient clinical improvement followed by a subsequent early relapse or exacerbation. The disease, in these cases, was moderate or severe, and Convalescent Plasma, IVIg, or MoAbs have been required to ensure clinical recovery. Interestingly, MoAbs are also beneficial in patients with primary antibody deficiencies [17], and available preparations of Ig replacement therapy might be already reasonably enriched with neutralizing antibodies [22]. However, we know that rituximab does not always lead to antibody deficiency [23]. Thus, it is also possible that not the anti-CD20 treatment itself but only its impact on B (and T) cell function might influence COVID-19 course and its long terms consequences. Interestingly, apart from immunoglobulin serum levels, response to vaccination is considered a functional measure of adaptive humoral response both during the diagnosis of PIDs and within the IVIg treatment indication for secondary hypogammaglobulinemia [24]. Considering that anti-SARS-CoV-2 specific antibodies and T cell response are now measurable and could discriminate between responders or non-responders vaccine (or previous infection), specific treatment or disease-related inadequate response to vaccination should thus be evaluated in future studies.

In summary, the role of different branches of immunological response during the COVID-19 infection is still not fully understood, and it is hard to define the

biological target to restore an efficient immunological function.

All these considered, we might also hypothesize that lymphoma treatment could influence disease course in terms of severity/oxygen requirement and ICU admission, rather than the middle and long-term overall survival. It would be thus interesting also to explore the impact of the different treatment categories on these items.

5. Open Questions

A prolonged and more severe COVID-19 course might impact patients' performance status after recovery. It would be interesting to know whether the patients, following COVID-19 infection, completed or not the therapeutic program and possibly quantify the rate of delayed or definitively stopped maintenance treatments with anti CD20. That might conversely influence long-term overall survival since infection. This aspect is detailed only by Cuneo et al. in the setting of CLL [25], and interestingly he observed that treatment initiation was conducted without delay in only 21% of participants centers; administration of ongoing treatment was delayed in 24% of centers, and in 1 center rituximab was suspended. No detailed data are available from studies evaluating this topic among Lymphoma patients [1-4,7,8].

6. Conclusion

In conclusion, the COVID-19 outbreak still represents a dramatic challenge and a severe threat worldwide; despite that, the increasing amount of knowledge of biological and immunological data needs to be rapidly translated into a reasoned clinical approach, ultimately leading to the

completion of the therapeutic program of hematological patients.

Potential conflicts of interest

The authors declare no potential conflicts of interest.

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