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Proceedings of the COVID-19 and Lymphoma Panel: January 12, 2022

A LYMPHOMA RESEARCH FOUNDATION WHITE PAPER

Introduction

On January 12, 2022, the Lymphoma Research Foundation convened an expert panel of medical and scientific advisors as part of a monthly meeting series, to discuss the current state of research regarding the COVID-19 vaccine and people with lymphoma. The panel discussed recommendations for oncologists caring for people with these cancers, as well as related scientific research and education programming.

This white paper reflects the panel discussion and the state of research as of the date of the above. Oncologists and other healthcare providers are encouraged to consult the most recent guidance from the Centers for Disease Control and Prevention (CDC) and other federal healthcare agencies when making treatment recommendations. Patients should consult with their own healthcare providers when making treatment decisions.

For additional information, members of the lymphoma community are also encouraged to visit the Lymphoma Research Foundation's COVID-19 Learning Center at lymphoma.org/covid19 and/or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.

The Foundation is grateful to the friends and family of Dr. Robert Schroeder whose support made this program possible.

Panel Participants

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Presentations

Introduction and Updates

Panel Chair Dr. Andrew Zelenetz of Memorial Sloan Kettering Cancer Center (MSKCC) opened the meeting with an overview of the changes that have occurred since the November 2021 meeting with regard to the emergence of the Omicron variant. Previous meetings had focused on getting lymphoma patients involved in prophylaxis clinical trials such as the one organized by Regeneron. However, within 48 hours of the previous meeting, it was determined that the Regeneron monoclonal antibody (mAb) therapy does not bind to the heavily mutated Omicron variant, and the study was discontinued. The field is changing quickly, and it is becoming increasingly difficult to determine the appropriate rules for vaccination as well as when to move to alternative agents. Since the previous meeting, though, a number of new agents have been authorized for use in the treatment and prevention of COVID-19, including several agents that are effective against the Omicron variant.

COVID-19 Therapeutic Landscape

Dr. Mini Kamboj of MSKCC began by emphasizing the unpresented impact of the Omicron variant on the treatment of COVID-19. Within a month of its emergence in the United States population, she reported that over 3,000 cases had been seen at MSKCC. While the percentage of patients who have been hospitalized with the Omicron variant has been lower than with previous surges, changes in the efficacy of various agents against the novel variant has shaken up the treatment landscape of COVID-19. An interactive portal is available from the National Institutes of Health (NIH) which compares the relative *in vitro* activity of various therapeutic agents against viral variants[1].

Monoclonal antibody landscape

Previously authorized mAb therapies, including casairivimab/imdevimab (REGEN-COV®) and bamlanivimab/tesevimab, have been found to have markedly reduced neutralization activity against the Omicron variant and are no longer being distributed. The impact on neutralization activity of other mAb therapies such as sotrovimab (Xevudy) and tixagevimab/cilgavimab (Evusheld) has been lower, but this activity has only been assessed in pseudovirus *in vitro* neutralization assays, and *in vivo* neutralization activity remains unclear. Panelists emphasized that the Omicron variant is relatively young and that the ability to obtain systematic *in vivo* data has been limited, particularly given the early geographic restriction of the variant.

A detailed description of mAb therapies currently in use is provided below:

- **Sotrovimab (Xevudy):** Noted by Dr. Kambuj as the most promising agent currently available, sotrovimab exhibits only a very mild reduction (less than 5-fold) in neutralization activity against the Omicron variant and is expected to retain much of its clinical activity. Sotrovimab is authorized for **treatment** of mild to moderate COVID-19 in people who are considered high risk for severe disease, which includes people with lymphoma. It is administered as a one-time intravenous dose, and access to a healthcare facility or infusion center may be a limitation for some.
- **Tixagevimab/cilgavimab (Evusheld):** Reduction in neutralization activity is slightly higher than for sotrovimab (12-30-fold), but the clinical impact of this reduction is unclear. Reductions in activity are relative, and starting efficacy is an important consideration (Evusheld was approximately 1000-times more potent than other mAbs against Delta). Evusheld is authorized as **pre-exposure prophylaxis** for people with moderate to severe immunosuppression (such as people with lymphoma) who are at high risk for progression to severe disease. It is not authorized as treatment for COVID-19. Evusheld is administered as two separate, consecutive injections intramuscularly.

1. Available at: https://opendata.ncats.nih.gov/variant/activity

Distribution of remaining mAb therapies was described as "opaque", and it is unclear what strategies or prioritization is in place based on clinical experience, meetings with state authorities, and information from the Centers for Disease Control and Prevention (CDC). The federal distribution of mAbs is weekly, and state and local departments regulate distribution beyond that point. There is a significant mismatch between the available supply for mAb therapies and the demand, which is expected to persist throughout the current surge.

Antiviral landscape

Since the previous Panel meeting, two new antivirals (Paxlovid and molnupiravir) have been authorized for the treatment of COVID-19, tripling the size of the COVID-19 antiviral treatment landscape. Modeling data suggest that the efficacy of available antiviral agents should not affected by mutations observed in the spike protein of Omicron, but *in vivo* data are not yet available.

A detailed description of currently available COVID-19 antiviral agents is provided below:

- **Nirmatrelvir/ritonavir (Paxlovid):** Noted by Dr. Kamboj as the most promising available COVID-19 therapeutic, Paxlovid is a protease inhibitor that disrupts viral replication. It is authorized for people 12 years of age or older (and greater than 40 kg) with mild-to-moderate COVID-19 who are at high risk for severe disease, and is used primarily in the ambulatory setting. It is most effective when used within 5 days of onset. There are a number of drug-drug interactions that can occur with ritonavir, which is used to increase concentrations of nirmatrelvir. Dose adjustments are required for patients with mild kidney impairment, and Paxlovid is not for patients with severe kidney or liver dysfunction.
- **Molnupiravir:** Molnupiravir has the same eligibility as Paxlovid, except that it is only authorized for adults 18 years of age or older due to concerns regarding bone-cartilage toxicity in children. Molnupiravir is a highly mutagenic drug and the real-world implications are still unknown. For this reason, and given it's reduced efficacy compared with other drugs, it is only to be used when other treatment options are not accessible or are contraindicated.
- **Remdesivir (Veklury):** Eligibility requirements for remdesivir are similar to those of other antiviral agents. The primary difference with remdesivir is the administration requirements; the drug is given intravenously over 3 consecutive days, which requires regular access to a healthcare facility or home infusion center. These requirements are a big lift for healthcare teams as well, especially considering existing staff shortages. While use of remdesivir was evaluated in the outpatient setting in the PINETREE trial,1 it may be used off-label for people with COVID-19 who are hospitalized for other reasons.

Federal distribution of antiviral treatments is done on an every-other-week basis. As with mAb therapies, there is a significant supply-demand mismatch, and antiviral stocks are often exhausted within 3 to 5 days.

COVID-19 vaccine updates

Since the November meeting, a third dose has been authorized as part of the primary series of the Pfizer-BioNTech vaccine for eligible children ages 5 to 11 years. A booster dose has also been authorized for children ages 12 to 15 years, and the interval from last dose in primary series to booster has been shortened for all mRNA vaccines (from 6 months to 5 months).

Discussion

COVID-19 Vaccination Recommendations

Dr. Kamboj and other panelists emphasized that all patients with lymphoma should be counseled to receive a third dose as part of their primary COVID-19 vaccination series. Convincing evidence is emerging that there are patients who do not mount an immune response after either of the first 2 doses who do produce a measurable antibody response after a third dose. Antibody levels have been observed in ranges that are associated with neutralization of the Delta variant, although the effects on Omicron remain to be seen. Given the availability of COVID-19 vaccines and the minor risk for side effects, a liberal vaccination approach (3 doses plus booster) is recommended for any cancer patient on active treatment or patients with hematologic malignancies who have been on active treatment within the past year. However, some patients may remain B cell-depleted for 18 months or longer, particularly those treated with obinutuzumab. B cell depletion appears to be more durable with this agent, which may be related to the dosage used and the longer half-life of the drug.

Coordination of Care

Across different institutions, coordination of the care of lymphoma patients who develop COVID-19 varies considerably. While some oncologists are fully responsible for the management of COVID-19 in their patients with lymphoma, some panelists noted that this responsibility is taken out of their hands and lies instead with either the patient's primary care provider or an external infectious disease team. In these settings, these external healthcare teams assume almost complete responsibility for COVID-19 treatment decision making. However, many lymphoma patients consider oncologists their primary care providers, which can make this fragmentation of care challenging. While this practice is intended to keep patients safe and reduce the risk of viral exposure for other high-risk patients, it complicates the coordination of care. Miscommunication and "gray zones" of responsibility but patients at risk for falling through the cracks, and oncologists still spend much of their day answering questions related to COVID-19 without being directly involved in the care of their patients.

Coordination of care and the use of COVID-19 therapeutics is also challenging for providers who practice at institutions with high volumes of patients who live out of state, such as at the Mayo Clinic and MSKCC. Because COVID-19 therapeutic are allocated at the state level, patients whose healthcare team is located out of state have difficulty accessing treatments, and it can be hard for oncologists to help coordinate their care.

Dr. Sonali Smith of the University of Chicago suggested that there is an opportunity for LRF to address the fragmentation of care of lymphoma patients during the COVID-19 pandemic.

Access and Availability

Panelists unanimously expressed difficulties regarding access to and availability of COVID-19 therapeutics and preventatives. The demand for Evusheld (pre-exposure prophylaxis) is high, and some institutions have enacted strict internal eligibility requirements to help ensure it is available to the patients who are most in need. High-priority candidates may include people who have had a transplant within the previous year who have acute graft versus host disease (GVHD), patients who have received chimeric antigen receptor (CAR) T-cell therapy within the last year, and those on B cell-depleting agents. Even with strict prioritization requirements, available supplies do not meet the demand. As one panelist shared, over a thousand patients were considered eligible for Evusheld therapy with only 48 available doses. It is difficult to predict how both supply and demand for Evusheld will change over the coming weeks and months as the course of the Omicron surge plays out. Any guidance that is made related to access to pre-exposure prophylaxis must be adapted based on changes to supply availability and community infection dynamics.

Access to antivirals poses unique challenges in addition to supply limitations. Whereas Evusheld is specifically authorized for people who are moderately to severely immunocompromised, the requirements for the use of antivirals are less explicit. In some locations, any doctor can prescribe Paxlovid, and there is a concern that otherwise healthy individuals who are fully vaccinated and boosted may be getting access to treatments over

immunosuppressed individuals. In other locations, distribution of antivirals may be controlled by a single provider or small group of individuals, such that access to antivirals becomes a matter of knowledge of the system. Another limitation is that whereas Evusheld is distributed directly to institutions to distribute among their patients, distribution of antivirals varies considerably from location to location. In some cases, antivirals are being delivered to general pharmacies, for example.

Recommendations

Access to Antivirals

Panelists emphasized that there is a need to ensure that antivirals are available to the patients who need them most. This is a concern not only for LRF and the lymphoma/ CLL community, but clinicians who care for other vulnerable populations as well. Panelists noted that other organizations, such as the Infectious Diseases Society of America, have already begun petitioning for a more rational prioritization of access to Paxlovid. Other societies and organizations that represent other immunocompromised patients, such as solid organ transplant recipients and rheumatologic or gastroenterology patients on disease-modifying agents, can be engaged to help support these efforts and broaden their impact.

Panelists agreed that outreach to the Department of Health and Human Services (DHHS) from the LRF on behalf of all immunocompromised patients, as defined by the CDC, would be productive; the LRF could request the prioritization of high-risk individuals for antiviral use. Such a letter could also include recommendations for adjustments to current acquisition and distribution methods to ensure better regulation of access so that these agents are available at the institutions with the most vulnerable patients. Diverse populations of immunocompromised people who would benefit from these changes should be emphasized to demonstrate the broader impact of such policies beyond lymphoma patients alone. Once completed, the letter can also be circulated among other professional organizations to help encourage and support them to undertake similar efforts to help the message resonates with as many potential allies and supporters as possible.

Included in the letter will be an invitation for members of the administration to meet with members of the panel to discuss specific concerns and recommendations. These discussions should include a balance of panelists from different states, institutions, and specialties to ensure all voices are represented.

One panelist also noted that efforts should be made to advocate for rational distribution of oral antivirals at the state level. While recommendations from the federal government are likely to help influence these practices to some extent, additional work can be undertaken at the state level as well.

Patient Education and Resources

A potential "Dear Doctor" letter was proposed that could be created to help patients discuss the recommendations provided by LRF with their healthcare providers. This would constitute a generic letter that includes broad guidelines and information about best practices for caring for lymphoma patients with COVID-19, including where to access additional resources. The American Society for Hematology (ASH) should be engaged in the drafting of this document to ensure alignment with their guidelines and current best practices, and updates can be made as needed. The potential drafting and circulation of such a resource will be discussed during the Panel's next regularly-scheduled meeting.

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