Cancerworld

COVID and haematological malignancies

Adriana Albini / 28 February 2023

On 24th January 2023, the first of three online seminars took place, which are part of the SPCC project “Cancer & Covid: Prevention and Treatment including Monoclonal Antibodies (MoABs)”. Carsten Bokemeyer, Director of the Department of Oncology and Haematology at Universitätsklinikum Hamburg-Eppendorf (UKE), Hamburg, Germany, chaired the meeting and introduced the subject. We might think that, after three years of pandemic, and reflecting upon how terribly serious it has been, particularly at the beginning, we are now moving into a much better place, and of course, this is partially true. However, especially for patients with a compromised immune system and/or haematological diseases, the Coronavirus is still a real burden and threat. We have a lot of measures now in terms of vaccination and new treatments, both antiviral and antibody, that can help manage the virus for patients with haematological diseases. Still, it is a complex situation. Dr. Bokemeyer works at a tertiary university cancer centre, which has employed many protective measures for patients with haematological malignancies throughout the pandemic,

starting from isolating patients to keep them alive when there was no treatment nor vaccination. Later, we learned that vaccination does not work as well in haematological patients with a compromised immune system. New drugs were introduced for treatment of Covid-19, which were quite successful, but different variants emerged, from the original Wuhan strain to the current Omicron. And all of them have a different morbidity for patients, a different mortality rate. Also, some of the drugs and some of the vaccines that were developed for earlier strains of the virus are not working as well anymore with the new mutations. Over the past four or five years, in parallel with the Covid-19 pandemic, new promising treatments have been introduced for patients with haematological diseases: monoclonal antibodies, bifunctional antibodies that target T-cells and lymphoma cells, or T-cells and myeloma cells, and CAR T-cells therapy. Many decision need to be taken to manage this group of patients in the Covid era.

Vaccination efficacy and Covid outcome in haematological patients

Carsten Niemann is Associate Professor, Head of CLL Lab, Chair of Nordic CLL study group, Department of Hematology, Rigshospitalet, Copenhagen, Denmark. Prof. Niemann started his presentation taking a step back, and looking at immune dysfunction across patients with haematological malignancies (HMs) and what has been done to address the outcome for these patients. A recent systematic review was published in Blood Advances by Khai Li Chai and co-workers. It looked through the literature to identify studies testing whether prophylaxis for patients with HMs could improve their outcome. The team found 21 completed randomized controlled trials and, quite surprisingly, for immunoglobulin replacement therapy, seven out of the eight studies included were more than 20 years old. Only five studies evaluated prophylactic antibiotics, and only seven vaccination. The researchers obviously had their criteria for inclusion, but still, we should consider whether we sufficiently test supportive care for patients with haematological malignancies. None or very few of the studies show a clear impact of prophylaxis on HM patient outcomes. But it seems, overall, that there could be a reduction in the risk of clinical infections with immunoglobulin replacement therapy. The team then looked into antibiotic prophylaxis, which is commonly used for specific subgroups of patients. The meta-analysis showed that prophylactic antibiotics had no effect on clinically documented infections. We know the risk of pneumocystis pneumonia when treating a patient for lymphoma or of fungal infections for AML, and so our therapy approaches can make the difference. This is a reminder that we really need to test these measures of supportive care. Moving on to vaccination, here is where we see the clearest improvement, with a 63% reduction in clinically documented infections. **Can vaccination improve the outcome for haematological patients?** A recent study by Yair Herishanu and his team (*Blood Advances*, 2022) looked at the serological response to mRNA based Covid-19 vaccination for patients with Chronic lymphocytic leukaemia (CLL). CLL, of course, is Prof. Niemann's specialty, but it is also a good model disease for haematological malignancies because both the treatment and the disease can cause immune dysfunction. The study compared the sustainability of a serological response for CLL patients with healthy controls. CLL patients showed a faster decline of serological response six months after vaccination. Patients on therapy are at higher risk of this decrease. We know from a number of studies that the serological response to Covid-19 vaccinations is lower for most patients with haematological malignancies. But here it also appears less sustainable.

Most clinicians treating patients with HMs, and probably the background population as well, were relieved, in early 2022, to see that the Omicron era produced much better outcomes for patients. Prof. Niemann and his team decided to investigate the clinical outcome for patients with CLL during Omicron. Looking at the hospital cohort of CLL patients diagnosed with Covid-19 in early 2022, they saw that the 30-day mortality was 23%, i.e., almost a quarter of patients. That was surprising because it was not what they experienced in their outpatient clinic. Looking at the population cohort, comprised of CLL patients with positive Covid-19 tests outside the hospitals, the outcome

looks much better with an overall 30-day mortality rate less than 2%. A patient with CLL who is in close contact with the hospital due to the haematological malignancy, or to comorbidity or to Covid-19, has a higher mortality risk. **Can we further identify the patients who have a good response? Could we identify biological markers or other markers?** Lee Greenberger and co-workers published an article late in 2022. They looked at the T-cell response in patients with haematological malignancies, because, as we know, serological conversion is not the whole story. Patients without serological response averaged a 45% response in T-cells. So, even when there is no serological conversion in patients with HMs, there is still a good chance of a T-cell response. It is important to capture both kinds of response. Furthermore, it is still possible to increase the serological response even in those patients with haematological malignancies who do not have a significant response even after the third dose. This holds true for most patients who receive no treatment for CLL but also for patients who do. Therefore, booster vaccination should be continued.

Prof. Niemann and colleagues tried to identify biomarkers early on for patients admitted to hospital with Covid-19. They used a TruCulture™ whole-blood ligand-stimulation assay. Normally, immune responses in patients with haematological malignancies are tested in the cell system or by measuring one type of cell at a time. But here the researchers aimed at testing whole-blood responses to standardised stimuli. The stimuli were applied to activate different Toll-like receptors, to activate the combined innate and acquired immune system. The team stimulated patients with LPS or antigen R-848. They could identify at the date of admission to hospital a signature in terms of cytokine releases upon the standardised stimuli to whole blood, which predicts whether the patient would progress to the peak severity group, needing support from a ventilator or dying, or be in the mild group, which only requires less than three litres of oxygen supply. This is one approach towards stratifying patients early on, not only using the information about their diagnosis but also that from molecular or functional tests. Next, the team also tried to use all the data that in Denmark can be acquired through electronic health records and health registries. From these records they could acquire all types of information, background medical history, hospitalisations, diagnoses in the past three years, prescription medication for the past year; also, vital parameters, laboratory tests, demographics. The team combined all of these into a data-driven approach. Regular conservative statistics would just look at whole cohorts or subgroups of patients, but they aimed to provide individual risk assessments for patients. And they wanted it to be a rolling model where they could actually predict the risk during each week. From testing positive for Covid-19, they would follow the patients for 12 weeks. They identified some patients with a very high-risk of dying and that risk seemed to be constant during the 12 weeks; other patients who would have a stepwise increased risk of dying, and patients who were at very low risk throughout the period. And that was just based on the routine data at time of admission and looking at the individual main risk factors. Among the top features identified were age, week after the first positive test, comorbidity, measured in terms of number of ordered medicines and whether the patient was already in hospital when testing positive, body mass index, and so on. Some specific medications had an impact, for example loop diuretics and laxatives, and encounter for other special examinations. Also, absolute lymphocyte count, and changes during the pandemic had impact on the individual risk assessment. This is just a different approach to assessing risk for patients. We need to test whether specific patients need specific interventions, vaccine, or prophylactic treatment. **But do we still need this for Covid-19?**

Looking at a chart of all patients with haematological malignancies in Denmark who tested positive during the different periods of Covid-19, against HM controls who did not test positive, we can see that those younger than 65-years of age did not have an excess mortality in 2022. The excess mortality for patients over 65 is much less with Omicron but is still increased. Going through each group of patients, colleagues of Prof. Niemann saw an excess mortality only in the >65 patients with CLL. These should be the patients for whom we need to do something more. We still see breakthrough infections despite patients being vaccinated four times since Covid-19 and receiving

passive immunisation (tixagevimab-cilgavimab). However, in the study recently published by James A. Davis and co-workers, most of the patients with B-cell malignancies did not get hospitalised and no fatal cases were found in retrospectively analysed medical records at their institution. **Does it actually help to vaccinate more times if we look at population data?** In the pre-Omicron era, more than three months since vaccination, HM patients had a significantly increased risk of dying from Covid-19. Those vaccinated within the previous three months had a better outcome. During the Omicron era, we can see that vaccination definitely narrows the gap between death in HM patients with Covid-19 and controls, although there is still a small excess.

To sum up: for patients with haematological malignancies, the more recent Covid-19 vaccination boosters and the more boosters, the better. Haematological malignancy as well as its treatment impair vaccine efficacy. Patients above 65-years of age with CLL still have increased mortality from Covid-19 during the Omicron era. And close contact with hospitals may be a good proxy for risk of death from Covid-19. We should definitely investigate further both molecular and data markers for Covid-19 risk to implement individualized supportive care and prophylactic meassures.

Covid-19 and Lymphomas: evolution of the interaction from the pandemic outbreak to today

Emanuele Zucca is Head of the Lymphoma Unit and Medical Oncology Consultant, Professor at the Oncology Institute of Southern Switzerland, Bellinzona, Switzerland. As at Jan 17, 2023, there had been reported to WHO more than 600 million cases of Covid-19 worldwide and nearly 7 million deaths. Even now that Europe and the United States have apparently entered the endemic stage of the Covid-19 outbreak, the virus is widespread, albeit significantly less fatal than it was in 2020, and is now causing only limited changes in public behaviour. We are less worried than we were; nevertheless, the endemic condition seems very likely to continue through the next months, unless a new immunity-evading variant emerges and causes a novel pandemic setting. Despite the continuous improvement in vaccines, therapeutics, and tests, the next stage remains highly uncertain. It seems likely that SARS-CoV2 will never be completely eradicated. The pandemic had a great impact on the clinical management of lymphoma patients, and this may still be an issue with the Omicron variant, although the disease appears to be much less fatal. An important point to remember here is that the improved outcome of Covid-19 in the general population is associated with vaccination and not independent from it. Vaccination has reduced the clinical risk of Covid-19 in most people.

COVID-19 in vaccinated patients with hematological malignancies

	N° patients	%
Stay during COVID-19		
Hospital	75	66.4
COVID-19 ward	59	83.8
ICU	16	14.2
Of which, invasive mechanical ventilation	10	8.8
Home	38	33.6
Overall mortality at 30 d	14	12.4
Attributable to COVID-19	9/14	64.3
+ Hematological malignancy	3/14	21.4
Contributable by COVID-19	4/14	28.6
+ Other reasons*	2/14	14.3
Not related to COVID-19	1/14	7.1
+ Hematological malignancy	1/14	7.1

Pagano et al. Blood 2022; 139:1588-1592

Covid-19 after *vs.* prior to vaccination in patients with hematological malignancies

- Severe or critical disease — 10% vs. 33% — p=.0242
- Hospitalization rate: — 17% vs. 50% — p=.0024
- Median disease duration — 16 vs. 22 days — p=.0094

Salvini et al. Am J Med 2022; 7:E321-E324.

In a pioneering study lead by Lennard Lee (*Lancet Oncology*, 2020), adult patients with cancer enrolled in the UK Coronavirus Cancer Monitoring Project (UKCCMP) cohort between March and May 2020. They were compared with a parallel non-Covid-19 UK cancer control population from the UK Office for National Statistics. The patients with haematological malignancies appeared to be at significantly increased risk of Covid-19 infection. The all-cause case– fatality rate in patients with cancer after Covid-19 infection was significantly associated with increasing age, and there was also an increased risk of death for the male gender. Patients with haematological cancer, diagnosed with Covid-19 and those with non-haematological cancer may present with very similar Covid symptoms. However, after adjustment for potential confounding variables of age and sex, patients with haematological malignancies tended to have a more severe or critical disease course, were significantly more likely to require high-flow oxygen and non-invasive intensive care unit. They also suffered higher risk of death compared with patients with non-haematological cancers and, of course, with the general population. Most lymphomas and particularly the low-grade, indolent subtypes have an increased incidence in the elderly and are associated with immunodeficiency. A narrative review published by Francesco Passamonti and colleagues (*Haematological Oncology*, 2022), looked at eight studies including over 2000 patients with lymphoma and Covid, mostly treated at the beginning of the pandemic. Overall, mortality rate was slightly over 30% for lymphoma patients. Today, things have improved. Vaccination has progressed across the world – albeit still not equitably, with developed nations vaccinating much faster than the rest. Moreover, we now have specific treatments for Covid-19. We have antiviral therapies and neutralising antibodies. We also have the possibility of prophylactic interventions. These are widely shown to be useful in the general population of elderly and frail patients, and are a must for all patients with immunodeficiency and/or lymphoma who are infected with the virus.

Evidence shows that patients with haematological cancer respond less well to vaccination in comparison with both solid cancer and healthy controls. Different haematological malignancies have different ratios of antibody responses to vaccination, with CLL ranking lowest, as it tends to cause severe disruption to the immune system. Patients with Non-Hodgkin Lymphoma (NHL) have slightly better responses. There are other factors associated with an imparied antibody response: if patients are receiving active treatment with CAR-T, for example, or with anti-CD20 antibodies. **Does vaccination work in patients receiving rituximab?** Rituximab is expected to blunt or even

entirely eliminate a humoral response to vaccination for several months after last exposure. T-cell responses may, however, provide some degree of protection or reduce severity of infection, justifying vaccination during or soon after completion of the therapy. A study published in 2021 by Sean Lim and his group, shows the importance of boosting. Individuals with Hodgkin lymphoma and aggressive B-cell non-Hodgkin lymphoma can develop robust serological responses as early as six months after treatment. Individuals vaccinated while receiving systemic anti-lymphoma therapy are unlikely to develop antibody responses and should be revaccinated after treatment completion. Revaccination six months after completion of anti-CD20 therapy is recommended. For patients treated only with chemotherapy without rituximab, earlier revaccination might also be effective, but more data are required to support this. Patients with CLL and indolent lymphomas might have impaired serological responses irrespective of their treatment history and might benefit from further measures to protect them against SARS-CoV-2, such as boosting with different vaccines and prophylactic monoclonal antibodies.

In an Australian study published in 2022, Brendan Beaton and his team comprehensively profiled both humoral, live viral neutralisation and cellular response to Covid-19 vaccination with the Pfizer-BioNTech mRNA vaccine. Patients with different types of indolent lymphoma and treatment responded differently. Namely, follicular lymphoma treated with rituximab and chemotherapy, and Waldenström macroglobulinemia patients treated with BTK (Bruton Tyrosine Kinase) inhibitors, showed reduced anti-spike IgG response, but preserved specific T-cell responses after vaccination. A paper by Steven Treon and colleagues in 2020 showed that BTK inhibitors may actually reduce the risk of severe lung disease in Covid-19 infection. This might be due to their capacity to block a chemokine release, but this is still a non-confirmed observation.

Livio Pagano and colleagues conducted a study using a multination survey approach – the EPICOVIDEHA survey (Epidemiology of Covid-19 Infection in Patients with Hematologic Malignancies: A European Hematology Association) – to capture outcomes for Covid-19 in vaccinated patients with hematologic neoplasms. Comorbidities, age, and non-controlled active lymphoma were found to be associated with reduced response and impaired outcome for Covid-19. The data are supporting a continued deployment of booster programs and ongoing public health guidance for this vulnerable group. Pagano and colleagues showed that the 30-day Covid mortality in vaccination patients is around 10%, one-third in comparison with the pre-vaccination year. They also found that appropriate and early treatment of Covid-19 has an impact on survival, with significant benefit deriving from monoclonal antibody administration, alone or combined with antivirals. In fact, antiviral drugs and monoclonal antibodies are valid treatment options for preventing the development of severe-critical Covid-19 in vulnerable patients, such as lymphoma patients, with mild-moderate disease. Passive immunisation with monoclonal antibodies against SARS-CoV-2 is an available strategy complementary to vaccination for patients who are unlikely to generate neutralising antibodies, for example, those with active lymphoma or prior immunosuppressive treatment. Nearly all the surveys and the conducted trials thus far published identify age and active lymphoma among the predictors of poor outcomes for a patient with concomitant lymphoma and Covid; also, patients with symptomatic Covid-19 needing hospitalisation and intensive care unit therapy have a much worse outcome. Non-vaccinated patients, as a whole, have in principle much higher risk of death.

A large population study from Israel, by Moshe Mittelman and colleagues, evaluated the relative effectiveness of the mRNA BNT162b2 vaccine in over 30,000 patients with haematological neoplasms compared with matched controls. Data on patients with haematological neoplasms after 2 vaccine doses were extracted and matched 1:1 with vaccinated controls. The analysis showed that vaccinated patients with haematological neoplasms, in particular those receiving treatment, suffer from more severe Covid-19 outcomes than vaccinated individuals with an intact immune system.

According to a French study, by Rémy Duléry and his group (*Am J Hematol*. 2021), patients treated with anti-CD20 monoclonal antibody and those with relapsed/refractory lymphoma were associated with prolonged length of in-hospital stay and decreased overall survival. Again, age and comorbidities were important outcome predictors. A large Italian survey of over 800 lymphoma patients, also indicates that admission in hospital for Covid is associated with higher mortality, all histologies taken into account. Today in Italy, the mortality rate for Covid-19 in lymphoma patients is around 13% at day-30. In a paper published in Blood Advances 2022, Carlo Visco and colleagues provided an easy-to-use prognostic model, which stratifies patients based on age >65, male gender, absolute lymphocyte counts, and platelet counts, into three prognostic groups with significantly different overall survival. Patients with no or one risk factor tend to have a good outcome. The majority of patients with four or five risk factors dies within one year from contracting Covid. The above mentioned EPICOVIDEHA survey suggested the benefit of vaccination against Covid-19 in patients with lymphomas and more in general, with haematological malignancies. The results of a prospective, cohort study by Marco Salvini and colleagues (*Am J Med* 2022) show that severe or critical disease was reduced from 33 to 10% in the vaccination year, hospitalisation from 50 to 17%, and disease duration from 22 to 16 days. So, there is much evidence in medical papers suggesting that vaccination is useful even if lymphoma patients may have a reduced response.

Aggressive lymphoma needs to be treated in spite of Covid-19 infection, although sometimes there might be challenging situations where life-saving treatments must be postponed. On the other hand, the pandemic has changed the approach for indolent lymphomas, because they are mostly a disease of the elderly, who are at higher risk. For these patients, vaccination against Covid-19 is strongly recommended. Safety is priority when treatment is not curative. We must raise the threshold for initiating treatment and increase the number of patients followed with watch-and-wait policy. We are treating symptomatic patients, but for those with localised disease we consider omitting or delaying and/or shortening radiotherapy treatment. Again, the already mentioned paper by Francesco Passamonti is a good summary of the present evidence, which indicates that vaccination is very important, and that exposed people should be treated with prophylactic approaches and monoclonal antibodies.