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Review

Impact of the COVID-19 pandemic on the diagnosis and treatment of onco-hematologic patients: a discussion paper

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ABSTRACT

We do not know the precise figure for solid organ tumors diagnosed each year in Spain and it is therefore difficult to calculate whether there has been a decrease in cancer diagnoses as a consequence of the pandemic. Some indirect data suggest that the pandemic has worsened the stage at which some non-hematological neoplasms are diagnosed. Despite the lack of robust evidence, oncology patients seem more likely to have a poor outcome when they contract COVID-19. The antibody response to infection in cancer patients will be fundamentally conditioned by the type of neoplasia present, the treatment received and the time of its administration.

In patients with hematological malignancies, the incidence of infection is probably similar or lower than in the general population, due to the better protective measures adopted by the patients and their environment. The severity and mortality of COVID-19 in patients with hematologic malignancies is clearly higher than the general population. Since the immune response to vaccination in hematologic patients is generally worse than in comparable populations, alternative methods of prevention must be established in these patients, as well as actions for earlier diagnosis and treatment.

Campaigns for the early diagnosis of malignant neoplasms must be urgently resumed, post-COVID manifestations should be monitored, collaboration with patient associations is indisputable and it is urgent to draw the right conclusions to improve our preparedness to fight against possible future catastrophes.

Keywords: COVID-19, SARS-CoV-2, solid organ tumors, hematologic malignancies, early detection.

Impacto de la pandemia de COVID-19 en el diagnóstico y tratamiento de los pacientes onco-hematológicos: un documento de opinión

RESUMEN

No conocemos con precisión la cifra nacional de tumores sólidos diagnosticados en España anualmente y por tanto se

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hace difícil calcular si ha habido una disminución de diagnósticos de cáncer como consecuencia de la pandemia. Algunos datos indirectos permiten sospechar que la pandemia ha empeorado el estadio en que se diagnostican algunas neoplasias no hematológicas. A pesar de no existir una evidencia robusta, los pacientes oncológicos presentan una mayor tendencia a tener una mala evolución cuando contraen COVID-19. La respuesta de anticuerpos frente a la infección en pacientes con cáncer va a estar condicionada fundamentalmente por el tipo de neoplasia presente, el tratamiento recibido y el momento de su administración.

En pacientes con hemopatías malignas la incidencia de infección es probablemente similar o inferior a la de la población general, debido a las mejores medidas de protección adoptadas por los pacientes y su entorno. La gravedad y letalidad de la COVID-19 en pacientes con hemopatías malignas es claramente más elevada que en la población general. Dado que la respuesta inmune a la vacunación es peor que en poblaciones comparables, hay que establecer métodos alternativos de prevención en estos pacientes, así como planes de diagnóstico y tratamiento precoces.

Hay que retomar las campañas de diagnóstico precoz de neoplasias malignas con urgencia, vigilar las manifestaciones post-COVID, colaborar con las asociaciones de pacientes y hacer planes urgentes para hacer frente con más eficiencia a potenciales catástrofes futuras.

Palabra clave: COVID-19, SARS-CoV-2, tumores de órgano sólido, hemopatías malignas, detección precoz,

INTRODUCTION

The information available on the impact of the COVID-19 pandemic on onco-hematologic patients generally focuses on determining the incidence of the disease in some groups of patients with certain processes and on their prognosis. In contrast, little information is available on the overall impact of this situation on care, clinical manifestations, vaccine protection, economic costs and other variables in patients with onco-hematologic diseases as a whole.

The Health Sciences Foundation (FCS) thought it pertinent to bring together a group of experts with different professional orientations who could shed light on broader aspects of the impact that the COVID-19 pandemic has had on these patients.

The members of the FCS Board of Trustees considered a series of questions related first to the problem in patients with solid organ tumors, then to patients with hematological malignancies and finally to possible solutions to some of the situations created.

To this end, professionals from Hematology, Oncology, Pharmacy, Ethics, Public Health, Intensive Care, Microbiology, Internal Medicine, Infectious Diseases and Health Management were brought together, trying to approach these issues with a multidisciplinary vision and reaching a consensus after discussion of the different items.

The following lines are the result of these discussions in which, in addition to reviewing the existing literature, a collegiate opinion is transmitted, where scientific evidence was not strong enough.

PART ONE - DIMENSION OF THE PROBLEM IN SOLID ORGAN TUMORS

HOW MANY PATIENTS WITH SOLID TUMORS WERE DIAGNOSED IN SPAIN IN 2019? ARE THERE FIGURES ON WHAT HAPPENED IN 2020 AND 2021?

Unfortunately, we are unable to provide precise figures that allow to compare the incidence of solid tumors in Spain during 2019 and beyond, as there is no nationwide population-based cancer registry.

If we refer to worldwide data, the "Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019)" estimates that there were 23.6 million new cases of cancer worldwide in 2019 (17.2 million if non-melanoma skin cancer is excluded) and 10.0 million cancer deaths worldwide, with an estimated 250 million (235-264 million) years lived with some disability (DALYs) due to cancer. Since 2020, this represented a 26.3% increase in new cases, a 20.9% increase in deaths, and a 16.0% increase in DALYs. Cancer was the second leading cause of deaths, after cardiovascular disease, years of life lost and DALYs globally in 2019 [1].

The Spanish Association Against Cancer (AECC) published in 2021 an extensive document on the impact of cancer in Spain, with an approach to inequality and social determinants [2] which puts cancer data in the context of our population imbalances. The document estimated the number of new cancer cases diagnosed in Spain in 2021 at 285,530. Of these, 119,682 occurred in women and 165,848 in men. The overall incidence rate was 603 episodes per 100,000 inhabitants (496 cases per 100,000 women and 715 per 100,000 men). The incidence increased, as expected, in the upper age ranges.

The most frequent types of cancers in our nation are colorectal (14.33%), prostate (12.30%), breast (12.02%), lung (10.37%) and skin tumors other than melanoma (7.77%).

The mortality estimate was 231 deaths per 100,000 population in 2021, 76% of which occurred in people aged 65 years or older. At the top of the mortality figures is lung cancer, followed by colorectal cancer.

In Spain, it is estimated that 15% of patients admitted to Intensive Care Units suffer from cancer, according to data from the ENVIN-HELICS study [3].

In our country, in some provinces that have a population registry, the association between socio-economic status and cancer incidence has also been evidenced, as in other European territories [4].

CONCLUSION:

In Spain, population-based cancer data are not available except in some regions and therefore, it is not possible to compare, up to this point, the incidence of cancer diagnoses immediately before and during the two years of pandemic.

IS THERE EVIDENCE THAT TUMORS DIAGNOSED IN THE PANDEMIC PERIOD HAVE BEEN DETECTED AT MORE ADVANCED STAGES?

It is still too early to say that the tumors diagnosed in 2020 and 2021 have been detected at more advanced stages than those diagnosed in previous years. It is suspected that the pandemic has had an effect on both the number of cases diagnosed and their stage, but to have real data to confirm this, it is necessary to wait at least one or two years and consolidate the incidence data for 2020 and 2021.

The data collected by the population-based cancer registries are the only ones that will make it possible to assess the impact of the pandemic on the general population. This is because these registries include information on all new cancer diagnoses occurring in a population, and are therefore free of selection bias. Population-based cancer registries, moreover, will make it possible to calculate valid survival indicators globally and by type of tumor, for the entire population, and separately for both sexes, by age group, tumor stage and even by other variables, such as the territory in which one resides or socioeconomic level.

Some countries and/or regions that had, since before the start of the pandemic, a Population-Based Cancer Registry (PBCR), have detected a decrease in the number of cancer cases diagnosed during 2020, and there is some evidence of possible diagnostic delays that may have resulted in later stage diagnoses and higher mortality [5-8]. These data, however, should be interpreted with caution, as most of the registries are still collecting and validating information, and their results are still provisional.

In Denmark, for example, between March and December 2020, 6% fewer new cancer cases were recorded than in the same months of the previous year, mainly due to a drop in cases diagnosed in the months of April and May, which did not recover in the months thereafter [6]. Despite this decline, no change to more advanced stages of cancers was observed in the subsequent months (until the end of 2020). According to the authors of this research, the lack of evidence of change to more advanced stages may be due, among other reasons, to the fact that in some cases the delays may have been only months, making it difficult to detect changes.

As already mentioned, the incidence of cancer is closely linked to social and economic conditions in Spain and other European countries [2,9-11]. Although the pandemic may have aggravated these inequalities, it cannot be ruled out that the possible delay in diagnosis may have affected the entire population to a greater or lesser extent - including those with a higher socioeconomic level, given that the pandemic has also caused delays in health care due to delays in the first consultations for fear of contact with the health system because of the risk of COVID-19 infection.

CONCLUSION:

In the absence of a national cancer registry, it is difficult to assess the impact of the pandemic on the detection of cancer cases in Spain in 2020 and 2021 and on the stage of tumors at diagnosis. Some international data suggest that the pandemic may have had a negative effect on cancer detection at early stages. It is necessary to develop a cancer surveillance system at the national level that is capable of collecting standardized and comparable data.

IS THERE EVIDENCE THAT PATIENTS WITH SOLID TUMORS ARE MORE PREDISPOSED TO DEVELOPING COVID? IS THE ANTIBODY RESPONSE TO AN EPISODE OF COVID WORSE IN THESE PATIENTS?

Patients with tumor disease seem to have a higher risk of developing SARS-CoV-2 infection, a fact that could be due to factors related to situations of immunosuppression associated with antineoplastic treatments and/or the tumor itself, or to the need for these patients to visit the health system frequently. This statement is based on weak scientific evidence, and there are even discordant conclusions and data between different series of oncology patients. This is due to the fact that the vast majority of studies retrospectively analyze cohorts of oncology patients, sometimes without a control group and with an over-representation of the first months of the pandemic (March-May 2020), a time when the diagnostic capacity of the different health systems was much lower than it is today.

Despite all these limitations, the current scientific literature suggests that oncology patients are at an increased risk of acquiring SARS-CoV-2 infection. A meta-analysis of studies evaluating patients with COVID-19 in China estimated a cancer prevalence of 1.4% in patients with SARS-CoV-2 infection, a prevalence much higher than that of the general population in China with malignancies (0.26%)[12].

A retrospective study in the USA with a population sample of more than 70 million patients and more than 2,000,000 oncology patients found 16,570 patients with COVID-19 of whom 1,200 were oncology patients. When the analysis was performed by different types of tumors, patients with hematological neoplasms (leukemia and non-Hodgkin's lymphoma) were at the highest risk, and in the case of patients with solid organ tumors, those with lung neoplasms were at the lowest risk [13]. The higher incidence in African-American patients also suggests that differences in access to the healthcare system, socioeconomic status and lifestyle may also be relevant factors in addition to the disease itself [14].

In a multinational study involving more than 1,800,000 individuals, 23,266 of whom were diagnosed with cancer, patients with malignancies had a higher risk (60%) of SARS-CoV-2 infection, with this association being greater in male patients over 65 years of age. Treatment with chemotherapy/immunotherapy increased the risk of infection and hospitalization [15].

Contrary to the previous studies, a retrospective work conducted in Italy in 2020, which included more than 200,000 patients with 10% of cancer patients, found a lower incidence of COVID-19 in oncology patients vs. the rest (11.7% vs. 16.2%) [16], but the design of this study has important flaws.

There is less doubt about the increased risk of hospitalization and development of severe forms of COVID-19 in patients with solid organ tumors [17].

Regarding the response of humoral immunity in oncology patients infected with SARS-CoV-2, there are few studies that evaluate the antibody response after the development of COVID-19 in cancer patients. This response seems to be conditioned by the type of neoplasm, antitumor treatment and the time elapsed between the treatment received and the episode of SARS-CoV-2 infection.

At the beginning of the pandemic, the first studies describing the antibody response in oncology patients were performed with rapid, qualitative diagnostic tests based on immunochromatographic techniques, with a lower sensitivity and specificity than the serological tests performed using ELISA/CLIA platforms currently available.

Two observational studies, one conducted in China and the other in France, suggested that the humoral response developed by oncology patients was lower than in the general population [18]. Subsequently, a third study conducted in Italy disagreed with the two previous studies and observed a similar IgG antibody response against SARS-CoV-2 in cancer patients compared to a control group of health care workers [19]. Patients in the French study had received cytostatic treatment during the previous 4 weeks, whereas in the Italian study this occurred in only 14% of cases. Cytostatic treatment in the 2-4 weeks prior to infection seems to be a relevant factor in the development of a poor humoral response [13,20].

Other treatments, such as anti-CD20 monoclonal antibodies and hematopoietic stem cell transplant recipients, are associated with lower seroconversion rates. In contrast, it appears that both immunotherapeutic treatments with checkpoint inhibitors and hormonal therapies are not associated with a lower development of antibodies against SARS-CoV-2.

Regarding the type of tumor, patients with hematological malignancies have lower seropositivity rates compared to those with solid organ tumors [21,22].

Failure to develop an adequate humoral response sometimes results in an inability to clear SARS-CoV-2 virus, and patients may have prolonged viral persistence, both systemic and respiratory, even for months [23,24].

CONCLUSION:

Despite the lack of robust evidence, oncologic patients seem to present a higher risk of SARS-CoV-2 infection.

The antibody response to infection in cancer patients will be fundamentally conditioned by the type of neoplasia present, the treatment received and the time of its administration.

ARE SOLID ORGAN NEOPLASMS AN INDEPENDENT FACTOR FOR POOR OUTCOME IN PATIENTS WITH COVID-19?

The available data on whether cancer is an independent risk factor for poor outcome in patients with COVID-19 are conflicting. Variables influencing outcome include age, general condition of patients at the time of exposure to the virus, comorbidities, aggressiveness and extent of the tumor, and the type of treatment administered during the exposure period.

In a recent study [25], retrospectively compared two cohorts of patients diagnosed with SARS-CoV-2 infection, one with cancer and one without cancer. Overall, there was higher mortality among patients diagnosed with cancer, but the heterogeneity of the oncology population was very important. Active or progressing cancer and recent treatment were significant prognostic factors in this study and others [26,27].

Other studies have failed to identify whether or not cancer "per se" is an independent risk factor for worse prognosis [28]. A large population-based study in Spain has found that the diagnosis of cancer, overall, was associated with higher mortality from COVID-19, especially those of recent diagnosis [29].

In any case, the mortality of oncology patients admitted for COVID-19 has been decreasing in successive waves, probably reflecting earlier diagnosis, better disease management and changes induced in the natural history of the disease by vaccinations and the different variants of the virus [30].

It is important to note that, especially during the most critical moments of the first wave, the diagnosis of cancer was a negative screening element for access to intensive care, regardless of the general condition prior to COVID-19 infection, its estimated survival or the stage of the disease. This led to the development of intensive care access criteria for patients with solid tumors published, along with other guidelines, by the Spanish Breast Cancer Research Group (Grupo Español de Investigación en Cáncer de Mama) [31]. The basic reason for this guideline was precisely to avoid that the mere diagnosis of cancer, without the necessary considerations of general condition, comorbidities and prior survival expectations, could become an independent factor in the care of patients with the consequent negative impact on their expectations of cure of the disease.

CONCLUSION:

There are no robust data to define precisely whether cancer "per se" conditions a worse prognosis of COVID-19. The higher mortality must be considered in the context of the stage of the disease, the recent treatments administered and the presence of comorbidities. The pandemic wave in which the episode occurred may have conditioned the application of restrictive intensive care measures to these patients in the early stages.

DOES A PATIENT WITH CANCER RESPOND EQUALLY TO VACCINATION AND IS EQUALLY PROTECTED THAN A PATIENT WITHOUT CANCER?

The series of the first part of the pandemic seemed to corroborate the higher risk of SARS-CoV-2 infection and a worse evolution of the same in the oncology patient [14,32-35]. Without curative weapons for the acute process, the idea of achieving immunity through vaccines was the big bet.

With little representation of tumor patients in phase III trials of COVID-19 vaccines, it seemed obvious to include them in the priority groups for vaccination along with other major immunocompromised patients, such as solid organ transplant recipients.

The proven safety of mRNA immunogens, and the absence of replicating virus in the rest of the approved vaccines, offered guarantees of safety and more advantages than disadvantages. It was necessary to wait for the demonstration of efficacy and tolerance as acceptable as that of the general population. There were other groups with greater uncertainty, especially with regard to the treatments they received (immunity enhancers, modified cells with immune function, etc.) and in clinical situations of special concern (neutropenia, severe immunosuppression, etc.).

With two years of experience in vaccination we know that, globally, cancer patients have a lower immune response to vaccines against COVID-19, but with a very pronounced gradient of efficacy [36-39].

The humoral response in oncologic patients varies from normal to a situation of total absence of demonstrable antibody production. On the other hand, the cellular response remains a background hope, of which we have less knowledge of its significance in this disease [40].

The type of tumor; its activity or remission; the time of evolution; the action of an active antiproliferative or biologic treatment or the time lapse since the patient received it, are determining factors in constructing the immune response. Other considerations such as age and comorbidities are important, as is the case in the control population [37].

Due to the lower quantitative response found in cohorts of patients with active tumors and in transplant recipients, it was precisely these groups in which immune boosting doses, the "boosters", were first tested [41,42]. The third doses rescued 40% of those who had not seroconverted with the first two doses from these groups [43-45]. Therefore, their standard primary immunization schedule has been agreed on three doses of vaccine (3 of mRNA). For those whose first immunization was with Adenovirus vector vaccines, it would be two doses with the Astra-Zeneca vaccine and a booster with mRNA and 1 or 2 doses of the Janssen vaccine -Ad26.COV2.s- and a booster with mRNA vaccine.

The intervals established between doses correspond to the recommended initial guidelines and the reminder doses advanced to three months, given the usual low response to the two initial doses and the need to generate an early response.

With patients treated with immune checkpoint inhibitors (ICIs), it was feared that there would be a higher incidence of side effects, both those that could be produced by the immunogen itself and by the potentiation that the monoclonal drugs used could have on the immune autoreactivity. The result has been a tolerance comparable to that of the general population and only more autoimmune adverse effects inherent to the treatment when more than one preparation is used in combination. This situation is already known without the intervention of vaccines. As with other types of vaccines, the immune potentiation of the vaccine response and its own response to the tumor has been proposed [46-48].

The quantitative humoral response is better studied in oncologic series than in the general population. Some of the series go as far as to analyze the results even with viral neutralization studies on cellular sample and some partially measure the response of cellular immunity [49]. The problem is the lack of correlation with clinical efficacy, explainable because the cohorts tested are of few patients; relatively recent so that their protective capacity in real life against infection and its severity can be compared. The change of viral variants and their remarkable capacity to evade the immunity generated by the vaccines in use is another confounding factor [50].

Vaccination remains the most important active pillar in the fight against COVID-19 and, therefore, all strategies aim at making the best use of available vaccines. Choosing those proven most effective, boosting improvement with dose spacing - (more efficacy and less toxicity) - when possible, and combining immunogens.

Research is underway on vaccines that induce response against more stable antigens of the virus to hinder escape of the immune response and to test routes of administration that block mucosal entry of the virus, enhancing both innate and selective barrier immunity.

CONCLUSION:

Vaccines tested against SARS-CoV-2 in patients with tumor disease elicit a positive humoral response although with a highly variable response gradient depending on tumor type, activity, treatment and time since receipt.

Practically all the cohorts studied have been performed with mRNA vaccines and some with Ad26.CoV2.s and a booster with mRNA, with similar results. The basic vaccination schedule for these patients is three doses.

There is not enough evidence of the benefit of the fourth dose, nor is there a correlation of clinical efficacy with humoral response.

WHAT HAVE BEEN THE CHANGES IN THE TREATMENT OF SOLID TUMORS THAT THE PANDEMIC HAS FORCED?

There is no doubt that the COVID-19 pandemic generated numerous changes in all the modalities of treatment of cancer patients, particularly in the first months of evolution, when many hospitals had to focus essentially on the treatment of COVID patients, temporarily abandoning other activities. The high incidence of infected healthcare professionals further complicated cancer care. This was compounded by the reluctance of many patients to go to hospitals for fear of becoming infected. These limitations affected all types of cancer treatment, albeit to varying degrees, as highlighted by the American Association for Cancer Research (AACR) [51].

Oncologic surgery, in general, was halted at most centers for several months, essentially because of the need to dedicate all intensive care beds to COVID patients. The American College of Surgeons recommended restricting surgeries to COVID-free centers and delaying longer operations when possible [52]. An exception to this situation was breast cancer surgery, which was maintained in some centers that were able to set up COVID-free areas, since patients usually do not require intensive care during the postoperative period. The reestablishment of major oncologic surgery only began to occur very gradually after the so-called first wave of the pandemic, but remained at low levels for many months.

Radiotherapy also suffered from serious organizational problems due to frequent infections of healthcare professionals and patients' fear of going to hospitals. Many patients experienced delays in treatment because of the organizational impact of the pandemic, especially in the first few months.

Chemotherapy treatment was initially withheld or delayed in many patients because of fears of inducing immunosuppression favoring COVID infection and/or worsening disease in the event of infection. However, this idea was later revised and it was found that chemotherapy per se did not increase the risk of COVID infection or death in most tumors [53]. An exception to this finding were patients with lung cancer (who usually have significant comorbidities) and patients with hematological malignancies, who receive treatments with corticosteroids and other suppressors of cellular immunity [54,55]. In any case, many oncology patients had their chemotherapy treatment suspended in the first year of the pandemic, due to the fear on the part of physicians and patients that this treatment could have negative consequences for the infection, which (together with the risk of infection in the hospital environment) increased the reluctance of patients to go to the hospital. In some cases, intravenous chemotherapy treatment was replaced by less myelosuppressive oral chemotherapy.

Immunotherapeutic anti-tumor treatments were also initially considered potentially dangerous to patients in the context of a COVID pandemic. This concept was further revised to the point where it was considered that treatment with immune checkpoint inhibitors could help prevent COVID infection [55].

Endocrine treatment of newly diagnosed localized hormone-sensitive breast cancer took on an important role in centers where surgery was problematic. Many patients received endocrine therapy as initial treatment of their operable cancers in order to inhibit tumor growth until curative surgery was feasible.

Finally, research treatments suffered a major setback during the first months of the pandemic [51]. Many trials had to stop recruiting patients and modify the follow-up of participants by using telematics methods instead. In 2020, the initiation of new studies also suffered a huge drop compared to previous years [56]. This situation began to improve in the second half of 2020, and has now normalized.

CONCLUSION:

Oncology treatment suffered a severe impact in all its modalities during the first months of the COVID pandemic, because of the reorganization of the health system to deal with the avalanche of COVID patients, the infection of health personnel, preconceived ideas about the dangerousness of some treatments, and the reluctance of patients to go to hospitals for fear of becoming infected. This situation improved in the second year of the pandemic and has normalized in the year 2022, although it is assumed that the consequences of the changes that have occurred will be felt over the next few years.

IS THERE A SARS-COV-2 VACCINE THAT IS MORE SUITABLE FOR CANCER PATIENTS?

Because cancer patients were excluded from the clinical trials conducted to develop the vaccines and support their licensed use, questions about whether the vaccines are safe in this vulnerable population and whether they provide adequate protection against severe forms of COVID-19 for people whose immune systems may be weakened by various medications could only be answered from the use of the vaccines in the general population and in several parallel studies [57,58]. We now have strong results and data demonstrating that vaccination against COVID-19 is safe, efficacious and effective in cancer patients. Most studies have been conducted with mRNA vaccines and people with cancer have an adequate protective immune response to vaccination, although the antibody titers achieved may be lower without experiencing more side effects than the general population [57,58].

Evidence suggests that a third "booster" injection could further increase the level of protection among this patient population. Several studies have shown that a booster vaccination in persons 60 years of age or older, after 5 months since completing their vaccination course, reduced the incidence of COVID-19 and severe disease. Booster doses can improve the immune response in cancer patients without sufficient protection after the second dose [59].

In the National Vaccination Strategy, all patients with compromised immune function, including cancer patients, have been prioritized for vaccination. In this group (the so-called Group 7) an mRNA vaccine (Pfizer or Moderna) has always been used for primary

vaccination. The third dose was considered an integral part of the complete regimen in this group and therefore a third dose of mRNA vaccine (Pfizer or Moderna) was used again regardless of the regimen initially received. In two systematic reviews [60,61] the risk of poor immune response in immunocompromised patients, especially solid organ recipients and patients with hematological malignancies, is evident. Although there is still a lack of data in this regard, the need to adopt strategies that seek to boost vaccination (additional doses of vaccines) and/or use monoclonal antibodies as pre-exposure prophylaxis, for example, is indicated. In a recently published meta-analysis [62], which included 82 studies, 94% of which used mRNA vaccines, concluded that after one dose of vaccine the seroconversion rate was less than 50% when comparing the results with those of immunocompetent patients and increased moderately after the second dose (60-90% depending on whether the patients had hematologic malignancy or solid cancer, respectively). The published work includes a systematic review of 11 studies showing that a third dose of an mRNA vaccine is associated with a higher rate of seroconversion among patients with hematologic or solid malignancies who initially respond poorly to previous doses of vaccine.

It is very important to consider the effect that certain treatments may have on the immune response to vaccination. Therefore, in some cases, the regimen must be adjusted individually. Strategies such as administering the vaccine between cycles of therapy and after appropriate waiting periods for patients receiving stem cell transplantation and immunoglobulin therapy can be used to reduce the risks and maintain the efficacy of vaccination. In an Omicron pandemic situation and more than 5 months after the third dose, this population group has been offered a booster dose. In this case, an mRNA vaccine (Pfizer, standard dose or Moderna, half standard dose) is again used.

CONCLUSION:

We now have strong data demonstrating that vaccination against COVID-19 is safe in cancer patients, although people with cancer have a protective immune response that is not as adequate as that of the general population. Evidence suggests that a third "booster" injection could increase the level of protection among this patient population. The vaccines that have shown the best results are mRNA vaccines, so they should be considered the most appropriate at this time.

PART TWO - COVID IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

WHAT HAS BEEN THE INCIDENCE OF COVID IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES? HAS COVID LED TO A DELAY IN THE DIAGNOSIS AND TREATMENT OF THESE PATIENTS?

Hematological malignancies are the fourth most frequently diagnosed group of cancers worldwide, with an annual incidence rate of 39.37 per 100,000 population in Europe in 2000-2002. They encompass a heterogeneous group of diseases with diverse etiology, presentation and prognosis. Currently, the World Health Organization (WHO) classification of hematological malignancies, first published in 2001 and subsequently updated in 2008 and 2016, is the gold standard for the study of these malignancies. However, these continuous refinements of definitions have posed significant challenges for population-based cancer registries to present complete and accurate data for the entire spectrum of hematologic malignancies and in particular for myeloid neoplasms (MN).

The actual incidence of COVID-19 in patients with hematologic malignancies is unknown, although we believe it has been lower than in the general population. This is the only explanation why the first articles referring to the first wave in Spain estimated an incidence of 0.7-3.9% in these patients [63] whereas in health care workers it reached 11%. There are several reasons that explain this lower incidence, such as the high degree of hygienic-sanitary commitment of these patients, with less social activity, habitual use of masks and distance from people with respiratory symptoms. We should also consider the possibility of under-diagnosis due to the distance from the hospital that these patients also had during the hardest periods of the pandemic. It is also unknown what has happened in the successive waves of the pandemic, although there are personal estimates that cases have been occurring steadily, but with a lower number of severe cases, probably due to the initial natural selection and the arrival of vaccines. However, mortality has been much higher than in other population groups, reaching 40.7% in the first wave and 24.8% in the second [64].

With regard to the diagnostic delay of hematological malignancies, data from a Spanish reference group in hematological molecular biology (Ramón García Sanz, personal contribution), which receives some 18,000 samples per year, suffered a 75% drop in the demand for tests during the months of March and April 2020, although it then recovered throughout the year to end up with an overall decrease of 1,400 samples (9%) over the entire year 2020. During 2021 this laboratory experienced an increase of 16% with respect to 2020, which is quite close to the data provided by the AECC study. However, it should be clarified that these variations affected mainly chronic myeloid leukemia and indolent lymphoproliferative syndromes, with hardly any effect on acute leukemias, multiple myeloma and aggressive lymphomas, so the real consequences on patients were less relevant.

CONCLUSION:

The incidence of COVID-19 has been lower in hematologic patients than in the general population, at least during the first wave, although severity and mortality have been higher.

There has been a delay in the diagnosis of malignant neoplasms that can be estimated at about 2 months and a reduction in the number of diagnoses estimated at approximately 15%.

ARE HEMATOLOGY INPATIENT UNITS MORE PROTECTED FROM NOSOCOMIAL OUTBREAKS OF COVID-19?

Probably yes, due to the additional protective measures that are contemplated in these units, although there is no clear evidence of this. Although there are several publications on outbreaks in hematopoietic stem cell transplantation (HSCT) units, there is little comparative evidence on hematology units compared to other hospital admission units [65,66]. In one of them, there was no difference between the hematology unit and other units in the incidence of cases in a nosocomial outbreak [67].

What hematologic patients with hematologic malignancies and recipients of HSCT certainly require is greater protection against COVID-19 infection given their higher risk of developing severe COVID-19. It is a fact that patients with hematologic malignancies and recipients of HSCT have a high mortality associated with COVID-19 (20-45%), although not all can be considered within this high mortality group, as will be discussed below [64].

The prevention of COVID-19 outbreaks in these units and the reduction of their clinical impact has been based on 3 points: preventive measures against infection; early detection of cases; and early treatment of infections or mild COVID-19 cases to avoid their progression to more severe forms [68].

Nosocomial infections account for 8% (67) (ranging from 4-12%) of cases seen in the hospital.

HEPA-filtered, positive-pressure rooms help protect patients from airborne infections such as SARS-CoV-2. However, if the patient has SARS-CoV-2 infection, he/she should be moved to a room without HEPA and positive pressure or disconnected if feasible, since, if the patient remains in such a room, and depending on the air circuit of the unit, he/she may pose a risk to staff and other patients in the room.

Healthcare personnel and accompanying persons/visitors are the other possible source of infection for admitted patients. One of the measures to prevent nosocomial infection is to prohibit visitors and to limit the number of accompanying persons as much as possible to essential cases. In those cases where a companion is authorized, the performance of PCR in nasopharyngeal exudate for SARS-CoV-2 before accessing the room and remaining in the unit without leaving it during the whole time, help to minimize the risk of transmission. Logically, accompanying patients with symptoms suspicious of COVID-19 should not be admitted and if they develop symptoms during admission, diagnostic studies should be performed using rapid techniques for SARS-CoV-2 as well as for other respiratory viruses.

To minimize transmission, preventive measures should be scrupulously observed. These measures should be taken not only in contact with patients, but also with other healthcare workers, particularly when eating or drinking together. In most cases of nosocomial acquisition of infection by healthcare workers, the index case is another healthcare worker [69].

It should be noted that during the first wave of SARS-CoV-2 infection, the percentage of asymptomatic infections was 40-50% [70], a percentage that has increased with the Omicron variant even in vaccinated individuals [71]. Therefore, symptom screening has relative efficacy in preventing transmission since more than 40% of infections are transmitted by individuals with asymptomatic infection [70].

The possible transmission from both sick and asymptomatic workers or visitors requires the systematic use of FFP2 masks in both patients and healthcare workers. [72], following the most recent CDC recommendation.

The other measure that contributes to the reduction of transmission is the correct and complete vaccination for SARS-CoV-2 since, in addition to preventing the disease, vaccines also reduce the risk of infection, although to a lesser degree. Therefore, all healthcare personnel and accompanying persons, if any, must be fully vaccinated. The presence of unvaccinated healthcare workers/companions is a risk that should not be accepted in these units.

Despite scrupulous adherence to protective measures, nosocomial infections can occur. For this reason, periodic repeated screening with PCR of all patients admitted to hematology units helps early detection and differentiated management, including transfer out of the unit and early treatment. Periodic screening of healthcare personnel encounters various difficulties, which means that it is not applied in the vast majority of centers.

If SARS-CoV-2 or mild COVID-19 infection is detected early, we now have both monoclonal antibodies and antivirals (oral and intravenous) that have been shown to be effective in preventing progression to more severe forms.

An additional measure of protection for our patients is pre-exposure prophylaxis by administration of monoclonal antibodies, Ronapreve (casirivimab/imdevimab) and Evusheld (cilgavimab/tixagevimab), the latter offering protection for >6 months after administration. The Ministry of Health has recently adopted criteria for the administration of these monoclonals as pre-exposure prophylaxis (https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid-19/prevencion-frente-a-la-covid-19/farmacos-con-indicacion-de-profilaxis-preexposicion/).

CONCLUSION:

Probably, although there is no clear evidence of it, the admission units of hematological/TPH patients are more protected from nosocomial acquisition of COVID than other areas of the hospital. This could be explained by strict compliance with the usual infection prevention measures and early detection of cases.

WHAT DO WE KNOW ABOUT COVID-19 AND CHRONIC MYELOID LEUKEMIA?

In published series on patients with onco-hematological

diseases with COVID-19, chronic myeloid leukemia (CML) has accounted for between 4.1 and 6.7% of cases [73,74].

Neither the incidence of COVID-19 nor the clinical course of the disease appear to be worse in CML patients than in people with the same comorbidity [75]. An Italian group has published experience with 8,665 CML patients of whom 217 (2.5%) had COVID-19 infection [76]. The severity of infection was generally comparable to that observed in the normal population (most were asymptomatic or had the mild form of the disease, and up to 170 patients did not require hospital admission). Twelve patients died, with a mortality rate of 5.5%, lower than that found in the available literature on other hematological malignancies, but still slightly higher than in the general Italian population (2.97%). As in the general population, age and cardiovascular risk factors were observed as adverse prognostic factors in patients with CML. Importantly, SARS-CoV-2 infection was associated with treatment discontinuation in up to a quarter of admitted patients and had negative effects on patient monitoring (prolongation of time between monitoring or not opting for planned treatment discontinuation strategies).

In a series of much smaller dimensions than the previous one and published with cases from the beginning of the pandemic (global CANDID study), a mortality rate of 13.7% was observed in 110 patients diagnosed with COVID-19 and CML in July 2020. It should be noted that most of the diagnoses were made after hospital admission [77].

There are several possible explanations for the fact that CML does not play as adverse a prognostic role as other onco-hematological malignancies. First, although immune system dysfunction at the time of disease diagnosis is well known, it has been shown how after treatment with tyrosine kinase inhibitors (TKIs) this immune response is restored [78]. In a study [79] data were collected from a large cohort of 6,883 CML patients, and only 12 cases of COVID-19 infection were confirmed, with a prevalence of 0.17%. The results of this study show that the incidence of COVID-19 infection is extremely low in CML patients treated with tyrosine kinase inhibitors (TKIs).

It is known that TKIs, far from producing immunosuppression (as occurs in most treatments used for other neoplasms), could potentiate the immune response against known viruses [80] (and presumably could occur against SARS-CoV-2). Similarly, the humoral immune response has been shown to be robust in CML patients, both after infection with COVID-19 and after vaccination. A study in 62 CML patients on TBI treatment observed seroconversion rates in 96% of patients, with the duration of the immune response being similar to that of healthy subjects [81]. The same group showed how the majority of CML patients with adequate humoral response after vaccination had neutralizing antibody response [76]. When the humoral immune response has been compared between subjects with different myeloproliferative neoplasms, the highest rate of seroconversion has been observed in patients with CML [76]. Finally, a Spanish group has recently shown how the cellular immune response measured by direct cellular cytotoxicity (DCS) studies against Vero E6 cells infected with SARS-CoV-2 is superior in patients with CML versus other hematological malignancies being very similar to that of healthy subjects [82,83].

CONCLUSION:

In patients with chronic myeloid leukemia (CML), neither the incidence nor the severity of COVID-19 appears higher than in the population with the same comorbidity. There is no evidence of the need to discontinue Tysosin Kinase Inhibitors in these patients when they acquire COVID-19. The vaccine-induced immune response appears comparable to that of the general population.

WHAT IS THE SITUATION OF COVID-19 IN PATIENTS WITH MULTIPLE MYELOMA?

Patients with multiple myeloma (MM) due to their multifactorial immunodeficiency have an elevated risk of infections caused by different etiological agents that constitute, in them, an important cause of morbidity and mortality [84-86]. Viruses have been shown, in recent studies, to be a frequent etiology of infections in patients with MM, particularly those affecting the respiratory tract [86,87].

It has not been surprising, therefore, that patients with MM are a population particularly vulnerable to SARS-CoV2 infection, with a high risk of poor outcome, meaning the need for hospitalization and risk of death [88,89].

Martinez-Lopez et al. [90,91] using three large databases of patients with MM (Hospital 12 de Octubre, EMEA, Global Network) have shown that the first impact of the pandemic has been that the number of new MM diagnoses was statistically lower in 2020 than in 2019.

The incidence of COVID-19 was higher in patients with MM than in other population groups and mortality in them was much higher than in the general population, standing at around 32% [90,91]. The most important factors associated with this high mortality were the presence of active or progressive MM, renal failure, advanced age and male sex.

Recent studies suggest that a substantial proportion of MM patients, especially those on treatment with anti-CD38 or B-cell maturation antigen (BCMA) therapies, do not develop anti-SARS-CoV-2 antibodies or have an insufficient response, even after full vaccination [92]. On day 50 after the second vaccine dose (mRNA or AZD1222 (AstraZeneca), only 53.5% of MM patients had a NAb titer of 50% or higher vs. 81% of controls.

In the publication by Van Oekelen et al.[93] 16% of 260 MM patients who received full vaccination with mRNA vaccines did not develop detectable IgG antibody titers to SARS-CoV-2 protein S at a median of 51 days after receiving the second dose of vaccine. In contrast, all age- and sex-matched controls had detectable anti-SARS-CoV-2 antibodies. Of the

41 patients without antibody responses, 24 (58.5%) were on anti-CD38 antibody therapy at the time of vaccination, 13 (31.7%) were on anti-BCMA antibody therapy, and 4 (9.8%) had undergone anti-BCMA CAR-T therapy more than 3 months previously.

These data suggest the need to monitor post-vaccination antibody titers in MM patients with the consequent application of personalized risk reduction measures in those who are unable to mount an adequate immune response to the vaccine. Unfortunately, such measures are far from clear and proven at present in patients with MM but could involve the administration of new doses of vaccine, or monoclonal antibodies on a prophylactic basis.

CONCLUSION:

Patients with Multiple Myeloma have a higher incidence of COVID-19 and a higher severity of infection, hospital admission and death. The response to conventional doses of vaccines is worse, especially in patients receiving anti-CD-38 and in those with anti-BCMA treatments. Patients who do not respond with significant elevation of antibody titer should be protected especially with a series of measures that have not been clearly defined by the corresponding agencies up to now.

WHAT IS KNOWN ABOUT COVID-19 IN LYMPHOMA PATIENTS?

Lymphomas are a heterogeneous group of cancers that are broadly divided into two main histological subtypes: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). NHL can spread to extranodal organs, bone marrow and spleen.

Along with rituximab chemotherapy, hypogammaglobulinemia, neutropenia and lymphopenia [94] contribute to immunosuppression in these patients.

In recent years, treatments with different mechanisms of action (monoclonal antibodies, biologic agents, cell therapy,..) have been approved, which have expanded the therapeutic arsenal available for the treatment of lymphomas.

Patients with lymphomas are underrepresented in COVID-19 disease series and it is unclear whether or not these patients are at higher risk of becoming infected with SARS-CoV-2 than other populations with the same co-morbidity. What seems less in doubt is that patients with lymphoma, co-infected with SARS-CoV-2 have a worse outcome [94]. A retrospective, multicenter, 19-center study in Madrid evaluated risk factors for mortality in adult patients with COVID-19 and lymphoma [95]. Overall 177 patients (55.9% men) with a median follow-up of 27 days and a median age of 70 years were included. At the time of COVID-19 diagnosis, 49.7% of patients were on active treatment. The overall mortality rate was 34.5%. Age older than 70 years, confusion, elevated urea concentration, high respiratory rate, hypertension, and cardiac disease were associated with an increased risk of mortality. Active disease significantly increased the risk of death. However, being on anti-tumor treatment did not modify the risk of mortality and no differences were found between the different therapeutic regimens. Persistence of COVID19-positive PCR after week 6 was significantly associated with increased mortality. This study confirms the increased mortality due to COVID-19 compared to the general population in patients with lymphoma. In view of these results, any interruption or delay in treatment initiation should be questioned since active treatment has not been shown to increase the risk of mortality and achieving disease remission may lead to better outcomes.

The Spanish Lymphoma Group (GELTAMO) also conducted a retrospective multicenter study that included patients with a histologic diagnosis of lymphoma and SARS-COV-2 infection before June 30, 2020 [96].

A total of 218 patients were included who had received a median of 1 line (0 - 7) of treatment, and 44.9% were on active treatment at the time of diagnosis of COVID infection. Only 6.4%, 1.8% and 0.9% of patients had previously received autologous or allogeneic hematopoietic progenitor transplantation or CAR-T cell therapy, respectively. Eighty-nine percent of patients were hospitalized, 71% required oxygen and 15% mechanical ventilation. With a median follow-up of 91.5 days (13-203), 65 patients had died (60 from COVID-19, 4 from lymphoma and 1 from other causes), with an estimated overall survival at 60 days of 68.6 %. Multivariate analysis showed that only age ≥70 years demonstrated independent influence on the risk of death.

In patients with aggressive B-cell lymphoma, active disease negatively impacted survival while, in patients with follicular lymphoma, it was active treatment of the underlying disease that negatively impacted survival. The results of this retrospective analysis confirm the high mortality of SARS-CoV-2 infection in patients with lymphoma, especially in those aged ≥70 years. In patients with aggressive B-cell lymphoma, control of the underlying disease seems essential to reduce the risk of mortality in case of infection whereas in patients with follicular lymphoma this should not be considered strictly necessary.

Regarding the immune response after SARS-CoV-2 infection, a prospective study (PROSECO) [97] analyzed the immune response of 457 patients with lymphoma who received two or three doses of the COVID-19 vaccine. Fifty-two percent of patients on active treatment had undetectable humoral response after two doses of vaccine. In addition, 60% of patients on anti-CD20 monoclonal antibody therapy had undetectable antibodies after complete vaccination within 12 months of receiving targeted antineoplastic therapy. However, 70% of individuals with indolent lymphoma had improved antibody responses after the booster dose and, in particular, 63% of all patients had T-cell-specific antigenic responses that increased after the third dose regardless of baseline disease treatment status. The results of this study and others emphasize the need for careful monitoring of specific anti-COVID19 immune responses to guide vaccination strategies for these patients.

It can be deduced from the above that patients with lymphoma should be treated in highly specialized centers where general procedures are in place to minimize the risk of COVID-19 spread. For indolent lymphoma/chronic lymphocytic leukemia/Waldenström's disease requiring therapy, greater flexibility in initiating therapy can often be explored. However, if indolent lymphoma requires treatment according to national consensus guidelines, then treatment should not be delayed. The type of therapy should be decided based on the most effective treatment and, only if it has comparable efficacy, should the least immunosuppressive alternative be considered [98].

For patients with aggressive histologic patterns (aggressive B-cell lymphoma, mantle cell lymphoma, T-cell lymphoma), delays in initiating treatment may result in a significant worsening of outcome. It is important to initiate treatment after the diagnosis is made, avoiding if possible more aggressive chemotherapy schedules that increase the duration of neutropenia and immunosuppression. Autologous hematopoietic stem cell transplantation should not be delayed in those diseases in which it is considered a curative therapeutic strategy; this concept also applies to treatment with CART cells. Allogeneic transplantation can eventually be delayed always taking into account risks/benefits for a given patient.

CONCLUSION:

It has not been demonstrated whether patients with lymphoma are more easily infected with SARS-CoV-2 but after infection, their severity and evolution is worse than that of the population with equal co-morbidity. The immune response in these patients after vaccination is worse than that of the normal population, which should be taken into account when scheduling revaccination and protecting these patients.

The risk of COVID-19 or COVID-19 itself should not postpone the necessary therapeutic interventions in these patients.

HOW SHOULD PATIENTS WITH HEMATOLOGIC MALIGNANCIES BE VACCINATED? ARE THEY A PREFERENTIAL GROUP FOR VACCINATION?

We have already mentioned the risks of acquisition of COVID-19 in different patients with solid tumors or hematological malignancies as well as their clinical course and risk of death in previous pages [99-102]. For all these reasons, vaccination of these patients and the healthcare personnel who care for them should be a priority.

Vaccines against SARS-CoV-2 have alleviated the immediate pandemic threat to patients with hematologic malignancies. However, the immune response to these vaccines is reduced by the immunosuppressive nature of the malignancies themselves and their treatments. Most of the available data regarding the efficacy of vaccination in patients with neoplastic diseases refer to mRNA vaccines, either BNT162b2 (BioNTech and Pfizer) or mRNA-1273 (Moderna). None of the papers published to date have described safety issues different from those reported in the general population [57,103]. In any case, the benefits of vaccination outweigh the potential adverse effects in patients with no known contraindications to the vaccine components.

As mentioned above, the immune response to vaccines against SARS-CoV2 may be suboptimal in patients with hematologic malignancies [104,105]. These patients have heterogeneous and highly attenuated serologic responses to two doses of BT162b2 compared to healthy individuals, regardless of age or type of treatment. Vaccine response is especially poor in patients treated with Bruton's tyrosine kinase (BTK) inhibitors, ruxolitinib, venetoclax and/or anti-CD20 antibodies [103]. Similarly, treatment with anti-CD38 or anti-BCMA has been significantly associated with a failure of vaccine response [106]. In a study involving 320 patients with multiple myeloma, only 84% of patients developed anti-spike antibodies after complete vaccination with BNT162b2 or 1273 mRNA, and with highly variable titers [93]. Patients undergoing hematopoietic precursor transplantation (autologous or allogeneic), patients undergoing systemic chemotherapy, or patients treated with imatinib, dasatinib, nilotinib, or gilteritinib more than 6 months prior to vaccination show a better serologic response after immunization with BNT162b2 [103].

Therefore, patients requiring treatment for a hematologic malignancy should be vaccinated, if possible, before initiating treatment with chemotherapy, cellular therapies, or T- or B-cell depleting treatments, but this should not delay urgent treatment. If feasible, vaccination should be completed at least 2 weeks before immunosuppressive treatment. For patients already started on disease-specific therapies, interruption of treatment during vaccination is not recommended. It is appropriate to delay vaccination for at least 3 months after B-cell depletion therapy or stem cell transplantation. In these patients, vaccination of family contacts is an essential preventive measure.

In patients undergoing hematopoietic cell transplantation (HSTC) or cellular therapy, and taking into account expert opinion, vaccination should be considered from 3-6 months after allogeneic HSCT, except if the patient is still on immunosuppression (cyclosporine, tacrolimus, etc) [107].

Vaccination with a COVID-19 vaccine should be considered starting 3-6 months after autologous HSCT. Patients with mild chronic GVHD and/or receiving > 0.5mg/kg /day of prednisolone (or equivalent) should be vaccinated. For patients with moderate/severe GVHD or with more intensive immunosuppressive therapy (high dose steroids >0.5mg/kg/day) it is advisable to individualize on a case-by-case basis.

Patients with suspected or confirmed prior COVID-19 infection should be vaccinated according to international guidelines, as immunity may decrease over time [108].

Despite these data the actual efficacy of SARSCoV2 vaccines in patients with hematologic malignancies and cell transplantation/therapy is not well defined. Further studies on

the value of booster doses and long-term efficacy are needed. It would be necessary, for example, to be able to determine antibody titers against SARS-CoV-2 in these patients to ensure that protective neutralizing antibody titers have been achieved. If not, a third booster dose could be administered. Eventually, a heterologous booster regimen could be considered in these patients [109,110]. However, interpretation of the immune response to vaccination is complex and requires consideration of underlying pathology, disease status, current or past treatment, interval between treatment and vaccination, age, type of vaccine, and correlation between antibody levels and clinical protection.

The occurrence of severe SARS-CoV-2 infections in fully vaccinated patients with hematologic malignancies underscores the importance of strict adherence to nonpharmacologic interventions, and vaccination of cohabitants while SARS-CoV-2 is circulating in the community.

CONCLUSION:

Despite the fact that patients with hematological malignancies present attenuated and heterogeneous serological responses after vaccination with BNT162b2 mRNA, vaccination in them and in the healthcare personnel who care for them and cohabitants should be a priority, since the benefits of vaccination outweigh the possible adverse effects.

Patients receiving active treatment with BTKIs, ruxolitinib, venetoclax, anti-CD20, anti-CD38 and anti-BCMA antibody therapies seem to be the most affected and could be unprotected against SARS-CoV-2 infection.

Patients undergoing hematopoietic precursor transplantation (autologous or allogeneic), patients undergoing systemic chemotherapy or patients treated with imatinib, dasatinib, nilotinib or gilteritinib more than 6 months prior to vaccination show a better serological response after immunization with BNT162b2.

PART THREE - PROPOSALS FOR POSSIBLE SOLUTIONS

COULD WE DEFINE WHAT WE MEAN BY POST-COVID OR LONG-COVID SYNDROME?

In our environment, COVID is already a mostly ambulatory disease due to the change in the clinical spectrum resulting from the predominant variants and the response of the population, mostly vaccinated. The percentage of patients requiring hospitalization has fortunately been much lower in recent months.

In the first phase of the epidemic, in addition to the drama of the clinical aspects of the acute illness caused by SARS-CoV-2 infection, there were a large number of convalescent patients who were not completely free of disease. They continued with some of the symptoms that defined their acute symptoms, such as dyspnea and cough, and others appeared that were either new or were in the background at the height of the primary infection, such as asthenia or reduced intellectual agility.

Patients had no evidence of viral activity, their complementary scans improved or normalized, but their symptoms persisted and did so in a very high percentage of patients and for no obvious and predictable reason. It always seemed that the more severe initially suffered more, but the moderate and mild ones were widely represented in this continuum.

Age, as in other aspects of the disease, was associated with persistent functional impairment, while in children the incidence was very low.

Primoinfection, objectively leaves measurable and evident organ sequelae [111], as occurred with the predecessor epidemics of SARS and MERS [112,113]. Respiratory function tests, especially pulmonary diffusion, radiology and certainly histology, attest to the same. It occurs in the lung and it occurs in other organs (heart, nervous system, intestine, skin...) [114-117].

The problem arises when there is no parallelism between symptoms and findings.

Persistent asthenia; "mental fog"; dyspnea; tachycardia on small efforts; and the sensation of respiratory ceiling become complaints that do not leave the patient. Unfortunately, much of the literature addressing this situation is based on hastily collected data, with a methodology of very dubious validation (telephone interviews, with little or no parallel clinical study and of course without a control population) [118-120].

Given the lack of specificity of the symptoms, the evidence that this occurs after other acute diseases and above all after prolonged admission to the ICU, post-COVID began to be a complex of symptoms that could include entities already described, such as those mentioned, and others with equivalent symptoms and for which we do not have a certain pathophysiological explanation, such as myalgic encephalomyelopathy (chronic fatigue), which has come to occupy a considerable space, almost epidemic, in second opinion consultations or consultations of patients awaiting diagnosis.

In any case, the entity had to be defined and by consensus it was considered as the set of persistent or new onset symptoms after the acute phase of COVID, three months after the onset of symptoms, which are not justified by any other pathological process.

The continuum of recovery from primoinfection and the lack of specificity of the set of symptoms has meant that it has not been accepted as an entity and in fact for cataloguing purposes a code has been generated as a non-specific state post-CovidU09.9 in the International Classification of Diseases (ICD).

Another significant fact is that, in the course of the pandemic, new cases are notably less numerous, and it is quite possible that vaccination has much to do with the evolution and resolution of patients who become infected [121].

Clinical follow-up should be in the hands of general practitioners who are familiar with and regularly see these patients. The comprehensive assessment will decide which complementary explorations should be performed, if any, or specific consultations to other specialties. There is no consensus nor is it possible to have an initial protocol, given the enormous range of symptoms.

There is a WHO platform for communicating cases of interest post-COVID with the idea of refining the series and guiding research to provide an answer to the symptoms.

There is no doubt that COVID-19 generates anatomical and functional sequelae and there is an increasing trickle of new complications related to reinfection and vaccines, where autoimmunity plays a pathogenic role (hyperthyroidism, hepatitis...), and will continue to generate post-COVID doctrine.

CONCLUSION:

Entering the third year of the pandemic, it has not yet been possible to define Post-Covid as a clearly differentiated entity. This concept includes symptoms directly related to the anatomical or functional sequelae of the acute process; chronic alterations comparable to those of other severe or critical illnesses, such as post-intensive care syndrome; symptomatic complexes that can be framed in entities already known and that can be seen after infectious diseases or processes of other etiology, such as chronic fatigue and finally persistent or new onset symptoms for which there is no immediate explanation after the resolution of the acute phase and which are being studied. With the course of the epidemic, the number of patients with persistent symptoms has decreased and it is likely that vaccination is the cause.

IS IT POSSIBLE TO SHORTEN HOSPITAL STAY AND ICU STAY?

During the SARS-CoV-2 coronavirus pandemic, one of the main problems, especially during the first wave, has been the saturation of the healthcare system. During these months, all hospitals and Intensive Care Units (ICU) have seen an increase in admissions of COVID patients, reducing to absolute limits the possibility of caring for other non-COVID patients. Hospital stay and ICU stay adjusted for pathology are indicators of quality, which are related to efficiency in the use of resources. The optimization of scarce resources entails the need to seek strategies to reduce hospital stays, especially in the ICU, without reducing the quality of care.

In ICUs, after patient stabilization, much of the stay is consumed in the management and treatment of complications such as delirium and ICU-acquired muscle weakness. The "ABCDEF" measurement packages, related to adequate pain management (A), daily mechanical ventilation weaning tests (B), adequate sedation (C), delirium prevention and management (D), early rehabilitation (E) and family presence and involvement (F), have been shown to reduce days of mechanical ventilation and ICU stay, as well as impacting other outcomes such as mortality. The nutritional approach to patients, identifying nutritional needs specific to each situation improves the functional capacity of patients, reducing sequelae and reducing days of hospital stay [122-125].

The participation in the team of professionals such as rehabilitators, physiotherapists, speech therapists, nutritionists and psychologists reduces the sequelae of patients. Prevention of healthcare-associated infections, especially catheter-related bacteremia, ventilator-associated pneumonia, urinary catheter-associated infection and multi-resistant microorganism (MDR) infections reduces ICU and hospital stays, patient morbidity and mortality, and resource consumption. The Zero projects of the Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC) and the Sociedad Española de Enfermería Intensiva y Unidades Coronarias (SEIUCC) have shown their effectiveness in reducing these types of infections [126,127].

Although there is no conclusive evidence, some studies propose that the use of early tracheostomy in some situations could reduce the number of days of mechanical ventilation. Education and training in the management of tracheostomized patients on the hospital ward may allow these patients to be cared for safely, reducing stays in critical care areas [128].

Interdisciplinary teamwork improves collaborative practice. Daily multidisciplinary sessions and structured information handoffs focus daily objectives and reduce communication and patient safety problems. The use of protocols and clinical practice guidelines reduces hospital stays and improves outcomes. In the surgical patient Enhanced Recovery After Surgery (ERAS) protocols combine evidence-based perioperative management that work synergistically to improve patients' functional recovery after surgery, minimizing the response to surgical stress, improving outcomes and process efficiency [129].

Clinical information systems and the use of technology help to speed up decision making, ensure continuity of care, reduce errors, especially in the safe use of medication, and allow the evaluation of results and the implementation of improvement actions.

Decision-making, especially in the most critically ill patients, requires adequate patient- and family-centered communication. Daily information and involvement of families in decision making reduces conflict. Adequacy of life-sustaining treatment, proactively identifying those patients who do not respond to therapeutic measures, and redirecting efforts to improve the physical, psychological and emotional well-being of the patient in end-of-life care, reduces hospital stays and improves patient and family satisfaction. These decisions should be made in consensus with the entire team, based on the best available evidence regarding prognosis and taking into account the patient's preferences. Conditional treatment" allows decisions to be adjusted in the context of uncertainty. In some cases, in agreement with the family, terminal extubation while ensuring comfort measures may be an alternative and allow the patient to be transferred to the hospital ward.

Intermediate Care Units allow the transfer of patients to hospital areas with sufficient technical and human resources to provide monitoring and care at a lower level than ICUs, but much higher than conventional hospitalization areas.

Rapid response teams aimed at detecting patients at risk of deterioration on hospital wards, through monitoring systems and predictive scores such as the National Early Warning Score (NEWS), have been shown to be effective in reducing complications such as cardiorespiratory arrests, ICU readmissions and non-indicated admissions.

Finally, home hospitalization can reduce hospital days and provide person-centered care.

CONCLUSION:

Hospital and ICU length of stay is a quality indicator that reflects the efficiency of the system. There are different strategies to optimize processes, especially focused on improving patient safety, reducing avoidable adverse events. Communication and teamwork lead to a collaborative practice that impacts on outcomes and reduces inefficiency and inadequate use of resources.

WHAT IS THE OPINION ABOUT MONOGRAPHIC HOSPITALS FOR PATIENTS WITH COVID? WHAT IS THE VISION OF THE HEALTH AUTHORITIES?

Crisis situations and major catastrophes test the elasticity and adaptability of a society and, in this case, of its healthcare system. In Spain, perhaps the most paradigmatic case is that of the Community of Madrid, which first used the pavilions of a large fairground (IFEMA) which were reconditioned to provide health care in record time. Care in such conditions proved efficient and effective [130-135].

Monographic hospitals have been another alternative both in Spain and abroad. In Spain, the experience of the monographic hospital "Enfermera Isabel Zendal", which was built in record time and with the idea of serving as a multifunctional center and as a pandemic hospital, has been particularly interesting. During the most acute moments of the pandemic, more than 9,000 patients passed through this center, representing slightly more than 10% of all those who required hospitalization in Madrid.

These centers, being monographic, have standardized management, medical and nursing protocols. They also allow the development of studies and research projects. These centers have also been used as mass vaccination centers (with more than 2 million doses administered).

As pointed out by the director of the WHO Health Catastrophe Committee, they play a very important role in the management of the pandemic at times of greatest pressure.

These experiences have shown the capacity to develop, equip and operate as effective health centers, structures not designed for that purpose and invite in our opinion that in a future disaster plan every large building, just as it has its fire plan, should also have a plan for potential reconversion into a place of reception and health care.

CONCLUSION:

The reconversion of large spaces and infrastructures into places of effective health care has been one of the experiences derived from this pandemic. The Community of Madrid, in particular, converted part of a large exhibition center into a COVID field hospital and subsequently built in record time a multifunctional pandemic hospital that is still in use today as a vaccination center and has a great structural flexibility that allows it to adapt to other tasks.

HOW CAN THE EFFICIENCY OF CANCER SCREENING SYSTEMS BE INCREASED IF THE PANDEMIC CONTINUES?

Basically, it can be answered with two major answers, one how to recover the lost time or rather the patients who have been deprived of screening during the time of the pandemic and secondly keeping in mind that screening is only a part of the spectrum of all cancer control activities, how to recover and transform to impact the final cancer outcomes in our society. It is estimated that at the European level there are more than 100 million screening studies that have not been performed [136,137]. At the Spanish level we have no data. This means, following theoretical models, that 5% of patients with breast cancer or 8% of patients with lung cancer progress from stage I to stage II, after about 6 months of disruption of screening campaigns. Evidently, everything seems to indicate that this delay or rather standstill leads to an increase in mortality. It also induces an increase in health care costs, since as a rule more advanced cancers tend to consume more resources than early cancers. Therefore, an urgent action is to resume screening campaigns in those processes that have been shown to increase survival, such as breast cancer, cervical cancer and colon and rectal cancer [138-140]. In addition, pilot programs in other tumors that might be amenable could be considered as part of a broad recovery and research program.

Fortunately, LM Kregting et al. [141] have devised different strategies for resumption of screening and evaluated their impact in the Netherlands. The 5 strategies they have proposed are: resume the program without trying to capture the lost patients; resume the program by continuing with the same dynamics, in the patients who could not follow it; resume the program to those who start but quoting them at a later date than those who are already in the program; postpone the whole program with those who start by moving them to a later date than those who are already in and increasing the age cut-off; and finally resume all activities as again and capture in an extraordinary way those who were lost during the hiatus, including the

possibility of increasing the age cut-off. In this theoretical, but very rational model, this last strategy appears to be the most beneficial in an important way, compared to the first four. The limitations to extrapolate this model to the rest of the countries are firstly the different organization and capacity of the screening systems, and possibly of the whole national health system, including private systems in a system like ours that could collaborate to recover. The second limitation is that these theoretical models were designed for a short pandemic period, approximately 3 to 6 months, and we have no idea what it would be like at present, where the pandemic has lasted more than 2 years and with a variable and irregular intensity throughout the same and in different territories, with situations of total disruption in the first 3 to 6 months and then with certain recoveries and blockages, depending on the nations, regions and even cities.

CONCLUSION:

It is absolutely necessary and advisable to urgently resume screening programs for breast, cervical and colon and rectal cancer in order to avoid further mortality, decrease the deterioration of quality of life and prevent an extraordinary consumption of health resources in our society.

Following theoretical models, the best strategy would be to resume screening, sizing and increasing the necessary resources and adding additional time in an amount similar to that lost in those patients who could not be screened because of the pandemic.

IS TELEMEDICINE USEFUL IN THE MANAGEMENT OF ONCO-HEMATOLOGY PATIENTS DURING THE COVID PANDEMIC?

WHO defines telemedicine as "the delivery of health services by health professionals through the use of technological platforms for prevention, diagnosis, treatment, follow-up, research and continuing education of health professionals" [142].

The pandemic caused by COVID-19 has led to the activation and acceleration of numerous healthcare innovation initiatives. Telemedicine, which was already gaining ground in recent years, has seen its use expand significantly during the pandemic.

At present, the development of telemedicine offers enormous advantages to the healthcare system, but also encounters a number of difficulties in its implementation [143-146]. Among the advantages it offers are:

- It allows patients to reduce travel by avoiding unnecessary transfers (saving time and money) and facilitates access to the consultation for patients with difficulties (physical or geographical).

- It improves the care pressure on physicians by reducing the overcrowding of consultations, allowing better management of uncertainty in a calmer environment and with more elements of judgment, which favors decision making.

- It allows healthcare centers to make more efficient use of equipment and material resources and to reinforce the image of innovation.

- It allows the system to make better use of resources and improve health management.

However, a number of barriers to telemedicine implementation are:

- Difficulty on the part of many patients to use this type of technological tools (either due to lack of skill or lack of the technology).

- The regulation of their use and the resolution of the legal issues they raise: Data protection law, patient protection law and the doctor-patient confidentiality relationship.

- The training of healthcare professionals and patients, both in the use of the available platforms and in the use of their rights and duties.

- Integration into the portfolio of services by healthcare managers and their incorporation into the complete healthcare process, making face-to-face and telematic consultations compatible, according to the evolutionary moment of the process and the circumstances.

- The use of secure technological platforms that make it possible to encrypt the information being exchanged. The use of social networks, instant messaging services or e-mail is illegal in this type of medical practice.

During this pandemic it was essential to implement measures to optimize resources and protect patients, family members and healthcare personnel from the risk of contagion, guaranteeing, as far as possible, continuity of care for oncology patients. Telemedicine has helped to reduce the pressure of care in health centers and hospitals and to maintain continuity of patient care, while facilitating the continuing education of medical professionals [147-153]. In this regard, most oncology services implemented telephone consultations (landline or mobile) and sometimes video calls (Skype or Facetime), although these do not comply with adequate privacy standards.

Most of the teleconsultations performed were in patients and situations of low complexity:

- Follow-up visits to patients known to the physician.

- Information on test results (especially if they do not show alterations).

- Control of oral treatments (hormone therapy and chemotherapy).

- Control of side effects.

- Symptom control.

- Palliative care with home care.

- Psychological support.

CONCLUSION:

The development and implementation of telemedicine systems is of vital importance in the current era. It is clear that telemedicine is one more tool at the service of the professional that most patients have accepted and appreciated.

In the future, it will be necessary to plan for telemedicine to be safe and of high quality, which should include training professionals, defining the type of consultations that can be performed telematically and drawing up clinical and legal protocols to regulate this medical practice. This cannot be done without adequate technological development of the centers with institutional and economic support.

WHAT HELP AND ADVICE REGARDING COVID HAVE ONCO-HEMATOLOGY PATIENTS RECEIVED THROUGH PATIENT ORGANIZATIONS?

Since the coronavirus was declared a global pandemic, a whole host of information and data has been heard on a daily basis, which cancer patients often find difficult to understand and interpret.

As patients, they know that having medical information in an accessible and intelligible language is vital for them and their families, but the information received from different media, social networks and the Internet increases the doubts and concerns of cancer patients.

The continuity of cancer treatments, prevention measures against the virus, how to act in the event of infection or doubts about the emotional processes linked to the pandemic are just some of the questions that patients and their families are asked on a daily basis.

In those moments of uncertainty, when it was not possible to go to the doctor's office normally or to talk to the doctor as before, GEPAC (Spanish Cancer Patients Group) carried out different projects. The GEPAC website was, and is, a source of confidence and peace of mind for patients. It is recognized as a Web Médica Acreditada (WMA)[154] and this is the reason for the creation, linked to it, of the Web:" coronavirus y cancer" [155].

Not leaving home, the uncertainty and health concerns that are added to the oncological process itself, can generate fear, stress, anxiety or nervousness in patients. For all these reasons, at the beginning of the pandemic, a free tool was offered to provide information from experts in the field and to resolve doubts. This was done through an online seminar entitled "COVID-19 and cancer. Resolve your doubts from home [156] .

In order to put an end to the doubts of cancer patients and their families in relation to legal aspects, an online seminar was held to answer the questions of all the attendees, especially those related to ERTES, ERES, sick leave, etc. This was entitled "Legal aspects related to COVID-19" [157].

The pandemic has also generated a whole host of new psychosocial needs in patients. In spite of this, it is sometimes difficult to have a professional close by who can advise and provide the necessary tools to manage all the feelings and emotions that may arise in relation to the VIDOC-19. After verifying the high demand for a Psycho-oncology service, the Guide for the management of the emotional impact during COVID-19 for cancer patients and our families [158] was published, offering the possibility of having, free of charge, a manual to help in the management of emotions.

In addition, as the audiovisual format was gaining special relevance and so that anyone who wished could get to know the information in the guide in a dynamic and visual way, five explanatory videos were made in which the psycho-oncologists explained the main aspects of the manual in a visual and dynamic way [157,159,160-163]

Faced with this new disease, hitherto unknown scenarios have been created that have had a strong impact on the Spanish Health System, as well as on people's lives. Confinement, fears, the change in medical processes or the decrease in quality of life itself may have had a strong effect on cancer patients and survivors.

For all these reasons, the study "Problems and needs of cancer patients in the face of COVID-19" [163] has been carried out to find out how this situation has affected patients, cancer survivors and patient associations in order to draw conclusions that will allow us to improve care now and in the face of the new future we are facing.

Following the results obtained with the aforementioned study, a digital social awareness campaign was carried out under the title "Don't let fear paralyze you", with the aim of putting an end to the current fear of going to the doctor and reminding people of the importance of continuing with check-ups, always with the necessary protective measures to avoid contagion.

Given the refusal to go to the hospital or primary care centers for fear of contagion, mainly in those at risk, such as cancer patients, elderly or chronic patients, in addition to the cancellation of appointments or the delay in diagnostic tests, we were facing a scenario of considerable danger to people's health.

For all the above reasons, it was decided that this initiative would feature nine short videos recorded in high quality that were disseminated on social networks. Three of them feature cancer patients, another three show people from society in general, and the remaining three have the participation of SEHH, SEOM and SEOR, inviting those who see these audiovisual pieces to go to the doctor for check-ups, consultations or any necessary tests or specialists without being afraid [164-173].

We applied to the Comisión Nacional de los Mercados y la Competencia (CNMC) for an exemption from the advertising computation and it was granted. Thanks to this, the different videos were broadcasted on television channels, which allowed us to bring the campaign to many more people.

But we have a long and difficult road ahead, and the consequences of what we have experienced so far and of what cancer patients continue to go through will be seen later on.

CONCLUSION:

The pandemic has affected cancer patients particularly with delays in diagnoses, difficulties in receiving treatments, cancelled check-ups and generation of fear and uncertainty. In these circumstances, patient organizations such as GEPAC have developed educational and informative tools and put in place services to try to minimize the tremendous impact that COVID-19 has meant and means for onco-hematological patients.

WHAT REFLECTIONS FROM THE PERSPECTIVE OF ETHICS ARE RAISED IN THIS PANDEMIC?

The current pandemic has gone through several phases, which, having very different characteristics, have raised different ethical problems. The first in time was the lack of foresight that such a thing could happen. Both politicians and the media conveyed to society the false certainty that everything was under control and that, therefore, the infection would only affect a small group of people, and moreover in very specific geographical areas, certainly in developing countries, and therefore far from our own. That had happened in 2012 with the outbreak of another coronavirus, the one causing the so-called Middle East Respiratory Syndrome (MERS), shortly after, in 2014-16, in Guinea with the Ebola outbreak in 2014-2016 and almost simultaneously with the Zica virus outbreak (2015-2016) in America. In all three cases it was possible to prevent the uncontrolled spread of the virus to other regions of the planet, preventing these epidemics from becoming pandemics.

In the collective imagination, three examples seem sufficient to draw some general conclusions. And the one that prevailed, both in the media and in political propaganda, was that the warning and control system for this type of threat in Western countries was so fast and effective that those horrible epidemics we find in history books could no longer occur, nor could pandemics such as the influenza pandemic suffered barely a century ago, between 1918 and 1920. Thanks to advances in medicine and public health, such things would "never happen again". We could sleep soundly. Such is the belief that was installed in the collective unconscious of our super-developed societies. The great and deadly epidemics were a thing of the past. Thanks to science, they had become a bad memory.

That was what the bulk of the population thought. But scientists, and more specifically, epidemiologists, were not so optimistic. They were warning of the opposite, that there was a high probability of the appearance of an infection, similar to those mentioned above, that would break through barriers and would not be possible to control in specific areas, taking on planetary dimensions and causing immense mortality. This was becoming increasingly possible, if only because of the accelerated process of globalization of life. Social mobility today is enormous, unparalleled in any other era in human history. The classic systems of epidemiological control of ports and borders, which in classical terminology were encompassed under the label of "foreign health", have become obsolete. Trade is the engine of commerce, and therefore the basic principle of the economy. Now we have a repeat of something that already arose in Europe during the cholera epidemics of the 19th century. Faced with these epidemics, doctors demanded that the political authorities implement the classic procedure from biblical times, the quarantine and isolation of cities and people. And so it was done, despite the angry protests of industrialists and merchants, who saw their businesses ruined, without, moreover, any substantial improvement in the course of the epidemic. Today, two centuries later, the conflict between the demands of medicine and the needs of the economy and commerce is being repeated, albeit elevated to a dimension that no human being of the 19th century would have been able to imagine. And the dilemma arises: two risks must be weighed, infection on the one hand and hunger on the other.

This dilemma, like any other, is artificial and therefore false. Dilemmas are usually poorly posed and poorly resolved problems. And this is because the possible courses of action in the face of a conflict are practically never reduced to two. The courses of action are always several, many, and our first moral obligation is to identify them, so that we can then choose the optimal course, which is always the one that most promotes the realization of all the values at stake, or harms them the least. There is no other morally correct course than the optimal one, even though its identification can be complex, and therefore very difficult. One of the great biases that hinder our decision-making processes is that, sometimes out of fear, and often because of the law of least effort, we artificially reduce all possible courses of action to two; that is, we turn problems into dilemmas, which facilitates decision-making, but at the price of ignoring the nuances of the intermediate courses, which are those among which the optimal solutions are always found. A logical error ends up generating a moral error.

It is common, when speaking of the ethical problems raised by the current pandemic, to refer to the lack of resources, to improvisation, to whether or not health professionals are obliged to put their lives at risk, to the fact that the epidemic has delayed or marginalized the care of other types of patients, such as oncology and hematology patients, with the serious damage this causes to their health and their lives, etc. And, indeed, these are all serious political, medical and ethical problems. But there is an earlier problem, which is the only one I will mention. It is a matter of broadening the perspective and seeing this pandemic for what it is, one of the consequences of our way of relating to nature, or if you prefer, to the environment. Why has it occurred? A simplistic answer would be to say that it is due to the existence of a virus that we have not been able to eradicate from the face of the earth, nor to control completely by means of vaccines and drugs. Therefore, as soon as our science provides us with more effective vaccines, or more powerful or more specific antivirals, everything will return to its normal course and we will forget about this as if

it were a bad dream.

This way of thinking, which is probably the most frequent today, is not correct; moreover, it is profoundly mistaken. We will never do away with viruses or microorganisms, if only because they are necessary, indispensable. The strategy of eradication, so typical of the time when vaccines, chemotherapy and antibiotics began to be used, is not correct. Why are antibiotic resistances increasing so much? Why do we ignore the enormous number of people who die due to such resistances, as if it were something purely circumstantial? We continue with the philosophy of "eradication" as a goal, despite the fact that it is already known to be incorrect. In fact, we have only managed to eradicate one virus, that of smallpox. This should be enough to make us think that the generalization of that model is incorrect. Life in general, and ours as part of life in general, is a complex system of equilibria, which we must alter or modify only with great care. The thesis, especially in Western culture, that human beings are the king of creation and can do with other things as they please, is not correct. Is this pandemic unrelated to the fact that we are altering the environment to the point of raising the temperature of the planet, causing phenomena such as the greenhouse effect, increasing the pollution of rivers and seas, deforesting forests and modifying the biological cycles of plants and animals in an increasingly evident way? Has this influenced the present pandemic?

CONCLUSION:

It is necessary to change our mentality, and moreover urgently. We cannot continue to maintain the thesis that has prevailed in Western culture for many centuries, according to which the human being is the king of creation, so that he can do with it as he pleases. This is not true. We are just one more of the living beings that inhabit it, and our life depends on the balance between all of them. If we deserve respect, and it seems that no one denies it, the other beings, and nature as a whole, must also deserve it. It is a known fact that the human being, as soon as he considers himself superior and does not take into account the context in which he lives, begins to make mistakes. And that is exactly what is happening to Western culture in this problem. It has also invaded all other cultural spaces and has become in the last centuries the planetary culture.

TRANSPARENCY STATEMENT

For transparency purposes, we inform you that GSK has collaborated in the financing of this publication. Its contents reflect the authors' own opinions, criteria, conclusions and/or findings, which may not necessarily coincide with those of GSK. GSK always recommends the use of its products in accordance with the data sheet approved by the health authorities.

REFERENCES

1. Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, Harvey JD, et al. Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. JAMA Oncol. 2022;8(3):420-44. DOI: 10.1001/jamaoncol.2021.6987
2. Fernández A, De Haro Gázquez D, B FnSn, Diez Muñiz E, Puyol Escolar M, Yélamos Agua C, et al. Impacto del cáncer en España: Una aproximación a la inequidad y los determinantes sociales. Availabe at: https://observatoriocontraelcanceres/informes/impacto-del-cancer-en-espana-una-aproximacion-a-la-inequidad-y-los-determinantes-sociales. 2021. DOI:
3. Olaechea Astigarraga PM, Álvarez Lerma F, Beato Zambrano C, Gimeno Costa R, Gordo Vidal F, Durá Navarro R, et al. Epidemiology and prognosis of patients with a history of cancer admitted to intensive care. A multicenter observational study. Med Intensiva (Engl Ed). 2021;45(6):332-46. DOI: 10.1016/j.medine.2021.05.003
4. Redondo-Sánchez D, Marcos-Gragera R, Carulla M, Lopez de Munain A, Sabater Gregori C, Jimenez Chillarón R, et al. Lung, Breast and Colorectal Cancer Incidence by Socioeconomic Status in Spain: A Population-Based Multilevel Study. Cancers (Basel). 2021;13(11). DOI: 10.3390/cancers13112820
5. Dinmohamed AG, Visser O, Verhoeven RHA, Louwman MWJ, van Nederveen FH, Willems SM, et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. Lancet Oncol. 2020;21(6):750-1. DOI: 10.1016/s1470-2045(20)30265-5
6. Skovlund CW, Friis S, Christensen J, Nilbert MC, Mørch LS. Drop in cancer diagnosis during the COVID-19 pandemic in Denmark: assessment of impact during 2020. Acta Oncol. 2022:1-4. DOI: 10.1080/0284186x.2021.2024879
7. Kaufman HW, Chen Z, Niles J, Fesko Y. Changes in the Number of US Patients With Newly Identified Cancer Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic. JAMA Netw Open. 2020;3(8):e2017267. DOI: 10.1001/jamanetworkopen.2020.17267
8. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol. 2020;21(8):1023-34. DOI: 10.1016/s1470-2045(20)30388-0
9. Nuñez O, Rodríguez Barranco M, Fernández-Navarro P, Redondo Sanchez D, Luque Fernández M, Pollán Santamaría M, et al. Deprivation gap in colorectal cancer survival attributable to stage at diagnosis: A population-based study in Spain. Cancer Epidemiol. 2020;68:101794. DOI: 10.1016/j.canep.2020.101794
10. Luque-Fernandez MA, Redondo-Sánchez D, Rodríguez-Barranco M, Chang-Chan YL, Salamanca-Fernández E, Núñez O, et al. Socioeconomic Inequalities in Colorectal Cancer Survival in Southern Spain: A Multilevel Population-Based Cohort Study. Clin Epidemiol. 2020;12:797-806. DOI: 10.2147/clep.S261355
11. Launoy G, Zadnik V, Coleman M P. Social Environment and Cancer in Europe: Springer; 2021.
12. Tian Y, Qiu X, Wang C, Zhao J, Jiang X, Niu W, et al. Cancer associates with risk and severe events of COVID-19: A systematic review

and meta-analysis. Int J Cancer. 2021;148(2):363-74. DOI: 10.1002/ijc.33213

13. Yazaki S, Yoshida T, Kojima Y, Yagishita S, Nakahama H, Okinaka K, et al. Difference in SARS-CoV-2 Antibody Status Between Patients With Cancer and Health Care Workers During the COVID-19 Pandemic in Japan. JAMA Oncol. 2021;7(8):1141-8. DOI: 10.1001/jamaoncol.2021.2159
14. Wang Q, Berger NA, Xu R. Analyses of Risk, Racial Disparity, and Outcomes Among US Patients With Cancer and COVID-19 Infection. JAMA Oncol. 2021;7(2):220-7. DOI: 10.1001/jamaoncol.2020.6178
15. Lee KA, Ma W, Sikavi DR, Drew DA, Nguyen LH, Bowyer RCE, et al. Cancer and Risk of COVID-19 Through a General Community Survey. Oncologist. 2021;26(1):e182-5. DOI: 10.1634/theoncologist.2020-0572
16. Serraino D, Zucchetto A, Dal Maso L, Del Zotto S, Taboga F, Clagnan E, et al. Prevalence, determinants, and outcomes of SARS-COV-2 infection among cancer patients. A population-based study in northern Italy. Cancer Med. 2021;10(21):7781-92. DOI: 10.1002/cam4.4271
17. Lee LYW, Cazier JB, Starkey T, Briggs SEW, Arnold R, Bisht V, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. Lancet Oncol. 2020;21(10):1309-16. DOI: 10.1016/s1470-2045(20)30442-3
18. Liu T, Zeng G, Tao H, Shi Y, Wang T, Liu T, et al. Low prevalence of IgG antibodies to SARS-CoV-2 in cancer patients with COVID-19. Int J Cancer. 2020. DOI: 10.1002/ijc.33148
19. Marra A, Generali D, Zagami P, Cervoni V, Gandini S, Venturini S, et al. Seroconversion in patients with cancer and oncology health care workers infected by SARS-CoV-2. Ann Oncol. 2021;32(1):113-9. DOI: 10.1016/j.annonc.2020.10.473
20. Esperança-Martins M, Gonçalves L, Soares-Pinho I, Gomes A, Serrano M, Blankenhaus B, et al. Humoral Immune Response of SARS-CoV-2-Infected Patients with Cancer: Influencing Factors and Mechanisms. Oncologist. 2021;26(9):e1619-e32. DOI: 10.1002/onco.13828
21. Thakkar A, Pradhan K, Jindal S, Cui Z, Rockwell B, Shah AP, et al. Patterns of seroconversion for SARS-CoV2-IgG in patients with malignant disease and association with anticancer therapy. Nat Cancer. 2021;2(4):392-9. DOI: 10.1038/s43018-021-00191-y
22. Cattaneo C, Cancelli V, Imberti L, Dobbs K, Sottini A, Pagani C, et al. Production and persistence of specific antibodies in COVID-19 patients with hematologic malignancies: role of rituximab. Blood Cancer J. 2021;11(9):151. DOI: 10.1038/s41408-021-00546-9
23. Sepulcri C, Dentone C, Mikulska M, Bruzzone B, Lai A, Fenoglio D, et al. The Longest Persistence of Viable SARS-CoV-2 With Recurrence of Viremia and Relapsing Symptomatic COVID-19 in an Immunocompromised Patient-A Case Study. Open Forum Infect Dis. 2021;8(11):ofab217. DOI: 10.1093/ofid/ofab217
24. Tepasse PR, Hafezi W, Lutz M, Kühn J, Wilms C, Wiewrodt R, et al. Persisting SARS-CoV-2 viraemia after rituximab therapy: two cases with fatal outcome and a review of the literature. Br J Haematol. 2020;190(2):185-8. DOI: 10.1111/bjh.16896
25. Lunski MJ, Burton J, Tawagi K, Maslov D, Simenson V, Barr D, et al. Multivariate mortality analyses in COVID-19: Comparing patients with cancer and patients without cancer in Louisiana. Cancer. 2021;127(2):266-74. DOI: 10.1002/cncr.33243
26. Bertuzzi AF, Ciccarelli M, Marrari A, Gennaro N, Dipasquale A, Giordano L, et al. Impact of active cancer on COVID-19 survival: a matched-analysis on 557 consecutive patients at an Academic Hospital in Lombardy, Italy. Br J Cancer. 2021;125(3):358-65. DOI: 10.1038/s41416-021-01396-9
27. Fu C, Stoeckle JH, Masri L, Pandey A, Cao M, Littman D, et al. COVID-19 outcomes in hospitalized patients with active cancer: Experiences from a major New York City health care system. Cancer. 2021. DOI: 10.1002/cncr.33657
28. Brar G, Pinheiro LC, Shusterman M, Swed B, Reshetnyak E, Soroka O, et al. COVID-19 Severity and Outcomes in Patients With Cancer: A Matched Cohort Study. J Clin Oncol. 2020;38(33):3914-24. DOI: 10.1200/jco.20.01580
29. Roel E, Pistillo A, Recalde M, Fernández-Bertolín S, Aragón M, Soerjomataram I, et al. Cancer and the risk of coronavirus disease 2019 diagnosis, hospitalisation and death: A population-based multistate cohort study including 4 618 377 adults in Catalonia, Spain. Int J Cancer. 2022;150(5):782-94. DOI: 10.1002/ijc.33846
30. Pinato DJ, Patel M, Scotti L, Colomba E, Dolly S, Loizidou A, et al. Time-Dependent COVID-19 Mortality in Patients With Cancer: An Updated Analysis of the OnCovid Registry. JAMA Oncol. 2022;8(1):114-22. DOI: 10.1001/jamaoncol.2021.6199
31. Martin M, Guerrero-Zotano A, Montero Á, Jara C, Filipovich E, Rojo F, et al. GEICAM Guidelines for the Management of Patients with Breast Cancer During the COVID-19 Pandemic in Spain. Oncologist. 2020;25(9):e1339-e45. DOI: 10.1634/theoncologist.2020-0363
32. Venkatesulu BP, Chandrasekar VT, Girdhar P, Advani P, Sharma A, Elumalai T, et al. A Systematic Review and Meta-Analysis of Cancer Patients Affected by a Novel Coronavirus. JNCI Cancer Spectr. 2021;5(2):pkaa102. DOI: 10.1093/jncics/pkaa102
33. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. JAMA Oncol. 2020;6(7):1108-10. DOI: 10.1001/jamaoncol.2020.0980
34. Berghoff AS, Gansterer M, Bathke AC, Trutschnig W, Hungerländer P, Berger JM, et al. SARS-CoV-2 Testing in Patients With Cancer Treated at a Tertiary Care Hospital During the COVID-19 Pandemic. J Clin Oncol. 2020;38(30):3547-54. DOI: 10.1200/jco.20.01442
35. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7. DOI: 10.1016/s1470-2045(20)30096-6
36. Chodick G, Tene L, Rotem RS, Patalon T, Gazit S, Ben-Tov A, et al. The Effectiveness of the Two-Dose BNT162b2 Vaccine: Analysis of Real-World Data. Clin Infect Dis. 2022;74(3):472-8. DOI: 10.1093/cid/ciab438
37. Tenforde MW, Patel MM, Ginde AA, Douin DJ, Talbot HK, Casey JD, et al. Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States. Clin Infect Dis. 2021. DOI: 10.1093/cid/ciab687
38. Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del

Barrio I, Alaguthurai T, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol. 2021;22(6):765-78. DOI: 10.1016/s1470-2045(21)00213-8

39. Thakkar A, Gonzalez-Lugo JD, Goradia N, Gali R, Shapiro LC, Pradhan K, et al. Seroconversion rates following COVID-19 vaccination among patients with cancer. Cancer Cell. 2021;39(8):1081-90.e2. DOI: 10.1016/j.ccell.2021.06.002
40. Fendler A, Shepherd STC, Au L, Wilkinson KA, Wu M, Byrne F, et al. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: The CAPTURE study. Nat Cancer. 2021;2:1321-37. DOI: 10.1038/s43018-021-00274-w
41. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. Jama. 2021. DOI: 10.1001/jama.2021.7489
42. Marion O, Del Bello A, Abravanel F, Couat C, Faguer S, Esposito L, et al. Safety and Immunogenicity of Anti-SARS-CoV-2 Messenger RNA Vaccines in Recipients of Solid Organ Transplants. Ann Intern Med. 2021;174(9):1336-8. DOI: 10.7326/m21-1341
43. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021. DOI: 10.1056/NEJMc2108861
44. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Ann Intern Med. 2021. DOI: 10.7326/l21-0282
45. Tsapepas D, Paget K, Mohan S, Cohen DJ, Husain SA. Clinically Significant COVID-19 Following SARS-CoV-2 Vaccination in Kidney Transplant Recipients. Am J Kidney Dis. 2021;78(2):314-7. DOI: 10.1053/j.ajkd.2021.05.004
46. Waissengrin B, Agbarya A, Safadi E, Padova H, Wolf I. Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. Lancet Oncol. 2021;22(5):581-3. DOI: 10.1016/s1470-2045(21)00155-8
47. Figueiredo JC, Ihenacho U, Merin NM, Hamid O, Darrah J, Gong J, et al. SARS-CoV-2 vaccine uptake, perspectives, and adverse reactions following vaccination in patients with cancer undergoing treatment. Ann Oncol. 2022;33(1):109-11. DOI: 10.1016/j.annonc.2021.10.004
48. Luo B, Li J, Hou X, Yang Q, Zhou Y, Ye J, et al. Indications for and contraindications of immune checkpoint inhibitors in cancer patients with COVID-19 vaccination. Future Oncol. 2021;17(26):3477-84. DOI: 10.2217/fon-2021-0288
49. Corti C, Antonarelli G, Scotté F, Spano JP, Barrière J, Michot JM, et al. Seroconversion rate after vaccination against COVID-19 in patients with cancer-a systematic review. Ann Oncol. 2022;33(2):158-68. DOI: 10.1016/j.annonc.2021.10.014
50. Fendler A, Shepherd STC, Au L, Wu M, Harvey R, Schmitt AM, et al. Omicron neutralising antibodies after third COVID-19 vaccine dose in patients with cancer. Lancet. 2022;399(10328):905-7. DOI: 10.1016/s0140-6736(22)00147-7
51. American Association for Cancer Research. AACR Report on the impactr of COVID-19 on cancer research and patient care. https://wwwaacrorg/wp-content/uploads/2022/02/AACR_C19CR_2022pdf, accesed Feb 13, 2022. 2022. DOI:
52. American College of Surgeons. COVID-19 Guidelines for Triage of Breast Cancer Patients. 2020. Available at https://wwwfacsorg/covid-19/clinical-guidance/elective-case/breast-cancer Accessed May 14, 2020. 2020. DOI:
53. Jee J, Foote MB, Lumish M, Stonestrom AJ, Wills B, Narendra V, et al. Chemotherapy and COVID-19 Outcomes in Patients With Cancer. J Clin Oncol. 2020;38(30):3538-46. DOI: 10.1200/jco.20.01307
54. García-Suárez J, de la Cruz J, Cedillo Á, Llamas P, Duarte R, Jiménez-Yuste V, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. J Hematol Oncol. 2020;13(1):133. DOI: 10.1186/s13045-020-00970-7
55. Lee LY, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet. 2020;395(10241):1919-26. DOI: 10.1016/s0140-6736(20)31173-9
56. Lamont EB, Diamond SS, Katriel RG, Ensign LL, Liu J, Rusli E, et al. Trends in Oncology Clinical Trials Launched Before and During the COVID-19 Pandemic. JAMA Netw Open. 2021;4(1):e2036353. DOI: 10.1001/jamanetworkopen.2020.36353
57. Goshen-Lago T, Waldhorn I, Holland R, Szwarcwort-Cohen M, Reiner-Benaim A, Shachor-Meyouhas Y, et al. Serologic Status and Toxic Effects of the SARS-CoV-2 BNT162b2 Vaccine in Patients Undergoing Treatment for Cancer. JAMA Oncol. 2021;7(10):1507-13. DOI: 10.1001/jamaoncol.2021.2675
58. Massarweh A, Eliakim-Raz N, Stemmer A, Levy-Barda A, Yust-Katz S, Zer A, et al. Evaluation of Seropositivity Following BNT162b2 Messenger RNA Vaccination for SARS-CoV-2 in Patients Undergoing Treatment for Cancer. JAMA Oncol. 2021;7(8):1133-40. DOI: 10.1001/jamaoncol.2021.2155
59. Fenioux C, Teixeira L, Fourati S, Melica G, Lelievre JD, Gallien S, et al. SARS-CoV-2 Antibody Response to 2 or 3 Doses of the BNT162b2 Vaccine in Patients Treated With Anticancer Agents. JAMA Oncol. 2022. DOI: 10.1001/jamaoncol.2021.7777
60. Galmiche S, Luong Nguyen LB, Tartour E, de Lamballerie X, Wittkop L, Loubet P, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. Clin Microbiol Infect. 2022;28(2):163-77. DOI: 10.1016/j.cmi.2021.09.036
61. Gong IY, Vijenthira A, Betschel SD, Hicks LK, Cheung MC. COVID-19 vaccine response in patients with hematologic malignancy: A systematic review and meta-analysis. Am J Hematol. 2022;97(4):E132-e5. DOI: 10.1002/ajh.26459
62. Lee A, Wong SY, Chai LYA, Lee SC, Lee MX, Muthiah MD, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. Bmj. 2022;376:e068632. DOI: 10.1136/bmj-2021-068632
63. Sanchez-Pina JM, Rodríguez Rodriguez M, Castro Quismondo N,

Gil Manso R, Colmenares R, Gil Alos D, et al. Clinical course and risk factors for mortality from COVID-19 in patients with haematological malignancies. Eur J Haematol. 2020;105(5):597-607. DOI: 10.1111/ejh.13493

64. Pagano L, Salmanton-García J, Marchesi F, Busca A, Corradini P, Hoenigl M, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA). J Hematol Oncol. 2021;14(1):168. DOI: 10.1186/s13045-021-01177-0

65. Jung J, Lee J, Jo S, Bae S, Kim JY, Cha HH, et al. Nosocomial Outbreak of COVID-19 in a Hematologic Ward. Infect Chemother. 2021;53(2):332-41. DOI: 10.3947/ic.2021.0046

66. Saidel-Odes L, Nesher L, Nativ R, Borer A. An outbreak of coronavirus disease 2019 (COVID-19) in hematology staff via airborne transmission. Infect Control Hosp Epidemiol. 2022;43(3):405-7. DOI: 10.1017/ice.2020.1431

67. Aghdassi SJS, Schwab F, Peña Diaz LA, Brodzinski A, Fucini GB, Hansen S, et al. Risk factors for nosocomial SARS-CoV-2 infections in patients: results from a retrospective matched case-control study in a tertiary care university center. Antimicrob Resist Infect Control. 2022;11(1):9. DOI: 10.1186/s13756-022-01056-4

68. Kaddu-Mulindwa D, Thurner L, Bewarder M, Murawski N, Ahlgrimm M, Pfuhl T, et al. Protection strategy against outbreak of COVID-19 at a tertiary hematology-oncology: strengths and pitfalls. Infect Agent Cancer. 2021;16(1):17. DOI: 10.1186/s13027-021-00356-5

69. Kaya Kalem A, Kayaaslan B, Eser F, Hasanoglu İ, Ayhan M, Coskun B, et al. Investigation of the relation between risk assessment of exposure and nosocomial SARS-CoV-2 transmission in healthcare workers: a prospective single-centre study. BMJ Open. 2022;12(1):e056858. DOI: 10.1136/bmjopen-2021-056858

70. Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic. Ann Intern Med. 2021;174(9):1344-5. DOI: 10.7326/l21-0491

71. Garrett N, Tapley A, Andriesen J, Seocharan I, Fisher LH, Bunts L, et al. High Rate of Asymptomatic Carriage Associated with Variant Strain Omicron. medRxiv. 2022. DOI: 10.1101/2021.12.20.21268130

72. Klompas M, Rhee C, Baker MA. Universal Use of N95 Respirators in Healthcare Settings When Community Coronavirus Disease 2019 Rates Are High. Clin Infect Dis. 2022;74(3):529-31. DOI: 10.1093/cid/ciab539

73. Yigenoglu TN, Ata N, Altuntas F, Bascı S, Dal MS, Korkmaz S, et al. The outcome of COVID-19 in patients with hematological malignancy. J Med Virol. 2021;93(2):1099-104. DOI: 10.1002/jmv.26404

74. Cattaneo C, Daffini R, Pagani C, Salvetti M, Mancini V, Borlenghi E, et al. Clinical characteristics and risk factors for mortality in hematologic patients affected By COVID-19. Cancer. 2020. DOI: 10.1002/cncr.33160

75. Delgado N, Torres A. What Do We Currently Know About Chronic Myeloid Leukemia (CML) and COVID-19? Curr Oncol Rep. 2022:1-6. DOI: 10.1007/s11912-021-01169-w

76. Harrington P, Doores KJ, Radia D, O'Reilly A, Lam HPJ, Seow J, et al. Single dose of BNT162b2 mRNA vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induces neutralising antibody and polyfunctional T-cell responses in patients with chronic myeloid leukaemia. Br J Haematol. 2021;194(6):999-1006. DOI: 10.1111/bjh.17568

77. Rea D, Mauro MJ, Cortes JE, Jiang Q, Pagnano KB, Ongondi M, et al. COVID-19 in patients with chronic myeloid leukemia: results from the international CML Foundation (iCMLf) CML and COVID-19 (CANDID) study. Blood. 2020;136(s1):649. DOI:

78. Hughes A, Yong ASM. Immune Effector Recovery in Chronic Myeloid Leukemia and Treatment-Free Remission. Front Immunol. 2017;8:469. DOI: 10.3389/fimmu.2017.00469

79. Breccia M, Abruzzese E, Bocchia M, Bonifacio M, Castagnetti F, Fava C, et al. Chronic myeloid leukemia management at the time of the COVID-19 pandemic in Italy. A campus CML survey. Leukemia. 2020;34(8):2260-1. DOI: 10.1038/s41375-020-0904-z

80. Vigón L, Luna A, Galán M, Rodríguez-Mora S, Fuertes D, Mateos E, et al. Identification of Immunological Parameters as Predictive Biomarkers of Relapse in Patients with Chronic Myeloid Leukemia on Treatment-Free Remission. J Clin Med. 2020;10(1). DOI: 10.3390/jcm10010042

81. Claudiani S, Apperley JF, Parker EL, Marchesin F, Katsanovskaja K, Palanicawandar R, et al. Durable humoral responses after the second anti-SARS-CoV-2 vaccine dose in chronic myeloid leukaemia patients on tyrosine kinase inhibitors. Br J Haematol. 2021. DOI: 10.1111/bjh.18001

82. Vigón L, García-Pérez J, Rodríguez-Mora S, Torres M, Mateos E, Castillo de la Osa M, et al. Impaired Antibody-Dependent Cellular Cytotoxicity in a Spanish Cohort of Patients With COVID-19 Admitted to the ICU. Front Immunol. 2021;12:742631. DOI: 10.3389/fimmu.2021.742631

83. Vigón L, Sánchez-Tornero A, Rodríguez-Mora S, García-Pérez J, Corona de Lapuerta M, Pérez-Lamas L, et al. Strong Cellular Immune Response, but Not Humoral, against SARS-CoV-2 in Onco-hematological Patients with Autologous Stem Cell Transplantation after Natural Infection. J Clin Med. 2022;11(8). DOI: 10.3390/jcm11082137

84. Brioli A, Klaus M, Sayer H, Scholl S, Ernst T, Hilgendorf I, et al. The risk of infections in multiple myeloma before and after the advent of novel agents: a 12-year survey. Ann Hematol. 2019;98(3):713-22. DOI: 10.1007/s00277-019-03621-1

85. Balmaceda N, Aziz M, Chandrasekar VT, McClune B, Kambhampati S, Shune L, et al. Infection risks in multiple myeloma: a systematic review and meta-analysis of randomized trials from 2015 to 2019. BMC Cancer. 2021;21(1):730. DOI: 10.1186/s12885-021-08451-x

86. Park H, Youk J, Kim HR, Koh Y, Kwon JH, Yoon SS, et al. Infectious complications in multiple myeloma receiving autologous stem cell transplantation in the past 10 years. Int J Hematol. 2017;106(6):801-10. DOI: 10.1007/s12185-017-2313-2

87. Lim C, Sinha P, Harrison SJ, Quach H, Slavin MA, Teh BW. Epidemiology and Risks of Infections in Patients With Multiple Myeloma Managed With New Generation Therapies. Clin Lymphoma Myeloma Leuk. 2021;21(7):444-50.e3. DOI: 10.1016/j.clml.2021.02.002

88. Chari A, Samur MK, Martinez-Lopez J, Cook G, Biran N, Yong K, et al. Clinical features associated with COVID-19 outcome in multiple

myeloma: first results from the International Myeloma Society data set. Blood. 2020;136(26):3033-40. DOI: 10.1182/blood.2020008150

89. Engelhardt M, Shoumariyeh K, Rösner A, Ihorst G, Biavasco F, Meckel K, et al. Clinical characteristics and outcome of multiple myeloma patients with concomitant COVID-19 at Comprehensive Cancer Centers in Germany. Haematologica. 2020;105(12):2872-8. DOI: 10.3324/haematol.2020.262758
90. Martinez-Lopez J, Hernandez-Ibarburu G, Alonso R, Sanchez-Pina JM, Zamanillo I, Lopez-Muñoz N, et al. Impact of COVID-19 in patients with multiple myeloma based on a global data network. Blood Cancer J. 2021;11(12):198. DOI: 10.1038/s41408-021-00588-z
91. Martínez-López J, Mateos MV, Encinas C, Sureda A, Hernández-Rivas J, Lopez de la Guía A, et al. Multiple myeloma and SARS-CoV-2 infection: clinical characteristics and prognostic factors of inpatient mortality. Blood Cancer J. 2020;10(10):103. DOI: 10.1038/s41408-020-00372-5
92. Terpos E, Rajkumar SV, Leung N. Neutralizing Antibody Testing in Patients With Multiple Myeloma Following COVID-19 Vaccination. JAMA Oncol. 2022;8(2):201-2. DOI: 10.1001/jamaoncol.2021.5942
93. Van Oekelen O, Gleason CR, Agte S, Srivastava K, Beach KF, Aleman A, et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. Cancer Cell. 2021;39(8):1028-30. DOI: 10.1016/j.ccell.2021.06.014
94. Bonuomo V, Ferrarini I, Dell'Eva M, Sbisà E, Krampera M, Visco C. COVID-19 (SARS-CoV-2 infection) in lymphoma patients: A review. World J Virol. 2021;10(6):312-25. DOI: 10.5501/wjv.v10.i6.312
95. Regalado-Artamendi I, Jiménez-Ubieto A, Hernández-Rivas J, Navarro B, Núñez L, Alaez C, et al. Risk Factors and Mortality of COVID-19 in Patients With Lymphoma: A Multicenter Study. Hemasphere. 2021;5(3):e538. DOI: 10.1097/hs9.0000000000000538
96. Martín García-Sancho A, Izuzquiza M, Bastos-Oreiro M, Baile S, Nistal M, Cortés A, et al. Outcomes of patients with Lymphoma and COVID-19: An observational cohort study from GELTAMO Spanish Group. Hematological Oncology. 2021;39, IssueS2. . DOI: 10.1002/hon.200_2880
97. Lim SH, Stuart B, Joseph-Pietras D, Johnson M, Campbell N, Kelly A, et al. Immune responses against SARS-CoV-2 variants after two and three doses of vaccine in B-cell malignancies: UK PROSECO study. Nat Cancer. 2022. DOI: 10.1038/s43018-022-00364-3
98. Buske C, Dreyling M, Alvarez-Larrán A, Apperley J, Arcaini L, Besson C, et al. Managing hematological cancer patients during the COVID-19 pandemic: an ESMO-EHA Interdisciplinary Expert Consensus. ESMO Open. 2022;7(2):100403. DOI: 10.1016/j.esmoop.2022.100403
99. Afshar ZM, Dayani M, Naderi M, Ghabarveisi F, Shiri S, Rajati F. Fatality rate of COVID-19 in patients with malignancies: a sytematic review and meta-analysis. J Infect. 2020. DOI: 10.1016/j.jinf.2020.05.062
100. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: A systematic review and meta-analysis of 3377 patients. Blood. 2020. DOI: 10.1182/blood.2020008824
101. Abdul-Jawad S, Beatson R, Lechmere T, Graham R, Alaguthurai T, Graham C, et al. BNT162b2 COVID-19 and ChAdOx1 nCoV-19 vaccination in patients with myelodysplastic syndromes. Haematologica. 2022. DOI: 10.3324/haematol.2021.280337
102. Avanzato VA, Matson MJ, Seifert SN, Pryce R, Williamson BN, Anzick SL, et al. Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer. Cell. 2020;183(7):1901-12.e9. DOI: 10.1016/j.cell.2020.10.049
103. Maneikis K, Šablauskas K, Ringelevičiūtė U, Vaitekėnaitė V, Čekauskienė R, Kryžauskaitė L, et al. Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study. Lancet Haematol. 2021;8(8):e583-e92. DOI: 10.1016/s2352-3026(21)00169-1
104. Addeo A, Obeid M, Friedlaender A. COVID-19 and lung cancer: risks, mechanisms and treatment interactions. J Immunother Cancer. 2020;8(1). DOI: 10.1136/jitc-2020-000892
105. Addeo A, Friedlaender A. Cancer and COVID-19: Unmasking their ties. Cancer Treat Rev. 2020;88:102041. DOI: 10.1016/j.ctrv.2020.102041
106. Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood. 2021;137(23):3165-73. DOI: 10.1182/blood.2021011568
107. The British Society of Blood and Marrow transplantation and Cellular Therapy. COVID-19 Vaccination sub-group. BSBMT&CT recommendations for the management of adult patients and allogeneic donors during the COVID-19 (causative agent the SARS-CoV-2 virus) outbreak. {https://bsbmtctorg/wp-content/uploads/2020/12/BSBMTCT-COVID-19-Guidelines-50-Dec-2020_finalpdf), Accesed february 1`, 2022 #12}. 2020. DOI:
108. McCaughan G, Di Ciaccio P, Ananda-Rajah M, Gilroy N, MacIntyre R, Teh B, et al. COVID-19 vaccination in haematology patients: an Australian and New Zealand consensus position statement. Intern Med J. 2021;51(5):763-8. DOI: 10.1111/imj.15247
109. Hill EM, Keeling MJ. Comparison between one and two dose SARS-CoV-2 vaccine prioritization for a fixed number of vaccine doses. J R Soc Interface. 2021;18(182):20210214. DOI: 10.1098/rsif.2021.0214
110. Hill JA. Humoral Immunity After mRNA SARS-CoV-2 Vaccination in Allogeneic HCT Recipients-Room for Improvement and Much to Learn. JAMA Netw Open. 2021;4(9):e2127454. DOI: 10.1001/jamanetworkopen.2021.27454
111. Caramaschi S, Kapp ME, Miller SE, Eisenberg R, Johnson J, Epperly G, et al. Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review. Mod Pathol. 2021;34(9):1614-33. DOI: 10.1038/s41379-021-00814-w
112. Ong KC, Ng AW, Lee LS, Kaw G, Kwek SK, Leow MK, et al. Pulmonary function and exercise capacity in survivors of severe acute respiratory syndrome. Eur Respir J. 2004;24(3):436-42. DOI: 10.1183/09031936.04.00007104
113. Park WB, Jun KI, Kim G, Choi JP, Rhee JY, Cheon S, et al. Correlation between Pneumonia Severity and Pulmonary Complications in Middle East Respiratory Syndrome. J Korean Med Sci. 2018;33(24):e169. DOI: 10.3346/jkms.2018.33.e169

114. Bellan M, Soddu D, Balbo PE, Baricich A, Zeppegno P, Avanzi GC, et al. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA Netw Open. 2021;4(1):e2036142. DOI: 10.1001/jamanetworkopen.2020.36142

115. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res. 2020;21(1):163. DOI: 10.1186/s12931-020-01429-6

116. Liang L, Yang B, Jiang N, Fu W, He X, Zhou Y, et al. Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge. J Korean Med Sci. 2020;35(47):e418. DOI: 10.3346/jkms.2020.35.e418

117. Guedj E, Campion JY, Dudouet P, Kaphan E, Bregeon F, Tissot-Dupont H, et al. (18)F-FDG brain PET hypometabolism in patients with long COVID. Eur J Nucl Med Mol Imaging. 2021:1-11. DOI: 10.1007/s00259-021-05215-4

118. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin Microbiol Infect. 2021;27(1):89-95. DOI: 10.1016/j.cmi.2020.09.023

119. van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers CP, Schers H, et al. Comprehensive Health Assessment 3 Months After Recovery From Acute Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 2021;73(5):e1089-e98. DOI: 10.1093/cid/ciaa1750

120. Carfì A, Bernabei R, Landi F. Persistent Symptoms in Patients After Acute COVID-19. Jama. 2020. DOI: 10.1001/jama.2020.12603

121. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis. 2022;22(1):43-55. DOI: 10.1016/s1473-3099(21)00460-6

122. Siddique SM, Tipton K, Leas B, Greysen SR, Mull NK, Lane-Fall M, et al. Interventions to Reduce Hospital Length of Stay in High-risk Populations: A Systematic Review. JAMA Netw Open. 2021;4(9):e2125846. DOI: 10.1001/jamanetworkopen.2021.25846

123. Collinsworth AW, Priest EL, Masica AL. Evaluating the Cost-Effectiveness of the ABCDE Bundle: Impact of Bundle Adherence on Inpatient and 1-Year Mortality and Costs of Care. Crit Care Med. 2020;48(12):1752-9. DOI: 10.1097/ccm.0000000000004609

124. Hunter A, Johnson L, Coustasse A. Reduction of intensive care unit length of stay: the case of early mobilization. Health Care Manag (Frederick). 2014;33(2):128-35. DOI: 10.1097/hcm.0000000000000006

125. Martins B, Oliveira RA, Cataneo AJM. Palliative care for terminally ill patients in the intensive care unit: Systematic review and metaanalysis. Palliat Support Care. 2017;15(3):376-83. DOI: 10.1017/s1478951516000584

126. Hsieh SJ, Otusanya O, Gershengorn HB, Hope AA, Dayton C, Levi D, et al. Staged Implementation of Awakening and Breathing, Coordination, Delirium Monitoring and Management, and Early Mobilization Bundle Improves Patient Outcomes and Reduces Hospital Costs. Crit Care Med. 2019;47(7):885-93. DOI: 10.1097/ccm.0000000000003765

127. Wang YY, Wan QQ, Lin F, Zhou WJ, Shang SM. Interventions to improve communication between nurses and physicians in the intensive care unit: An integrative literature review. Int J Nurs Sci. 2018;5(1):81-8. DOI: 10.1016/j.ijnss.2017.09.007

128. Mata-Castro N, Sanz-López L, Pinacho-Martínez P, Varillas-Delgado D, Miró-Murillo M, Martín-Delgado MC. Tracheostomy in patients with SARS-CoV-2 reduces time on mechanical ventilation but not intensive care unit stay. Am J Otolaryngol. 2021;42(2):102867. DOI: 10.1016/j.amjoto.2020.102867

129. Shimabukuro-Vornhagen A. Intensive Care Unit Organization and Interdisciplinary Care for Critically Ill Patients with Cancer. Crit Care Clin. 2021;37(1):19-28. DOI: 10.1016/j.ccc.2020.09.003

130. Nuño González A, Magaletskyy K, Martín Carrillo P, Lozano Masdemont B, Mayor Ibarguren A, Feito Rodríguez M, et al. Are Oral Mucosal Changes a Sign of COVID-19? A Cross-Sectional Study at a Field Hospital. Actas Dermosifiliogr (Engl Ed). 2021;112(7):640-4. DOI: 10.1016/j.ad.2021.02.007

131. Martín Delgado MC, Avilés-Jurado FX, Álvarez Escudero J, Aldecoa Álvarez-Santuyano C, de Haro López C, Díaz de Cerio Canduela P, et al. [Consensus document of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC), the Spanish Society of Otorhinolaryngology and Head and Neck Surgery (SEORL-CCC) and the Spanish Society of Anesthesiology and Resuscitation (SEDAR) on tracheotomy in patients with COVID-19 infection]. Med Intensiva (Engl Ed). 2020;44(8):493-9. DOI: 10.1016/j.medin.2020.05.002

132. Hernández-Tejedor A, Munayco Sánchez AJ, Suárez Barrientos A, Pujol Varela I. The challenge of an intensive care unit in a fairground. Med Intensiva (Engl Ed). 2020;44(8):521-2. DOI: 10.1016/j.medin.2020.04.008

133. Díaz-Garzón J, Oliver P, Crespo G, Duque M, Fernandez-Calle P, Gómez M, et al. Experience on how to implement a preanalytical and POCT unit in Madrid's IFEMA field hospital during this unprecedented COVID-19 emergency. Biochem Med (Zagreb). 2020;30(3):030403. DOI: 10.11613/bm.2020.030403

134. Candel FJ, Canora J, Zapatero A, Barba R, González Del Castillo J, García-Casasola G, et al. Temporary hospitals in times of the COVID pandemic. An example and a practical view. Rev Esp Quimioter. 2021;34(4):280-8. DOI: 10.37201/req/041.2021

135. Aranguren-Oyarzábal A, Segura-Bedmar M, Calvo-Alcántara MJ. Ifema hospital model. Implementation and start-up of the Pharmacy Department. Farm Hosp. 2020;44(7):57-60. DOI: 10.7399/fh.11491

136. Sud A, Jones ME, Broggio J, Loveday C, Torr B, Garrett A, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. Ann Oncol. 2020;31(8):1065-74. DOI: 10.1016/j.annonc.2020.05.009

137. Thierry AR, Pastor B, Pisareva E, Ghiringhelli F, Bouché O, De La Fouchardière C, et al. Association of COVID-19 Lockdown With the Tumor Burden in Patients With Newly Diagnosed Metastatic Colorectal Cancer. JAMA Netw Open. 2021;4(9):e2124483. DOI: 10.1001/jamanetworkopen.2021.24483

138. Yabroff KR, Wu XC, Negoita S, Stevens J, Coyle L, Zhao J, et al. Association of the COVID-19 Pandemic with Patterns of Statewide

Cancer Services. J Natl Cancer Inst. 2021. DOI: 10.1093/jnci/djab122

139. Edge R, Meyers J, Tiernan G, Li Z, Schiavuzzi A, Chan P, et al. Cancer care disruption and reorganisation during the COVID-19 pandemic in Australia: A patient, carer and healthcare worker perspective. PLoS One. 2021;16(9):e0257420. DOI: 10.1371/journal.pone.0257420
140. Peacock HM, Tambuyzer T, Verdoodt F, Calay F, Poirel HA, De Schutter H, et al. Decline and incomplete recovery in cancer diagnoses during the COVID-19 pandemic in Belgium: a year-long, population-level analysis. ESMO Open. 2021;6(4):100197. DOI: 10.1016/j.esmoop.2021.100197
141. Kregting LM, Kaljouw S, de Jonge L, Jansen EEL, Peterse EFP, Heijnsdijk EAM, et al. Effects of cancer screening restart strategies after COVID-19 disruption. Br J Cancer. 2021;124(9):1516-23. DOI: 10.1038/s41416-021-01261-9
142. World Health Organization, Ryu S. Telemedicine: Opportunities and Developments in Member States: Report on the Second Global Survey on eHealth 2009 (Global Observatory for eHealth Series, Volume 2. Healthc Inform Res 2012 Jun; 18(2): 153–155. Published online 2012 Jun 30 doi: 104258/hir2012182153. 2009;Available at: http://www.who.int/goe/publications/goe_telemedicine_2010.pdf
143. Cremades M, Ferret G, Parés D, Navinés J, Espin F, Pardo F, et al. Telemedicine to follow patients in a general surgery department. A randomized controlled trial. Am J Surg. 2020;219(6):882-7. DOI: 10.1016/j.amjsurg.2020.03.023
144. Moazzami B, Razavi-Khorasani N, Dooghaie Moghadam A, Farokhi E, Rezaei N. COVID-19 and telemedicine: Immediate action required for maintaining healthcare providers well-being. J Clin Virol. 2020;126:104345. DOI: 10.1016/j.jcv.2020.104345
145. Mitchell J. From telehealth to e-health: the unstoppable rise of e-health. Canberra, Australia: National Office for the Information Technology. 1999.
146. Bird KT. Telemedicine; concept and practice. Springfield, Illinois1975.
147. Sirintrapun SJ, Lopez AM. Telemedicine in Cancer Care. Am Soc Clin Oncol Educ Book. 2018;38:540-5. DOI: 10.1200/edbk_200141
148. Portnoy J, Waller M, Elliott T. Telemedicine in the Era of COVID-19. J Allergy Clin Immunol Pract. 2020;8(5):1489-91. DOI: 10.1016/j.jaip.2020.03.008
149. Calton B, Abedini N, Fratkin M. Telemedicine in the Time of Coronavirus. J Pain Symptom Manage. 2020. DOI: 10.1016/j.jpainsymman.2020.03.019
150. Mars M. Medicolegal, ethical, and regulatory guidelines pertaining to telehealth. . In: Gogia S e, editor. Fundamentals of Telemedicine and Telehealth Cambridge: Elsevier; 2020 p 297-303 2020.
151. Ekeland AG, Bowes A, Flottorp S. Effectiveness of telemedicine: a systematic review of reviews. Int J Med Inform. 2010;79(11):736-71. DOI: 10.1016/j.ijmedinf.2010.08.006
152. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. N Engl J Med. 2020;382(18):1679-81. DOI: 10.1056/NEJMp2003539
153. Pearce C. Worldwide initiatives. . In: Gogia S e, editor. Fundamentals of Telemedicine and Telehealth Cambridge: Elsevier; 2020 p 331-342 2020.
154. Grupo Español de Pacientes con cáncer. Available at: https://wmacombes/es/homephp.
155. Grupo Español de Pacientes con Cáncer. COVID-19 y cáncer. 2021. Available at: https://appswhoint/gb/COVID-19/pdf_files/2021/28_03/20210328-%20Full%20reportpdf.
156. Grupo Español de Pacientes con Cáncer. COVID-19 y cáncer: Resuelve tus dudas desde casa. 2020. Available at: https://youtube/hd592N0O9iE.
157. Cuadrado-Lavín A, Olmos JM, Cifrian JM, Gimenez T, Gandarillas MA, García-Saiz M, et al. Controlled, double-blind, randomized trial to assess the efficacy and safety of hydroxychloroquine chemoprophylaxis in SARS CoV2 infection in healthcare personnel in the hospital setting: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21(1):472. DOI: 10.1186/s13063-020-04400-4
158. Grupo Español de Pacientes con Cáncer. Guía para el manejo del impacto emocional durante la COVID-19 para pacientes con cáncer y nuestras familias. 2020. Available at: http://wwwgepaces/web2016/wp-content/uploads/2020/05/GU%C3%8.
159. Grupo Español de Pacientes con Cáncer, Panera-Hernández C. COVID-19 Guía para el manejo del impacto emocional durante la COVID-19 para pacientes con cáncer y sus familias. 2020. Available at:https://youtube/kilU-XaUOfo.
160. Grupo Español de Pacientes con Cáncer, M. RC. Guiá para el manejo del impacto emocional durante la COVID-19 en pacients con cáncer y sus familias. 2020. Available at: https://youtube/aZWpa8iBY8Y.
161. Grupo Español de Pacientes con Cáncer, Rojas Casares M. Guiá para el manejo del impacto emocional durante la COVID-19 en pacients con cáncer y sus familias. Cuidarnos para poder cuidar. 2020. Available at: https://youtube/UPa3ehVFBFs.
162. Grupo Español de Pacientes con Cáncer, M. J-M. Guiá para el manejo del impacto emocional durante la COVID-19 en pacients con cáncer y sus familias. El duelo. 2020. Available at: https://youtube/tnSjNWWY5H4.
163. Grupo Español de Pacientes con Cáncer. Problemas y necesidades de los pacientes con cáncer frente a la Covid-19. 2020. :Available at:http://wwwgepaces/web2016/wp-content/uploads/2020/11/.
164. Grupo Español de Pacientes con Cáncer, Rodríguez-Lescure A. Que el miedo no te paralice. 2020. Available at:https://wwwyoutubecom/watch?v=GHDrjFLdtOw&list=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&index=1.
165. Grupo Español de Pacientes con Cáncer, García Sanz R. Que el miedo no te paralice. 2. 2020. Available at: https://wwwyoutubecom/watch?v=2336rzEUJ5E&list=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&index=2
166. Grupo Español de Pacientes con Cáncer, Contreras Martínez J. Que el miedo no te paralice. 3. 2020. Available at: https://wwwyoutubecom/watch?v=noUM3O3XLaE&list=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&index=3.
167. Grupo Español de Pacientes con Cáncer. Que el miedo no te paralice. 4. 2020. Available at: https://wwwyoutubecom/watch?v=tPl0NkWQyZQ&list=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&index=4.

168. Grupo Español de Pacientes con Cáncer. Que el miedo no te paralice 6. 2020. Available at: https://wwwyoutubecom/watch?v=6kZeG2QGFNU&tlist=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&tindex=5.

169. Grupo Español de Pacientes con Cáncer. Que el miedo no te paralice. 7. 2020. Available at: https://wwwyoutubecom/watch?v=cchOn0rQpsM&tlist=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&tindex=6.

170. Grupo Español de Pacientes con Cáncer. Que el miedo no te paralice. 8. 2020. Available at: https://wwwyoutubecom/watch?v=t1sJS7njISU&tlist=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&tindex=7.:

171. Grupo Español de Pacientes con Cáncer. Que el miedo no te paralice. 9. 2020. Available at: https://wwwyoutubecom/watch?v=skIVMg0fM2A&tlist=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&tindex=8.

172. Grupo Español de Pacientes con Cáncer. Que el miedo no te paralice.10. 2020. Available at: https://wwwyoutubecom/watch?v=enMaEmrP9w4&tlist=PLgJri5GPa_FvYqqv7gzKdT-_edbzGZsF8&tindex=9.

173. Grupo Español de Pacientes con Cáncer, Rojas Casares M. 2020.