HBV Reactivation in Hemato-Oncologic Patients with COVID-19

Subjects: Infectious Diseases

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Onco-hematologic patients are highly susceptible to SARS-CoV-2 infection and, once infected, frequently develop COVID-19 due to the immunosuppression caused by tumor growth, chemotherapy and immunosuppressive therapy. In addition, COVID-19 has also been recognized as a further cause of hepatitis B virus (HBV) reactivation, since its treatment includes the administration of corticosteroids and some immunosuppressive drugs.

Keywords: COVID-19 ; SARS-CoV-2 ; hepatitis B virus ; reactivation ; chemotherapy ; prevention

1. Introduction

The reactivation of hepatitis B virus (HBV) is a frequent event in onco-hematologic patients, both hepatitis B surface antigen (HBsAg)-positive and HBsAg-negative/hepatitis B core antibody (HBcAb)-positive ones, since the covalently closed circular DNA (cccDNA) remains a small microsome in the nucleus of infected hepatocytes even after patients have recovered, acting as a template for HBV-DNA synthesis and able to induce HBV reactivation. The immunosuppression induced by the growth of the tumor and by antineoplastic treatments is the main cause of this reactivation.

2. HBV Reactivation in Patients with Hemato-Oncologic Malignancies and Its Prevention

Before starting any antineoplastic treatment, hemato-oncologic patients should be tested for serum HBsAg and HBsAb, and the positive patients also for the serum HBV-DNA load. Being at a high risk of HBV reactivation, HBsAg-positive patients with cancer have to undergo prophylaxis with a high genetic barrier nucleus(t)side analogue (ETV, TDF or TAF) to be started one–two weeks before antineoplastic therapy [1], whereas pre-emptive therapy with the same nucleus(t)side analogues is considered sufficient for HBsAg-negative/HBcAb-positive patients who are at a lower risk of HBV reactivation; an exception should be made for the HBsAg-negative/HBcAb-positive patients intending to receive treatment with anti-CD20 antibodies or to undergo stem cell transplantation (SCT), who would need nucleus(t)side analogues in prophylaxis [2][3][4].

Of note, pre-emptive therapy with high genetic barrier nucleo(t)side analogues implies the determination of HBV-DNA serum levels every 1–3 months during antineoplastic treatment and the subsequent post-treatment follow-up. Once started, nucleo(t)side analogue prophylaxis should be continued throughout the antineoplastic therapy and a 12-month post-treatment follow-up, which should be extended for a further 6 months for patients treated with anti-CD20 antibodies or SCT [5][6][7].

The published studies on HBV reactivation in cancer patients concern patients unprotected by high genetic barrier nucleo(t)side analogues. It has been estimated that anticancer therapy induces HBV reactivation in 41–53% of HBsAg-positive subjects and in 8–18% of those that are HBsAg-negative/HBcAb-positive [8][9], with rituximab, alemtuzumab, anthracyclines, fludarabine and high-dose corticosteroids being the drugs most frequently involved. Some authors have highlighted that the type of malignancy also plays a role in the development of HBV reactivation [10][11][12]. In a retrospective study on 156 HBsAg-positive neoplastic patients undergoing chemotherapy, the incidence of severe HBV exacerbation was 25% in those with hematological malignancies, and 4.3% in those with solid tumors; of note, this rate was 40% in patients receiving rituximab-based chemotherapy and 4.1% in those treated with rituximab-free chemotherapy [13].

Numerous studies concern the reactivation of HBV in HBsAg-negative/HBcAb-positive onco-hematologic patients not protected by a high genetic barrier nucleus(t)side analogue. Wu et al. [14] reported a 5.7% incidence rate in leukemia patients receiving chemotherapy and a 2.2% in those who underwent SCT [14].

Hui et al. [15] found a 3.3% HBV reactivation in 244 patients with malignant lymphoma, with a higher reactivation rate in those treated with rituximab plus corticosteroids.

In a prospective study performed by Yeo et al. [16], in patients with diffuse large B-cell lymphoma (DLBCL), HBV reactivation occurred in 23.8% of the 21 receiving R-CHOP and in none of the 25 treated with CHOP.

In 150 patients with lymphoma receiving rituximab-based chemotherapy, Hsu et al. [17] found an incidence of HBV reactivation of 10.4 per person per year and the development of a hepatic flare in 6.4% of cases [17].

Matsui et al. [18] followed up with 59 patients with lymphoma under R-CHOP treatment, and found HBV reactivation in 6.8% of cases.

Ji et al. [19] reported HBV reactivation in 1 patient out of 43 with DLBCL treated with R-CHOP. The different frequency of HBV reactivation in HBsAg-negative/HBcAb-positive patients with onco-hematologic malignancies across the above-mentioned studies reflects differences in selection criteria, duration and the quality of the follow-up, type of onco-hematologic malignancy, degree of patients' immunosuppression and type of antineoplastic treatment. Taken together, however, these studies indicate that HBV reactivation affects 2–10% of HBsAg-negative/HBcAb-positive patients, the highest rates occurring in those treated with rituximab-based chemotherapy.

3. SARS-CoV-2 Infection and COVID-19 in Onco-Hematologic Patients

Cancer patients are at a high risk of developing severe COVID-19 once infected with SARS-CoV-2 [20][21][22][23][24][25]. Due to their low or absent host immune response, this virus is free to replicate and spread in patients with neutropenia, aplasia, bone marrow hypoplasia or neoplastic bone marrow disease, with massive direct cell damage; serous dangers are also exerted in patients with indolent chronic hematological diseases, in those who have undergone a bone marrow transplant and in those receiving or having recently received immunosuppressive therapy or chemotherapy [24][26][27][28][29][30]. In contrast, SARS-CoV-2 infection can induce an immunological hyperactivation and cytokine storm with consequent indirect tissue damage in patients with onco-hematological diseases involving antigen-presenting cells, T lymphocytes, NK or histiocytes [26][27][28][29][30][31][32]. This can also occur in patients with multiple myeloma on immunomodulatory therapy and in those with chronic myeloproliferative diseases [26][27][28][29][30][32].

The management of cancer patients during the SARS-CoV-2 pandemic has been complex. The real need of patients to access health facilities should be carefully assessed through an online triage to distinguish between deferrable and non-deferrable hospitalization needs. During a pandemic wave, hospitalization could be postponed by 12 weeks for patients waiting for a non-urgent transplantation and for those with stabilized diseases [33][34][35][36]. Patients on the waiting list for allogeneic transplantation should start conditioned chemotherapy only after the arrival of the donor cells and cryopreservation.

It has been recommended by several scientific societies (the European Society for Medical Oncology, the American Society of Clinical Oncology, the National Comprehensive Care Network, the Commission on Cancer, the National Institute for Health and Care Excellence in the UK and the American Society of Radiation Oncology) that a diagnostic molecular nasopharyngeal swab should be performed to detect SARS-CoV-2 RNA by PCR in all patients with cancer who have signs or symptoms of an influenza-like illness (ILI), in those who have been in contact with individuals with SARS-CoV-2 infection and in those who have been in hyperendemic areas; the positive ones should be admitted to dedicated care facilities until the RNA test is negative in at least two consecutive swabs [37][38][39][40][41].

Patients with hematological cancer should be advised to minimize hospital visits to prevent SARS-CoV-2 infection and to remain in telephone and audiovisual contact with the medical staff in care. The use of telemedicine can be of considerable support in the management of onco-hematological patients who can receive useful information on the behaviors to be followed, the modulation of therapy and any possible need they may have [37][41][42][43]. When necessary, onco-hematologic patients who have completed the SARS-CoV-2 vaccination course may be admitted with caution to healthcare facilities if they test negative with a SARS-CoV-2 RNA nasopharyngeal swab and have no ILI symptoms nor contact with SARS-infected subjects.

Most of the published studies on the efficacy of the COVID-19 vaccine report data obtained with the administration of two doses. Taken together, these studies demonstrate a good vaccine efficacy in the general population and lower efficacy in cancer patients [44][45][46][47]. In fact, Embi et al. [45] found that two doses of the COVID-19 mRNA vaccine prevented hospitalization in 90% of immunocompetent subjects, in 77% of immunocompromised patients and in 75% of cancer patients. In a retrospective, multi-center cohort study on 184,485 US cancer veterans, Wu et al. [46] evaluated COVID-19

mRNA vaccination as effective in approximately 60% of patients, ranging from 54% in patients on endocrine therapy or chemotherapy to 85% in those left untreated in the last 6 months [46]. Therefore, even if somewhat less effective than in normal subjects, COVID-19 vaccination is of great use for onco-hematologic patients. The need to vaccinate infection immunosuppressed and cancer patients against SARS-CoV-2 with a complete vaccination cycle (three vaccine doses) and with additional doses eventually required by the evolution of the pandemic and the duration of vaccine protection was clearly demonstrated in a UK study performed by Hippisley-Cox on a prospective cohort of 6,952,440 vaccinated subjects, of whom 5,150,310 received two doses of vaccine and the remaining ones a single dose. The study highlighted risk factors for death from COVID-19 to be moderate or high intensity chemotherapy (HR 3.63 and 4.3, respectively), stem cell transplantation within the last six months (HR 2.5), hematological cancer (HR 1.86) and cancer of the respiratory tract (HR 1.35) [47]. There was then the clear indication that oncologic patients should be given priority in COVID-19 vaccination over healthy citizens. This is true even today, since the administration of the fourth dose of RNA vaccine has begun in high-income countries with priority for the elderly and cancer patients.

However, there are concerns regarding the vaccination of numerous patients due to insufficient information, misinformation transmitted by social and mass media, the wavering decisions of some governments and patient fears of worsening the precarious equilibrium of the diseases. Evidence of these concerns was provided by Mejri et al. [48], who interviewed 329 Tunisian cancer patients; the vaccination acceptance rate was 50.5%, while 28.3% refused and 21.2% remained undecided and did not get vaccinated. The most frequent reasons for non-acceptance were the fear that the COVID-19 vaccine was not sufficiently effective and that it could negatively affect the course of the disease and the efficacy of treatments in place. This is a useful indication for physicians and psychologists to better target their work in convincing cancer patients that this vaccine is effective, safe and well-tolerated by almost everyone.

The reasons for vaccine hesitancy are heterogeneous and complex [49]. Three main motivations were identified by the SAGE group: contextual influences (e.g., socioeconomic and political), individual and social influences (e.g., social or personal experiences) and problems related to the vaccine and its administration (e.g., perceived benefits and risks and attitudes of health care providers) [50]. In June–August of 2020, there were conflicting views on the need for a COVID-19 vaccine, attributable to several factors that helped create vaccine hesitancy, including the perceived low risk of COVID-19 infection, vaccine-specific concerns and low adherence to COVID-19 information sources [51][52][53]. This hesitancy has also arisen among a significant number of physicians, and this has further increased hesitation about the COVID-19 vaccine in the general population. It is reasonable to hypothesize that vaccine hesitation could be lessened if it were administered by family doctors and doctors involved in the clinical and therapeutic follow-up of patients with long-lasting diseases, as it commonly occurs for onco-hematological patients. Trust in long-time respected doctors can increase patient confidence in the vaccine, and the practice of vaccination can increase doctors' confidence in a vaccine whose benefits they have directly assessed.

4. HBV Reactivation in Patients with COVID-19

There is little information on HBV reactivation in patients with COVID-19 due to the short time elapsed since the start of the COVID-19 pandemic. Wu et al. [19] published the case of a 45-year-old male affected by HBsAg-positive chronic hepatitis treated with adefovir dipivoxil and ETV, who was hospitalized for COVID-19. He was HBsAg-positive and HBeAg/HBeAb-negative, his serum aminotransferases were normal and HBV-DNA was undetectable. The patient was treated with methylprednisolone and developed a moderate HBV reactivation identified by a moderate increase in aminotransferases serum values and by a moderate HBV-DNA load. TDF was added to therapy and HBV reactivation rapidly resolved. The nasopharyngeal molecular swab to detect SARS-CoV-2 RNA became permanently negative and the patient recovered from COVID-19 [54].

Aldhaleei et al. [55] published the case of a 35-year-old man hospitalized for unconsciousness, which developed after an episode of vomiting, and was found positive for SARS-CoV-2 infection. He was jaundiced with serum aminotransferases over 100 times the higher value of the normal, had elevated serum bilirubin and slightly reduced serum albumin levels; a brain CAT scan did not show pathological findings. He was HBsAg-positive, HBV-DNA-positive, HBcAb IgM-positive, HBeAg-negative and HBeAb-positive. No corticosteroids nor immunosuppressive drugs were administered except for supportive therapy and entecavir one mg per day. Liver disease gradually resolved, and the SARS-CoV-2 RNA test became negative. In the absence of information on HBV markers prior to admission and relying on HBeAb positivity, the authors hypothesized the diagnosis of severe HBV reactivation related to SARS-CoV-2 infection, but the possibility of an acute hepatitis B concomitant with SARS-CoV-2 infection could not be excluded.

In a prospective cohort study of 600 COVID-19 patients, 61 were found to be HBsAg-negative/HBcAb-positive and were followed up with to identify a possible HBV reactivation during corticosteroid and/or immunosuppressive therapy. Out of

the 61, 38 received ETV prophylaxis (0.5 mg/day) and 23 remained untreated. HBV-DNA became detectable in 2 of 23 untreated patients and in none of 38 in the prophylaxis group, suggesting that entecavir was effective in preventing HBV reactivation [56].

References

1. American Cancer Society. Welcome to the COVID-19 and Cancer ECHO Series. Available online: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf (accessed on 3 May 2022).
2. Hwang, J.P.; Somerfield, J.J.; Hammond, S.P.; Wang, S.H.; Alston-Johnson, D.E.; Cryer, D.R.; Hershman, D.L.; Loehrer, A.P.; Sabichi, A.L.; Symington, B.E.; et al. Hepatitis B virus screening for patients with cancer before therapy: American Society of clinical oncology provisional clinical opinion update. J. Clin. Oncol. 2015, 33, 2212–2220.
3. Terrault, N.A.; Lok, A.S.F.; McMahon, B.J.; Chang, K.M.; Hwang, J.P.; Jonas, M.M.; Brown, R.S., Jr.; Bzowej, N.H.; Wong, J.B. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018, 67, 1560–1599.
4. European Association for the Study of the Liver (EASL). EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J. Hepatol. 2017, 67, 370–398.
5. Cholongitas, E.; Haidich, A.B.; Apostolidou-Kiouti, F.; Chalevas, P.; Papatheodoridis, G.V. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: A systematic review. Ann. Gastroenterol. 2018, 31, 480–490.
6. Zhang, M.Y.; Zhu, G.Q.; Shi, K.Q.; Zheng, J.N.; Cheng, Z.; Zou, Z.L.; Huang, H.H.; Chen, F.Y.; Zheng, M.H. Systematic review with network meta-analysis: Comparative efficacy of oral nucleos(t)ide analogues for the prevention of chemotherapy-induced hepatitis B virus reactivation. Oncotarget 2016, 7, 30642–30658.
7. Tsai, Y.F.; Hsu, C.M.; Hsiao, H.H. Management of Hepatitis B Virus Reactivation in Malignant Lymphoma Prior to Immunosuppressive Treatment. J. Pers. Med. 2021, 11, 267.
8. Lau, G.K.K.; Yiu, H.H.Y.; Fong, D.Y.T.; Cheng, H.C.; Au, W.Y.; Lai, L.S.F.; Cheung, M.; Zhang, H.-Y.; Lie, A.; Ngan, R.; et al. Affiliations expand Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. Gastroenterology 2003, 125, 1742–1749.
9. Huang, Y.H.; Hsiao, L.T.; Hong, Y.C.; Chiou, T.J.; Yu, Y.B.; Gau, J.P.; Liu, C.Y.; Yang, M.H.; Tzeng, C.H.; Lee, P.C.; et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J. Clin. Oncol. 2013, 31, 2765–2772.
10. Lalazar, G.; Rund, D.; Shouval, D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br. J. Haematol. 2007, 136, 699–712.
11. Kusumoto, S.; Tanaka, Y.; Mizokami, M.; Ueda, R. Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. Int. J. Hematol. 2009, 90, 13–23.
12. Liang, R. How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 2009, 113, 3147–3153.
13. Shih, C.A.; Chen, W.C.; Yu, H.C.; Cheng, J.S.; Lai, K.H.; Hsu, J.T.; Chen, H.C.; Hsu, P.I. Risk of severe acute exacerbation of chronic HBV infection cancer patients who underwent chemotherapy and did not receive anti-viral prophylaxis. PLoS ONE 2015, 10, e0132426.
14. Wu, T.; Wu, N.; Ma, Y.X.; Wu, J.; Gao, Y.; Pan, X.B. Role of hepatitis B antibody in predicting reactivation of resolved hepatitis B virus infection in leukemia patients. Antivir. Res. 2020, 177, 104765.
15. Hui, C.K.; Cheung, W.W.; Zhang, H.Y.; Au, W.Y.; Yueng, Y.H.; Leung, A.Y.; Leung, N.; Luk, J.M.; Lie, A.K.; Kwong, Y.L.; et al. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology 2006, 131, 59–68.
16. Yeo, W.; Chan, T.C.; Leung, N.W.; Lam, W.Y.; Mo, F.K.; Chu, M.T.; Chan, H.L.; Hui, E.P.; Lei, K.I.; Mok, T.S.; et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J. Clin. Oncol. 2009, 27, 605–611.
17. Hsu, C.; Tsou, H.H.; Lin, S.J.; Wang, M.C.; Yao, M.; Hwang, W.L.; Kao, W.Y.; Chiu, C.F.; Lin, S.F.; Lin, J.; et al. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: A prospective study. Hepatology 2014, 59, 2092–2100.
18. Matsui, T.; Kang, J.H.; Nojima, M.; Tomonari, A.; Aoki, H.; Yamazaki, H.; Yane, K.; Tsuji, K.; Andoh, S.; Andoh, S.; et al. Reactivation of hepatitis B virus in patients with undetectable HBsAg undergoing chemotherapy for malignant lymphom

a or multiple myeloma. J. Med. Virol. 2013, 85, 1900–1906.

19. Ji, D.; Cao, J.; Hong, X.; Li, J.; Wang, J.; Chen, F.; Wang, C.; Zou, S. Low incidence of hepatitis B virus reactivation duri ng chemotherapy among diffuse large B-cell lymphoma patients who are HBsAg-negative/ HBcAb-positive: A multicent er retrospective study. Eur. J. Haematol. 2010, 85, 243–250.
20. Xie, J.; Tong, Z.; Guan, X.; Du, B.; Qiu, H. Clinical Characteristics of Patients Who Died of Coronavirus Disease 2019 in China. JAMA Netw. Open. 2020, 3, e205619.
21. Desai, A.; Sachdeva, S.; Parekh, T.; Desai, R. COVID-19 and Cancer: Lessons from a Pooled Meta-Analysis. JCO Glo b. Oncol. 2020, 6, 557–559.
22. Zheng, R.S.; Sun, K.X.; Zhang, S.W.; Zeng, H.M.; Zou, X.N.; Chen, R.; Gu, X.Y.; Wei, W.W.; He, J. Report of cancer ep idemiology in China, 2015. Zhonghua Zhong Liu Za Zhi 2019, 41, 19–28.
23. Richardson, S.; Hirsch, J.S.; Narasimhan, M.; Crawford, J.M.; McGinn, T.; Davidson, K.W.; The Northwell COVID-19 R esearch Consortium; Barnaby, D.P.; Becker, L.B.; Chelico, J.D.; et al. Presenting haracteristics, Comorbidities, and Out comes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020, 323, 2052–2059.
24. Mehta, V.; Goel, S.; Kabarriti, R.; Cole, D.; Goldfinger, M.; Acuna-Villaorduna, A.; Pradhan, K.; Thota, R.; Reissman, S.; Sparano, J.A.; et al. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. Cancer Disc ov. 2020, 10, 935–941.
25. Grasselli, G.; Zangrillo, A.; Zanella, A.; Antonelli, M.; Cabrini, L.; Castelli, A.; Cereda, D.; Coluccello, A.; Foti, G.; Fumag alli, R.; et al. COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020, 323, 1574–1581.
26. Sica, A.; Casale, D.; Rossi, G.; Casale, B.; Ciccozzi, M.; Fasano, M.; Ciotti, M.; Sagnelli, E.; Papa, A.; Sagnelli, C. The i mpact of the SARS-CoV-2 infection, with special reference to the hematological setting. J. Med. Virol. 2020, 93, 223–23 3.
27. Yigenoglu, T.N.; Ata, N.; Altuntas, F.; Bascı, S.; Dal, M.S.; Korkmaz, S.; Namdaroglu, S.; Basturk, A.; Hacıbekiroglu, T.; Dogu, M.H.; et al. The outcome of COVID-19 in patients with hematological malignancy. J. Med. Virol. 2021, 93, 1099–1104.
28. Aries, J.A.; Davies, J.K.; Auer, R.L.; Hallam, S.L.; Montoto, S.; Smith, M.; Sevillano, B.; Foggo, V.; Wrench, B.; Zegocki, K.; et al. Clinical Outcome of Coronavirus Disease 2019 in Haemato-oncology Patients. Br. J. Haematol. 2020, 190, e6 4–e67.
29. Martín-Moro, F.; Marquet, J.; Piris, M.; Michael, B.M.; Sáez, A.J.; Corona, M.; Jiménez, C.; Astibia, B.; García, I.; Rodríg uez, E.; et al. Survival study of hospitalised patients with concurrent COVID-19 and haematological malignancies. Br. J. Haematol. 2020, 190, e16–e20.
30. Yang, F.; Shi, S.; Zhu, J.; Shi, J.; Dai, K.; Chen, X. Clinical characteristics and outcomes of cancer patients with COVID -19. J. Med. Virol. 2020, 92, 2067–2073.
31. Sica, A.; Sagnelli, C.; Casale, B.; Svanera, G.; Creta, M.; Calogero, A.; Franco, R.; Sagnelli, E.; Ronchi, A. How Fear of COVID-19 Can Affect Treatment Choices for Anaplastic Large Cell Lymphomas ALK+ Therapy: A Case Report. Healthc are 2021, 9, 135.
32. Sagnelli, C.; Celia, B.; Monari, C.; Cirillo, S.; De Angelis, G.; Bianco, A.; Coppola, N. Management of SARS-CoV-2 pne umonia. J. Med. Virol. 2021, 93, 1276–1287.
33. He, W.; Chen, L.; Chen, L.; Yuan, G.; Fang, Y.; Chen, W.; Wu, D.; Liang, B.; Lu, X.; Ma, Y.; et al. COVID-19 in persons with haematological cancers. Leukemia 2020, 34, 1637–1645.
34. Kumar, D.; Dey, T. Treatment delays in oncology patients during COVID-19 pandemic: A perspective. J. Glob. Health 20 20, 10, 010367.
35. Rubinstein, S.M.; Steinharter, J.A.; Warner, J.; Rini, B.I.; Peters, S.; Choueiri, T.K. The COVID-19 and Cancer Consorti um: A Collaborative Effort to Understand the Effects of COVID-19 on Patients with Cancer. Cancer Cell 2020, 37, 738–741.
36. Matsuo, T.; Kobayashi, D.; Taki, F.; Sakamoto, F.; Uehara, Y.; Mori, N.; Fukui, T. Prevalence of Health Care Worker Bur nout During the Coronavirus Disease 2019 (COVID-19) Pandemic in Japan. JAMA Netw. Open. 2020, 3, e2017271.
37. Richards, M.; Anderson, M.; Carter, P.; Ebert, B.L.; Mossialos, E. The impact of the COVID-19 pandemic on cancer car e. Nat. Cancer 2020, 1, 565–567.
38. Steimer, M.; Leabo, J.; Wang, H.; Heyer, D.; Addison, N.; Bowles, N.; Cannon, T.L.; Cuevo, R.; Ershler, W.B.; Shafer, D.; et al. Remote Home Monitoring of Patients With Cancer During the COVID Pandemic: A Pilot Study. JCO Oncol. Pr. 2021, 17, e1286–e1292.

39. Dietz, J.R.; Moran, M.S.; Isakoff, S.J.; Kurtzman, S.H.; Willey, S.C.; Burstein, H.J.; Bleicher, R.J.; Lyons, J.A.; Sarantou, T.; Baron, P.L.; et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the CO VID-19 pandemic. the COVID-19 pandemic breast cancer consortium. Breast Cancer Res. Treat. 2020, 181, 487–497.
40. Shinder, B.M.; Patel, H.V.; Sterling, J.; Tabakin, A.L.; Kim, I.Y.; Jang, T.L.; Singer, E.A. Urologic oncology surgery during COVID-19: A rapid review of current triage guidance documents. Urol. Oncol. 2020, 38, 609–614.
41. ESMO—European Society for Medical Oncology. Guidelines|ESMO—European Society for Medical Oncology. Availabl e online: https://www.esmo.org/guidelines/cancer-patientmanagement-during-the-COVID-19-pandemic (accessed on 3 May 2022).
42. Monaghesh, E.; Hajizadeh, A. The role of telehealth during COVID-19 outbreak: A systematic review based on current evidence. BMC Public Health 2020, 20, 1193.
43. Rosenbaum, L. Facing COVID-19 in Italy—Ethics, Logistics, and Therapeutics on the Epidemic's Front Line. N. Engl. J. Med. 2020, 382, 1873–1875.
44. Hippisley-Cox, J.; Coupland, C.A.; Mehta, N.; Keogh, R.H.; Diaz-Ordaz, K.; Khunti, K.; Lyons, R.A.; Kee, F.; Sheikh, A.; Rahman, S.; et al. Risk prediction of COVID-19 related death and hospital admission in adults after COVID-19 vaccinati on: National prospective cohort study. BMJ 2021, 374, n2244.
45. Giesen, N.; Sprute, R.; Rüthrich, M.; Khodamoradi, Y.; Mellinghoff, S.C.; Beutel, G.; Lueck, C.; Koldehoff, M.; Hentrich, M.; Sandherr, M.; et al. 2021 update of the AGIHO guideline on evidence-based management of COVID-19 in patients with cancer regarding diagnostics, viral shedding, vaccination and therapy. Eur. J. Cancer 2021, 147, 154–160.
46. Embi, P.J.; Levy, M.E.; Naleway, A.L.; Patel, P.; Gaglani, M.; Natarajan, K.; Dascomb, K.; Ong, T.C.; Klein, N.P.; Liao, I. C.; et al. Effectiveness of 2-dose vaccination with mRNA COVID-19 vaccines against COVID-19-associated hospitalizat ions among immunocompromised adults—Nine states, January-September 2021. MMWR Morb. Mortal. Wkly Rep. 202 1, 70, 1553–1559.
47. Wu, J.T.; La, J.; Branch-Elliman, W.; Huhmann, L.B.; Han, S.S.; Parmigiani, G.; Tuck, D.P.; Brophy, M.T.; Do, N.V.; Lin, A.Y.; et al. Association of COVID-19 vaccination with SARS-CoV-2 infection in patients with cancer: A US nationwide Ve terans Affairs study. JAMA Oncol. 2022, 8, 281–286.
48. Mejri, N.; Berrazega, Y.; Ouertani, E.; Rachdi, H.; Bohli, M.; Kochbati, L.; Boussen, H. Understanding COVID-19 vaccin e hesitancy and resistance: Another challenge in cancer patients. Support Care Cancer 2022, 30, 289–293.
49. Larson, H.J.; Jarrett, C.; Eckersberger, E.; Smith, D.M.D.; Paterson, P. Understanding vaccine hesitation about vaccine s and vaccination from a global perspective: A systematic review of published literature, 2007–2012. Vaccine 2014, 32, 2150–2159.
50. MacDonald, N.E. SAGE Working Group on Vaccine Hesitancy Vaccine Hesitancy hesitancy: Definition, scope and dete rminants. Vaccine 2015, 33, 4161–4164.
51. Lang, R.; Benham, J.L.; Atabati, O.; Hollis, A.; Tombe, T.; Shaffer, B.; Burns, K.K.; MacKean, G.; Léveillé, T.; McCormac k, B.; et al. Attitudes, behaviours and barriers to public health measures for COVID-19: A survey to inform public health messaging. BMC Public Health 2021, 21, 765.
52. Benham, J.L.; Atabati, O.; Oxoby, R.J.; Mourali, M.; Shaffer, B.; Sheikh, H.; Boucher, J.C.; Constantinescu, C.; Parsons Leigh, J.; Ivers, N.M.; et al. COVID-19 Vaccine–Related Attitudes and Beliefs in Canada: National Cross-sectional Surv ey and Cluster Analysis. JMIR Public Health Surveill. 2021, 7, e30424.
53. Benham, J.L.; Lang, R.; Kovacs Burns, K.; MacKean, G.; Léveillé, T.; McCormack, B.; Sheikh, H.; Fullerton, M.M.; Tan g, T.; Boucher, J.; et al. Attitudes, current behaviours and barriers to public health measures that reduce COVID-19 tran smission: A qualitative study to inform public health messaging. PLoS ONE 2021, 16, e0246941.
54. Wu, Y.F.; Yu, W.J.; Zhen, R.B.; Jiang, Y.H.; Chen, Y.; Zhang, B.; Li, X.P.; Zhang, J.T.; Wang, Y.P.; Li, Q.; et al. COVID-19 or treatment associated immunosuppression may trigger hepatitis B virus reactivation: A case report. World J. Clin. Cas es 2021, 9, 5266–5269.
55. Aldhaleei, W.A.; Alnuaimi, A.; Bhagavathula, A.S. COVID-19 Induced Hepatitis B Virus Reactivation: A Novel Case Fro m the United Arab Emirates. Cureus 2020, 12, e8645.
56. Rodríguez-Tajes, S.; Miralpeix, A.; Costa, J.; López-Suñé, E.; Laguno, M.; Pocurull, A.; Lens, S.; Mariño, Z.; Forns, X. L ow risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. J. Viral H epat. 2021, 28, 89–94.