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Complications of Treatment

SARS-CoV-2 and cancer: Are they really partners in crime?

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ABSTRACT

The outbreak of the SARS-CoV-2 pandemic has overwhelmed health care systems in many countries. The clinical presentation of the SARS-CoV-2 varies between a subclinical or flu-like syndrome to that of severe pneumonia with multi-organ failure and death. Initial reports have suggested that cancer patients may have a higher susceptibility to get infected by the SARS-CoV-2 virus but current evidence remains poor as it is biased by important confounders. Patients with ongoing or recent cancer treatment for advanced active disease, metastatic solid tumors and hematological malignancies are at higher risk of developing severe COVID-19 respiratory disease that requires hospitalization and have a poorer disease outcome compared to individuals without cancer. However it is not clear whether these are independent risk factors, or mainly driven by male gender, age, obesity, performance status, uncontrolled diabetes, cardiovascular disease and various other medical conditions. These often have a greater influence on the probability to die due to SARS-CoV-2 then cancer. Delayed diagnosis and suboptimal cancer management due to the pandemic results in disease upstaging and has considerable impact cancer on specific death rates. Surgery during the peak of the pandemic seems to increase mortality, but there is no convincing evidence that adjuvant systemic cancer therapy and radiotherapy are contraindicated, implicating that cancer treatment can be provided safely after individual risk/benefit assessment and some adaptive measures. Underlying immunosuppression, elevated cytokine levels, altered expression of the angiotensin converting enzyme (ACE-2) and TMPRSS2, and a prothrombotic status may fuel the effects of a SARS-CoV-2 in some cancer patients, but have the potential to be used as biomarkers for severe disease and therapeutic targets. The rapidly expanding literature on COVID-19 should be interpreted with care as it is often hampered by methodological and statistical flaws.

Introduction

The SARS-COV-2 is a novel coronavirus that has been identified after an outbreak of unusual pneumonia in Wuhan, China. The genome of the virus has been sequenced and assigned GeneBank accession number MN908947 [1]. Phylogenetically it belongs to the genus Betacoronavirus (subgenus Sarbecovirus) and has similarities with the other human betacoronaviruses SARS-CoV-1 [2] and MERS-CoV [1]. There is also 96% concordance with the genome of a bat coronavirus suggesting its potential origin [3,4]. SARS-CoV-2 contains a single strand RNA associated with a nucleoprotein within a capsid comprised of matrix protein. Four main structural proteins are encoded by ORFs10, 11 near the 3́-terminus [4,5]. The virus has a specific tropism for the upper airways and lung, cardiovascular and bowel tissue, but can also be detected in faeces [6], urine and blood samples [7,8]. Pharyngeal virus shedding is particularly high during the first week of

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symptoms (more than $7x10^8$ RNA copies per throat swab) [9]. However patients are already contagious in the presymptomatic period [8,10]. Although in most cases the salivary viral load declined with time, viral RNA was detected up to 25 days after symptom onset [10]. Asymptomatic shedding is reported [11,12,13]. Seroconversion [14] occurred after a 7–12 days in 50% of patients [8,15]. Enzyme immune assay of IgG and IgM against internal viral nucleoprotein (NP) and surface spike protein receptor domain (RBD) showed correlation [16] between antibody response and neutralizing antibody titer [10]. Ambiguity remains over the expected acquired immunity and its duration in both in the general population and in individuals with a severe underlying condition, as well as in the different age groups [17,18]. There is a broad range of clinical presentations of a SARS-CoV-2 viral infection varying from subclinical infection, sensation of a mild cold or flu to severe bilateral pneumonia, multiorgan failure, thrombotic events and death [19]. Common symptoms include fever, sore throat, fatigue, dyspnea and cough, diarrhea, anosmia and neurological symptoms [15,20]. The incubation period is 1–14 days (on average 3–7 days) [21]. Data from the WHO stated an overall case fatality rate of COVID-19 of about 1–7%. Mortality is the highest in the elderly, obese and in people with a pre-existing condition such as cardio-vascular disease, pulmonary disease, hypertension, diabetes and cancer [22]. Unfortunately, the disease may less frequently also become life-threatening in the population under the age of 50 with no prior underlying condition [23]. Children under the age of 9 have a mild course in nearly all cases although a new kind of disease entity during the COVID-19 period has been observed which resembles Kawasaki disease [24]. Postmortem research revealed that tissue responses to SARS-CoV-2 infection are distinct in different organs [25,26]. In comparison with observations made during the SARS-CoV-1 and MERS outbreaks, SARS-CoV-2 has similarities in risk group spread, but the case fatality rate of SARS-CoV-2 appears to be lower [2]. Today the virus is widely spread throughout the world and declared by the WHO as a pandemic. Enormous efforts are ongoing to develop a preventive vaccine, but this is beyond the scope of this paper.

COVID-19 and cancer

Susceptibility of cancer patients for SARS-CoV-2 infection

In an early report Yu J et al [27] suggested that patients with cancer seem more likely to be diagnosed with COVID-19. Twelve out of 1524 (0.79%) of patients admitted to the Department of Radiotherapy and Medical Oncology of the Zhonghan Hospital of Wuhan University had clinical COVID-19, compared to 0.37% in the general population of Wuhan in the same time period (OR 2.31, 95% CI 1.89–3.02). The authors hypothesized that this may be explained by immune suppression due to cancer treatment but in the aforementioned study only 41.7% of patients were receiving chemotherapy or radiotherapy at the time of diagnosis. He et al [28] found that case rate for COVID-19 in hospitalized subjects with hematological cancers (13/128: 10%) was similar to that in health care providers (16/226:7%). In a meta-analysis of studies incorporating ten or more patients with cancer and COVID-19, [29] the overall prevalence of cancer in patients with COVID-19 was 2.0% (95% CI 2.0–3.0%). These authors did not provide data on the prevalence of COVID-19 in the respective control populations. Data from Gustave Roussy Cancer Centre showed that 18% of the 7251 in- and outpatients, and 156/1302 (12%) of the hospitalized patients tested between 14 March and 15 April 2020 were positive for SARS-CoV-2 by real time PCR. The infection rate was 2.1% compared to 0.25% in the French population (test rate 0.71%, 25% testing positive) [30]. Our group looked for Sars-CoV-2 antibodies (LIAISON® SARS-CoV-2 S1/S2 IgG test, Diasorin) in ambulatory and hospitalized patients attending the multidisciplinary oncology unit of the Antwerp University hospital and in volunteering 80 oncology health care providers from 21 March till 15 May 2020 and found positivity in respectively 76/850 (8.5%) and 13/80 (16%). Similar testing in about the same time period in 850 health care providers in Belgian hospitals showed 8.4% had Sars-CoV-2 antibodies compared to 6.9% in the Belgian population (unpublished data). Although the above data suggest that cancer patients may have slightly higher risk of acquiring SARS-CoV-2 they are biased several confounders. Particularly differences in the definition of testing criteria, used assays and imbalances in age, gender and comorbidity between the cancer patients and the general populations are crucial factors involved. Therefor it is currently impossible to ascertain that cancer patients are more susceptible for SARS-CoV-2 infections [31].

Morbidity and mortality in cancer patients with COVID19

An important question is whether cancer patients are more likely to develop severe and/or lethal complications after being infected by the SARS-CoV-2 virus. In a small retrospective series of 28 cancer patients with COVID-19 in Wuhan, 15 patients (53.6%) had developed serious complications and 8 (28.6%) had died. Most had metastasized disease (10/28) and many of them had lung cancer (7/28). The major causes of death were adult respiratory distress syndrome (ARDS), pulmonary embolism, septic shock and acute myocardial infarction [32,33]. Liang et al [34] found that patients with cancer often had more severe morbidity (defined as the composite of admission to the intensive care unit requiring invasive ventilation or death): severe events occurred in 7 (39%) of 18 patients with cancer compared to 124 (8%) of 1,572 patients without cancer (P = .0003). Particularly patients who had undergone chemotherapy or cancer surgery in the past month were at greater risk (3 [75%] of 4 patients) versus those who had not (6 [43%] of 14 patients; odds ratio [OR] = 5.34, P = .0026 in an analysis adjusting for risk factors including age, smoking history and other comorbidities). In multivariate analysis, cancer history was also associated with the highest risk for severe events (OR = 5.399, P = .003). Similar high mortality rates were reported in small series on hematological patients in China and cancer patients in Northern Italy [28,35]. In a multicenter study including 105 patients with cancer and 536 age-matched non-cancer patients with confirmed COVID-19 it was shown that COVID-19 patients with cancer had higher likelihood in all severe outcomes (mortality OR 2.34, 95% CI 1.15–4.77). Patients with hematological cancers, lung cancer, or metastatic cancer (stage IV) had the highest frequency of major adverse events [36]. In a large Italian study looking at 9280 patients with PCR-confirmed CARS-CoV-2 infection [37] 9.5% of the men had a cancer diagnosis (prostate 28%, kidney/bladder 17%, colorectal 15%, leukemia/lymphoma 11%, lung 3%)). There were no data published for women with cancer in that study. Men with cancer were more frequently hospitalized and had a higher mortality compared to non-cancer males (respectively 67.9% vs 47% and 17.4% vs 6.9%). Strikingly, prostate cancer patients receiving androgen deprivation treatment had a significantly lower probability to develop a clinical SARS-CoV-2 infection then other cancer patients (OR: 5.17; 95% CI 2.02–13.40) which may be explained by downregulation of the TMPRSS2 expression (see below). In The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) multicenter observational registry clinical data of 200 patients with COVID19 and thoracic cancers, diagnosed between March 26 and April 2020 were included [38]. One hundred fifty two (76%) patients were hospitalized and 66 (33%) died. Strikingly only 13 (10%) of 134 patients who met criteria for intensive care unit (ICU) admission were admitted to ICU. Hampered by limited numbers, this study did not suggest that type of systemic therapy and immunotherapy affected the survival of the patients with COVID-19. The study did not capture many patients with surgery or radiotherapy. However it is striking that in times of prioritizing ICU admission many of these patients did not receive optimal ICU care and this needs further attention.

Recently a report on the outcome of a larger group of patients with cancer and COVID-19 in New York city was published [39]. In this study 334 (6%) out of 5688 patients with proven COVID-19 had a cancer diagnosis (57, 56, 23, 18 and 116 with respectively breast,

prostate, lung, urothelial and colon cancer). In the overall group there was a higher risk for intubation in the cancer population (RR: 1.89; 95% CI: 1.31–2.61) but no significant differences in mortality between the cancer and non-cancer patients (respectively 11.07% vs 9.67%). Stratifying patients by age maintained these effects for the older age groups. However, the cancer patients younger than 50 years had a significantly higher death rate (RR: 5.01; 95% CI: 1.55–16.2). A team from Gustave Roussy did not find convincing evidence that cancer patients are more aggressively affected by SARS-CoV-2. After the first case early March 2020 they reorganized cancer care, maximizing protective measures for patients and medical staff, while maintaining an optimal level of cancer care. Mortality due to COVID19 was 14.8% in the 3616 cancer patients hospitalized between 14 March and 15 April 2020, compared to 18.3% in the general French population [30]. Data from 137 patients with cancer and COVID-19 in their unit showed that an ECOG performance status greater than 1 was a predictor of clinical worsening in patients with the virus on both univariate (HR, 4.6; 95% CI, 2.2–10.0; P < .0001) and multivariate (HR, 3.9; 95% CI, 1.8–8.7; P = .008) analysis. Additionally, on univariate analysis patients with hematologic malignancies and individuals who received chemotherapy for their disease within the past 3 months also had a higher risk for a poor outcome (respectively HR, 2.7; 95% CI, 1.3–5.5; P = .008; and HR, 2.60; 95% CI, 1.32–5.13; P = .06). However, these differences were not significant in multivariance analysis. It is important to mention that chemotherapy only correlated with a greater chance of clinical deterioration in patients with active metastatic disease, and there was no observed effect related to treatment with immunotherapy or targeted agents in the past 3 months. The OpenSAFELY study, looking at factors associated with 5683 COVID-19-related hospital deaths in the linked electronic health records of 17 million adult NHS patients clearly showed that mortality was higher in cancer patients with solid tumors the first 5 years after treatment and lifelong for patients with hematological tumors (Fig. 1). An important finding of this study was that male gender (HR 1.99; 95% CI 1.80–2.10), age (with a very strong gradient), ethnicity (adjusted HR 1.71; 95% CI 1.44–2.02), uncontrolled diabetes (HR 2.26 95% CI: 2.18–2.56), obesity (with a very strong gradient) and various other medical conditions often had a higher impact on the probability to die of SARS-CoV-2 then cancer (Fig. 1) [40]. These cofactors should be taken into account in all future analysis on the mortality of SARS-Cov-2 in patients with cancer. As age is the major determinant of the outcome in COVID19, age-adjusted estimations are to be made mandatory.

Although most guidelines advice to delay cancer treatment in patients with clinical COVID-19 [41–43], it remains unclear how cancer treatment affects the natural course of a SARS-CoV-2 infection [44–48]. Evidence is emerging that surgery increases treatment related morbidity and mortality [36,49,50]. In the series of Dai et al [36] two out of 8 (25%) cancer patients having surgery within 40 days of COVID-19 died. An international cohort study at 235 hospitals in 24 countries included all patients undergoing surgery who had SARS-CoV-2 infection confirmed 7 days before or 30 days after surgery [51]: 835 (74%) patients had emergency surgery and 280 (24.8%) elective surgery. Thirty day mortality of the entire population was 24.8%, mainly secondary to pulmonary complications (occurring in 51.2% of patients). In an adjusted analysis 30 day mortality was associated with male sex (OR 1.75; 95% CI 1.28–2.4), age above 70 years (2.3; 95% CI 1.65–3.22), American Society of Anesthesiologists grades 3–5, malignant versus benign diagnosis (OR 1.55; 95%CI 1.01–2.39), emergency versus elective surgery (OR 1.67; 95% CI1.06–2.63) and major versus minor surgery (OR 1.52; 95% CI 1.01–2.31). This type of cohort analysis is certainly influenced by selection bias, but it is clear that surgery in a patients with COVID-19 is accompanied with hazards much higher than

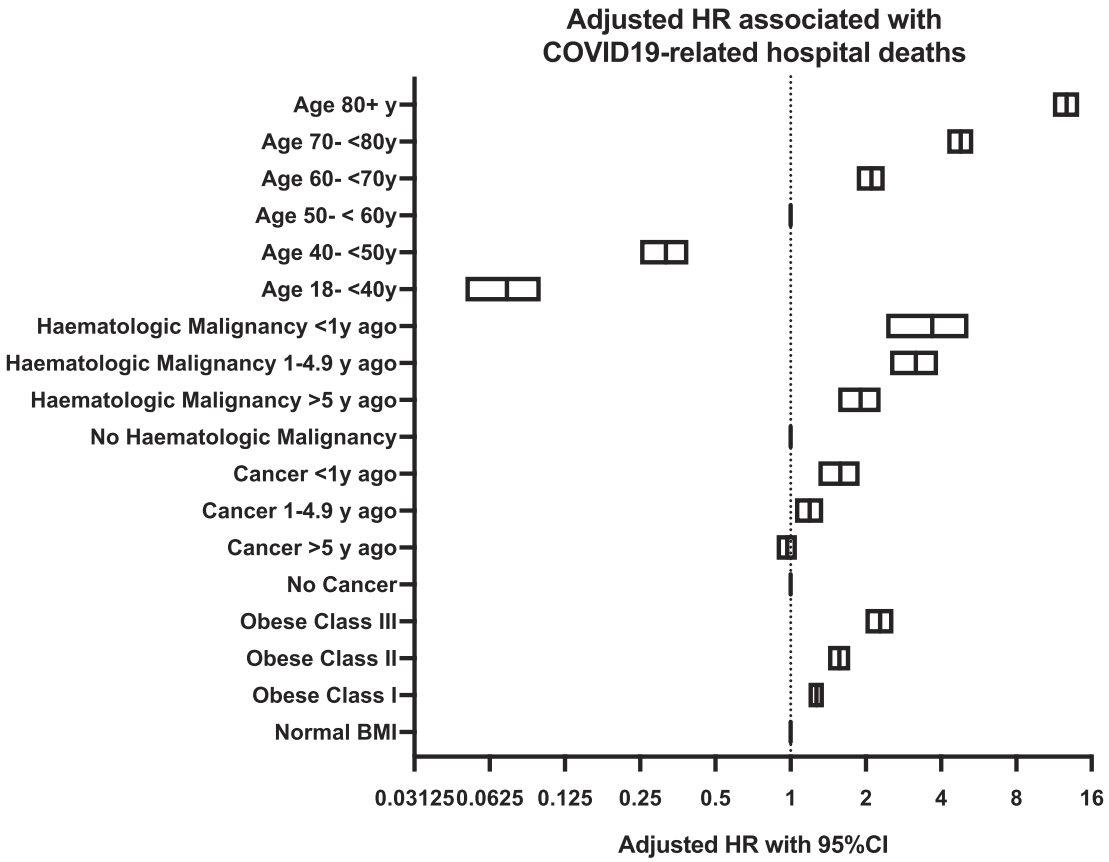

Fig. 1. Adjusted hazard ratios associated with hospital related deaths after COVID-19 according to age, body mass index (BMI) and time after diagnosis for solid and hematological cancers (based on Williamson et al, ref 40).

seen in normal circumstances. Screening for COVID-19 prior to surgery is mandatory to minimize surgical risk, but in our experience this is currently not sufficiently sensitive to completely avoid that screen negative patients develop COVID-19 a few days after surgery. However, the available tests and tests strategies evolve rapidly.

It is advised to delay systemic cancer treatment during the SARS-CoV-2 pandemic, but specific evidence on the risks of having anticancer treatment shortly after of before COVID-19 is scarce [52]. In some series but not in others, chemotherapy received in the last 14 days seems to affect the prognosis. Current data are not conclusive as they a are often biased by the populations compared: that is, in some studies the receipt of chemotherapy is in patients with advanced aggressive tumors in later lines (e.g. pancreatic cancer, small cell lung cancer) against patients not receiving chemotherapy, in others in first line with immunotherapeutic agents or tyrosine kinase inhibitors or in patients with a medical history of cancer, treated with surgery years before. In a small study of Dai et al [36] death rate was double amongst patients having chemotherapy and triple in patients treated with immunotherapy compared to non-cancer patients. In an hypothesis raising paper Solodky et al [53] showed that only 3/10 (30)% of cancer patients with PCR-confirmed Sars-CoV-2 infection had detectable antibodies against the virus 15 days after the clinical start of the infection compared to 10/14 (71%) of control patients ($p = 0.04\%$). Strikingly 6 of the 7 seronegative patients had received cytotoxic treatment or major surgery in the previous 4 weeks. Longitudinal additional data are necessary to confirm whether the immune response to SARS-CoV-2 is influenced by cancer treatment [54]. The best data on COVID19 mortality in cancer patients on chemotherapy or other anticancer treatments are provided by the prospective cohort study of Lee LY et al [55]. This observational study was initiated by the UK Coronavirus Cancer Monitoring Project (UKCCMP) and analyzed data of 800 patients with a diagnosis of cancer and symptomatic COVID19. Risk of death was significantly associated with advanced patient age (OR 9.42; 95% CI 6.56–10.02), male gender (OR 1.67; 95% CI: 1.19–2.34) and the presence of comorbidities such as hypertension (OR 1.95; 95% CI: 1.36–2.80) and cardiovascular disease (OR 2.32; 95% CI: 1.47–3.64). Mortality of the 281 patients that had received cytotoxic chemotherapy within 4 weeks before being tested positive for COVID 19 was similar compared to cancer patients who had not received recent chemotherapy (OR 1.18; 95% CI 0.81–1.72). These authors did not find a significant effect on mortality in patients on immunotherapy, hormone therapy, targeted therapy, radiotherapy us within the past 4 weeks. As total cases per treatment type remain low, further research is necessary to elucidate the impact of systemic cancer treatment on the clinical and immunological behavior of SARS-CoV-2. Although chemotherapy may be an immune suppressant for patients, especially in high doses, no really increased susceptibility to viral infections has ever been demonstrated, except for direct immunosuppressive anti-lymphocytes agents, or myeloablative regimens. In fact some antineoplastic agents have been included in clinical trials for COVID19, including actinomycin D, bevacizumab, nivolumab and proteasome inhibitors, thereby exploring in a repurpose indication their antivascular, immunomodulatory and antiviral properties (eg NCT04343144)

COVID-19 and delay of cancer care

The collateral effects on the health care system, being overwhelmed by COVID-19 [56,57], are likely to become the most dominant drivers of increased cancer mortality during and after the first wave of the pandemic [58–63]. Data from the nationwide Netherland Cancer Registry between February 24, 2020 and April 12, 2020 (during the peak of the epidemic) showed a reduction of 26% in cancer diagnosis (excluding skin cancer) and for skin cancer this was even 60% [64]. Sud et al [65] estimated that the indirect impact of the battle against COVID-19 may cost 18.000 additional lives in cancer patients in the United Kingdom next year. They found a 60% reduction in attendance for chemotherapy and an average 75% drop in cancer referrals for early diagnosis, resulting in a potential upstaging at diagnosis and a delay of surgery, radiotherapy and systemic treatment. However this estimation comes from a country were the health system was at the verge of collapsing with the outbreak of the pandemic and cannot be generalized for other countr[i]es with a lower prevalence of the disease or a better organized health care system. It is of paramount importance that during possible future outbreaks of SARS-CoV-2 cancer patients should not be stigmatized to be too vulnerable to start or continue treatments of proven value, propending for delays or no treatment at all. Adaptations of cancer care by means of protective measures, social distancing, minimizing the number of hospital attendances, aggressive testing for SARs-CoV-2 in patients and health care providers, telemonitoring, artificial intelligence and better knowledge of risk factors for severe morbidity can all be helpful to provide cancer care safely in times of COVID-19 [66]. Stepwise implementation of the above measures allowed our team of the Multidiciplinary Oncology Unit of the Antwerp University Hospital in the period of March 1st till May 31 th 2020 to deliver 2925 cycles of systemic treatment to our cancer patients, compared to 2742 in the same time period of 2019 (+7%), despite a reduction of outpatient visits (4848 in 2020 compared to 6015 in 2020: −18%) (manuscript in preparation)

Potential biomarkers to identify high risk patients and targets for treatment

The angiotensin converting enzyme receptor and TMPRSS2

The SARS-CoV-2 virus uses the angiotensin converting-enzyme related carboxypeptidase 2 (ACE-2) receptor to enter the cell. The ACE-2 receptor is widely expressed in nasopharyngeal, respiratory, gastrointestinal and cardiovascular tissues [67], but also on some hematopoietic cells such as monocytes and macrophages [8,68]. This receptor tropism is thought to determine pathogenicity and explain the symptomatology of COVID-19 [8]. Similar to SARS-CoV, SARS-COV-2 uses a highly glycosylated homotrimeric spike (S) protein for receptor binding and virus entry [69]. The S protein of SARS-CoV-2 consists of two subunits S1 and S2. Entry depends on binding of the S1 unit to the ACE-2 receptor, allowing viral attachment to the surface of the target cells [70,71]. The serine protease TMPRSS2 then primes the S protein by triggering S protein cleavage at the S1/S2 and the S2′ site [72]. This process is driven by the S2 unit undergoing dramatic conformational changes after activation to expose the receptor binding domain (RBD) [73,74]. Binding of the RBD to ACE-2 receptor leads to disconnection of the S1 from the S2 protein thereby promoting S2-mediated virus-host membrane fusion and viral entry [75]. Taking into account the crucial role of the RBD in this process it becomes an attractive target for treatment. Chen et al [69] could clone two human blocking monoclonal antibodies using SARS-CoV-2 RBD-specific memory B cells isolated from recovered COVID-19 patients which specifically block the interaction between SARS-CoV-2 RBD and the ACE-2 receptor. These antibodies hold great promise to be used as therapeutic and prophylactic agents [76].

TMPRSS2 is a member of the family of Type II Transmembrane Serine proteases (TTSPs) that are involved in multiple physiological processes particularly in host immunity. Steroid hormones may enhance TMPRSS2 expression through binding their respective nuclear receptors for responsive elements (eg GRE, ERE) thereby modulating the immune response [77,78]. Earlier studies show that androgen and androgen deprivation, respectively, increase and decrease transcription of TTPRSS2 in the lung, which may explain the increased susceptibility of men to develop severe COVID-19 [79]. The serine protease inhibitor camostat mesylate is a TMPRSS2 inhibitor that blocks SARS-CoV-2 viral entry and may be an off-label treatment option as this drug has been approved for human use in Japan [72,80,81]. According to the Human Protein Atlas high expression levels of TMPRSS2 are found in prostate

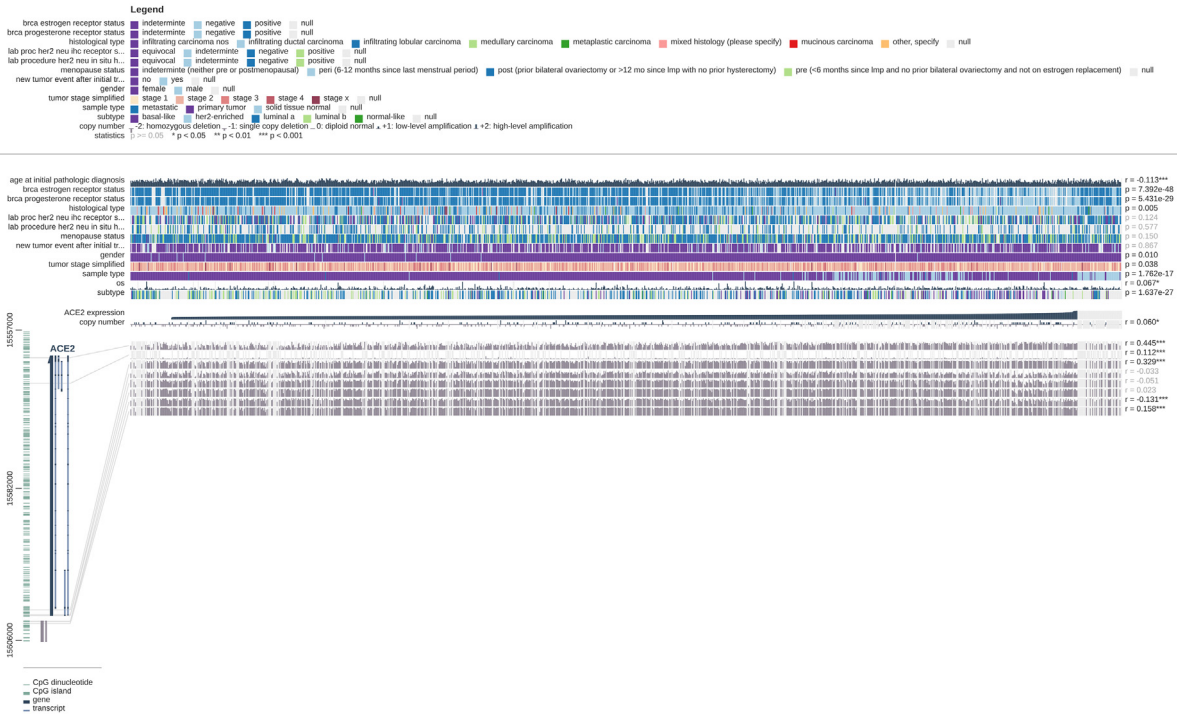

Fig. 2. ACE2 and breast cancerMEXPRESS visualization (https://mexpress.be, PMID: 31114869) of the TCGA expression/Infinium DNA methylation data for ACE2 in breast invasive carcinoma (n = 1268) (A) The default view, in which the samples are sorted by their ACE2 expression levels and the samples without expression data were removed. The figure and the statistics on the right hand side show significant cpg probe methylation correlation with gene expression (P-values) or Pearson correlations (+ or −) between ACE2 expression and gene region specific DNA methylation. (B) All breast cancer samples have been divided into two groups based on their ACE2 expression level (high/low expression). The horizontal lines at each probe location indicate the median percentage of methylation (B-value of 1 = 100% DNA methylation), whereas the vertical lines mark the range between the 25th and the 75th percentile.

cancers while a few renal, urothelial, lung, colorectal and pancreatic cancers showed weak to moderate membranous and/or granular cytoplasmic immunoreactivity and other tumor types were negative (The Human Protein Atlas). A provocative recent study by Montopoli et al [37] showed that downregulation of the expression of TMPRSS2 by androgen deprivation therapy decreased the susceptibility of prostate cancer patients to develop COVID-19, suggesting new therapeutic options. Hormonal manipulations (such as estrogens, luteinizing hormone releasing hormone agonists) could be considered as preventive measures in specific contexts. It is worth mentioning that the effect of TMPRSS2/ERG gene fusions had differing effects on radio- and chemosensitivity depending on cell line and fusion type, suggesting that binding and altered expression of this gene by a SARS-CoV-2 infection may have implications for effectivity of treatment of cancer patients [82].

ACE-2 is a membrane protein that inactivates angiotensin 2 and is endocytosed together with SARS-CoBV-2, resulting in a reduction of cellular ACE-2 and subsequent increase of serum angiotensin II [83]. Angiotensin converting enzyme (ACE) converts Angiotensin I to Angiotensin II [84]. This peptide exerts its activity mainly through the Angiotensin II Type 1 receptor (AT1R) and has several effects, such as vasoconstriction, increase of vascular endothelium permeability and pro-inflammatory signaling with a resulting cytokine profile very similar to the one seen in COVID-19 patients [85]. A SARS-Cov-2 infection can trigger increased NF-kB and STAT3 signaling, which in turn can activate the IL-6 amplifier (a mechanism for hyperactivation of NF-kB) thereby inducing various pro-inflammatory cytokines and chemokines (including IL6) [86]. By this mechanism lymphoid cells and myeloid cells (eg. activated T-cells and macrophages) are recruited in the infected lesions reinforcing the IL-6 signaling in a positive feedback loop. Hypothetically the age dependent enhancement of the IL-6 amplifier may be one of the explanations of the age-dependent increase in COVID-19 mortality [86]. Therefore the IL6 signaling loop is an important potential target for treatment.

ACE-2 expression is suppressed by the SARS-CoV-1 spike protein and the severity of lung injury caused by SARS-CoV-1 is inversely correlated to ACE-2 levels in animal models [83]. The same could very well be true for SARS-CoV-2, although to date, that remains hypothetical. If so this could provide the rationale that explains why patients with hypertension, diabetes or cancer seem to be at higher risk for developing severe disease [87]. In these patients, the Renin/Angiotensin/Aldosterone System (RAAS) system is often already out of balance, with more Angiotensin II signaling and lower ACE-2 expression levels [88]. Epigenetic mechanisms seem important to control ACE-2 gene expression, but apparently also play a crucial role in the pathophysiology and disease severity of COVID19 [89]. Oxidative stress induced by viral infections exacerbates DNA methylation defects, probably resulting in ACE-2 hypomethylation and enhanced viremia. In human lung tissues gender and biological age related differences in DNA methylation at sites in the ACE-2 gene were identified [89 90]. Demethylation of interferon regulated genes, NFkB and cytokines in certain disease (eg lupus) are likely to exacerbate the immune response to SARS-CoV-2 and increase the likelihood of cytokine storm [91]. Drugs regulating the epigenetic control of the ACE-2 gene may be used in prevention strategies and treatment of COVID-19 [91].

Preclinical studies have provided compelling evidence that the RAAS is involved in regulating almost all hallmarks of cancer [92]. Signaling in the RAAS shapes the microenvironment, can facilitate or inhibit growth and tumor dissemination and has been shown to affect cell proliferation, migration, invasion, metastasis, apoptosis, angiogenesis, cancer-associated inflammation, immunomodulation, and tumor fibrosis/desmoplasia. Angiotensin II (AngII)/AT1R-mediated effects on tumor vasculature can impair tumor perfusion and oxygenation, resulting in hypoxia and acidosis within the tumor stroma which leads to up-regulation of various cytokines, growth factors, and transcription factors [including HIF (hypoxia-inducible factor), VEGF, and

TGF-beta) [87]. The net effect of this is an immunosuppressive microenvironment. Generally, the AngII/AT1R axis is considered to favor tumor growth, whereas AngII/AT2R and Ang(1–7)/MAS signaling have opposing effects [93]. Overexpression of AT1R is associated with more aggressive tumor behavior (larger tumors, higher grade, and higher vascular density) and worse outcomes [92,94]. An analysis of TGCA data shows that ACE-2 is overexpressed in some cancers including lung, cervical, pancreatic and renal carcinomas [95–97]. By contrast the expression of ACE2 is significantly decreased in breast, prostate and liver cancer compared to normal adjacent tissue [44]. There is no correlation between ACE2 expression and prognosis for most tumor types except of lung adenocarcinoma, hepatocellular carcinoma, endometrial carcinoma and renal papillary carcinoma [98]. High ACE-2 expression is positively correlated with the level of immune infiltration of macrophages, B cells, CD4 + T cells neutrophils and dendritic cells in endometrial carcinoma [98]. The effects of high ACE-2 expression on cancer related outcome vary enormously, and are highly dependent on the underlying tumor origin and stage (Fig. 2). However, the gene expression level of ACE-2 may indicate the susceptibility to SARS-CoV-2 infection, while TMPRSS2 plays a supporting role [95]. ACE inhibitors (suppressing Angiotensin II synthesis) or Angiotensin Receptor Blockers (ARB's, blocking AT1R signaling) can have a therapeutic potential in this context [81]. Basic and meta-analytic studies have shown that these drugs reduce the metastatic features of tumors [99]. Further studies are needed to assess the role of ACE-2 inhibitors in the prevention and treatment of SARS-CoV-2 infections. The current available data can be used for biocomputional drug repurposing studies [100]. The important role of the renin-angiotensin system may also explain the mode of activity of chloroquine by modifying ACE-2 affinity to the viral spike protein due to altered glycosylation [101] although its role in the treatment of SARS-CoV-2 remains controversial.

Cytokine signaling

Cytokines are molecular messengers of the innate and adaptive immunity that enable cells of the immune system to communicate over short distances in a paracrine and autocrine manner. According to their biological properties they can be classified into three groups: T-helper (Th) 1, Th 2 and Th17 respectively regulating cellular immune response, humoral immune response and inflammatory response. Proinflammatory cytokines (such as IL-1, IL6, IL8, IL 12, IL 18, IL 33, GM-CSF, TGF-beta TNF-alpha) stimulate inflammatory reaction and are involved in chemoattraction of inflammatory cells. On the other hand anti-inflammatory cytokines (IL-1 receptor antagonist, IL-4, IL-10, IL-11, IL-13) control proinflammatory cytokine activity in a fine tuned system. Some cytokines, such as interferon alpha, IL-6, and TGF-beta, can be anti- or proinflammatory dependent on a specific context [102,103]. As explained above a SARS-CoV-2 infection triggers cytokine release, which is playing an important role in the immune response of the host [104]. In the asymptomatic and early phase of the disease the majority of patients is able to clear the virus through cytokine mediated mechanisms [105]. Cytokine levels are elevated in a gradual way in most patients with COVID19 [84,105,106]. Accumulating evidence shows that a subgroup of patients with COVID-19 develops a cytokine storm syndrome which resembles the cytokine profile seen in patients with secondary hemophagocytic lymphohistiocytosis (sHLH) [10]. This is an under-recognized, hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia with multiorgan failure, often triggered by viral infections [107]. It should be mentioned that cytokine storm and HLH are superimposable but not identical entities across a spectrum of pathologies [108]. The cytokine storm is thought to elicit cardinal features of HLH [109]. Confirmatory laboratory findings including dropping cell counts, low erythrocyte sedimentation rate, increased ferritin, natural killer cell dysfunction, and hemophagocytosis that were considered to be unique to hemophagocytic disorders, are increasingly recognized in several infectious or even allergic mediated cytokine storm syndromes [110]. Additionally hemophagocytosis is not typically found in pathology reports from COVID-19 patients. Only one case report from Japan, describes hemophagocytosis in the lungs, spleen, and lymph nodes [111]. Common findings in COVID-19 patients are features of both exudative and organizing diffuse alveolar damage, desquamation, squamous metaplasia of the epithelial cells, organizing hyaline membranes, inflammatory cell infiltration with prominent plasma cells in the alveolar septa and also intra-alveolar hemorrhage, vascular congestion, hyperplasia of type 2 pneumocytes and multinucleated syncytial cells [112]. On the other hand in cancer patients with malignancy related HLH, hemophagocytosis was seen in up to 70% with findings including sinusoidal infiltration of bland histiocytes containing erythrocytes, admixed with occasionally lymphocytes and neutrophils, together with highly activated macrophages including phagocytes in the red pulps [113]. These discrepancies indicate the need for additional research to understand the real reciprocal implications within the current clinical landscape.

Inflammatory mediators play a key role in the pathogenesis of ARDS, a primary cause of death in patients infected with SARS-CoV or MERS-CoV [114]. Cytokine surges can trigger uncontrolled epithelial cell proliferation and impaired tissue remodeling during later stages of the disease, inducing lung dysfunction, pulmonary fibrosis and death. In the study of Huang et al [7] on the clinical presentation of COVID-19 in Wuhan initial plasma concentrations of IL-1beta, IL1RA, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNgamma, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFalpha, and VEGF concentrations were higher in ICU patients and non-ICU patients compared to healthy adults. Plasma levels of IL5, IL12p70, IL15, Eotaxin, and RANTES were similar between healthy adults and patients with COVID-19. Further comparison between ICU and non-ICU patients showed that plasma concentrations of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFalpha were higher in ICU patients than non-ICU patients. In a meta-analysis on more the 1302 patients with COVID-19 IL-6 levels were consistently elevated in most patients at hospitalization, and in patients requiring ICU admission levels were even 3 times higher [115].

It is well known that inflammatory cytokines have a key role in the initiation, progression and metastasis of cancer [116–120]. The combined action of cytokines (particularly IL-1 beta, IL-6, TNF, IL-8, IL-17), produced by the neoplastic cells via multiple mechanisms, modulates cell response of the host immune system. High cytokine levels have been correlated to advanced stage and poor prognosis for many cancer types such as breast, prostate and colon cancer [121]. Our group could show that patients with metastatic breast cancer had IL-6 and IL-8 serum levels which were 5–10 times higher than in patients with early stage breast cancer [121,122]. Interestingly also patients with early stage breast cancer with microscopic bone marrow involvement had increased serum IL-8 levels compared with those without bone marrow involvement ($P = 0.0334$), and a poorer prognosis. These findings confirmed the observations of others that high cytokine levels are stage dependent, but can be present in patients with occult disease and play a role in tumor dormancy. High cytokine levels can also be induced by chemo- and radiotherapy [123]. In a recent study it was shown that hospitalized non-COVID-19 cancer patients with a rash secondary to cytostatic or targeted treatment and elevated IL-6 and TNF-α were nearly 6 times more likely to die over the course of follow-up [124]. Upregulation of inflammatory cytokines is not unique for cancer patients and is also seen in patients with diabetes, cardiovascular disease, autoimmune disorders, obesity and other diseases [125,126]. It is tempting to hypothesize that particularly patients with comorbidity, metastatic solid cancer and hematological tumors can have elevated cytokine levels, implicating that an additional SARS-CoV-2 infection makes them more prone to develop an uncontrolled "cytokine storm". Profiling of cytokines, particularly IL6 and IL10, may be used in the clinic to identify (cancer) patients at high risk to develop severe COVID19 [127]. This has important therapeutic implications as inhibitors of cytokines recently also came available to block a potentially

fatal cytokine surge [128–131]. The use of JAK1- and JAK2 inhibitors, such as Baricitinib, in patients with severe COVID-19 has been proposed as antiviral effects of interferons are mediated by JAK-STAT signaling [132]. Myo-inositol, a polyol already in use for treating respiratory distress syndrome in newborns may also be beneficial to manage severe SARS-CoV-2. It reduces IL-6 levels and blocks the inflammatory cascade [133]. A case report suggested that Tocilizumab, an anti-IL6 receptor antibody, can be successfully used to treat COVOD-19 related respiratory failure [134]. A recent randomized study showed that an early short course of methylprednisolone in patients with moderate to severe COVID-19 significantly reduced escalation of care from ward to ICU, new requirement of mechanical ventilation, length of hospital stay and mortality, probably by minimizing the excessive immune response and cytokine surge [135].

In an earlier study IL-6 injection into animal models significantly increased neutrophil counts in the blood [136]. In patients with COVID-19, neutrophilia is a source of excess neutrophil extracellular traps (NETs). Excess NET formation induces mucus accumulation in the lungs and potentially drives several severe respiratory pathologies including ARDS [137]. Indeed, neutrophilia was a predictor of poor outcome for patients with COVID-19, while the neutrophil-to-lymphocyte ratio was an independent severity factor in another report [138–140]. In the study of Zhang et al high levels of IL-6 and IL-8 during treatment were observed in patients with severe or critical disease and correlated with decreased lymphocyte count [95]. These authors concluded that COVID-19 severity seemed to be related mostly to host factors such as age, lymphocytopenia, and is associated cytokine storm, whereas viral genetic variation did not significantly affect the outcomes. NETs also induce arterial and venous thrombosis, a feature commonly reported in patients with severe COVID-19 infection [141]. When we consider the neutrophil variations typically induced during cancer treatment, cytokine signaling through these mechanisms provides an additional potential link of COVID-19 severity with cancer.

Coagulopathy

A hallmark of severe COVID-19 is coagulopathy which is mainly prothrombotic with high levels of D-Dimers and fibrinogen and a low anti-thrombin III [18,142]. Coagulation factors and platelets are directly implicated in the immune response triggered by cytokine signaling induced by the SARS-CoV-2 sepsis [143,144]. In addition the immobilization of the severely ill patients, comorbidity and the presence of a cancer are well known thrombogenic risk factors with mutually reinforcing clotting hazard [145]. This results in venous thromboembolism, pulmonary congestion, and arterial occlusive events. The microvascular thrombosis in the lungs is an important factor causally related to ARDS [142,146]. An autopsy study in 12 consecutive COVID-19 positive patients revealed deep venous thrombosis in 7 patients (58%) in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients. In all patients, SARS-CoV-2 RNA was detected in the lung at high concentrations; viremia in 6 of 10 and 5 of 12 patients demonstrated high viral RNA titers in the liver, kidney, or heart [147]. About 71.4% of patients dying of COVID-19 met the criteria of disseminated intravascular coagulation compared to 0.6% in the surviving patients [138]. There is evidence that the use of tissue plasminogen activator (tPA) in this setting may be of therapeutic value [148,149]. Recent data also show prophylactic doses of low molecular weight heparin (LMWH) or unfractionated heparin reduces the mortality in severely ill COVID-19 patients with coagulopathy [150]. The use of therapeutic doses is not supported by evidence but seems reasonable taking into account the sometimes occult occlusive events in the autopsy findings [151,152].

Several malignancies and also some of anticancer treatments are related to higher risk to develop thrombotic events which can be venous or arterial but can also be related to thrombotic microangiopathy or disseminated intravascular coagulation [145]. Mechanisms for cancer-associated thrombosis were recently reviewed in detail by Razak et al [145]. Tumor cells and cells in the tumor microenvironment can produce proteins creating procoagulant status such as tissue factor (TF), podoplanin, plasminogen activator inhibitor (PAI-1), cytokines (eg TNF-alpha, IL-1beta, VEGF, G-CSF), neutrophil extracellular traps, mucins, and others. Site of the cancer (eg pelvic tumor), stage of disease, histology and time after diagnosis are strongly related to thrombotic risk. Particularly in patients with regional and distant disease the risk to have a venous thrombotic event is significantly higher compared with patients with local disease, and this is correlated with a worse clinical outcome [153,154]. Neither all malignancies nor treatments are thrombogenic. The highest incidence of thrombotic events is reported in mucin-producing adenocarcinomas, pancreas and gastrointestinal tract malignancies, lung cancer, and ovarian cancer while this is less frequent in breast and renal cell carcinoma and rarely in patients with prostate cancer, melanoma, and cancer of unknown primary origin [155]. Some types of chemotherapy and targeted drugs result in a 2–7 fold increase of thrombosis (eg bevacizumab), but others do not [145] Similarly some endocrine treatments, such as tamoxifen, are thrombogenic while aromatase inhibitors and luteinizing hormone-releasing hormone (LHRH) agonists are not [156]. Thus, assuming that all cancer patients are at increased risk of thrombosis than the average population is rather an over-simplification and a case by case evaluation should be more appropriate. Preexisting comorbidity but also severity of SARS-CoV-2 infection, immobilization, surgery, venous access ports, type and stage of the disease and current treatment should be taken into account on an individual basis to estimate the thrombotic risk. Predictive risk models are now available to identify patients most benefitting from thromboprophylaxis, and are likely to improve prognosis [153]. COVID-19 can, as with other forms of sepsis, further disturb the normal clotting homeostasis less or more in specific clinical settings, and this should be included in risk assessments. Elevated D-Dimers, degradation products of cross-linked fibrin, can be used to identify patients at high risk for thrombotic events [157]. An extremely elevated D-dimer has been found to be uniquely associated with serious illness, mainly including venous thromboembolism, sepsis and/or cancer [157].

Conclusion

While a world-wide huge effort to collect data on COVID19 and cancer has been performed over the last months, the available results should be interpreted with care as methodological flaws and poor statistics dilute their impact. Current evidence does not prove convincingly that cancer patients are at a clearly increased risk to develop clinical COVID-19 and are more prone to hospitalization, and intensive care management. Many accumulating and maybe more important entangled cofactors are involved such as older age, comorbidity and obesity, which are often correlated to cancer risk. The present data suggest that particularly patients with ongoing treatment for active locally advanced and metastatic solid tumors and hematologic cancers have a poorer outcome and higher mortality after SARS-CoV-2 infection, but this seems not the case for other cancer settings [56]. Mechanistically this association seems logic as the interaction between the host immune environment and cancer or SARS-CoV-2 infections uses similar pathways in advanced disease settings. Alterations in ACE-II and TMPRSSII expression, cytokine signaling, hypercoagulability, immune response can fuel and reinforce each other, bringing the human body in severe disequilibrium. They can be used as biomarkers to identify patients at high risk for serious complications and mortality. Delay and lack of optimal cancer treatment during the COVID-19 pandemic will be an important cause of additional cancer mortality. Therefore it is of paramount importance to continue treatment of cancer patients as much as possible in times of SARS-Cov-2, introducing protective measures for patients and medical staff, assessing clinical benefit and risks on an individual basis and if necessary adapting treatment modalities. Prevention of thrombotic events, and early detection as well as

treatment of a cytokine storm may be valuable options to improve the prognosis of cancer patients. Selection of cancer patients on an individual basis and timing for (adapted) treatment after a COVID-19 episode [158] is the only way to obtain an optimal balance to maximize SARS-CoV-2 and cancer cure, awaiting an effective preventive vaccine.

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