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Coronavirus infection and immune system: An insight of COVID-19 in cancer patients

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ABSTRACT

The novel coronavirus respiratory illness (COVID-19) is a public health emergency of global concern. Patients with cancer are at high risk of infections, due to an overall immunocompromised status. However, this connection is not straightforward for coronavirus (CoV) infection, in which the host immune response is the main driver of tissue damage. We performed a thorough review of data on CoV pathogenesis and morbidity rate in cancer patients, through the analysis of the previous CoV pandemics. Considering the interaction between CoV and the host immune system, cancer patients receiving immunotherapy might be more at risk for an aberrant immune response in case of infection, and might therefore deserve additional precautions. The limited available data do not allow us to provide practical indications for the management of cancer patients in this critical situation. Efforts should be made to prospectively collect data, to identify effective interventions to guide treatment decision.

1. Introduction

On December 31st 2019 a cluster of pneumonia of unknown cause was first detected in Wuhan, the capital of Hubei Chinese province, and reported to the World Health Organization (WHO) Country Office in China (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). The causal agent of this respiratory syndrome was identified as a novel Coronavirus (CoV) of zoonotic origin, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus started to spread rapidly on Chinese territory and beyond, and on January 30th the WHO declared its outbreak a public health emergency of international concern. The most common clinical manifestations of SARS-CoV-2 infection are fever, cough, and dyspnea, however also muscle pain, diarrhea, headache, sore throat, ageusia and anosmia have been frequently described. While the majority of people show only mild symptoms, a subset of infected subjects worsens to pneumonia, multi-organ failure, and eventually death. On February 11th 2020, the WHO named this novel viral respiratory illness Coronavirus Disease 19 (COVID-19). As of June 2020, SARS-CoV-2 has spread over 200 countries worldwide, with more than 10 million affected subjects, and number of confirmed deaths exceeding 500.000 (Source, 2020a).

From the beginning of the 21st century, novel CoV have periodically emerged in different areas of the world. In 2002, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) reportedly infected near 10.000 people, with 916 deaths worldwide during the epidemic. In 2012, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first identified, and is still ongoing in 27 countries worldwide, with nearly 2.500 infected subjects and 850 deaths (World Health Organization, 2020a, b; Koh and Sng, 2010).

Worldwide health services are presently facing the challenge of COVID-19 pandemic, which is wide spreading rapidly and severely. Health care providers are changing their daily clinical practice in view of the current emergency, and some categories of patients are considered more at risk than others. Patients with cancer have historically been judged at high risk of infections, due to an overall immunocompromised status. However, this connection is not straightforward for CoV infection, both due to the peculiar pathogenesis of CoV in humans and to different mechanisms of action of novel oncologic treatments.

In this article we provide an overview of the complex interaction between CoV and the immune system, and analyze similarities and differences among the three CoV (SARS-CoV, MERS-CoV, and SARS-CoV-2). We also suggest practical indications to guide decision-making,

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in view of the available data on COVID-19 diffusion risk in the oncologic population, with specific considerations for patients receiving immunotherapy.

2. Immune system and cancer

The immune system has a fundamental role in cancer pathogenesis (Oberg et al., 2019; Guo and Cui, 2019). The paradigm of tumor cell proliferation and spreading has changed after the inclusion of immune system evasion among the hallmarks of cancer (Hanahan and Weinberg, 2011). According to the theory of immune-surveillance, the immune system exerts a continuous monitoring, able to recognize and eliminate potential tumorigenic cells. As so, cancer cells must develop the ability to bypass the immune system control, thereby evading eradication. Tumor-associated inflammation further contributes to tumorigenesis, by supplying tumor cells with growth factors, pro-angiogenic factors, and extracellular matrix-modifying proteins, which eventually favor tumor cells proliferation and metastases (Grivennikov et al., 2010).

Thus, cancer itself seems to develop in an immunocompromised field, supporting the concept that oncologic patients are more at risk of infections. This risk is further increased by certain oncologic treatments: cytotoxic chemotherapy negatively impacts on bone marrow production, with decrease in white cell count; bone directed radiotherapy may similarly affect white cell production, while skin and mucosal radiation cause irritation, epithelial lesions and subsequent infections. Major surgery in cancer patients is associated with the activation of pro-inflammatory processes, followed by post-operative immunosuppression (Menges et al., 2012). Long-lasting treatment with high-dose corticosteroids, commonly used as supportive therapy for patients with cancer, have detrimental effects on neutrophil function, humoral and cell-mediated immunity, increasing the overall infective risk (Kaltsas and Sepkovitz, 2012). In clinical practice, preventive measures for subjects undergoing systemic anti-cancer treatment are commonly implemented, as serologic screening for certain chronic infections (e.g. hepatitis B [HBV] and C virus [HCV]), and pneumococcal and/or seasonal flu vaccinations (Ariza-Heredia and Chemaly, 2015) Other measures commonly adopted consist in the use of granulocyte colony stimulating factors (G-CSF) and antibiotics for chemotherapy induced neutropenia, either in the prophylactic or therapeutic setting (Becker et al., 2020).

In the last few years, oncologic treatments have significantly changed with the advent of immunotherapy agents targeting the immune-checkpoint inhibitors (ICIs) (Robert et al., 2015; Reck et al., 2016; Motzer et al., 2015; Migden et al., 2018; Ferris et al., 2016). These include monoclonal antibodies against the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), the anti-programmed cell death 1 (PD-1) and its ligands (PD-L1 and PD-L2). The natural function of checkpoint inhibitors is to halt the immune response. Blocking these molecules release the brakes of the immune system, which is reinforced to fight against tumor cells. ICIs have become part of standard treatment for several solid tumors, as melanoma, non-small cell lung cancer (NSCLC), renal cell and urothelial carcinoma, cutaneous squamous cell carcinoma, and head and neck squamous cell carcinoma (Robert et al., 2015; Reck et al., 2016; Motzer et al., 2015; Migden et al., 2018; Ferris et al., 2016). Thus, most oncologic patients have changed their features of immunocompromised subjects, rather their immune system is reinforced by the oncologic treatment they receive. This might translate into a distinct susceptibility of oncologic patients towards CoV infections, as explained in the further section.

3. Coronaviruses and cancer

SARS-CoV, MERS-CoV and SARS-CoV-2 all belong to the subfamily Coronavirinae, in the family Coronaviridae. Table 1 shows the main characteristics of the three CoV. Periodically, CoV outbreaks unpredictably occur and have rapid diffusion, possibly inducing fatal infections and representing a serious threat to human health. The absence of approved vaccines or drugs for the treatment of infections, together with the wide range of animal reservoirs for new CoV occurrence, make this infective danger even more harmful. Fatality rate ranges from 9.14 % for SARS-CoV (Source, 2020a), to 34.4 % for MERS (World Health Organization, 2020a), to around 5% for SARS-CoV-2 (with 506.041 deaths out of 10.268.839 confirmed cases as of June 30th 2020) (Source, 2020a). Epidemiologic studies confirm a higher fatality rate of all three CoV infections in subjects with comorbidities (cardiovascular disease, obesity, diabetes, and chronic kidney disease). Advanced age and male sex both represent additional recognized risk factors for poor outcomes (Hui et al., 2018; Extance, 2020). Tobacco smoke has been recognized as a risk factor for MERS-CoV infection, but not confirmed in SARS-CoV and SARS-CoV-2. Interestingly, review of mortality and morbidity reports of previous CoV pandemics do not show an increased fatality rate in patients undergoing chemotherapy, solid organ transplantation or other immunosuppressive therapy. There is only one report on the features of MERS-CoV infection among patients with cancer during the outbreak in 2015. In this small population of oncologic patients (n = 19), only 15.8 % of them survived the infection, with a case fatality rate (CFR) more than doubled compared with the CFR of non-oncologic patients (Jazieh et al., 2020). Accumulating data on COVID-19 reveal that, as for other CoV pandemics, patients with cancer did not seem to be more prone to develop infection. Of course, a possible confounding factor might be a higher rate of protective measures adopted by this high-risk population of subjects in view of a pandemic. The widest report on COVID-19 diffusion in China revealed a 0.9 % incidence of cancer among 1099 infected patients (Guan et al., 2020). A recent report from the National Health Commission of the People's Republic of China, which collected 1590 cases of laboratory-confirmed COVID-19 admitted to 575 hospitals, found that 1 % of subjects had a history of cancer (Liang et al., 2020). Authors comment this prevalence is higher than that observed in the overall Chinese population according to 2015 epidemiology statistics (0.29 %) (Zheng et al., 2019). However, as assessed by Xia et al. (2020) the small sample size and heterogeneity of data of this population of patients, make the correlation between COVID-19 and cancer not clear. Moreover, the vague definition of cancer history does not distinguish long-term survivors with diagnosis of previous cancer, from patients receiving active systemic treatment. As assessed by Wang et al. (Wang and Zhang, 2020), 12 out of 16 patients included in the report by Liang et al. (2020) had no clear immunocompromised condition (i.e. only 4 patients had undergone surgery or chemotherapy within the previous month). Two more Chinese reports on COVID-19 positive patients highlight a higher incidence rate for subjects with cancer with the epicenter of the epidemics, with lung cancer being fairly the most common diagnosis (Zhang et al., 2020; Yu et al., 2020). However, data suggest that advanced age, hospital admission and recurrent hospital visits might be critical risk factors, outweighing cancer diagnosis. Overall, these evidences suggest that COVID-19 diffusion in cancer patients is not prominent as expected for other viral infections, rather is as contagious as for the general population.

4. Immune system and coronaviruses

Unlike other common viral agents (e.g. Adenovirus, Rhinovirus, Norovirus, Influenza, Respiratory Syncytial Virus), CoV have not shown to cause a more severe disease in immunocompromised subjects. For this family of viruses, the host innate immune response appears the main driver of tissue damage during infection. There are many similarities between the pathogenesis of different CoV, mainly due to the high genomic similarity among these viruses, as well as significant differences (Gralinski and Baric, 2015). Along with direct viral pathogenicity, the host inflammatory response plays a crucial role in CoV induced lung injury. In some individuals, the trigger of an exaggerate immune response through the production of chemotactic factors lead to

Table 1
Characteristics of the three Coronaviruses.

	SARS-CoV	MERS-CoV	SARS-CoV-2
Date of onset, place	November 2002, Guandong (China)	June 2012, Jeddah (Saudi Arabia)	December 2019, Wuhan (China)
Number of affected countries	29	27	213*
Confirmed cases	8.096	2.494	10 185 374*
Case fatality rate	9.3 %	34.4 %	5.3 %*
Age, years (range)	39.9 (1 – 91)	56 (14 – 94)	< 1– > 80
Reproductive number, R_0	1.4–5.5	< 1	2.2–2.6
Epidemic doubling time (days)	4.6 – 14.2	90	6.4
Incubation time (days)	2–7	6	4–14
Hospitalization rate	Most cases	Most cases	98.4 per 100.000*
Community attack rate	10 – 60 %	4 – 13 %	30 – 40 %

Abbreviations: CoV, coronavirus; MERS, Middle-East Respiratory Syndrome; SARS, severe acute respiratory syndrome.
* Updated June 30th 2020, 1.00 pm (sources: https://www.cdc.gov/coronavirus/2019-ncov/coviddata/covidview/index.html; https://www.who.int/emergencies/diseases/novel-coronavirus-2019).

uncontrolled inflammation and tissue damage (Prompetchara et al., 2020). CoV act on both innate and adaptive immune response mechanisms. The host innate immune system recognizes viral Pathogen-Associated Molecular Patterns (PAMPs) through Toll-like receptors (TLRs). This interaction activates the Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NFkB) transcription factor and Mitogen-Activated Protein Kinases (MAPK), leading to the expression of pro-inflammatory factors (Kawai and Akira, 2010). CoV infection promotes interferon (IFN) I synthesis and stimulation of signaling pathways (as NFkB, MAPKs, and JAK-STAT), triggering cell phagocytosis, dendritic cells (DCs) maturation, and immune cells chemotaxis. Studies on MERS-CoV show that the virus can directly infect macrophages and DCs, resulting in dysregulation in antigen presentation and cytokine production (Ying et al., 2016). This results in the activation of the inflammatory cascades contributing to both viral control and tissue damage (Vardhana and Wolchok, 2020).

Type I and III IFN represent the major antiviral molecules to limit initial CoV spread, through the promotion of intracellular antiviral defenses in epithelial cells and the recruitment of immune cells (Vardhana and Wolchok, 2020; Nelemans and Kikkert, 2019). Also T cells, both CD4+ and CD8 + T cells, play a significant antiviral activity. CD8 + T cells account for the majority of inflammatory infiltrate in the pulmonary interstitium of patients with COVID-19, playing both an antiviral cytotoxic effect as well as self-induced tissue injury (Li et al., 2020). Histopathological findings of patients with SARS-CoV pneumonia show signs of non-specific inflammatory response (e.g. edema, immune cells infiltration), but also severe degeneration and damage of alveolar epithelial cells (Zhang et al., 2020). A study of hospitalized patients with severe COVID-19 revealed high levels of circulating pro-inflammatory cytokines (as IL-1, IL-2, IL-6, IL-7, IL-8, IL-10, IL-21, G-CSF, IP-10, MCP-1, MIP-1A, and TNF) (Huang et al., 2020). This so-called “cytokine storm”, in line with SARS-CoV and MERS-CoV infections, leads to the accumulation of cells and fluid within lung tissue, with diffuse alveolar damage resulting in respiratory failure (Mahallawi et al., 2018; Wong et al., 2004). There is evidence that dysregulation in the innate immune response contributes to the clinical presentation of patients with severe COVID-19. High IL-6 levels have been shown to correlate with the need for mechanical ventilation and mortality in Chinese hospitalized patients (Chen et al., 2020). Indeed, the therapeutic weapon to counter-attack the cytokine storm-related tissue damage consists in the use of antibodies targeting IL-6 (tocilizumab), and IL-1 (canakinumab, anakinra). SARS-CoV-2 also acts on lymphocytes, especially T lymphocytes, dysregulating immune response through the hyper-production of pro-inflammatory cytokines (Newton et al., 2016). Indeed, lymphopenia is one of the most common features of patients with COVID-19. A retrospective report from a Chinese hospital on 452 patients with confirmed COVID-19 compared difference in the expression of infection related biomarkers between severe and non-severe cases (Qin et al., 2020). Most patients had lymphopenia, high levels of inflammation biomarkers (e.g. C-reactive protein [CRP], procalcitonin, erythrocyte sedimentation rate, serum ferritin) and circulating cytokines (TNF-α, IL-1 and IL-6) and chemokines (IL-8). Severe cases had higher leukocyte and neutrophil counts, with lower lymphocyte count and subsequent higher NLR. Based on these data, authors suggest that hyper-inflammatory response together with T-cells’ consumption, play a major role in SARS-CoV-2 pathogenesis, as observed in SARS-CoV and MERS-CoV infections (Mahallawi et al., 2018). Specifically, SARS-CoV-2 infection is characterized by persistent antigenic T cells’ activation leading to an exhaustive status, rather than a failure to activate T cells’ responses (Vardhana and Wolchok, 2020).

5. Coronaviruses, immune system and cancer: the showdown

In light of this evidence, people with cancer may paradoxically be protected from excessive immune system stimulation of CoV infections. Table 2 outlines the characteristics of immune mechanisms involved in the following conditions: CoV infection, cancer, chemotherapy and immunotherapy. Cancer itself determines an immunocompromised status in the host, which is modulated by immunosuppressive treatments, as cytotoxic chemotherapy (Emens and Middleton, 2015). This might partially explain why cancer did not seem to represent a significant risk factor during the two last SARS-CoV and MERS-CoV epidemics. Limited data on COVID-19 case series are available to date, suggesting that cancer diagnosis is under-represented in patients with COVID-19, compared with other comorbidities (e.g. cardiovascular disease, diabetes, obesity).

However, cancer treatment has substantially changed over the last years, with less patients receiving chemotherapy and a growing proportion of patients treated with immunotherapy and targeted therapy (e.g. tyrosine kinase inhibitors [TKIs]). This means that, within the subpopulation of cancer patients, at least three categories can be distinguished on the basis of the oncologic treatment they receive and subsequent immune status impairment. The first group includes patients treated with cytotoxic chemotherapy, and therefore severely immunocompromised. The second includes patients receiving oral anticancer agents (e.g. TKIs, targeted therapy, hormonal treatment) and monoclonal antibodies (e.g. drugs targeting the epidermal growth factor receptor [EGFR], and anti-angiogenic drugs), with an overall less impact on the immune system. The last includes patients treated with immunotherapy. For this latter group of patients, SARS-CoV-2 infection may represent a serious threat. In fact, the immune system of patients receiving immunotherapy is reinforced by the treatment itself and might show aberrant responses to external factors. PD-L1 blockade could theoretically increase the immune system hyperactivation during COVID-19 (i.e. the cytokine storm), possibly worsening the outcomes of the infection (Moore and June, 2020).

In patients responding to treatment (accounting for 20–40 % of

Table 2
Immune mechanisms involved in CoV infection, cancer, chemotherapy and immunotherapy (responsive and resistant immune system).

Host condition	Neutrophils, monocytes	T cells	B cells	Dendritic cells	Other cell populations, soluble mediators
CoV infection	↑ cytokine production	↑ activation ↑ Th17 polarization ↑ CD4+ apoptosis ↓ CD4+ recruitment in lung tissue	↑ complement protein production (C3a, C5a)		↑ IL-1, IL-6, IL-8, IL-10, IL-21
		↑ CD8+ infiltration in lung tissue ↑ viral clearance and immune injury ↓ T reg ↑ cytokine production ↑ neutrophils and monocytes recruitment		↓ maturation process ↓ MHC class I expression ↓ viral Ag presentation	↑ MIF, MCP-1 ↑ TNF α/β ↑ type I IFN ↑ VEGF
Cancer	↑ polarization of N2 immunosuppressive neutrophils	↑ T reg ↑ Th 17	↑ B reg	↓ tumor Ag expression	↑ TNF α
	↑ anti-inflammatory M2 macrophages	↑ expression of immune checkpoint ligands ↑ exhaustion		↓ MHC class I and II expression	↑ TGF β ↑ IL-10
	↑ MDSC	↓ proliferation and activation			↑ IFN-γ production
Cytotoxic chemotherapy	↓ MDSC activity (gemcitabine, 5FU, CDDP, doxorubicin)	↑ CD8+ cross priming (gemcitabine, anthracyclines) ↑ CD4+ phenotype expression (cyclophosphamide, paclitaxel) ↓ T reg activity (cyclophosphamide, 5FU, paclitaxel, CDDP)		↑ activation (anthracyclines, taxanes, cyclophosphamide, vinca alkaloids, methotrexate)	↑ IFN-γ production ↑ CXCL10 ↑ IL-1 β ↑ tumor cell recognition and lysis (cyclophosphamide, 5FU, paclitaxel, CDDP, doxorubicin)
Immunotherapy (responsive immune system)		↑ tumor Ag-specific T cell response ↑ T cell migration and activation ↑ CD8+ tumor infiltrating lymphocytes			↑ IFN-γ production ↑ co-stimulatory molecules expression (CD80, CD86, OX40, GITR, CD40)
Immunotherapy (resistant immune system)	↑ MDSC	↑ T reg ↑ Th 2 ↓ priming ↓ T cell function		↓ migration and maturation	↓ chemokines expression (epigenetic silencing) ↑ PD-L1, endothelin B receptor
		↓ T CD8+ tumor cell recognition ↑ expression of immune checkpoint molecules (TIM-3, LAG-3, VISTA, BTLA) ↑ exhaustion		↓ tumor Ag expression ↓ MHC class I and II expression	↑ CD73-adenosine ↑ IFN-γ pathway ↑ VEGF ↑ IL-8

Abbreviations: Ag, antigen; BTLA, B- and T-lymphocyte attenuator; CD, cluster of differentiation; CDDP, cisplatin; CXCL10, C-X-C motif chemokine 10; GITR, glucocorticoid-induced TNFR-related protein; IFN, interferon; IL, interleukin; LAG-3, lymphocyte activation gene 3; MCP-1, monocyte chemoattractant protein 1; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MIF, macrophage migration inhibitory factor; PD-L1, programmed-death ligand 1; TGF, transforming growth factor; Th, T helper cell; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TNF, tumor necrosis factor; T reg, T regulatory cell; VEGF, vascular endothelial growth factor; VISTA, V-domain Ig suppressor of T cell activation; 5FU, 5-fluorouracil.

patients across different studies), their lively immune response often correlates with immune-related adverse events (irAEs) onset. Interestingly, immunosuppressive drugs for the treatment of severe COVID-19 cases have become part of the therapeutic arsenal of oncologists for the treatment of steroid-refractory severe irAEs (e.g. tocilizumab) (Kim et al., 2017). There is plenty of evidence that irAEs correlate with a higher efficacy of immunotherapy, suggesting that mounting an adequate immune response harms both the tumor and the host (Indini et al., 2019). However, there are significant differences in the kinetics of irAEs onset during immunotherapy, suggesting that the immune system activation promoted by immune-checkpoint inhibitors varies over time, and might therefore have a different role also in the susceptibility, development, and complication of infections (Martins et al., 2019).

PD-L1 inhibitors could improve control of chronic viral infections, through the depletion and exhaustion of T cells. Blocking the PD-1/PD-L1 axis restored the immune functions of exhausted CD8 + T cells, thereby improving the virus clearance in mice chronically infected with lymphocytic choriomeningitis virus (LCMV) (Barber et al., 2006). Preliminary results suggested that treatment with anti-PD1 might improve the outcomes of patients with progressive multifocal leukoencephalopathy due to the JC virus (Koralnik, 2019). However, this benefit was observed only in patients with JC virus-specific CD4 + T cells, showing features of exhausted lymphocytes.

Patients with SARS-CoV-2 infection have a markedly decreased number of NK and CD8 + T cells, which also an exhausted profile with increased expression of the NK group member A (NKG2A) receptor (Zheng et al., 2020). Interestingly, this pattern of functional exhaustion is restored in patients convalescing after COVID-19 treatment, with consequently reduced expression of NKG2A (Zheng et al., 2020). Moreover, significant and durable immunological changes have been shown in patients reaching recovery after COVID-19, including increased antibody-secreting cells, T helper, activated CD4+ and CD8 + T cells, and IgM and IgG antibodies against SARS-CoV-2 (Thevarajan et al., 2020).

The majority of patients receiving immunotherapy, however, show either primary or acquired resistance to treatment, partially due to an immune system persistently dampened by the tumor (Sharma et al., 2017). Curiously, CoV infection in humans shares the same mechanisms involved in immunotherapy acquired resistance, as production of IFN, activation of JAK-STAT pathway and NFkB. On the other hand, PD-1 blockade shifts the balance of antigen-induced cellular reactivity toward a pro-inflammatory T helper (Th)1/Th17 response (Dulos et al., 2012). The consequence of this shift is the enhanced production of IFN γ, IL-2, TNF α, IL-6, and IL-17, and reduced Th2 cytokines IL-5 and IL-13, as observed in severe cases of COVID-19. Polarization of immune response towards a pro-inflammatory profile correlates with lower efficacy of immunotherapy and tumor progression. High NLR at baseline, a marker of subclinical inflammation, correlates with poor survival outcomes and reduced response to immunotherapy.

Along with the presence of comorbidities, recognized risk factors for COVID-19 include male sex, obesity, and older age. Intriguingly, all these factors impact on the host immune system, and have recently been addressed as crucial determinants of response to immunotherapy. There are sex-related differences in hormones (estrogen, progesterone, and androgens) and sex-chromosome-related genes, which make women more prone to mount a stronger immune response compared to men. The incidence of autoimmune diseases is fairly high in female population, while males show a higher risk of cancer throughout their lifetime (Wang et al., 2019). Consistently, male patients seem to benefit more from immunotherapy compared with women (Wang et al., 2019). Regarding obesity, increased body-mass index (BMI) has been correlated with greater survival in patients with chronic conditions, as heart disease, chronic obstructive pulmonary disease (COPD) and kidney disease. This so-called “obesity paradox” has not a clear role in patients with cancer, since higher BMI correlates with increased risk of cancer incidence (Lennon et al., 2016). However, the pro-inflammatory status promoted by adipocytes might explain the correlation of BMI with improved activity and efficacy of immunotherapy in patients with metastatic melanoma (McQuade et al., 2018). Increased age confers immune dysregulation, with fewer naïve CD4+ and CD8 + T cells, decreased regulatory and memory T cells, and an overall pro-inflammatory profile. These changes together shape a condition of immune-senescence, leading to a more restricted repertoire of T cells which might be more prone to develop an exhausted profile during viral infections (Vardhana and Wolchok, 2020). Data on older adults receiving immunotherapy for cancer suggest that the efficacy is similar to that in younger patients, even though older patients tend to have higher incidence of irAEs (Kanesvaran et al., 2018).

Overall, evidence suggests that the interplay between immune system of oncologic patients receiving immunotherapy and SARS-CoV-2 infection is extremely complex. What happens when a reinforced immune system faces tumor cells and CoV infected cells at the same time? Is the immune system helpful or rather an obstacle? This population of patients deserve specific attention and need tailored recommendations in this challenging situation.

6. Recommendations for clinical practice: how oncologists face the pandemic

Clinical practice of health-care workers worldwide has substantially changed during the present pandemic (Indini et al., 2020a). Patients with an immunocompromised status, like those with cancer, are considered particularly vulnerable and at risk of infection. On the other hand, most treatment procedures in oncology cannot be delayed without compromising the efficacy of treatment itself, and in some cases the benefit of ensuring a well-delivered anti-cancer treatment plan outweighs the risk of COVID-19 infection. In the current situation, the main goal to safeguard patients’ care is to guarantee the provision of oncologic services, looking after preservation of both patients and health-care workers. This consideration has led to the rapid draft of medical oncologists’ guidelines for patients’ management during the pandemic (You et al., 2020; Lambertini et al., 2020; Cortiula et al., 2020; Source, 2020b). General measures aiming at the maintenance of COVID-free oncologic services include: use of protective devices, patients’ triage with on-site temperature tests before accessing the hospital, and questions regarding contact and travel history in high-risk areas (Wang et al., 2020). In case of suspected symptoms (e.g. fever, cough, dyspnea), blood tests, imaging and rhino-pharingeal swab are performed. The same measures are used for visitors and caregivers, together with reduction of access for these people during visits and hospitalization.

Reduction in patients’ hospital access has been implemented with the use of phone calls and online exchange of clinical documentation, to replace follow up (i.e. non-urgent) visits of disease-free patients. Phone calls are also used to avoid hospital access of patients with fever and/or respiratory symptoms, with subsequent redirection to family doctors for home care or, whenever required, to hospitalization (Wang et al., 2020). For patients receiving active oncologic treatments, customization of treatment strategy is needed in order to minimize their presence in hospitals. Proposals in this regard include change of intravenous anticancer drugs to orally administered drugs, if available (e.g. etoposide, vinorelbine), and arranging home administration of oral or subcutaneous anticancer agents; adjustment of chemotherapy schedules, favoring those not requiring frequent hospital admissions (e.g. avoiding drugs with weekly administration if an alternate schedule is feasible); temporary breaks for patients with slowly evolving metastatic cancer, extending disease assessment frequency.

Along with the implementation of such measures, prioritization of patients by diagnosis and/or type of anticancer treatment should be pursued. Patients with lung cancer diagnosis seem to be more at risk for severe COVID-19, and therefore deserve more careful evaluation

(Passaro et al., 2020). Data from the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry, which have been presented at the American Association of Medical Oncology (ASCO) 2020 annual meeting, suggest high mortality and low admission to intensive care rates in patients with thoracic malignancies (Garassino et al., 2020). Among patients with lung cancer, the overall severity of COVID-19 is high, however there does not seem to be an increased risk of severe disease in patients receiving immunotherapy (Horn et al., 2020; Luo et al., 2020).

In a recent report, Kutikov et al. (2020) proposed some interesting starting points to guide decision making during pandemic on the basis of a risk assessment for cancer treatment delay. Decision regarding surgery, radiotherapy and medical treatment delays are made after a risk-to-benefit evaluation between the risk of cancer progression due to delay (based tumor type and stage of disease) and risk for significant COVID-19 associated morbidity (based on age and presence of comorbidities). Other relevant elements to consider in decision making are the intent of treatment strategy (i.e. curative vs non-curative), and the patients' life expectancy (Kutikov et al. (2020)).

To date, no specific recommendations have been given on the management of patients receiving immunotherapy. Considering the interplay between CoV and the immune system, these patients might be more at risk for an aberrant immune response in case of CoV infection, and therefore deserve additional precautions. This scenario is even more complex, since patients experiencing disease response and/or with history of irAEs might be more at risk, compared to patients whose disease has progressed during immunotherapy (i.e. with primary/acquired resistance). Furthermore, no markers for early diagnosis can be used to guide decision making in the present situation. Patients with severe COVID-19 present high levels of inflammatory markers (e.g. CRP) and lactate dehydrogenase (LDH), lymphopenia, and high NLR, which are common features also of patients with cancer.

Considering all the above-mentioned issues, we propose a list of clinical and laboratory values (displayed in Table 3), which clinician should consider to evaluate the risk of oncology patients in the actual COVID-19 emergency. These clinical and laboratory variables have been recently grouped to form a risk assessment score, which is currently undergoing validation in the clinic (Indini et al., 2020b). Evidence suggests there is a strong rationale supporting the role of the immune system in CoV infection and patients with cancer, with a complex interplay between pro-inflammatory and immune-suppressive elements which substantially differs among patients receiving different types of treatment. Given the lack of data in this field to date, the assumption of a precise role of these variables is only speculative. Prospective collection of data might help to translate these observations in clinical practice, creating a scoring system to be used as an integrative tool to guide the risk-to-benefit consideration and treatment decision in specific subgroups of patients. Customization of cancer treatment should be pursued, in order to provide patients with the best care in this critical situation.

7. Conclusion

At the present time, precise data on the pathogenesis of COVID-19 and subsequent risk of morbidity in patients with cancer are lacking. Evidences suggest that this risk might be different depending on the oncologic treatment received. There is a strong rationale supporting an increased risk of COVID-19 morbidity in patients treated with immunotherapy and, in this subset of patients, a potential higher risk for those experiencing disease responses to treatment and/or with a history of irAEs. However, with data available we still cannot provide practical indications for the management of oncologic patients in this critical situation. Efforts should be made to prospectively collect data, in order to identify effective interventions to guide treatment decision during the pandemic.

Table 3
Clinical and laboratory values for risk evaluation in patients with cancer during COVID-19.

Variables	
Patient characteristics	
Sex	F vs M
Age	< 70 vs ≥ 70
BMI	< 30 vs ≥ 30
Comorbidities[a]	NO vs YES
History of autoimmune disease	NO vs YES
Concomitant steroid treatment[b]	NO vs YES
Disease characteristics	
Thoracic tumor	NO vs YES
History of thoracic RT*	NO vs YES
Treatment characteristics	
Line of treatment	Adjuvant vs metastatic
Type of treatment	HT/TT/TKIs/mAb vs CT vs IT/CT + IT
History of irAEs**	NO vs YES
Laboratory values	
NLR	< 5 vs ≥ 5
LDH	< ULN vs ≥ ULN
CRP	< ULN vs ≥ ULN

Abbreviations: BMI, body-mass index; COVID-19, novel coronavirus disease; CRP, C-reactive protein; CT, chemotherapy; F, female; HT, hormonal therapy; irAEs, immune-related adverse events; IT, immunotherapy; LDH, lactate dehydrogenase; M, male; mAb, monoclonal antibody; NLR, neutrophil-to-lymphocyte ratio; RT, radiotherapy; TKIs, tyrosine kinase inhibitors; TT, targeted therapy; ULN, upper limit of normal.

[a] Comorbidities include: hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, chronic systemic infections.

[b] Concomitant steroid treatment includes continuous therapy with > 10 mg daily of prednisone equivalent, lasting for more than 1-month period.

* only for patients with extra-thoracic tumors.

** only for patients treated with IT or IT + CT.

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CRediT authorship contribution statement

Alice Indini: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Erika Rijavec:** Investigation, Methodology. **Michele Ghidini:** Investigation, Methodology. **Claudia Bareggi:** Visualization, Writing - review & editing. **Monica Cattaneo:** Visualization, Writing - review & editing. **Barbara Galassi:** Visualization, Writing - review & editing. **Donatella Gambini:** Visualization, Writing - review & editing. **Francesco Grossi:** Funding acquisition, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

F. Grossi declares the following conflicts of interest: Consulting or Advisory Role for MSD Oncology, Bristol-Myers Squibb, AstraZeneca, Roche, Pfizer, Bayer. Speakers' Bureau: MSD Oncology, Bristol-Myers Squibb, AstraZeneca, Roche, Pierre Fabre, Amgen, Celgene, Eli Lilly, Pfizer. Research Funding: Bristol-Myers Squibb. Travel, Accomodations, Expenses: Bristol-Myers Squibb, MSD, Roche, AstraZeneca, Pierre Fabre, Celgene, Amgen, Eli Lilly, Novartis. All remaining authors have declared no conflicts of interest.

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